Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Netupitant / palonosetron (as hydrochloride)

Proprietary Product Name: Akynzeo

Sponsor: Specialised Therapeutics Australia Pty Ltd[1]

October 2016

TGA Health Safety Regulation

[1] Post registration the sponsorship for Akynzeo has changed to Mundipharma Pty Ltd, GPO Box 5214, Sydney NSW 2001.

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
5-HT_3	Serotonin
5-HT_3 RA	5-HT_3 receptor antagonist
AC	anthracycline-cyclophosphamide
ADR	adverse drug reaction
AE	adverse event
ALT	Alanine aminotransferase
APD	action potential duration
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	area under the concentration time curve
AUC_{inf}	area under the concentration versus time curve up to infinity
$AUC_{0-\infty}$	area under the concentration versus time curve up to infinity
AUC_{0-t}	area under the concentration-time curve from time zero to time t
AUC_{0-tz}	area under the concentration-time data profile from administration until the last sampling point (tz) equal or above LLOQ.
BA	bioavailability
BCRP	breast cancer resistance protein
BD	twice daily
BE	bioequivalence
BP	British Pharmocopeia
bpm	beats per minute
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CINV	Chemotherapy induced nausea and vomiting
CL/F	apparent clearance

Abbreviation	Meaning
CLCR	Creatinine clearance
C_{max}	peak drug concentration
CNS	central nervous system
CTZ	chemoreceptor trigger zone
CYP	Cytochrome P450
CYP3A4	Cytochrome P450 isoenzyme 3A4
ECG	Electrocardiogram
ED50	Median (50%) effective dose
EMA	European Medicines Agency
EPAR	European public assessment reports
EviQ	Evidence based cancer treatments (online)
ESMO	European Society for Medical Oncology
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed dose combination
G-CSF	granulocyte colony-stimulating factor
GD	gestation day
GDH	glutamate dehydrogenase
GGT	gamma-glutamyl transpeptidase
GLP	Good Laboratory Practice
GM-CSF	granulocyte macrophage colony-stimulating factor
h	hour/s
Hb	haemoglobin
HEC	highly emetogenic chemotherapy
hERG	human Ether-à-go-go Related Gene

Abbreviation	Meaning
IV	Intravenous
MASCC	Multinational Association of Supportive Care in Cancer
MCH	mean corpuscular haemoglobin
MCV	mean corpuscular volume
MEC	moderately emetogenic chemotherapy
MedDRA	The Medical Dictionary for Regulatory Activities
mL	Millilitre
ms	Millisecond
NaCl	sodium chloride
NK1	Neurokinin 1
NK1 R	NK1 receptor
OR	Odds ratio
PBAC	Pharmaceutical Benefits Advisory Committee
PBRER	Periodic Benefit-Risk Evaluation Report
PBS	Pharmaceutical Benefits Scheme
PD	Pharmacodynamics
PET	positron emission tomography
PI	Product Information
PK	Pharmacokinetics
PND	postnatal day
PopPK	population PK
PRAC	EMA Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	preferred term
QTcF	Fridericia-corrected QT interval
QTcV	Van de Water corrected QT interval

Abbreviation	Meaning
SAE	serious adverse event
SD	Standard Deviation
SDH	sorbitol dehydrogenase
SDS	surfactant sodium dodecylsulfate
SE	sucrose lauric ester
SOC	System Organ Class
SMQs	Standardised MeDRA queries
t½	half-life
t½z	apparent terminal elimination half-life
TEAE	treatment emergent adverse events
TGA	Therapeutic Goods Administration
US	United States
V/F	Absolute volume of distribution
V_z/F	volume of distribution
λ	blood/plasma concentration ratio
µg	Microgram

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity (netupitant)/new fixed dose combination
Decision:	Approved
Date of decision:	4 May 2015
Date of entry onto ARTG	6 May 2015
Active ingredients:	Netupitant and palonosetron (as hydrochloride)
Product name:	Akynzeo
sponsor's name and address:	Specialised Therapeutics Australia Pty Ltd[2] PO Box 250, Kew East VIC 3102
Dose form:	Capsule
Strength:	Netupitant/palonosetron 300 mg and 0.5 mg
Container:	Blister pack AI/AI
Pack size:	Blister pack containing 1 capsule
Approved therapeutic use:	*Akynzeo is indicated in adult patients for:* *Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.* *Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.*
Route of administration:	Oral (PO)
Dosage:	The recommended dose is one capsule approximately one hour prior to the start of each chemotherapy cycle. The concomitant use of dexamethasone is recommended.
ARTG number:	222237

[2] Post registration the sponsorship for Akynzeo has changed to Mundipharma Pty Ltd, GPO Box 5214, Sydney NSW 2001.

Product background

This AusPAR describes the application by the sponsor, Specialised Therapeutics Australia Pty Ltd, to register a new chemical entity, netupitant, in the fixed-dose combination (FDC) of netupitant 300 mg and palonosetron 0.5 mg for the following indication:

> *Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.*
>
> *Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.*

The proposed dosing regimen is 300 mg netupitant and 0.5 mg palonosetron one hour prior to the start of each chemotherapy cycle.

Palonosetron is a 5-HT_3 receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors. Palonosetron is already registered as a single agent for the same indication as a solution for injection. In this application a new dose form and route of administration is proposed for palonostron in the FDC with netupitant.

Netupitant is a selective high-affinity antagonist of human substance P, neurokinin 1 (NK1) receptors, with little or no affinity for serotonin (5-HT_3), dopamine, and corticosteroid receptors.

Chemotherapy induced nausea and vomiting (CINV) can lead to metabolic problems such as fluid and electrolyte balance disturbances and nutritional status deficiencies, psychological problems, decision by physician to reduce chemotherapy dose intensity, or decision by the patient to stop potentially beneficial cancer treatment.

CINV is classified as either acute (occurring within the first 24 hours after chemotherapy) or delayed (occurring after the first 24 hours, extending until the fifth day). The development of acute emesis is known to largely depend on serotonin (5-HT_3). CINV is mainly due to input from the chemoreceptor trigger zone (CTZ). The neurotransmitters serotonin and dopamine stimulate the vomiting centre indirectly via stimulation of the CTZ. The 5-HT_3 receptor has been shown to selectively participate in the emetic response, thus providing a physiological explanation for the clinical anti-emetic effects of 5-HT_3 receptor antagonists.

Delayed emesis during chemotherapy treatment has been largely associated with the activation of tachykinin family neurokinin 1 (NK1) receptors by substance P. Netupitant and palonosetron can contribute to the inhibition of substance P mediated response. Palonosetron can enhance the prevention of delayed emesis provided by netupitant.

The clinical anti emetic efficacy of 5-HT_3 receptor antagonists and NK1 R antagonists is considered to be complementary: the major effect of 5-HT_3 receptor antagonists is in the control of the acute phase of CINV, while the additional benefit of NK1 R antagonists is mostly seen in the control of the delayed phase of CINV.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 6 May 2015.

Palonosetron 250 µg/5 mL solution for intravenous (IV) injection received registration on the Australian Register of Therapeutic Goods (ARTG) 26 June 2006and is indicated *'for prevention of nausea and vomiting induced by cytotoxic chemotherapy'*.

Oral palonosetron is not registered in Australia but is approved in the United States (US) and European Union (EU) as a 0.5 mg dose, for prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

At the time the TGA considered this application; a similar application had been approved in or was under consideration in the countries as shown in Table 1.

Table 1 Overseas regulatory status

Country	Submisiion/ approval date	Indication
United States	10 October 2014	Akynzeo is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. Akynzeo is an oral fixed combination of palonosetron and netupitant: palonosetron prevents nausea and vomiting during the acute phase and netupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy.
Europe	CHMP Final Opinion expected on 26 March 2015	
Switzerland	Application made on 4 July 2014	
Israel	Application made on 23 October 2014	
Singapore	Application made on 22 December 2014	
Philippines	Application made on 23 December, 2014	
Malaysia	Application made on 24 December, 2014	

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Introduction

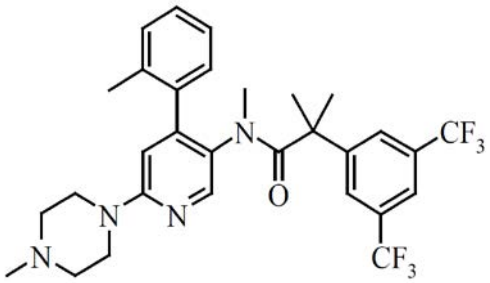
The sponsor has applied to register Akynzeo fixed dose combination hard gelatin capsules containing 300 mg netupitant and 0.5 mg palonosetron (as hydrochloride). The combination capsule contains three netupitant tablets 100 mg and one palonosetron softgel capsule 0.5 mg.

The proposed shelf life for the unopened product is 24 months 'Store below 30°C' in the original container and protected from light. , however this is not supported by the stability studies conducted.[3]Netupitant and palonosetron hydrochloride are not subject to British Pharmacopeia (BP)/European Pharmacopeia (Ph.Eur.) or US Pharmacopoeia (USP) monographs.

Drug substance (active ingredient)

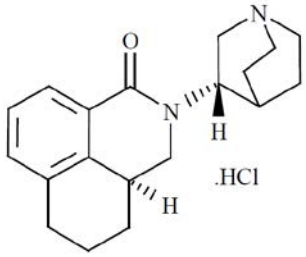
The drug substance, netupitant, has the following structure as shown in Figure 1.

Figure 1. Chemical structure of netupitant



The drug substance, palonosetron hydrochloride, has the structure show in Figure 2.

Figure 2. Chemical structure of palonosetron hydrochloride



Drug product

The proposed product is a single combination capsule.

[3] Based on the stability presented for both the primary and supportive stability studies, a storage condition of 'Store below 25°C' is supported by the data.

Netupitant

Netupitant tablets are a conventional immediate release formulation. The tablets are manufactured by conventional processes, by mixing, wet granulation, drying, milling, screening, blending and compression.

Netupitant was shown to be suitably stable under stressed, accelerated and long term conditions in the Drug Master File (DMF).

Palonosetron

Palonosetron softgel capsules areplain, round to oval, opaque, light beige, liquid filled, soft gelatin capsules, comprising 0.5 mg palonosetron fill solution encapsulated in Size 1.5 oval softgel capsule shells. The softgel capsules are manufactured by conventional processes, by compounding, mixing and encapsulation.

Netupitant-palonosetron combination capsules

The combination capsule is composed of one Size 0 hard gelatin capsule. Each capsule contains three intermediate netupitant tablets and one intermediate palonosetron softgel capsule. For the encapsulation process, the hard gelatin capsule is opened, three intermediate netupitant tablets followed by one intermediate palonosetron softgel capsule are filled into the hard gelatin capsule body, and then the hard gelatin cap is placed on the body and the capsule is closed.

Based on the stability presented for both the primary and supportive stability studies, a storage condition of 'Store below 25°C' is supported by the data.

Biopharmaceutics

Seven Biopharmaceutic/Bioavailability/Bioequivalence studies were presented.

Netupitant

Absolute netupitant bioavailability data are not available in humans. However, based on the results of two studies, which examined the safety, tolerability and pharmacokinetics (PK) of ascending doses of I.V. netupitant in healthy volunteers (Studies BP17085 and NETU-11-01), the bioavailability of netupitant in man is thought to be greater than 60%.

Palonosetron

Absolute bioavailability of palonosetron had not been determined in the present submission. However, The European Public Assessment Reports (EPAR) PI for Aloxi (palonosetron) 0.5 mg soft capsules indicates that palonosetron is well absorbed with an absolute bioavailability reaching 97%.

Advisory committee considerations

The PSC considered the application to register Akynzeo capsule containing netupitant 300 mg and palonosetron hydrochloride 0.5 mg as a new combination.

The PSC advised that it had no further questions for the sponsor. The PI and CMI should be amended to reflect the recommendations of the PSC.

Quality summary and conclusions

Netupitant 300 mg and palonosetron (as hydrochloride) 0.5 mg capsules in blister packs are recommended for approval subject to resolution of the following:

- Clarification of the statement 'Each Akynzeo hard capsule shell contains 7 milligrams of sorbitol.' in the PI.
- Confirmation that the text height on the blister labels will meet the requirements of Therapeutics Goods Order (TGO 69).
- Confirmation that a test for Uniformity of Dosage Units by 2.9.40 will be included in the Certified Product details (CPD) submitted to the TGA.

III. Nonclinical findings

Introduction

General comments

The overall quality of the non-clinical dossier was good with all pivotal studies conducted according to Good Laboratory Practice (GLP).

Pharmacology

Primary pharmacology

Without prophylactic therapy most cancer patients experience Chemotherapy induced nausea and vomiting (CINV). The neural circuits involved in emesis are complex and not fully elucidated and involve inputs from the abdominal vagus via the nucleus tractus solitarius and from the chemoreceptive trigger zone in the area postrema. These inputs are integrated in a central pattern generator to stimulate the vomiting response. Neurotransmitter receptor systems involved in the mediation of signals leading to nausea and vomiting include dopaminergic (D2), cholinergic (muscarinic), histaminergic (H1), serotonergic (5-HT_3), and neurokinin NK1 systems. The corresponding receptors are potential targets for antiemetic drugs. The FDC Akynzeo combines antagonists at two of these receptors; palonosetron, an antagonist at serotonin receptors (5-HT_3 R) and netupitant, an antagonist at NK1 Rs.

Primary pharmacodynamic studies with netupitant established affinity and selectivity for recombinant human NK1 Rs with the isoelectric point (pKi) 9.0. pKi values for other NK receptors were human NK2 5.8, human NK3 7.49, rodent NK1 8.1, canine NK1 8.6, and guinea-pig NK3 5.8. pKi values for major human metabolites M1, M2 and M3 at hNK1 Rs were 9.0, 9.0 and 9.1 respectively, suggesting these metabolites are also active. M4, a minor metabolite in humans, also bound to hNK1 Rs (pKi 8.8) and human NK3 receptors (pKi 5.57). An in vitro functional assay using Chinese Hamster Ovary (CHO) cells expressing hNK1 showed that netupitant behaves as a competitive antagonist.

Netupitant antagonised emesis in ferrets induced by various emetogens and antagonised acute and delayed emesis induced by cisplatin for up to 72 hours (50% effective dose (ED50) approximately 0.2 mg/kg orally (PO)). Plasma levels of netupitant which produced 90 to 95% inhibition of cisplatin induced emesis between 40 to 72 hours post dosing were in the range 40 to 60 ng/mL, significantly below the anticipated clinical peak plasma concentration (C_{max})(567 ng/mL). Motion induced emesis was blocked by netupitant in the shrew (ED50 approximately 0.1 mg/kg PO). Netupitant inhibited NK1 agonist induced foot

tapping in Mongolian gerbils (ED50 0.5 mg/kg PO, 1.5 mg/kg intraperitoneally (IP). Complete inhibition of foot tapping was achieved at a plasma concentration of 40 ng/mL in 75% of gerbils, consistent with the findings in ferrets. In the gerbil model, metabolites M1 (ED50 5.4 mg/kg IP, 2.4 mg/kg PO) and M3 (ED50 1.2 mg/kg IP) were also active in this screen. Metabolite M2 was not active by the IP route (ED50 > 10 mg/kg IP), but resulted in 70% inhibition at 10 mg/kg PO. The reason for the lower effective dose by the PO route than the IP dose for netupitant and metabolites is unclear.

Netupitant combined with dexamethasone and palonosetron combined with dexamethasone were effective in preventing emesis induced by cisplatin in castrated male ferrets during the first 24 hours following cisplatin dosing. The combination of netupitant (0.3 or 1 mg/kg) and palonosetron (0.1 mg/kg) plus dexamethasone was also effective in preventing emesis during this period. None of the treatment regimens (either drug alone or combination) was effective in reducing retching and vomiting during the following 24 to 48 hours. Cisplatin induced decreases in food consumption and water consumption and increases in kaolin consumption were not affected significantly by regimens of netupitant or palonosetron alone, combined together, or by aprepitant/ondansetron.

Overall, nonclinical in vitro and in vivo data support the proposed clinical indication. Netupitant in combination with palonosetron was more effective than either drug alone.

Secondary pharmacodynamics and safety pharmacology

In in vitro screening assays of receptors and ion channels, netupitant showed some interaction with histamine H2 and adenosine A3 receptors, and dopamine and 5-HT re-uptake sites (respective inhibition: 95%, 78%, 67% and 53% at 10 µM; no binding at 0.1 µM), with only weak binding to H2 at 1 µM (38% inhibition). Netupitant also showed significant binding to the L-type calcium (Ca^{2+}) channel (diltiazem) binding site (Ki 1.2 µM). Binding assays with metabolites M1, M2, M3 and M4 showed inhibition of noradrenaline uptake 50% inhibitory concentration (IC_{50}) (1.3 µM) and dopamine uptake (IC_{50} 0.48 µM) by M1, and inhibition of noradrenaline uptake (58%) and dopamine uptake (81%) by M3 only at 10 µM. Similar to netupitant, M1, M2 and M3 showed binding to the L-type Ca^{2+} channel (Ki 0.5, 7.9 and 1.6 µM, respectively). Binding to L-type calcium channels might play a role in the cardiac effects observed in some studies (discussed below). The effective concentrations in vitro were > 100 fold higher than the anticipated free fraction of netupitant or metabolites at the clinical C_{max} (netupitant 9.8 nM, M1 0.71 nM, M2 8.9 nM and M3 1.16 nM based on free factions of 0.01, 0.01, 0.02 and 0.01, respectively). If the IC_{50}/Ki values are compared with the combined clinical free fraction C_{max} (approximately 20 nM) of netupitant and the 3 metabolites, the exposure margins are low.

Specialised safety pharmacology studies covered the cardiovascular, respiratory, renal, gastrointestinal systems and some aspects of the central nervous system (CNS). There was no evidence of effects on the function of respiratory (dog, 50 mg/kg), renal (rat, 100 mg/kg) and gastrointestinal (rat, 100 mg/kg) systems at plasma C_{max} of 1,140 (dog) and 3860 (rat) ng/mL, compared with compared with the anticipated C_{max} of 567 ng/mL in patients.

Extensive in vitro cardiovascular safety studies were conducted with netupitant and metabolites M1, M2, and M3. In isolated dog myocytes, netupitant, M1 and M3 (not M2) caused detectable inhibition of the rapid component of delayed rectifier potassium (K^+) current (which is conducted by the human Ether-à-go-go Related Gene (hERG) channel) at concentrations ≥ 3 µM (14 to 25% at 3 µM). A single non GLP study examined the effects of netupitant and the metabolites on inhibition of hERG K^+ currents expressed in CHO cells. IC_{50} or Ki values (µM) for this inhibition were netupitant 0.76, M1 0.84, M2 43 and M3 4.4,

which are > 50 fold higher than the clinical free fraction C_{max} for the parent and metabolites (see Table 2 below).

Table 2. Effects of netupitant and active metabolites on cardiac conduction in vitro

In vitro assay	Netupitant	M1	M2	M3	IC50/C_{max} ratio†
L-type Ca2+ channel (diltiazem) binding, Ki (µM)	1.2	0.5	7.9	1.6	122, 699, 888, 1379
CHO cells - hERG K+ currents, IC50 (µM)	0.76	0.84	43	4.4	78, 1175, 4831, 3793
Dog myocytes - rapid component of delayed rectifier potassium current	21% inhibition at 3 µM	25% inhibition at 3 µM	No effect at 30 µM	14% inhibition at 3 µM and 57% at 30 µM	-
Dog Purkinje fibres – action potential duration	Decrease at 3 µM	Decrease at 3 µM	Decrease at 30 µM	Decrease at 30 µM	-
Dog papillary muscles - action potential duration (APD)	No effect at 3 µM	No effect at 30 µM	No effect at 30 µM	Prolonged APD50,70,90 at > 3 µM and APD70 at ≥ 0.3 µM at 1 Hz by 14-18 ms	-
Clinical free fraction C_{max} (nM)*	9.8	0.715	8.9	1.16	-

†Ratio of IC_{50} or Ki to clinical free fraction C_{max} for netupitant, M1, M2, M3; * Based on C_{max} of 980, 71.5, 445.7 and 116.0 nM and free fraction of 0.01, 0.01, 0.02 and 0.01 for netupitant, M1, M2 and M3, respectively. ms = milliseconds

In isolated dog Purkinje fibres netupitant and M1 reduced action potential duration(APD) at 50, 70 and 90% (APD50, APD70 and APD90) at 3 µM, and M2 and M3 had similar effects at 30 µM (no effects at 3 µM). Netupitant at concentrations up to 3 µM (maximum concentration tested) and metabolites M1 and M2 at concentrations up to 30 µM had no effects on action potential parameters in dog papillary muscles in vitro. Metabolite M3 did increase the duration of action potentials (APD50, 70, 90) at concentrations 0.3 to 30 µM by 14 to 18 ms.

In vivo cardiovascular safety studies were conducted in three species with netupitant, metabolites M1, M2 and M3 and palonosetron/netupitant combinations by IV injection.

There were some small increases in APD recorded from anaesthetised guinea pigs dosed with M3 at 0.3 to 3 mg/kg (APD70 and APD90: 10 to 16% at 0.3 to 3 mg/kg); sinus period was also increased, indicating bradycardia. The combination of palonosetron and netupitant caused dose dependent, significant increases in APD (by 19 to 38% in APD70 and APD90) at doses ≥ 0.3 palonosetron/0.03 netupitant mg/kg IV in the unpaced heart. No significant effects in the paged heart.

In rabbits netupitant (30 mg/kg) or metabolite M2 (30 mg/kg) had no effects on arterial pressure or electrocardiogram (ECG) parameters. Metabolite M1 (1 mg/kg) caused increases in diastolic pressure (+2%), and RR (+51%) and QT (+16%) intervals (no effects on Fridericia-corrected QT interval (QTcF) in the heart's electrical cycle at 15 minutes post dose. Metabolite M3 (1 mg/kg) caused a transient fall in arterial pressure, long lasting bradycardia, and prolonged QT interval (corrected QTcF not significantly increased). Two animals had premature ectopic beats, pairs, runs, ventricular bigeminist and tachycardia. The combination of netupitant and palonosetron (30/3 mg/kg) caused significant hypotension (systolic arterial pressure -23%, diastolic arterial pressure -33%) and bradycardia (RR +31%) at 15 min, and significantly increased QT interval (QT +41%) at 10 minutes (QTcF +34%, non-significant).

QT interval (corrected and uncorrected) prolongation was observed after 8 days at 50 mg/kg/day in dogs (Day 14: QT +11%, QTcF +8%, Van de Water corrected QT interval (QTcV) +9%), with plasma netupitant C_{max} of approximately 4,000 ng/mL and M1 C_{max} approximately 3,500 ng / mL (other metabolites not measured), although in another study no effect on QT intervals was observed after 5 days at the same dose. Conversely, in one single high dose study in dogs (100 mg / kg) QT shortening (QT -23%, QTcV -12%, QTcQ -13% between 5 and 8 h; QTcF unaffected) was observed, associated with tachycardia (+ 36 beats per minute (bpm)) and hypertension (mean arterial pressure + 14 mmHg). QT prolongation (QT + 26%, QTcF + 12%, QTcV + 14% on Day 12) was also seen after 5 days at 30 mg/kg/day (C_{max} 4,000 to 9,000 ng/mL) with metabolite M1 (no effects at 5 mg/kg/day, plasma M1 C_{max} approximately 1500 ng/mL), associated with bradycardia (RR +43%). No studies with other metabolites were conducted in dogs. In repeat dose toxicity studies, there were small (approximately 10% or 10 to 20 ms), but significant, increases in QT and QTc (QTcF and QTcV) at the highest dose (10 mg/kg/day), particularly in males in the 9 month study and in females in the 3 month combination study. Uncorrected QT prolongation was also observed after 23 days at ≥ 15 mg/kg/day, associated with bradycardia. In a safety pharmacology study following combined doses of palonosetron and netupitant (10/10 and 10/50 mg/kg) for 7 days, there was a dose-dependent decrease in atrio-ventricular conduction and in ventricular depolarisation rate associated with a slight prolongation of ventricular repolarisation. Plasma C_{max} values in the dog studies are compared with the clinical C_{max} in the following table.

Table 3. Comparison of plasma C_{max} in dogs with clinical C_{max}

	Netupitant	M1	M2	M3	Animal/human ratio†
Repeat dose 9 month study at 10 mg/kg/day	1,024	1,595	439	97	1.8, 41, 1.7, 1.4
Safety pharmacology 2 week study at 50 mg/kg/day	4,240	3,980	ND	ND	7.5, 102, -, -
Safety pharmacology 2 week study with M1 30	-	9,060	-	-	-, 232, -, -

	Netupitant	M1	M2	M3	Animal/human ratio†
mg/kg/day					
Safety pharmacology 2 week study with M1 5 mg/kg/day	-	1,510	-	-	-, 39, -, -
Repeat dose combination 3 month study at 10/10 mg/kg/day	839	1,345	407	77	1.5, 34, 1.5, 1.1
Clinical C_{max}*	567	39	265	69	-

* From population pharmacokinetic Study NETU-10-02 for netupitant and clinical Study NETU-10-09 for metabolites; † For netupitant, M1, M2 and M3, respectively; ND, no data.

High levels of netupitant and M1 in heart tissues were detected in dogs after repeated dosing. The mean concentrations at 50 mg/kg/day for 5 days were 16,600 ng/g for netupitant, 94,100 ng/g for M1, below the limit of quantification (LOQ) for M2, and 1,430 ng/g for M3, and higher levels were detected after 4 weeks (40,400, 128,000 and 5,060 ng/mL for netupitant, M1 and M3, respectively). The heart concentrations of netupitant and metabolites M1 and M3 were around 10, 20 and 8 fold higher than the plasma C_{max}, respectively. It appears netupitant, M1 and M3 accumulates in the heart tissue. Relatively high levels of netupitant-related materials (measured as radioactivity after dosing with radiolabelled netupitant) were also detected in rats in the tissue distribution studies (myocardium/plasma ratio 6 to 14 at most time points after a single dose).

Histological lesion of myodegeneration was only reported in rats at very high doses (100 mg/kg/day for 4 weeks, netupitant area under the concentration time curve (AUC) AUC_{0-24h} approximately 300 times clinical $AUC_{0-\infty}$. No myocardial lesions were seen in dogs.

The sponsor suggested that the cardiac effects were mainly attributable to M1 because of high M1 levels detected in dog plasma and heart tissues and similar cardiovascular findings in dogs dosed with M1 or netupitant. However, studies with M2 and M3 also indicated that these metabolites in addition to netupitant and M1 may contribute to the cardiovascular effects, for example, M3 caused APD prolongation in dog papillary muscles while M1, M2 and netupitant had no effects. Based on L-type Ca^{2+} channel binding and hERG inhibition, M2 is the least potent while netupitant and M1 are most potent in affecting cardiac conduction.

The above in vitro and in vivo study findings indicate that netupitant affects cardiac conduction probably by binding to the L-type Ca^{2+} channel and inhibiting the hERG channel and causes bradycardia and prolongation of APD. Netupitant and palonosetron may have additive effects on cardiac conduction. Some potential for cardiovascular effects in patients taking the netupitant/palonosetron combination exists based on the observations in the nonclinical studies.

No evidence of CNS effects was observed in any of the repeat dose toxicity studies, although distribution of netupitant and/or metabolites to brain was evident in rats. Netupitant alone had no pro convulsant activity in rats (100 mg/kg single dose). No neurological effects were detected in an Irwin battery in a non GLP study in rats. A non GLP study on the abuse potential of the combination of palonosetron and netupitant was conducted in baboons. Oral doses of the combination at up to 10/0.02 mg/kg/day (netupitant/palonosetron) for one month did not result in withdrawal or dependence symptoms.

Pharmacokinetics

Absorption

In rats and dogs time of C_{max} values were mostly between 2 to 8 hours with some exceptions and these were comparable to the human values reported to be between 4 and 5 hours. In animals (rat, dog and monkey) oral bioavailability ranged from 34 to 100%. Sub dose proportional increases in exposure to netupitant and metabolites were seen with increasing dose in rats and dogs. In rats both netupitant and M1 showed accumulation with rates ranging from 1.3 to 5 times for netupitant and up to 10 times for M1 while in dogs accumulation of netupitant was slight to moderate and accumulation of M1 was moderate to high (up to 11 times). In rats and dogs the apparent half-life for netupitant was around 10 hours but was much longer during the recovery phase (up to 38.4 hours).

Distribution

Plasma protein binding by netupitant and major metabolites was high in humans (> 99% for netupitant, M1 and M3, 98% for M2) and laboratory animal species. The volume of distribution was high in laboratory animal species, around 11.5 L/kg in rats, 13.8 L/kg in dogs and 10 L/kg in monkeys. Netupitant was rapidly distributed to most organs in rat whole body autoradiography studies and penetration to brain and testes was demonstrated. Drug associated radioactivity was generally eliminated from the tissues in parallel with plasma.

Metabolism

Metabolites were formed by N-demethylation (M1), oxidation (M2, and subsequently M6, M8), methyl hydroxylation (M3), hydroxylation (M5), and glucuronidation (M6-G and M8-G). Cytochrome P450 (CYP) CYP3A4 catalysed the formation of two metabolites M1 and M2. The human metabolites M1, M2, M3, and M4 (minor metabolite < 10% parent in humans) were all detected in dog plasma and bile, and M1, M2 and M3 in rat plasma and bile. The oxidative metabolite M4 was detected in humans late in the development of the drug. It was detected and described in dog plasma in an in vivo metabolism study. In repeat dose toxicity studies the metabolic profile of netupitant in dogs and rats was similar with M1 shown to be the predominant metabolite in both species. Production of M3 was higher in rat bile than in dog in vivo metabolism studies. In humans M3 accounted for a greater proportion of drug related material than in rats or dogs.

Excretion

Netupitant is cleared by metabolism and biliary excretion. Excretion of netupitant and/or its metabolites was almost exclusively via the faeces in rats and dogs. Urinary excretion was also not a significant excretory route in humans.

Conclusion

The pharmacokinetic profiles in the laboratory animal species (particularly those used in the pivotal repeat dose toxicity studies) were sufficiently similar to allow them to serve as appropriate models for the assessment of drug toxicity in humans. Significant accumulation of netupitant and M1 was noted in repeat dose studies.

Pharmacokinetic drug interactions

Since netupitant is predominantly metabolised by cytochrome P450 isozyme 3A4 (CYP3A4) to M1 and M2, CYP3A inhibitors or inducers may alter the plasma

concentrations of netupitant and metabolites. However, as all 3 major metabolites are pharmacologically active, the net effects on efficacy and safety might not be significantly affected. There are no data on the clearance of the metabolites.

Netupitant is a competitive inhibitor of CYP3A4 inhibition constant (Ki) 1.1 μM, IC_{50} 1.7 μM). M1 and M2 are also inhibitors of CYP3A4 with IC_{50} values similar to those for netupitant. The Ki or IC_{50} values were approximately 50 times the combined free fraction C_{max} of netupitant and metabolites (approximately 20 nM) in patients. The potential for drug - drug interactions via CYP3A4 inhibition is low. Netupitant inhibited CYP2C9 only at high concentrations (IC_{50} approximately 20 μM; Ki 25 μM). Netupitant and its metabolites, M1 and M2 were not inhibitors of CYP1A2, 2C19, or 2D6. Significant metabolic drug - drug interactions in man are not anticipated for compounds metabolised mainly by CYP1A2, 2C9, 2C19 or 2D6.

No induction of CYP1A2, CYP2C9, CYP2C19 and CYP3A4 was seen with netupitant and major metabolites. Studies in human liver microsomes suggest that drug - drug interactions are unlikely with cyclophosphamide and vincristine but may be possible with docetaxel. In human liver microsomes, netupitant inhibited hydroxylation of docetaxel with an IC_{50} of 3.7 μM.

In vitro studies investigated the potential for the interaction of netupitant and metabolites M1, M2 and M3 with the human ABC (efflux) transporters breast cancer resistance protein (BCRP) (ABCG2/MXR), BSEP (ABCB11/sPgp), MRP2 (ABCC2) and MDR1 (ABCB1/P-gp) and the human uptake transporters OATP1B1 (OATP2, OATP-C), OATP1B3 (OATP8), OAT1, OAT3, OCT1 and OCT2. Netupitant and/or its metabolites inhibited BCRP (IC_{50} 6.0, 8.6, 22.6 and 10.6 μM for netupitant, M1, M2 and M3, respectively), OCT1 (IC_{50} 8.1, 19.0, 7.4 and 4.4 μM for netupitant, M1, M2 and M3, respectively), MDR1 (IC_{50} 4.95, 8.0 and 5.35 μM for M1, M2 and M3, respectively), OATP1B3 (IC_{50} 4.3 and 9.6 μM for M2 and M3, respectively). Results of inhibition studies with Caco - 2 cell monolayers showed permeability glycoprotein (P-gp) inhibition (by 55%) at 5 μM (no effects at 1 μM). The IC_{50} values were > 200 fold higher than the combined clinical free fraction C_{max} of netupitant and metabolites (approximately 20 nM). Drug - drug interactions via transporters in patients are unlikely.

Toxicology

Acute toxicity

The acute oral toxicity of netupitant was assessed in single dose studies in mice, rats and dogs. None of the studies was GLP compliant. The maximum non lethal oral dose in rats was 1,500 mg/kg and in dogs was 400 mg/kg dose. A maximum non lethal dose was not determined in mice where the lowest dose tested (1,000 mg/kg) was lethal.

In mice doses ≥ 1,000 mg/kg causes inflammation and necrosis in the liver, spleen and mesenteric and mandibular lymph nodes. Signs of phospholipidosis were also present in these tissues and were also present in the lung. In rats single doses (≥ 1,500 mg/kg) caused inflammation and necrosis in liver and doses of 2,000 mg/kg necrosis of mesenteric lymph nodes, skeletal muscle, stomach and duodenum. There were also signs of phospholipidosis in these tissues and in the lung.

Single doses 200 to 400 mg/kg in dogs had minimal effects with a slight increase in the occurrence of vacuolated macrophage infiltration in gall bladder at the highest dose and the appearance of foamy alveolar macrophages in the male animal at this dose. These macrophage changes are consistent with phospholipidosis, similar to those seen in rodents. Dogs were also dosed with daily ascending single doses (3, 10, 30, 30, 60, 100,

150 mg/kg). At the end of this dosing sequence some lymphocyte depletion was noted in lymphoid tissues and there was necrosis of parietal cells in the stomach mucosa.

Acute toxicity of netupitant is moderate with significant mortality and evidence of necrosis in several tissues following single doses. No pharmacokinetic data was submitted for doses in the range of those used in the single dose studies. The doses at which this toxicity occurred were probably much higher than the anticipated clinical exposure.

Repeat dose toxicity

Repeat dose toxicity studies with netupitant alone were conducted in three species: mouse, rat, and dog. The maximum doses employed in these studies were 450 mg/kg/day in the mouse, 300 mg/kg/day in the rat and 10 mg/kg/day in the dog. Studies of up to 13 weeks duration were conducted in mice, 26 weeks duration in rats and 39 weeks duration in dogs. The daily dosing regimens in these studies are quite different from the anticipated clinical use which involves single doses likely to be separated by periods of several weeks. The effects seen in repeat dose studies were, however, similar to those seen following much higher single doses.

Repeat dose studies with palonosetron/netupitant combinations were conducted in two species: rats and dogs. The maximum doses employed in these studies were palonosetron 60/netupitant 30 mg/kg/day in rats and palonosetron 15/netupitant 15 mg/kg/day in dogs. Studies of up to 13 weeks duration were conducted in both species and were GLP compliant.

Relative exposure

Exposure ratios have been calculated based on animal: human plasma AUC from time 0 to 24 hours post dose ($AUC_{0\text{-}24h}$) for netupitant and the three major metabolites. Human reference values for netupitant (AUC = 17,284 ng.h/mL) are from population pharmacokinetic Study NETU-10-02 and values for exposure to metabolites are from clinical Study NETU-10-09 in cancer patients (AUC = 4,851; 5,102; 5,687 ng.h/mL for M1; M2 and M3 respectively). Since the metabolites are active and had very similar binding affinity to NK1 R, AUC values in animals and humans were combined for animal: human exposure comparison. For assessing repeat dose toxicity, AUC values in animals given daily doses are multiplied by 21 since the typical human dosing is every 21 days.

Table 4. Relative exposure to netupitant and metabolites in repeat dose toxicity studies

Study duration	Dose (mg/kg/day) [Palonosetron]	$AUC_{0-24\,h}$ (ng·h/mL)$	Exposure ratio*	Study duration	Dose (mg/kg/day) [Palonosetron]	$AUC_{0-24\,h}$ (ng·h/mL)$	Exposure ratio*
Mouse (CD-1)				Dog (Beagle)			
4 weeks	3	5,070	3.2	4 weeks	1	5,275	3.4
	10	30,221.5	19		3	15,039	9.6
	30	138,416	88		5	36,690	23
13	1	949.8	0.6		15	98,240	63

Study duration	Dose (mg/kg/day) [Palonosetron]	$AUC_{0-24\,h}$ (ng·h/mL)[$]	Exposure ratio*	Study duration	Dose (mg/kg/day) [Palonosetron]	$AUC_{0-24\,h}$ (ng·h/mL)[$]	Exposure ratio*
weeks	3	7,623.8	4.9		50	229,735	147
	10	40,261	26	4 weeks	3 [10]	12,365	7.9
Rat (Wistar)					7.5 [15]	31,445	20
4 weeks	3	24,540	16		15 [15]	73,485	47
	10	51,590	33	13 weeks	1	4,894	3.1
	30	93,225	60		3	10,425	6.6
4 weeks	3 [10]	19,140	12		10	34,284	22
	10 [18]	36,885	24	13 weeks	1 [3]	5,287.5	3.4
	30 [60]	56,304	36		3 [5]	17,702	11
13 weeks	3	22,870	15		10 [10]	47,840	31
	10	48,225	31	9 months	1	7,427	4.7
	30	83,896	54		3	19,434	12
13 weeks	1 [2]	21,300	14		10	59,890	38
	3 [6]	20,003	13				
	10 [18]	38,061	24				
	10 [0]	43,448	28				
26 weeks	1	8,295	5.3				
	3	28,171	18				
	10	50,013	32				
Human (Cancer patients)							
steady state	[300/0.5 mg]†	32,924‡	–				

[$] AUC values of netupitant, M1, M2 and M3 combined; * Animal $AUC_{0-24\,h}$ x21/human $AUC_{0-\infty}$; †Fixed dose combination 300/0.5 mg netupitant/palonosetron ; ‡ $AUC_{0-\infty}$

Major toxicities

The major target organs for netupitant were the liver and lymph nodes. Vacuolated macrophage infiltration and vacuolation; histological signs indicative of phospholipidosis; were apparent in these and other organs and tissues, most notably lung and spleen. The precise relationship between the generalised phospholipidosis and the more severe effects seen in some tissues is not clear.

Signs of phospholipidosis (cellular vacuolation, foamy macrophages) were present in multiple organs (including liver), principally lung and lymphoid tissue, in the repeat dose studies in rats at > 3 mg/kg/day and dogs > 5 mg/kg/day and also after a single, high dose of netupitant in rats, and to a lesser extent, in mice and dogs. The severity of phospholipidosis generally increased with dose and dosing duration but a clear dose response was often not apparent. Histocytosis, histiocytic aggregates and syncythial macrophages in spleen and lymph nodes described in the 13 and 26 week rat study at > 3 mg/kg/day (foamy macrophages only reported in lungs, not in lymph nodes as described in other studies) might be related to phospholipidosis. Phospholipidosis was shown to be partially reversible (in some cases completely) upon cessation of treatment, but in the long term study in rats dosed with netupitant for 26 weeks, no reversal was apparent after 8 weeks of recovery.

Phospholipidosis is not an unexpected finding as the structure of netupitant has features (cationic, amphiphilic) common to many other drugs (for example, amiodarone, fluoxetine) which produce this effect. It is important to note that many drugs produce this effect, which is unrelated to the principal pharmacological action of the drugs. Drug induced phospholipidosis is thought to be an adaptive response and does not indicate a toxic condition. Definitive evidence for this theory is, however, still lacking except for isolated studies (for example,[4]). Various mechanisms may be involved in the production of phospholipidosis. These include impairment of lysosomal enzyme activity, increased phospholipid synthesis and impaired membrane recycling and lysosomal enzyme sorting dynamics. These mechanisms are not mutually exclusive. Phospholipidosis and associated organ dysfunction have been reported in humans for some cationic amphiphilic drugs (for example, amiodarone), but many drugs causing phospholipidosis are well tolerated in patients. Phospholipidosis observed in animal studies with netupitant is considered clinically relevant.

Elevations of serum cholesterol and serum phospholipids were seen in the repeat dose studies in rats and dogs with netupitant alone and in the combination studies with palonosetron in rats. The effects were not consistent, being present in one gender in some studies and the other gender in other studies. In the amiodarone induced animal model of phospholipidosis elevations of cholesterol and phospholipids have been reported[5] and it is possible that the elevations seen following netupitant may be associated with phospholipidosis. Netupitant and metabolites M1, M2 and M3 were screened in vitro for the ability to induce phospholipid accumulation in fibroblasts prepared from bovine corneas. Netupitant and the three metabolites were positive in the test at all non toxic concentrations.

Some red blood cell indices were reduced in rats in some studies haemoglobin ((Hb), haematocrit, mean corpuscular haemoglobin (MCH), mean corpuscular volume (MCV)) but the effect was not consistent across genders and was not clearly dose related. The effect

[4] Cartwright, M.E. et al. Phospholipidosis in neurons caused by posaconazole, without evidence for functional neurologic effects. *Toxicologic Pathology* 2009; 37: 902-910.
[5] Mesens, N. Phospholipidosis in rats treated with amiodarone: serum biochemistry and whole genome micro-array analysis supporting the lipid traffic jam hypothesis and the subsequent rise of the biomarker BMP. *Toxicologic Pathology* 2012; 40: 491-503.

appeared more marked following intravenous administration, which is not the proposed dosing route.

Elevations of liver enzymes (sorbitol dehydrogenase (SDH), gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT)), increases in liver weight, hepatocellular vacuolation, hypertrophy and necrosis were seen in rats following doses of 30 mg/kg/day (exposure ratio (ER 54)). At this and lower exposures increased liver weights, histological signs of hypertrophy and vacuolation were also apparent. In dogs at > 10 mg/kg/day (ER 22) reversible liver enlargement was observed in males together with histological signs of hypertrophy, in addition to increased serum transaminases (ALT, GGT and glutamate dehydrogenase (GDH)) at > 15 mg/kg/day (ER 63) and hepatocellular necrosis at 50 mg/kg/day (ER 147). The effects on the liver were generally reversible with the cessation of dosing. Increased liver weights were also seen in the combination studies with palonosetron in rats and dogs and hepatocellular hypertrophy in rats (see Combination Studies below). The N observable effect level (NOEL) for histopathological lesions in the liver in both species was 3 mg/kg/day (ER 18 for rats, 12 for dogs).

Inflammation and necrosis of mesenteric and mandibular lymph nodes were seen in mice (450 mg/kg/day), rats (≥ 30 mg/kg/day) and dogs (≥ 15 mg/kg/day). At lower doses foamy/vacuolated/syncytial macrophages were observed in these and other lymphoid tissues in all species. Inflammation was probably related to phospholipidosis, but it is unclear whether necrosis was secondary to phospholipidosis.

Weight loss was seen in rats (≥ 30 mg/kg) and dogs (≥ 15 mg/kg), accompanied by necrosis/degenerative changes in the gastric mucosa. At lower doses foamy/vacuolated macrophages were present in this tissue.

Cardiac effects are discussed above.

Metabolites

The role of metabolites in the toxicity seen in animals following administration of netupitant is not clear. The major metabolites M1, M2 and M3 and metabolite M4 all have similar binding affinity to NK1 Rs, and M1, M2 and M3 also bind to the diltiazem site on Ca^{2+} channels with M1 having slightly higher affinity than netupitant and the other metabolites at this site. It seems plausible that the effects of these metabolites are probably quite similar to those of the parent compound. In both in vitro and in vivo cardiovascular safety studies the actions of the netupitant and the metabolites were generally qualitatively similar. Thus in species where significant amounts of these metabolites are formed the overall effect would be expected to be similar to sustained exposure to the parent compound. In a qualitative in vitro screen for the ability to induce phospholipid accumulation, netupitant and metabolites M1, M2 and M3 were all positive. Thus it is possible that these metabolites contributed to the phospholipidosis seen in the repeat dose toxicity studies. The sponsor indicated in the nonclinical overview that 'The in vitro and in vivo data support the conclusion that the toxicity of netupitant is due predominantly to the M1 metabolite.' There is not enough evidence supporting the sponsor's statement.

Combination studies with palonosetron

Toxicity of the netupitant/palonosetron combination was investigated in rats and dogs. In the 13 week combination study in rats liver weights were increased in animals receiving netupitant and palonosetron alone and in animals receiving the 6/3 mg/kg/day and 18/10 mg/kg/day palonosetron/netupitant combinations although not all increases in both genders were statistically significant. Histological evidence of hypertrophy was observed in male animals receiving netupitant alone at 10 mg/kg/day and in females

receiving 10 mg/kg/day netupitant alone or in combination with palonosetron 18 mg/kg/day (no difference between netupitant alone and the combination).

In the 4 week combination study in rats which employed simultaneously increasing doses of both netupitant and palonosetron the principal findings were histological changes similar to those seen in studies with netupitant alone: hepatocellular hypertrophy more frequent in females and syncytial macrophages in mesenteric lymph nodes in both sexes. Both effects increased with netupitant (and palonosetron) dose. The effects were comparable to those seen with netupitant alone at the same doses.

In the 13 week combination study in dogs some prolongation of uncorrected QT intervals (males and females) and corrected QT intervals (females only) was observed at various times during the dosing phase in animals receiving 10/10 mg/kg/day (discussed above). These small effects were not apparent at the end of the recovery period. Similar ECG findings were seen in the 4 week combination study. In addition, some CNS toxicity ranging from tremors at 15/7.5 mg/kg/day to seizures at 20/15 mg/kg/day were observed. As a result the higher palonosetron dose was reduced to 15 mg/kg/day after 11 days of treatment. These observations are consistent with known effect of palonosetron. and seizures following intravenous palonosetron have been reported in patients[6,7]. No evidence of tremors or seizures was observed in any study with netupitant alone.

Genotoxicity

Netupitant was evaluated for its genotoxic potential in Salmonella typhimurium and Escherichia coli, L5178Y/TK+/- mouse lymphoma cells in vitro and in a rat bone marrow micronucleus assay. Netupitant was negative in all the tests and is unlikely to pose a mutagenic or clastogenic risk to humans. Ames tests were also performed on the metabolite M4 and two impurities, and the results were negative. No genotoxicity studies were performed with the major human metabolites, M1, M2 and M3, and this issue was addressed by the rat micronucleus test where exposure to metabolites would have occurred.

Carcinogenicity

No studies submitted. This is acceptable given the proposed indication, intermittent treatment schedule, and the lack of genotoxicity.

Reproductive toxicity

Reproductive toxicity was assessed in rats and rabbits in GLP compliant studies. The studies investigated potential effects on male and female fertility (rats), embryofoetal toxicity (rats and rabbits) and pre/postnatal development (rats). Adequate animal numbers were used in the pivotal studies and treatment periods were mostly appropriate. The male fertility study, however, employed a pre mating dosing period of only two weeks. The sponsor was requested to provide justifications for the shorter pre mating dosing period in the assessment of effects on male fertility. The sponsor's response that a 2 week study with an appropriate dose setting has equal potential in detecting the toxicity on male reproductive organs is accepted.

Toxicokinetic data were obtained from animals in the embryofoetal development studies. Animal: human exposure ratios in rabbits were calculated using combined netupitant parent and metabolites exposure based on AUC and C_{max}. In the rat embryofoetal

[6] Zambelli, A. et al. Seizure associated with palonosetron. *Support Care Cancer* 2009; 17: 217.
[7] Park, P-G. et al. Seizure developed after palonosetron intravenous injection during recovery from general anesthesia, A case report. *Korean J Anesthesiol*. 2012; 63(2): 173–176.

development study, only the parent drug was measured; there were no toxicokinetic data on the metabolites. Since the Day 1 toxicokinetic values for netupitant in pregnant rats were similar to the values in non-pregnant female rats in the 4 week repeat dose toxicity study, the exposure ratios for the rat embryofoetal development study are estimated based on toxicokinetic data in female rats in the 4 week repeat dose study (Study 1006011).

Table 5. Relative exposure in reproductive toxicity studies

Species	Study	Dose (mg/kg/day)	C_{max} (ng/mL)*	$AUC_{0-24\ h}$ (ng·h/mL)*	Exposure ratio	
					C_{max}	AUC#
Rat (Wistar)	Embryofoetal development ‡	3	1,189	24,900	1.3	9
		10	2,737	55,940	2.9	20
		30	4,960	105,040	5.3	38
Rabbit (Himalayan)	Embryofoetal development	3	110	816	0.12	0.3
		10	419	6,290	0.45	2.3
		30	956	16,150	1.0	5.9
Human (Cancer patients and population PK)	Steady state	[300/0.5 mg]†	940	32,924	–	

* Sum of netupitant and M1, M2 and M3 C_{max} or AUC; ‡ C_{max} and AUC values from the 4 week repeat dose toxicity study in female rats (Study 1006011); # = animal AUC_{0-24h} x 12 (dosing period):human plasma $AUC_{0-\infty}$; †Fixed dose combination 300/0.5 mg netupitant/palonosetron.

The level of exposure to netupitant and active metabolites achieved in the embryofoetal development studies was low (up to 5 in rats and 1 to rabbits) based on C_{max} and the exposure ratios based on AUC were up to 38 in rats and 6 in rabbits.

Placental transfer and excretion in milk were not examined in the studies.

Netupitant at doses up to 30 mg/kg/day had no effect on the fertility of either male or female rats although the high dose (30 mg/kg/day) did cause reduced weight gain in both males and females.

In the fertility study in rats (Report no. 1008497), corpora lutea, implantations and litter values in the high dose group (30 mg/kg/day) were significantly decreased compared with the vehicle control group. However, the values were within normal limits for this strain of rat and the decrease was not considered biologically significant (historical control data for these parameters in HanIbm: WIST rats from the study laboratory [information redacted] were provided.

Netupitant had minimal effects on embryofoetal development in the rat. Doses of 30 mg/kg/day did cause some growth retardation (indicated by reduced foetal weights) and there were small increases in the incidence of tarsal hyperflexion (1.3% compared with 0.4% in the vehicle control group). This variation, however, was not accompanied by alterations in the skeleton or soft tissues and do not indicate teratogenicity. In the rabbit

study increased numbers of minimally/partially fused sternebrae were observed at doses ≥ 10 mg/kg/day (7.9% and 15% at 10 and 30 mg/kg/day, respectively, compared with 0% in the vehicle control group), associated with low foetal weight at 30 mg/kg/day.

One curious observation was the occurrence of cleft palate in pups from one rat litter (100 mg/kg/day) and one rabbit litter (30 mg/kg/day) in the non pivotal studies in each species. The 100 mg/kg/day dose was not employed in the pivotal study in rats but the effect was not seen again in rabbits at 30 mg/kg/day in the pivotal study and may have been due to chance.

In the pre-/post-natal development study, rat pups from dams receiving ≥ 10 mg/kg/day from gestation day (GD) 6 to postnatal day (PND) 21 showed significantly reduced body weight at birth. Pups from these groups showed delayed attainment of air righting reflex but no other developmental effects including motor activity and water maze performance. Mating performance, fertility and gestation length of the F1 generation were unaffected by F0 treatment and no effects were seen in F2 litters.

Pregnancy classification

The sponsor has proposed Pregnancy Category B2[8] for the FDC of palonosetron and netupitant. The pregnancy category for palonosetron is B1.[9] Based on the animal study findings (partially fused sternebrae in rabbits and reduced foetal weights in rats), Pregnancy Category B3[10] is considered appropriate for netupitant. Because of the lack of embryofoetal development studies with the combination, pregnancy category B3 is considered appropriate for the combination based on the animal findings with netupitant.

Local tolerance

Local tolerance by IV infusion was assessed in rabbits. Local reactions were observed in the ear veins in the vehicle (propylene glycol) group and at 1 mg/kg (vein bluish, dilated) and 3 mg/kg (vein bluish, dilated and swollen; ear bluish and swollen). All the effects were reversible over 14 days. Animals treated with 10 mg/kg were sacrificed on Day 2 with necrotic lesions in the ear. Local intravenous tolerance was also examined in several IV repeat dose studies in rats and dogs, using 5% glucose as the dosing vehicle. Reactions at the injection site included perivascular/vascular inflammation, endothelial hyperplasia, granulation tissues, and thrombi after repeated dosing.

Only mild and transient signs of dermal irritation were observed in rabbits at 1 hour, following application of 0.5 g netupitant and no skin reactions were observed 24 hours after treatment. Netupitant showed no evidence of dermal sensitisation in guinea pigs. Netupitant caused some transient reddening of the conjunctivae and is considered non irritating to the eye. The intravenous formulation of netupitant caused haemolysis of human heparinised whole blood and precipitation in plasma at concentrations

[8] Pregnancy Category B2: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

[9] Preganacy Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

[10] Pregnancy Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

≥ 250 µg/mL. These results suggest that netupitant has local irritant and haemolytic potential when given intravenously at high concentrations and/or at high speed.

Antigenicity

Netupitant was tested in male guinea pigs for active and passive systemic anaphylaxis. No antigenicity and hence anaphylactic potential was observed in either the active or passive part of the study.

Phototoxicity

Netupitant was negative for phototoxicity in the 3T3 Neutral Red uptake phototoxicity test.

Impurities

Two impurities were negative in bacterial point mutation tests.

Paediatric use

Akynzeo is not proposed for paediatric use and no specific studies of netupitant in juvenile animals were submitted.

Nonclinical summary

- The overall quality of the non-clinical dossier was good with all pivotal toxicity studies conducted according to GLP.
- Primary pharmacodynamic studies with netupitant established affinity and selectivity for the human NK1 R (pKi 9.0). Netupitant was effective in preventing emesis induced by chemical emetogens in ferrets and emesis induced by motion in shrews. The netupitant/palonosetron combination was more effective than either drug alone. Three major human metabolites (M1, M2 and M3) had similar affinity for NK1 to netupitant. Nonclinical pharmacodynamics data support the proposed clinical indication.
- Netupitant and metabolites M1, M2, M3 and M4 were evaluated in screens of receptors, transporters and ion channels employing both radioligand displacement and functional assays. Interaction of netupitant with the histamine (H2), adenosine (A3), DA and 5-HT reuptake sites was observed at 10 µM (no interaction at 0.1 µM). M1 had a greater inhibitory activity on noradrenaline (IC_{50} 1.3 µM) and dopamine (IC_{50} 0.48 µM) uptake than netupitant, but toxicity studies showed no CNS toxicity (see below for cardiac effects). Netupitant and the active metabolites showed binding to the L-type Ca^{2+} channel, with M1 being most potent.
- Netupitant did not have any notable effects on CNS or respiratory function following oral administration. Netupitant at high concentrations affects cardiac conduction probably by binding to the L-type Ca^{2+} channel and inhibiting the hERG K^{+}channel and causes bradycardia and prolongation of APD. Netupitant and palonosetron may have additive effects on cardiac conduction. Some potential for cardiovascular effects exists in patients taking the netupitant and palonosetron combination.
- Pharmacokinetic studies in laboratory animal species showed moderate to high bioavailability by oral dosing. Netupitant is highly plasma protein bound in animals and humans (> 99%). Netupitant had a high volume of distribution in nonclinical species and was rapidly distributed to most organs in rats. Penetration to brain and

testes was demonstrated. CYP3A4 catalysed the formation of two metabolites M1 and M2. Netupitant and metabolites inhibited CYP3A4, with IC_{50}/Ki values approximately 50 times the combined free fraction C_{max} of netupitant and metabolites in patients, suggesting low potential for interactions with CYP3A4 substrates. Excretion of netupitant and/or its metabolites was almost exclusively via the faeces. Netupitant and/or major metabolites inhibited transporters (BCRP, OCT1, MDR1, OATP1B3 and P-gp) only at high concentrations. Drug-drug interactions via transporters in vivo are unlikely. Studies in human liver microsomes suggest that drug-drug interactions are unlikely with cyclophosphamide and vincristine but may be possible with docetaxel.

- Single high doses in rodents caused inflammation and necrosis in several tissues, including liver, stomach and mesenteric lymph nodes. Signs of phospholipidosis were also present in these and other tissues especially the lung.
- The major target organs identified in the repeat dose toxicity studies in rats and dogs were liver and lymph nodes. Inflammation and/or necrosis occurred in these tissues only following exposure to high doses. Accompanying or possibly underlying these toxicities were signs of phospholipidosis (foamy/vacuolated macrophages). Signs of phospholipidosis were also apparent in other tissues notably lung and spleen. All the effects were generally reversible with the cessation of dosing, although in rats dosed with netupitant for 26 weeks phospholipidosis was still evident after 8 weeks of recovery. Toxicity findings with the netupitant/palonosetron were similar to those with netupitant alone except for neurological effects (tremors and seizures) due to palonosetron at high doses.
- The potential genotoxicity of netupitant was investigated in a standard battery of tests. The results were negative in all tests and netupitant is unlikely to pose a mutagenic or clastogenic risk to humans.
- No carcinogenicity studies were conducted with netupitant. This is acceptable for the proposed indication and dosing regimen.
- Netupitant had no effects on fertility in rats. Foetal weights were reduced in rats and rabbits at 30 mg/kg/day and the incidence of minimally/partially fused sternebrae was increased in rabbits at > 10 mg/kg/day. In rats receiving ≥ 10 mg/kg/day from GD 6 to PND 21, pup body weights at birth were reduced, and air righting reflex was delayed.
- Netupitant did not show evidence of antigenicity or phototoxicity.

Nonclinical conclusion

- Affinity and selectivity of netupitant and major human metabolites (M1, M2 and M3) for recombinant human NK1 Rs was established in vitro. Pharmacological activity in relevant animal models was demonstrated.
- In vitro and animal studies indicate potential for affecting cardiac conduction and causing QT interval prolongation in patients taking the netupitant and palonosetron combination.
- Toxicity to the liver and lymph nodes and phospholipidosis in multiple organs were identified in repeat dose studies and after a high single dose.
- Netupitant is unlikely to pose a mutagenic or clastogenic risk to humans.
- A Pregnancy Category of B3 is recommended on nonclinical grounds.
- Revisions to the draft Product Information were also recommended to the Delegate but these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings and population pharmacokinetics is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Clinical rationale

Chemotherapy induced nausea and vomiting (CINV) can lead to metabolic problems such as fluid and electrolyte balance disturbances and nutritional status deficiencies, psychological problems, decision by physician to reduce chemotherapy dose intensity, or decision by the patient to stop potentially beneficial cancer treatment.

CINV is classified as either acute (occurring within the first 24 hours after chemotherapy) or delayed (occurring after the first 24 hours, extending until the fifth day). The development of acute emesis is known to largely depend on serotonin (5-HT_3). CINV is mainly due to input from the chemoreceptor trigger zone (CTZ). The neurotransmitters serotonin and dopamine stimulate the vomiting centre indirectly via stimulation of the CTZ. The 5-HT_3 receptor has been shown to selectively participate in the emetic response, thus providing a physiological explanation for the clinical anti-emetic effects of 5-HT_3 receptor antagonists. The pathophysiology of delayed emesis is less understood and multiple mechanisms may contribute to it, including substance P, which belongs to the neurokinin (NK) family of neuropeptides and exerts its biological effects via interaction with the NK1 R.

According to the sponsor, 5-HT_3 and NK1 R antagonists are among the drugs of choice for optimal anti-emetic prophylaxis in cancer patients receiving chemotherapy, and current clinical practice guidelines generally recommend that patients receiving highly or moderately emetogenic chemotherapy regimens should be treated with a combination of a 5-HT_3 receptor antagonist, NK1 R antagonist and a systemic corticosteroid. The clinical anti-emetic efficacy of 5-HT_3 receptor antagonists and NK1 R antagonists is considered to be complementary: the major effect of 5-HT_3 receptor antagonists is in the control of the acute phase of CINV, while the additional benefit of NK1 R antagonists is mostly seen in the control of the delayed phase of CINV. The sponsor was of the opinion that the clinical significance of this association provides a strong rationale for the development of a fixed combination of the two agents. The proposed palonosetron/netupitant FDC is composed of palonosetron (a registered 5-HT_3 receptor antagonist), and a new molecular entity, netupitant (a NK1 R antagonist).

In addition, it was felt that a fixed dose combination product could improve patient compliance due to a simplification and convenience of treatment regimen and hence increase adherence to guidelines for administration of both a 5-HT_3 and NK1 R antagonist for control of CINV. Moreover, the long half-lives of both components (approximately 40 and 90 hours for palonosetron and netupitant, respectively) suggested that a single oral dose administered on Day 1 of chemotherapy could be sufficient to protect patients from both acute and delayed CINV, allowing further simplification of treatment regimen and increasing patient compliance. According to the sponsor, the EU Committee for Medicinal Products for Human Use (CHMP) had agreed that the rationale for the development of the proposed fixed dose combination was based on valid therapeutic principles.

Contents of the clinical dossier

The submission contained the following clinical information:

- 23 clinical pharmacology studies, including 20 that provided pharmacokinetic data and 4 that provided pharmacodynamic data.
- 1 population pharmacokinetic/pharmacodynamic analyses.

- 1 pivotal efficacy/safety study (Study NETU-08-18; oral netupitant/palonosetron FDC 300/0.5 mg versus oral palonosetron 0.50 mg, moderately emetogenic chemotherapy (MEC), single and multiple chemotherapy cycles).
- 1 dose finding study (Study NETU-07-07; netupitant 100 mg+palonosetron 0.50 mg, netupitant 200 mg+palonosetron 0.50 mg and netupitant 300 mg+palonosetron 0.50 mg versus palonosetron 0.50 mg alone, highly emetogenic chemotherapy (HEC), single cycle).
- 1 other efficacy/safety study; (Study NETU-10-29; supportive safety study, netupitant/ palonosetron FDC 300/0.5 mg versus aprepitant+palonosetron, MEC and HEC, multiple cycles).
- 3 bridging studies (PALO-10-01 [non-inferiority study comparing efficacy of single dose oral palonosetron 0.50 mg versus single dose IV palonosetron 0.25 mg, HEC, single cycle]; PALO-03-13 [dose finding study; oral palonosetron 0.25 mg, 0.50 mg and 0.75 mg versus IV palonosetron 0.25 mg, MEC, single cycle]; PALO-03-14 [open label, uncontrolled study on efficacy and safety of oral palonosetron 0.75 mg in MEC, multiple cycles]).
- 2 efficacy/safety studies not relating to proposed indications (Study NETU-08-03, assessing the use of netupitant in patients with overactive bladder; Study NETU09-11, assessing the use of netupitant/palonosetron FDC in an acute pain model); 3 studies involving IV palonosetron (Studies PALO-99-03, PALO-99-04, and PALO-99-05; IV palonosetron versus other 5-HT_3 receptor antagonists); Integrated Summary of Efficacy, Integrated Summary of Safety.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

The clinical studies reviewed in this evaluation were in compliance with the Note for Guidance on Good Clinical Practice.[11]

Pharmacokinetics

Studies providing pharmacokinetic data

Table 5 below shows the studies relating to each pharmacokinetic topic.

Table 6. Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	Bioequivalence† - Single dose	NETU-11-02	BE of late Phase 1 and Phase 3 FDC
		NETU-09-07	BE of FDC and free combination
		NETU-08-12	BE of formulations utilised

[11] CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice

PK topic	Subtopic	Study ID	*
			during drug development
	Bioavailability (BA)	BP17408	BA of two netupitant forms with and without food.
		NETU-11-23	BA of netupitant administered as three FDC forms
	Influence of food	NETU-10-12	Effect of food and age on FDC
		NP16600	Effects of food and age on netupitant
	Dose proportionality	NP16603	Single ascending doses of netupitant
	Bioavailability during multiple-dosing	NP16601	Multiple ascending doses of netupitant
	ADME	NETU-09-21	Mass balance
PK in special populations	Target population	NETU-10-02	PPK/PPD
	Hepatic impairment	NETU-10-10	Effect of hepatic impairment on PK of FDC
PK interactions	CYP3A4 inhibitor and inducer	NETU-10-11	PK FDC in presence of ketoconazole and rifampicin
	CYP3A4 substrates	NP16599	Effect of netupitant on the PKs of midazolam and erythromycin
	Components of FDC	NETU-06-06	Netupitant with palonosetron
		NETU-06-27	Netupitant with palonosetron
	Netupitant versus dexamethasone	NETU-06-07	Examine the effects of netupitant on dexamethasone PK
	Netupitant with oral digoxin	NETU-07-01	Effects of netupitant on the PKs of steady-state digoxin
	FDC and oral contraceptives	NETU-10-08	Effect of FDC on the PK of ethinylestradiol and levonorgestrel
	Chemotherapy drug interactions	NETU-10-09	Effects of netupitant on the PK profile of 3 different

PK topic	Subtopic	Study ID	*
	in cancer		chemotherapeutic agents

BA – Bioavailability BE – Bioequivalence * Indicates the primary aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

Absorption/Distribution/Metabolism/Excretion (ADME)

Following administration of the proposed commercial FDC (300 mg/0.5 mg) to healthy subjects the C_{max} $AUC_{0-\infty}$, T_{max} and half-life (t½) values for netupitant were 453 ng/mL, 13,862 ng.h/mL, 5.00 hours and 76.62 h, respectively, and for palonosetron component were: 1271 ng/mL, 48,165 ng.h/mL, 3.00 hours and 37.22 hours, respectively.

Absolute netupitant bioavailability data are not available in humans; however, it is thought to be greater than 60%. The EPAR PI for Aloxi 500 µg soft capsules indicates that palonosetron has an absolute bioavailability of 97%.

A bridging study of late Phase I and Phase III FDC formulations with the proposed commercial FDC indicated that the formulations were bioequivalent. The FDC and free combination of netupitant 2 times 150 mg capsules and palonosetron 0.50 mg were bioequivalent. The surfactant sodium dodecylsulfate (SDS) and sucrose lauric ester (SE) formulations of netupitant were bioequivalent.

As netupitant has not been previously approved for marketing there are no relevant registered products for this component of the FDC, whereas, the palonosetron component of the FDC is similar to but not identical with the capsule formulation currently approved for use in Europe. It should be noted that only palonosetron IV is approved for use in Australia.

Administration of the FDC following a high fat breakfast increased the C_{max} and AUC_{inf} values of netupitant by 1.18 fold and 1.16 fold, respectively, compared to when the FDC was administered in the fasted state. By contrast, food did not affect the PK of palonosetron. Other studies indicated that the C_{max} and AUC_{inf} values of netupitant were increased by as much as 1.89 and 1.53 fold, respectively, when netupitant was administered under fed conditions compared to the fasted state.

For netupitant doses from 10 mg to 300 mg, there was a statistically significantly greater than proportional increase with dose in C_{max}, AUC_{last} and $AUC_{0-\infty}$ for netupitant.

Following one week daily oral dosing with 100 mg, 300 mg or 450 mg netupitant there was an increase in netupitant $AUC_{0-23.5}$ of approximately 3 times after 7 days dosing for all three dose levels.

Following oral capsule doses of 300 mg and 450 mg of netupitant containing the surfactants SDS and SE, respectively, the apparent volume of distribution (Vz/F) values were 1842 L and 3090 L respectively.

The high volume of distribution for netupitant indicates that the drug is highly distributed in tissues outside the plasma and interstitial fluid.

In humans, netupitant was highly bound (> 99%) to plasma proteins, with both albumin and α1-acid glycoprotein contributing to the high plasma binding of this drug, and the mean percentage of free drug was 0.33%. The fraction of drug in erythrocytes was approximately 13%.

The major elimination route for netupitant related entities was the hepatic/biliary route.

Four potentially active netupitant metabolites have been detected in human plasma (M1, M2, M3 and M4). CYP3A4 was responsible for the formation of three major netupitant metabolites (M1, M2 and M3). A minor metabolite, M4, was identified late in the development process. The exposure to the three major metabolites of netupitant, M1, M2 and M3 was equivalent to 29%, 14%, and 33%, respectively, of the systemic exposure to netupitant. By contrast, the minor metabolite M4 accounted for approximately 7% of parent drug exposure. The T_{max} values for the M1, M2 and M3 metabolites were 10.00 h, 2.00 hours and 24.00 hours, respectively, and the t½ values were 64.77 hours, 17.10 hours and 41.49 hours, respectively.

Following administration of C_{max} 60 µCi [^{14}C]-netupitant, approximately 50% of the administered radioactivity was recovered within 120 hours, whereas, by 696 hours post dose 70.7% of the total radioactivity was recovered in the faeces. Of all of the netupitant related material excreted by this time 86.49% was excreted in the faeces and a further 4.75% of drug related material was excreted in the urine.

Intra- and inter-individual variability of pharmacokinetics

Inter-subject variability of netupitant PK was high with a variability of 42% and 48% for AUC_{0-t} and C_{max}, respectively, following a 200 mg dose and 47% and 56% for AUC_{0-t} and C_{max}, respectively, following a 600 mg dose. For palonosetron, inter-subject variability was lower with variability of 25% and 29% for AUC_{0-t} and C_{max}, respectively, following a 0.5 mg dose and 20% and 23% for AUC_{0-t} and C_{max}, respectively, following a 1.5 mg dose.

The PopPK analysis estimated inter-subject variability in netupitant C_{max} and AUC_{inf} was 38.2% and 57% for C_{max} and AUC_{inf}, respectively following a 300 mg dose of netupitant. For 0.50 mg palonosetron, the final palonosetron model predicted an inter-subject variability of 28.3% and 33.4% for C_{max} and AUC_{inf}. The PopPK also indicated that the estimated inter-individual variability on clearance was 65.4% and 26.2% for netupitant and palonosetron, respectively and intra subject variability for netupitant and palonosetron was estimated at 37.3% and 17.2%, respectively.

Pharmacokinetics in the target population

The population pharmacokinetic (PopPK) analysis of concentration data following administration of the FDC and oral dexamethasone 20 mg in patients receiving moderately emetogenic chemotherapy indicated that netupitant PKs could be characterised by a 2 compartment model with an estimated median systemic clearance (CL) of 20.5 L/h and a large apparent volume of the central compartment (V2), estimated to be 486 L. The mean C_{max} and AUC_{inf} values for netupitant were estimated to be 567 ng/mL and 17284 ng.h/mL, respectively and the median T_{max} was 3.61 h. For palonosetron, a 2 compartment model with first-order absorption and elimination was identified as providing the best fit for the data and estimated median CL and V2 were 7.64 L/h and 367 L, respectively. The mean C_{max} and AUC_{inf} values for palonosetron were estimated to be 1,378 ng/mL and 68,611 ng.h/mL, respectively and the median T_{max} was 2.30 hours.

Pharmacokinetics in subjects with impaired hepatic function

Following administration of the FDC, subjects with mild hepatic impairment displayed small, not significant, increases of 11% and 14% in the C_{max} values of netupitant and palonosetron, respectively, compared to subjects with normal hepatic function, whereas, netupitant $AUC_{0-\infty}$ was 19% higher and palonosetron $AUC_{0-\infty}$ was significantly higher by 33% in subjects.

In subjects with moderate hepatic impairment, exposure to netupitant was significantly higher compared to matching healthy subjects with an increase of 70% for C_{max} and 143% for $AUC_{0-\infty}$, whereas, for palonosetron, although C_{max} was similar in the two groups, $AUC_{0-\infty}$ was significantly higher, by 62%, in the moderately impaired group.

The variability in netupitant PK was higher in subjects with mild and moderate hepatic impairment than in matching healthy subjects.

Pharmacokinetics in subjects with impaired renal function

No studies have examined the PK of the FDC in subjects with renal impairment.

Pharmacokinetics according to age

In healthy elderly (≥ 65 years of age) compared to younger subjects (18 to 45years) the C_{max} and $AUC_{0-\infty}$ of netupitant were 1.36 and 1.25 fold higher and the C_{max} and $AUC_{0-\infty}$ of palonosetron were also significantly higher (1.1 and 1.37 fold, respectively). By contrast, the results of the PopPK study (NETU-10-02) indicated that age was not a significant covariate in the PopPK models developed for either netupitant or palonosetron.

Pharmacokinetics in other special populations

The PopPK study indicates that race and gender were not significant covariates in the final PK models for either netupitant or palonosetron. It should be noted that the PopPK analysis was not deemed adequate for evaluation of factors such as gender and race as the population examined was primarily female (approximately 96%) and Caucasian (approximately 86%).

Pharmacokinetic interactions in healthy subjects

Netupitant C_{max} and $AUC_{0-\infty}$ were significantly increased by 25% and 140%, respectively, when the FDC was co-administered with the CYP3A4 inhibitor ketoconazole compared to when the FDC was administered alone and the formation of the metabolites M1 and M3 were delayed with T_{max} increasing by 8 fold and 2 fold, respectively. By contrast, ketoconazole had little to no effect on the PK of palonosetron.

Co-administration of the CYP3A4 inducer rifampicin with the FDC resulted in a significant decrease in netupitant C_{max} and AUC_{inf} (-62% and -83%, respectively) compared to when the FDC was administered alone. For the palonosetron component of the FDC, rifampicin co-administration did not significantly affect palonosetron C_{max}; however palonosetron AUC_{inf} was significantly lower.

Co-administration of netupitant with midazolam induced a small reduction in the C_{max} and AUC_{inf} of netupitant with decreases of approximately 7% and 9%, respectively, when compared to netupitant alone. By contrast, exposure to the CYP3A4 substrate midazolam was significantly increased when taken in combination with netupitant compared to administration of midazolam alone with C_{max} increasing by approximately 40% and $AUC_{0-\infty}$ by approximately 250%.

When netupitant was co-administered with the CYP3A4-substrate erythromycin, netupitant C_{max} was 18% higher when given in combination compared to when administered alone and AUC_{inf} decreased by approximately 12%. For erythromycin, the C_{max} and $AUC_{0-\infty}$ increased by approximately 92% and 56% respectively when given in combination with netupitant compared to when it was administered alone.

Co-administration of netupitant with palonosetron had little effect on the C_{max} and AUC_{inf} of netupitant, whereas for palonosetron, the C_{max} and AUC_{inf} were 15% and 10% higher, respectively when palonosetron was co-administered with netupitant compared to when it was administered alone. These small differences in the PK of palonosetron are unlikely to be clinically significant.

Co-administration of netupitant significantly increased the exposure to the corticosteroid dexamethasone in a dose and time dependant manner. Dexamethasone trough plasma concentration (C_{min}) on Days 2 to 4 was increased approximately 2.8, 4.3 and 4.6 fold with co-administration of 100, 300 and 450 mg netupitant, respectively. The apparent terminal

elimination half-life (t½z) of dexamethasone was increased by 1.9 to 3.2 hours on Day 1 and by 2.0 to 2.4 hours on Day 4.

The PK of digoxin was not affected by co-administration of netupitant.

Following co-administration of contraceptives and the FDC the C_{max} of ethinylestradiol was unchanged, whereas, the AUC_{inf} was 12% higher compared to when the contraceptive was given alone. Similarly, for levonorgestrel the C_{max} was unchanged by the co-administration of FDC, whereas the AUC_{inf} was significantly higher (40%).

Pharmacokinetic interactions in patients

Compared to when IV docetaxel and oral palonosetron were co-administered, administration of docetaxel with the FDC resulted in 1.49 and 1.35 fold increases in the docetaxel C_{max} and AUC_{0-t}, respectively. For etoposide, the AUC_{0-t} in the FDC period was approximately 21% higher than in the reference period, whereas, etoposide C_{max} values were similar in both treatment periods. For cyclophosphamide, the C_{max} and AUC_{0-t} values were 27% and 20% higher, respectively, following co-administration of the FDC compared to the period in which palonosetron was administered with cyclophosphamide.

In vitro interactions

Netupitant concentrations of 0.2, 2 and 20 μM and M1, M2 and M3 at concentrations of 0.02, 0.2 and 2 μM did not induce CYP1A2, CYP2C9, CYP2C19 or CYP3A4 activity in human hepatocytes.

Limitations of Pharmacokinetics studies

No studies have examined the PK of the FDC in the target population who were not receiving concurrent chemotherapy (for example, docetaxel).

Due to the low number of subjects (n = 2) included in the PK analysis of subjects with severe hepatic impairment the effect the PK of the FDC are unknown. Overall, hepatic impairment appears to result in increased inter-subject variability in netupitant PK as well as increases in exposure to both netupitant and palonosetron.

No studies have examined the PK of the FDC in subjects with renal impairment. Although the oral ADME study indicated that only low levels of netupitant related material were excreted in urine (4.75%) and therefore impaired renal function is unlikely to induce significant changes in the PK of netupitant, as netupitant is a new chemical entity and given that the FDC has not been previously described or registered the evaluator believes that a study of the FDC in patients with impaired renal function is appropriate.

As stated by the evaluator there are some issues with the modelling data that prohibit an accurate comparison of the PopPK results relating to age with those from Study NETU-10-12.

As stated by the evaluator, the populations modelled were primarily female (approximately 96%) and Caucasian (approximately 86%). Therefore, due to the small number of males (n = 4 to 5) and non-Caucasian subjects (n = 16) included in the analyses, it may not have allowed an accurate determination of the importance of these covariates and further analysis regarding gender and race may be required.

Comparison of the PK results in Study NETU-06-07 with those in Study NP16603, where the same doses of netupitant were administered (that is, 100, 300 and 450 mg), indicates that netupitant AUC_{inf} was significantly lower in Study NETU-06-07. Therefore, a study examining the effect on netupitant PK when netupitant is co-administered with dexamethasone is warranted.

The effect of digoxin on netupitant PK was not examined.

The effect of the contraceptive administration upon the PK of the FDC was not examined.

Population pharmacokinetics

Studies providing pharmacokinetic/pharmacodynamic data

The following study provided population pharmacokinetic (PopPK)/pharmacodynamic (PD) data:

Study NETU-08-18, a Phase III, multicenter, multinational, randomised, double blind, double dummy, parallel group, stratified study assessing efficacy and safety of a single oral dose of a fixed combination of netupitant and palonosetron (300 mg/0.50 mg) given with oral dexamethasone versus oral palonosetron (Aloxi) and oral dexamethasone prior to MEC. The study enrolled adult chemotherapy naïve male and female patients with a diagnosis of malignant solid tumour requiring treatment with an anthracycline and cyclophosphamide containing MEC regimen on Day 1 of each cycle

Evaluator's conclusions on pharmacokinetics

Overall, the modelling process performed by the sponsor was conducted and reported in accordance with the guideline.[12] The base, error and covariate models were all developed in accordance with the guidance. Appropriate diagnostic statistics and plots were provided for the models for netupitant and palonosetron but not for the M1, M2 and M3 metabolites. There were some inconsistencies whereby ALAG was excluded from early models, only to appear in the final models.

The sponsor's PopPK model for netupitant was confirmed by the external validation. However, the final model does not contain any covariate effects and does not provide any useful information with regard to individualisation of dosing. As would be expected from the previous data, it was not possible to describe a dose or concentration effect relationship because the 300 mg dose level would be expected to achieve maximum effect. There was no obvious relationship between dose or concentration and adverse effects, but this may have been limited by the paucity of subjects having adverse effects.

In the opinion of the evaluator, the models for the M1, M2 and M2 metabolites have serious limitations. The proportion of the dose converted to the metabolite was assumed from prior data and also assumed to be the same for all the subjects. There were no data for the output of each of the metabolites, either in urine or faeces. This means that volume of distribution was not estimable. In the equation for the metabolite, V/F and apparent clearance (CL/F) are interrelated. Hence, the inability to estimate V/F also translates to an inability to estimate CL/F. This explains why the estimates for V/F and CL/F were highly sensitive to the initial estimates.

However, although the estimates of V/F and CL/F from the models for the M1, M2 and M3 metabolites are not reliable, these models could still be used to reliably estimate AUC and C_{max} for the metabolites, because these are descriptive parameters. These parameters did not have any relationship with either efficacy or toxicity.

With regard to the palonosetron model, the validation did not confirm the model submitted by the sponsor. The sponsor's choice of a two compartment model may have been informed by knowledge of the intravenous PK of palonosetron (as shown in Figure 3).[13] Although the intravenous data for palonosetron are consistent with a two compartment model, the redistribution phase appears to be rapid, and of less than 0.5 hours duration.

[12] CHMP/EWP/185990/06 Guideline on Reporting the Results of population Pharmacokinetic Analyses
[13] Shah et. al. Pharmacokinetic evaluation and safety profile of a 15-minute versus 30-second infusion of palonosetron in healthy subjects *J Clin Pharmacol* 2006; 46: 1139-1145.

Figure 3. Plasma concentrationtime profile of palonosetron following intravenous administration (reproduced from Figure 1[13])

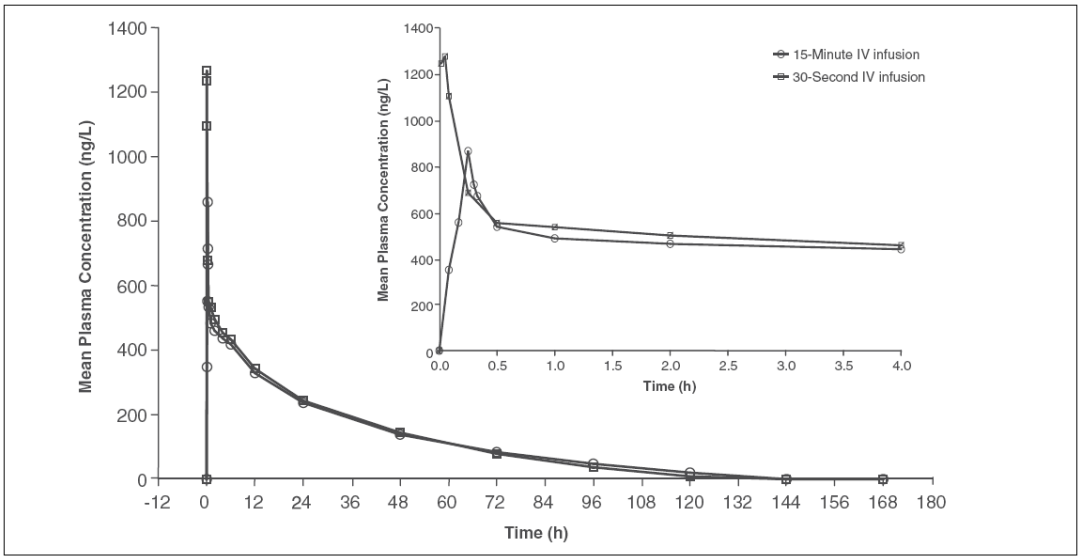


Figure 1. Mean plasma concentrations of palonosetron following 15-minute and 30-second infusions in healthy subjects. Inset shows mean plasma concentration-time profiles over the first 4-hour period.

Hence, following oral absorption, and with the data available to the sponsor, in the opinion of the PopPK evaluator the intercompartment PK parameters for palonosetron are inestimable and a one compartment model is more appropriate for the data.

There was also disagreement between the sponsor's covariate model and that of the external validation. The sponsor's model indicated V/F was proportional to weight, or body size, which is consistent with the known characteristics of palonosetron. However, an effect of creatinine clearance (CLCR) on CL/F is inconsistent. The fraction of palonosetron excreted unchanged in the urine is 40%. Hence, although CLCR would be expected to have an impact on CL/F it is not plausible that it would be the principal covariate effect on CL/F.

The PopPK evaluator recommends accepting the PopPK model for netupitant but rejecting the models for M1, M2, M3 and palonosetron. The models did not identify any important information that should be included in the PI or that impact upon efficacy, safety or the proposed dosing regimen for the netupitant/palonosetron FDC. The effect of age observed in Study NETU-10-12 was not confirmed in the PopPK analyses of netupitant or palonosetron in Study NETU-08-18. In Study NETU-10-12 the mean ratio (90% confidence interval (CI)) elderly subjects / adult subjects was 136.36 (95.87 to 193.96) for netupitant C_{max} and 124.91 (95.29 to 163.75) % for $AUC_{0\text{-}inf}$. Also for palonosetron, the mean ratio (90% confidence interval (CI)) elderly subjects/adult subjects was 110.44 (95.96 to 127.11) for C_{max} and 136.89 (117.44 to 159.56) % for $AUC_{0\text{-}inf}$. However, in Study NETU-08-18, age was examined as a continuous variable rather than a categorical variable, and as a consequence comparisons between the two studies are limited. The effects of age described in Study NETU-10-12 would not be clinically significant.

There was insufficient representation of male gender in the datasets (< 10%) to examine sex as a covariate. However, the representation of Asian race was > 10% andit was reasonable to examine this covariate in the modelling.

Pharmacodynamics studies providing pharmacodynamic data

Table 6 below shows the studies relating to each pharmacodynamic topic and the location of each study summary

Table 7. Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	Effect on nausea and vomiting	NP16602	Ability of netupitant to inhibit apomorphine-induced nausea and/or emesis.
	NK1 R occupancy	NETU-06-08	Netupitant dose that provides a NK1 R occupancy of at least 90% at a time point close to expected C_{max}
Secondary Pharmacology	Thorough QT	NETU-07-20	Effect of FDC on QT interval

* Indicates the primary aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication. ‡ And adolescents if applicable.

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

Mechanism of action

Netupitant is a NK1 R antagonist and therefore blocks the action of emetogens at the NK1 R. Palonosetron is a registered 5-HT_3 receptor antagonist.

Primary pharmacodynamic effects

At plasma netupitant concentrations of > 50 ng/mL there was an inverse relationship between plasma netupitant concentration and the incidence of vomiting. Retching was also reduced in subjects treated with netupitant; however, there was no observable trend between concentration groups. By contrast, nausea tended to increase with netupitant concentration to levels above that seen in placebo treated subjects.

Netupitant is a potent selective NK1 R antagonist that blocks NK1 Rs in the human brain for a relatively long time. At 6 hours post administration of 100, 300 or 450 mg netupitant, netupitant related NK1 R occupancy of ≥ 90% was identified in the occipital cortex and frontal cortex, as well as for striatum (for 300 and 450 mg netupitant) and anterior cingulate (for 100 and 450 mg netupitant).

Secondary pharmacodynamic effects

Administration of netupitant in combination with palonosetron, in contrast to moxifloxacin, had little to no effect on heart rate corrected QT interval. Healthy males administered 450 mg netupitant demonstrated a reduction in performance of two tasks (digit vigilance and numeric working memory) and a lowering of selfrated alertness were observed at around 8 hours post dose.

Time course of pharmacodynamic effects

Following administration of 100 mg, 300 mg or 450 mg of netupitant, NK1 R occupancy in various regions of the brain was maximal at approximately 6 hours following dosing. Netupitant receptor occupancy slowly decreased up until 96 hours following dosing and

ranged from 48.5 to 85.5%, 76 to 94.0% and 82.5 to 96.5% for the 100 mg, 300 mg and 450 mg doses, respectively.

Relationship between drug concentration and pharmacodynamic effects

The incidence of vomiting decreased as netupitant levels increased. Although there was a clear relationship between the degree of NK1 R occupancy in striatum and plasma concentrations of netupitant, overall there was only a small trend in NK1 R occupancy as the dose of netupitant increased. The PopPK study concluded that there did not appear to be any overt relationship or trend between exposure parameters for netupitant (and its metabolites) and the safety and efficacy parameters studied.

Limitations of pharmacodynamic studies

The effects of gender on Pharmacodynamics (PDs) have not been examined.

PD interactions between the FDC and other drugs have not been examined.

The PK/PD data suggests that earlier treatment with the FDC than that proposed may result in enhanced anti-emetic effectiveness and the absence of PD data examining administration of the FDC at a range of times prior to chemotherapy is a limitation of this application.

Dosage selection for the pivotal studies

The FDC formulation comprises of oral palonosetron 0.50 mg and oral netupitant 300 mg. The dose selection of palonosetron was based mainly on the dose finding Phase III Study PALO-03-13, which tested oral palonosetron doses of 0.25 mg, 0.50 mg and 0.75 mg. According to the sponsor, the selection of palonosetron dose range to be tested in this Phase III study was based mainly on results from two Phase II oral and IV dose response studies (Studies 2332 and 2330). Results of Study 2332 indicated that a plateau in palonosetron efficacy was observed starting at 10 μg/kg (corresponding to a fixed dose of approximately 0.75 mg). The complete response of the lowest oral palonosetron dose (0.3 to 1 μg/kg) was higher and the response of the 3 μg/kg (corresponding to a fixed dose of approximately 0.25 mg) was lower than expected. Results of Study 2330 showed that the minimal effective dose in preventing CINV was 3 μg/kg. Based on these data, oral palonosetron 0.25 mg, 0.50 mg and 0.75 mg were selected to be tested in the dose finding Study PALO-03-13, conducted from 2005 to 2006, assessing efficacy in a single cycle of MEC. In addition, an open label, uncontrolled Study PALO-03-14, was conducted concurrently with PALO-03-14 to assess the safety (primary objective) and the efficacy of a single oral dose of palonosetron in the prevention of CINV in repeated and consecutive MEC cycles, and the 0.75 mg oral dose was chosen for this study to represent the highest oral dose tested in PALO-03-13.

Results for Study PALO-03-13 showed that all 3 oral palonosetron doses (0.25 mg, 0.50 mg and 0.75 mg) were found to be non-inferior to IV palonosetron 0.25 mg (currently approved formulation in Australia for prevention of nausea and vomiting induced by cytotoxic chemotherapy) in preventing MEC induced nausea and vomiting with regards to the primary efficacy endpoint of the proportion of patients with complete response[14] during the first 24 hours after the administration of chemotherapeutic agent (that is, acute phase). Although analyses of secondary efficacy endpoints did not reveal any clear differences between the 3 oral doses and the IV palonosetron dose, a comparison of the 3 oral dose groups indicated that the oral palonosetron 0.50 mg and 0.75 mg doses tended to show higher anti-emetic efficacy than the oral palonosetron 0.25 mg dose. Safety analyses did not raise any safety concerns for all 3 doses. Based on the study results, the sponsor concluded that palonosetron 0.50 mg was the lowest effective oral palonosetron dose in the prevention of CINV following MEC chemotherapy. Results for Study PALO-03-

[14] defined as no emesis and no rescue medication use.

14 showed that oral palonosetron 0.75 mg administered in repeated (up to a maximum of four) consecutives cycles of chemotherapy showed continued efficacy for the prevention of MEC induced nausea and vomiting, and did not trigger any safety concerns. Based on the results of these studies and the fact that oral palonosetron 0.50 mg has been approved in the US and EU for the treatment of MEC induced nausea and vomiting, oral palonosetron 0.50 mg was chosen to be the palonosetron dose for the netupitant/palonosetron FDC.

As oral palonosetron 0.50 mg is not registered for the prevention of nausea and vomiting induced by HEC, and as its efficacy in HEC had only been explored in a Phase II study, Study PALO-10-01 was later conducted from 2011 to 2012 to support the efficacy of oral palonosetron 0.50 mg in the prevention of HEC-induced nausea and vomiting in comparison to IV palonosetron 0.25 mg, focusing on the 0 to24 hours period (that is, acute phase). Results supported the choice of palonosetron 0.50 mg for the FDC. Analyses of the primary efficacy outcome showed non-inferiority of oral palonosetron 0.50 mg compared with IV palonosetron 0.25 mg in terms of complete response rate in the acute phase. There was also no statistically significant difference (that is comparable efficacy) between the 2 treatment groups with regards to complete response rate in the delayed (24 to 120 hours interval) and overall (0 to 120 hours interval) phases as well as the other study secondary efficacy endpoints in all 3 phases (acute, delayed and overall).

The dose selection of netupitant for the FDC was based mainly on the dose finding Phase II Study NETU-07-07, which tested 3 different single oral doses of netupitant (100 mg, 200 mg and 300 mg) or placebo, each combined with a fixed oral dose of palonosetron (0.50 mg) and given with oral dexamethasone prior to HEC. The selection of the dose range to be tested in this study was based on earlier pre-clinical studies which evaluated the clinical pharmacology of netupitant using an apomorphine challenge model (NP16602) and a NK1 R binding assay study (NETU-06-08). The results of these 2 studies suggested that the therapeutic dose in humans was likely to be in the 100 to 300 mg dose range. Results of Study NETU-07-07 showed that there was a statistically significant treatment difference between the netupitant 300 mg plus palonosetron 0.50 mg group and the palonosetron 0.50 mg alone group in the percentage of patients with complete response in the acute phase (0 to 24 hour interval; treatment difference of 8.8%, in favour of netupitant 300 mg), while the treatment differences from the palonosetron alone group were not statistically significant for the netupitant 100 mg and netupitant 200 mg groups. Complete response rates in the delayed phase (24 to 120 hours interval) and the overall phase (0 to 120 hours) were comparable among the 3 netupitant doses and were statistically significantly higher for all 3 doses compared to palonosetron alone. Statistical analyses comparing the 3 netupitant doses to one another showed that netupitant 300 mg was statistically significantly superior to both lower doses (100 mg and 200 mg) for endpoints of complete response, no emesis and complete protection[15] in the acute phase. Netupitant 300 mg was also found to be statistically significantly superior to netupitant 100 mg for the endpoint of proportion of patients with no significant nausea in the overall and delayed phase). Safety analyses did not raise any safety concerns for the administration of palonosetron combined with netupitant at doses of 100 mg, 200 mg or 300 mg. Based on the efficacy and safety results of this Phase II dose ranging study, the dose of oral netupitant to be used in combination with 0.50 mg oral palonosetron for the FDC was identified to be 300 mg.

Comment: The rationale for the selection of the palonosetron and netupitant doses for the FDC formulation is sound.

[15] Defined as no emesis, no rescue medication and no significant nausea

Efficacy

Studies providing efficacy data

One pivotal efficacy study (NETU-08-18), one efficacy/safety study (Study NETU-10-29) as well as 3 bridging studies (PALO-10-01, PALO-03-13 and PALO-03-14) provided efficacy data to support the application.

Evaluator's conclusions on efficacy

Overall, the study design, study inclusion and exclusion criteria, and study endpoints of the clinical studies submitted were appropriate. The primary and secondary endpoints of the studies allowed evaluations of the effect on various symptoms and combinations of symptoms of CINV (nausea, significant nausea, emesis, need for rescue medication, no emesis plus no rescue medication [complete response; CR], no emesis plus no rescue medication plus no significant nausea [complete protection], no emesis plus no rescue medication plus no nausea [total or complete control]) in the acute, delayed and overall phases of CINV, of netupitant/palonosetron FDC compared to palonosetron alone (Study NETU-08-18), of concomitant administration of netupitant and palonosetron compared to palonosetron alone (Study NETU-07-07) and of netupitant/palonosetron FDC compared to aprepitant+palonosetron (Study NETU-10-29; exploratory comparison). Baseline demographic and disease characteristics were comparable among treatment groups in each study, and were consistent with the target patient population.

Overall, efficacy results supported the anti-emetic efficacy of oral netupitant 300 mg plus palonosetron 0.50 mg in acute and delayed phases of CINV with MEC and HEC, as well as efficacy over repeated cycles of chemotherapy. Primary and main secondary efficacy analyses in the clinical studies submitted showed that there was better anti-emetic efficacy in terms of the endpoint of CR rate for oral netupitant 300 mg plus palonosetron 0.50 mg compared to oral palonosetron 0.50 mg alone, with statistical significance achieved for all three phases (delayed [25 to 120 hours], acute [0 to 24 hours] and overall [0 to 120 hours]) in studies NETU-08-18 (MEC) and NETU-07-07 (HEC).

In NETU-08-18 there was a treatment difference (netupitant/palonosetron FDC over palonosetron alone) of 7.4%, 3.4% and 7.7% in the delayed, acute and overall phases, respectively, while in NETU-07-07 the treatment differences (netupitant 300 mg + palonosetron over palonosetron alone) were 10.2%, 8.8% and 13.2%, respectively. Although no formal comparison was performed against comparators other than oral palonosetron, a numerical advantage of netupitant/palonosetron FDC was shown versus aprepitant + palonosetron in Study NETU-10-29 (MEC and HEC) in CR rate in the delayed and overall phases (treatment difference of 5.5% and 4.9% in the delayed and overall phases, respectively; treatment difference of -1.3% in the acute phase).

Further analyses looking at efficacy in MEC (studies NETU-08-18 and MEC subgroup of NETU-10-29) and HEC (studies NETU-07-07 and HEC subgroup of NETU-10-29) supported the anti-emetic efficacy of oral netupitant 300 mg plus palonosetron 0.50 mg for both MEC and HEC. Complete response rates for netupitant/palonosetron FDC were generally comparable between Study NETU-08-18 and the MEC subgroup of Study NETU-10-29 for all 3 phases (NETU-08-18: CR rates of 66.6% to 85.0% across the 3 phases; NETU-10-29: CR rates of 79.6% to 93.2% across the 3 phases). CR rates were comparable between netupitant/palonosetron FDC and aprepitant + palonosetron in the MEC subgroup of Study NETU-10-29 in the delayed, acute and overall phases.

Complete response rates for oral netupitant 300 mg plus palonosetron 0.50 mg were generally comparable between Study NETU-07-07 (netupitant + palonosetron) and the HEC subgroup of Study NETU-10-29 (netupitant/palonosetron FDC) for all 3 phases (NETU-07-07: CR rates of 89.6% to 98.5% across the 3 phases; NETU-10-29: CR rates of

83.8% to 91.9% across the 3 phases). A numerical advantage of netupitant/palonosetron FDC was shown versus aprepitant + palonosetron in the HEC subgroup of Study NETU-10-29 in the delayed and overall phases (treatment difference of 30.1% and 26.1% in the delayed and overall phases, respectively). In addition, in Study NETU-10-29, exploratory subgroup analyses by chemotherapy emetogenicity for the endpoint of complete response showed that percentages of patients with CR in the netupitant/palonosetron FDC group were generally comparable between MEC (81.7%, 93.2% and 79.6% for the delayed, acute and overall phases of Cycle 1, respectively) and HEC subgroups (87.8%, 91.9% and 83.8%, respectively), as were the percentages of patients with no significant nausea in the netupitant/palonosetron FDC group (MEC: 85.5%, 90.2% and 84.7% for the delayed, acute and overall phases of Cycle 1, respectively; HEC: 83.8%, 91.9% and 82.4%, respectively).

Results in study PALO-10-01 supported efficacy of the palonosetron component of the FDC in HEC, showing non-inferiority of oral palonosetron 0.50 mg compared with IV palonosetron 0.25 mg in terms of CR rate in the acute phase in patients receiving HEC (treatment difference of 3.21%, 99% CI: -2.74% to 9.17%), and no statistically significant difference between oral palonosetron 0.50 mg and IV palonosetron 0.25 mg with regards to CR rate in the delayed and overall phases in patients receiving HEC (delayed phase: treatment difference of 1.4%, p = 0.637; overall phase: treatment difference of 3.5%, p = 0.269).

Analyses of other secondary efficacy endpoints generally supported the results of primary and main secondary efficacy endpoints. Efficacy endpoints of no emesis, no significant nausea, and complete protection (no emesis, no rescue medication, and no significant nausea) showed that oral netupitant 300 mg plus palonosetron 0.50 mg had statistically significantly better efficacy compared to oral palonosetron 0.50 mg alone in the delayed and overall phases in Studies NETU-08-18 (MEC; netupitant/palonosetron FDC) and NETU-07-07 (HEC; netupitant + palonosetron).

With regards to efficacy over repeated cycles of chemotherapy, 2 studies collected efficacy data over multiple cycles of chemotherapy (NETU-08-18 in MEC and safety Study NETU-10-29 in MEC and HEC). Overall, the results indicated that the anti-emetic effect of the FDC was maintained over multiple cycles of chemotherapy. Results in Study NETU-08-18 showed that the CR rates were higher for netupitant/palonosetron FDC than for palonosetron alone in each phase and each cycle up to Cycle 6, with treatment differences more pronounced in the delayed and overall phases. The range of treatment differences across Cycles 2 to 6 in the delayed phase was 5.6% to 12.9%, in the acute phase was 3.0% to 7.8%, and in the overall phase was 5.2% to 13.6%. The proportions of patients with no significant nausea were also higher for the netupitant/palonosetron FDC than for palonosetron alone in each phase and each cycle up to Cycle 6, with treatment differences more pronounced in the delayed and overall phases. The range of treatment differences across Cycles 2 to 6 in the delayed phase was 4.4% to 9.2%, in the acute phase was 1.6% to 3.4%, and in the delayed phase was 2.8% to 4.7%.

Results in Study NETU-10-29 showed that in Cycles 2 to 6, the proportion of patients with CR was numerically higher for the netupitant/palonosetron FDC group than the aprepitant+palonosetron group in particular in the delayed and overall phases. Results in the acute phase were more similar between groups. The range of treatment differences across Cycles 2 to 6 in the delayed phase was 3.3% to 7.0%, in the acute phase was -3.4% to 4.8%, and in the overall phase was 2.5% to 5.7%. Analyses of the proportion of patients with no significant nausea showed similar pattern. In Cycle 2 percentages of patients with no significant nausea were comparable between netupitant/palonosetron FDC and aprepitant+palonosetron for all phases (treatment differences ranging from 0.3% in the overall phase to 2.6% in the acute phase). Starting from Cycle 3 and up to 6, the proportion of patients with no significant nausea was numerically higher for the netupitant/palonosetron FDC group than the aprepitant+palonosetron group, in particular

in the delayed and overall phases (range of differences 5.4% to 11.1% in the delayed phase and 5.4% to 9.9% in the overall phase). The range of treatment differences across cycles 3 to 6 in the delayed phase was 5.4% to 11.1%, in the acute phase was 1.9% to 8.9%, and in the overall phase was 5.4% to 9.9%.

The study population in Study NETU-08-18 comprised mainly of females (98.1%; 1422 out of 1450). This was expected as the protocol specified chemotherapy regimen is mostly indicated for breast cancer. However, in Studies NETU-07-07 (HEC) and NETU-10-29 (MEC and HEC), male patients made up 57% and 50% of the respective study populations. In addition, subgroup analyses in Studies NETU-07-07 and NETU-10-29 showed that there was anti-emetic efficacy with oral netupitant 300 mg plus palonosetron 0.50 mg in both male and female subgroups. Results in Study NETU-07-07 showed that CR rate in the overall phase was numerically higher for oral netupitant 300 mg plus palonosetron 0.50 mg compared to palonosetron alone, for both male and female patients, although the treatment difference from palonosetron alone was smaller in male patients (94.8% versus 83.3%; treatment difference of 11.5%, p = 0.030) than in female patients (82.8% versus 67.2%; treatment difference of 15.5%, p = 0.057). Results in Study NETU-10-29 showed that percentages of patients with CR in the netupitant/palonosetron FDC group were generally comparable between male (85.7%, 94.2% and 82.5% for the delayed, acute and overall phases of Cycle 1, respectively) and female patients (80.6%, 91.6% and 78.7% respectively). Subgroup analyses by gender for the endpoint of no significant nausea showed that percentages of patients with no significant nausea in the netupitant/palonosetron FDC group were also generally comparable between male (82.5%, 87.7% and 81.8% for the delayed, acute and overall phases of Cycle 1, respectively) and female patients (87.7%, 93.5% and 86.5%, respectively). The clinical overview submitted was reviewed and did not raise any additional concerns.

Safety

Studies providing safety data

The following studies provided evaluable safety data:

Pivotal efficacy study

In Study NETU-08-18, the following safety data were collected:

- General adverse events (AEs) were assessed by the investigator obtaining and recording all AEs at each scheduled visit.
- AEs of particular interest were cardiac and CNS or psychiatric treatment emergent AEs (TEAEs). These AEs of special interest were selected and identified by standardised MedDRA queries (SMQs). According to the sponsor, these analyses of AEs of special interest were not done due to specific safety concerns, but to fulfil a requirement of the regulatory authority, with an objective of showing that there were no clusters of cardiac, CNS or psychiatric TEAEs in the study. In particular, special attention on CNS and psychiatric events of special interest was done to isolate possible signs of drug abuse and to support pre-clinical data showing no evidence of physical dependence potential for the netupitant/palonosetron FDC.
- Laboratory tests performed included haematology, blood chemistry (urea, creatinine, total bilirubin, alkaline phosphatase, ALT, AST, sodium, potassium, chloride,

bicarbonate, calcium, albumin, total protein, blood glucose, total creatine kinase (CK), CK-MB fraction[16] and myoglobin), and urinalysis.

- Other safety endpoints included vital signs, 12-lead ECG, left ventricular ejection fraction (LVEF), cardiac Troponin I (cTnI) levels.

The dose response and other efficacy studies provided safety data, as follows:

- Study NETU-07-07 provided data on AE s, vital signs, laboratory evaluations (haematology, blood chemistry and urinalysis) and 12-lead ECG.
- Study NETU-10-29 provided data on AE s, vital signs, laboratory evaluations (haematology, blood chemistry and urinalysis), 12-lead ECG, LVEF, and cTnI levels, performed according to the schedule.
- Studies PALO-10-01, PALO-03-13 and PALO-03-14 provided data on AEs, vital signs, laboratory evaluations (haematology, blood chemistry and urinalysis) and 12-lead ECG.

Patient exposure

In Study NETU-08-18, a total of 1,450 patients were treated with study medication, 724 in the netupitant/palonosetron FDC group and 726 in the palonosetron alone group. Over the complete study period, 164 (11.3%) patients overall received 1 dose of study drugs (90 [12.4%] and 74 [10.2%] in the netupitant/palonosetron FDC and palonosetron alone groups, respectively), 591 (40.8%) patients received 4 doses of study drugs (280 [38.5%] and 311 [42.9%], respectively) and 382 (26.3%) patients received 6 doses of study drugs (194 [26.8%] and 188 [25.9%], respectively). The median number of days on study drugs was 4.0 in both treatment groups.

In Study NETU-07-07, a total of 679 patients were treated with study medications, 136, 135, 138, 136 and 134 in the palonosetron alone, palonosetron+netupitant 100 mg, palonosetron+netupitant 200 mg, palonosetron+netupitant 300 mg, and aprepitant+ondansetron groups, respectively. The median duration of treatment with the study drugs was 4.0 days in all treatment groups.

In Study NETU-10-29, a total of 412 patients were treated with study medications, of which 308 were exposed to the netupitant/palonosetron FDC and 104 to aprepitant+palonosetron during Cycle 1. Over the complete study period, patients in the netupitant/palonosetron FDC group (N = 308) received a mean standard deviation (SD) of 4.7 (2.19) netupitant/palonosetron FDC capsules on Day 1.

Patients in the aprepitant+palonosetron group (N = 104) received a mean (SD) of 5 (2.36) aprepitant capsules and 5 (2.36) palonosetron capsules on Day 1, 4.9 (2.35) aprepitant capsules on Day 2, and 5.0 (2.29) aprepitant capsules on Day 3 (aprepitant was given for 3 days of the treatment cycle and palonosetron was given on Day 1 only). The median number of days on netupitant/palonosetron FDC capsules was 5.0 in the netupitant/palonosetron FDC group. The median number of days on aprepitant and palonosetron was 15.0 and 5.0, respectively, in the aprepitant+palonosetron group.

In Study PALO-10-01, a total of 739 patients were treated with study medications, of which 370 received oral palonosetron, and 369 received IV palonosetron. The median duration of treatment with the study drugs was 1.0 days in both treatment groups. A summary of the extent of exposure to study medication in Study PALO-03-was provided (see Attachment 2). A summary of the extent of exposure to study drug in study PALO-03-

[16] The CPK-MB test is a cardiac marker used to assist diagnoses of an acute myocardial infarction. It measures the blood level of CK-MB, the bound combination of two variants (isoenzymes CKM and CKB) of the enzyme phosphocreatine kinase.

14was provided (see Attachmetn 2). Overall in study PALO-03-14, the study medication was administered in 654 out of 661 cycles (98.9% of cycles).

Comment: Overall, the study drug exposure is adequate to assess the safety profile of netupitant/palonosetron FDC.

Safety issues with the potential for major regulatory impact

No safety issues with potential for major regulatory impact were listed.

Postmarketing data

No postmarketing data were available.

Evaluator's conclusions on safety

Overall, safety results did not raise any major safety concerns. In the Cycle 1 safety population of Study NETU-08-18 (MEC), the percentages of patients with any study drug related TEAEs were comparable between the netupitant/palonosetron FDC group and the palonosetron alone group (8.1% versus 7.2%). The most commonly reported study drug related TEAE by preferred term in the netupitant/palonosetron FDC group was headache (3.3% versus 3.0% in the palonosetron alone group) and constipation (2.1% versus 2.1%). Safety results in Study NETU-07-07 (HEC) showed similar findings. The percentages of patients with any study drug related TEAEs were comparable between the netupitant 300 mg plus palonosetron 0.50 mg group and the palonosetron alone group (15.4% versus 12.5%). The most commonly reported study drug related TEAE by preferred term in the netupitant 300 mg plus palonosetron group was hiccups (5.1% versus 3.7% in the palonosetron alone group). Although the percentages of patients with any study drug related TEAEs were higher in the netupitant/palonosetron FDC group (10.1%) compared to the aprepitant+palonosetron group (5.8%) in Study NETU-10-29, most of these study drug related TEAEs were mild or moderate in intensity. Only one (0.2%) patient (in the netupitant/palonosetron FDC group) experienced a severe study drug related TEAE (acute psychosis; serious adverse event (SAE)). The most commonly reported study drug related TEAE by preferred term in the netupitant/palonosetron FDC group was constipation (3.6% versus 1.0% in the aprepitant+palonosetron group) and headache (1.0% versus 1.0%).

In Study NETU-08-18, there were no deaths in the netupitant/palonosetron FDC group in 1 (compared to one death in the palonosetron alone group). There were also no deaths in the netupitant 300 mg plus palonosetron 0.50 mg group in Study NETU-07-07 (also no death in the palonosetron alone group). In Study NETU-10-29, the incidence of death was higher in the netupitant/palonosetron FDC group (16 deaths; 5.2%) compared to the aprepitant+palonosetron group (1 death; 1.0%). However, the most common cause of death in the netupitant/palonosetron FDC group was disease progression (5 patients) and lung/pulmonary embolism (2 patients), with other causes of deaths reported in 1 patient each. In addition, none of the deaths were considered related to study drugs.

In Study NETU-08-18, the percentages of patients with any SAEs in the Cycle 1 were comparable between the netupitant/palonosetron FDC group and the palonosetron alone group (1.8% versus 1.7%). The most commonly reported SAE by preferred term in the netupitant/palonosetron FDC group was febrile neutropenia (0.6% versus 0.4% in the palonosetron alone group). There were no study drug related SAEs in Cycle 1. In Study NETU-07-07, there were no SAEs in the netupitant 300 mg plus palonosetron 0.50 mg group (compared to 2.2% in the palonosetron alone group). In Study NETU-10-29, the percentages of patients with any SAEs were comparable between the netupitant/palonosetron FDC group and the aprepitant+palonosetron group (16.2%

versus 18.3%). The most commonly reported SAEs by preferred term in the netupitant/ palonosetron FDC group were febrile neutropenia (1.9% versus 1.0% in the aprepitant+palonosetron group) and vomiting (1.6% versus 1.0%). Two study drug related SAEs were reported in 2 (0.6%) patients in the netupitant/ palonosetron FDC group (ventricular extrasystoles; acute psychosis) compared with none in the aprepitant+palonosetron group.

The percentages of patients with any TEAEs leading to discontinuation of study drug were comparable between netupitant/palonosetron FDC and palonosetron alone (Study NETU-08-18; 1.0% versus 0.6%), between netupitant 300 mg plus palonosetron 0.50 mg and palonosetron alone (Study NETU-07-07; 0% in both groups), and between netupitant/palonosetron FDC and aprepitant+palonosetron (Study NETU-10-29; 9.1% versus 12.5%). Analyses of haematology, blood chemistry, urinalysis, 12-lead ECG and vital signs did not raise any safety concerns in Studies NETU-08-18, NETU-07-07 and NETU-10-29. Assessment of drug abuse potential did not raise any safety concerns.

Analyses of safety over repeated chemotherapy cycles did not raise any safety concerns. In the multiple cycle extension safety population in Study NETU-08-18, the percentages of patients with any study drug related TEAEs was comparable between the netupitant/palonosetron FDC group and the palonosetron alone group (10.1% versus 7.5%). Consistent with the findings in Cycle 1, the most commonly reported study drug related TEAE by preferred term in the netupitant/palonosetron FDC group in the multiple cycle extension was headache (3.5% in the versus 2.8% in the palonosetron alone group) and constipation (2.0% versus 2.2%). There were no deaths in the netupitant/palonosetron FDC group in the multiple cycle extension (compare with one death in the palonosetron alone group). In the multiple cycle extension safety population, the percentages of patients with any SAEs was comparable between the netupitant/palonosetron FDC group and the palonosetron alone group (3.6% versus 2.3%). Consistent with the findings in Cycle 1, the most commonly reported SAEs by preferred term in the netupitant/palonosetron FDC group was febrile neutropenia (0.9% versus 0.6% in the palonosetron alone group) and neutropenia (0.9% versus 0.2%). None of the SAEs were considered study drug related.

In Study NETU-10-29, the percentage of patients with any study drug related TEAEs in both treatment groups showed a general decreasing trend over the first 6 cycles, from an overall incidence of 4.6% in Cycle 1 (5.2% and 2.9% in the netupitant/palonosetron FDC and aprepitant + palonosetron groups, respectively) to 1.2% in Cycle 6 (1.6% and 0%, respectively). The incidence of study drug related TEAEs was generally similar between the treatment groups within each cycle from Cycles 1 to 6. The only study drug related TEAE that was reported by ≥ 2% patients in any treatment group, for Cycles 1 through 6, was constipation (incidence in Cycle 1 of 2.3% in the netupitant/palonosetron FDC versus 0% in the aprepitant+palonosetron group; incidence in Cycle 2 of 2.5% versus 0%). The incidence of death was highest in Cycle 1 (7 deaths [overall incidence of 1.7%]; all in netupitant/palonosetron FDC group) while the incidence of death in Cycles 2 to 6 was low (0.3% to 1.2%). The incidence of SAEs was generally comparable from Cycles 1 to 6 (incidence range of 2.9% to 5.3%). The incidence of SAEs was generally similar between the treatment groups within each cycle from Cycles 1 to 6.

First round benefit-risk assessment

First round assessment of benefits

The benefits of Akynzeo in the proposed usage are:

- Prevention of acute as well as delayed nausea and vomiting associated with initial and repeat courses of both highly emetogenic and moderately emetogenic cancer chemotherapy.
- Potential improved medication compliance as oral FDC formulation offers simpler dosing regimen.

Overall, efficacy results supported anti-emetic efficacy of a single oral dose of netupitant/palonosetron FDC in acute and delayed phases of CINV with MEC and HEC, as well as efficacy over repeated cycles of chemotherapy.

Efficacy analyses results showed that there was a statistically significantly higher proportion of patients with complete response (no emesis and no rescue medication) with netupitant/palonosetron FDC compared to palonosetron alone in patients on MEC in the acute (0 to 24 hours) and delayed (25 to 120 hours) phases (Study NETU-08-18: treatment difference [netupitant/palonosetron FDC over palonosetron alone] of 3.4% [p = 0.047] and 7.4% [p = 0.001] in the acute and delayed phases, respectively). There was also a statistically significantly higher proportion of patients with complete response with netupitant 300 mg + palonosetron 0.50 mg compared to palonosetron alone in patients on HEC in the acute and delayed phases (Study NETU-07-07: treatment difference [netupitant 300 mg+palonosetron over palonosetron alone] of 8.8% [p = 0.002; CMH test] and 10.2% [p = 0.016; CMH test] in the acute and delayed phases, respectively).

Analyses of other efficacy endpoints generally supported the results of the endpoint of complete response. Efficacy endpoint of the proportion of patients with no emesis showed statistically significant differences ($p < 0.05$) between oral netupitant 300 mg plus palonosetron 0.50 mg and oral palonosetron 0.50 mg alone in the acute, delayed and overall phases in studies NETU-08-18 (netupitant/palonosetron FDC versus palonosetron alone; acute phase: 90.9% versus 87.3%; delayed phase: 81.8% versus 75.6%) and NETU-07-07 (netupitant 300 mg + palonosetron versus palonosetron alone; acute phase: 98.5% versus 89.7%; delayed phase: 91.9% versus 80.1%). Endpoints of the proportion of patients with no significant nausea, and with complete protection (no emesis, no rescue medication, and no significant nausea) also showed statistically significant differences between oral netupitant 300 mg plus palonosetron 0.50 mg and oral palonosetron 0.50 mg alone (in favour of the former) in the delayed and overall phases in studies NETU-08-18 and NETU-07-07.

With regards to efficacy over repeated cycles of chemotherapy, analyses of efficacy data over multiple cycles of chemotherapy in Study NETU-08-18 (MEC) and safety Study NETU-10-29 (MEC and HEC) showed that the anti-emetic effect of the FDC was maintained over multiple cycles of chemotherapy. Results in Study NETU-08-18 showed that the proportions of patients with complete response and those with no significant nausea were higher for netupitant/palonosetron FDC than for palonosetron alone in each phase (acute, delayed and overall) and each cycle up to Cycle 6, with treatment differences more pronounced in the delayed and overall phases. Results in Study NETU-10-29 showed that in Cycles 2 to 6, the proportion of patients with complete response was numerically higher for the netupitant/palonosetron FDC group than the aprepitant+palonosetron group particularly in the delayed and overall phases, while that in the acute phase was more similar between treatment groups.

First round assessment of risks

The risks of Akynzeo in the proposed usage are:

- headache
- constipation.

Overall, safety results did not raise any major safety concerns. In both Studies NETU-08-18 (MEC) and NETU-10-29 (MEC and HEC), the most commonly reported study drug related TEAE by preferred term in the netupitant/palonosetron FDC group was headache (Study NETU-08-18 cycle one: 3.3% versus 3.0% in the palonosetron alone group; Study NETU-10-29: 1.0% versus 1.0% in the aprepitant+palonosetron group) and constipation (Study NETU-08-18 Cycle one: 2.1% versus 2.1%; Study NETU-10-29: 3.6% versus 1.0%). In Study NETU-07-07 (HEC), the most commonly reported study drug related TEAE by preferred term in the netupitant 300 mg plus palonosetron group was hiccups (5.1% versus 3.7% in the palonosetron alone group).

The majority of study drug related TEAEs were mild to moderate in intensity. The incidence of severe study drug related TEAEs in the netupitant/palonosetron FDC group was 0.7% (5 out of 725) in Study NETU-08-18 Cycle 1 (versus 0% [0 out of 725] in the palonosetron alone group) and 0.3% (1 out of 308) in Study NETU-10-29 (versus 0% [0 out of 104] in aprepitant+palonosetron group), and that of netupitant 300 mg + palonosetron was 0% (0 out of 136) in Study NETU-07-07 (versus 1.5% [2 out of 136] in the palonosetron alone group). The incidence of drug related SAEs was also low. There were no study drug related SAEs in Study NETU-08-18 (Cycle 1) and in Study NETU-07-07 and only two study drug related SAEs were reported in 2 (0.6%) patients in the netupitant/ palonosetron FDC group (ventricular extrasystoles; acute psychosis) in Study NETU-10-29.

Analyses of safety over repeated chemotherapy cycles did not raise any safety concerns. In the multiple cycle extension safety population in Study NETU-08-18, the percentages of patients with any study drug related TEAEs was comparable between the netupitant/palonosetron FDC group and the palonosetron alone group (10.1% versus 7.5%). Consistent with the findings in Cycle 1, the most commonly reported study drug related TEAE by preferred term in the netupitant/palonosetron FDC group in the multiple cycle extension was headache (3.5% in the versus 2.8% in the palonosetron alone group) and constipation (2.0% versus 2.2%). The majority of study drug related TEAEs were mild to moderate in intensity. The incidence of severe study drug related TEAEs in the netupitant/palonosetron FDC group was 0.2% (1 out of 635; versus 0.2% [1 out of 651] in the palonosetron alone group). There were no study drug related SAEs in either treatment groups. In Study NETU-10-29, the percentage of patients with any study drug related TEAEs was generally similar between the treatment groups within each cycle from cycles 1 to 6, and showed a general decreasing trend over the first 6 cycles, from an overall incidence of 4.6% in Cycle 1 (5.2% and 2.9% in the netupitant/palonosetron FDC and aprepitant+ palonosetron groups, respectively) to 1.2% in cycle 6 (1.6% and 0%, respectively). The only study drug related TEAE that was reported by ≥ 2% patients in any treatment group, for Cycles 1 through 6, was constipation (incidence in Cycle 1 of 2.3% in the netupitant/palonosetron FDC versus 0% in the aprepitant+palonosetron group; incidence in Cycle 2 of 2.5% versus 0%).

First round assessment of benefit-risk balance

The benefit-risk balance of Akynzeo, given the proposed usage, is favourable.

Overall, efficacy results supported anti-emetic efficacy of oral netupitant 300 mg plus palonosetron 0.50 mg in acute and delayed phases of CINV with MEC and HEC, as well as efficacy over repeated cycles of chemotherapy. Efficacy analyses results showed that there was a statistically significantly higher proportion of patients with complete response with netupitant/palonosetron FDC compared to palonosetron alone in patients on MEC in the acute and delayed phases (Study NETU-08-18: treatment difference [netupitant/palonosetron FDC over palonosetron alone] of 3.4% and 7.4% in the acute and delayed phases, respectively). There was also a statistically significantly higher proportion of patients with complete response with netupitant 300 mg + palonosetron

0.50 mg compared to palonosetron alone in patients on HEC in the acute and delayed phases (Study NETU-07-07: treatment difference [netupitant+palonosetron over palonosetron alone] of 8.8% and 10.2% in the acute and delayed phases, respectively). Analyses of other efficacy endpoints generally supported the results of the endpoint of complete response. Analyses of efficacy data over multiple cycles of chemotherapy showed that the anti-emetic effect of the FDC was maintained over multiple cycles of chemotherapy.

Overall, safety results did not raise any major safety concerns. In both Studies NETU-08-18 (MEC) and NETU-10-29 (MEC and HEC), the most commonly reported study drug related TEAE by preferred term in the netupitant/palonosetron FDC group was headache and constipation, while in Study NETU-07-07 (HEC), the most commonly reported study drug related TEAE by preferred term in the netupitant 300 mg plus palonosetron group was hiccups. The majority of study drug related TEAEs were mild to moderate in intensity. The incidence of severe and serious drug related TEAEs was low. Analyses of safety over repeated chemotherapy cycles did not raise any safety concerns.

First round recommendation regarding authorisation

It is recommended that the application for registration of Akynzeo for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic and moderately emetogenic cancer chemotherapy be approved. This is subject to incorporation of suggested changes to proposed PI.

Clinical questions

Pharmacokinetics

1. Although the palonosetron oral softgel capsules used in the FDC are similar to the currently approved formulation, the two formulations are not identical; why has the sponsor not examined the effects of these formulation differences on the PK of the palonosetron component?
2. Can the sponsor please provide an explanation as to why food has a much greater effect on netupitant PK in Studies BP17408 and NP16600 compared with Study NETU-10-12.
3. Can the sponsor please provide an explanation for the increased variability in netupitant PK that occurs as a result of hepatic impairment?
4. As comparison of the PK results regarding netupitant when given in combination with dexamethasone (Study NETU-06-07) and in Study NP16603, where the same doses of netupitant were administered (that is, 100, 300 and 450 mg), indicate that netupitant AUC_{inf} was significantly lower in Study NETU-06-07, can the sponsor please explain this discrepancy.
5. As the 'investigational plan' section of Study Report NETU-08-18 indicated that the subset of patients in which the PK of the FDC were to be determined numbered approximately 500 it is not clear why the data for only 117 to 118 patients was included in the PopPK modelling studies. Therefore, can the sponsor please provide details concerning how the sub-population for the PopPK study was selected?
6. The populations modelled in the PopPK were primarily female (approximately 96%) and Caucasian (approximately 86%). Therefore, due to the small number of male (n = 4 to 5) and non-Caucasian subjects (n = 16) included in the analyses, it may not have

allowed an accurate determination of the importance of these covariates. Can the sponsor please justify the use of this population in the modelling studies?

Pharmacodynamics

7. One of the TEAEs of special interest that was identified in the pivotal study and was assessed by the investigator as being possibly related to study drugs was mood alteration during Cycle 2. This TEAE was of moderate intensity and resolved after 13 days with no specific therapy. In addition, Study NP16603 identified 2 out of 4 subjects who experienced decreased vigilance, alertness and memory impairment. Therefore, can the sponsor please provide a summary of all the data related to the central effects of the FDC on alertness, mood and memory?
8. The PK/PD data suggests that earlier treatment with the FDC than that proposed may result in enhanced anti-emetic effectiveness. Therefore, in the absence of data examining a range of times of FDC administration prior to chemotherapy how was the proposed 1 hour's pre-chemotherapy time point chosen?

Second round evaluation of clinical data submitted in response to questions

For details of theSponsor's responses and the evalautor's comments on these responses, please see Attachment 2 Second Round Evaluation of clinical data submitted in response to questions.

Second round benefit-risk assessment

Second round assessment of benefits

No clinical questions were raised pertaining to efficacy. Accordingly, the benefits of Akynzeo are unchanged from those identified inthe First round evaluation.

Second round assessment of risks

No clinical questions were raised pertaining to safety. Accordingly, the risks of Akynzeo are unchanged from those identified in the First round evaluation.

Second round assessment of benefit-risk balance

The benefit-risk balance of Akynzeo, given the proposed usage, is favourable.

Second round recommendation regarding authorisation

It is recommended that the application for registration of Akynzeo for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic and moderately emetogenic cancer chemotherapy be approved.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP) (Akynzeo EU-RMP version 1.0 (undated; data lock point 31 August 2013) with the Australian Specific Annex (ASA) version 1.0 (dated 28 February 2014)) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 8.

Table 8. Summary of Ongoing safety concerns

Summaroy of ongoing safety concerns	
Important identified risks	None
Important Potential risks	QT/QTc interval prolongation Anaphylaxis, anaphylactic/anaphylactoid reactions and shock Constipation related complications Convulsive reactions Liver transaminases increase Interactions with CYP3A4 inhibitors and inducers Interaction with corticosteroicds
Missing information	Effects on pregnancy and lactation Effects on fertility Patients with end stage renal disease undergoing haemodialysis

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities for all the ongoing safety concerns in the EU-RMP and the ASA. No additional pharmacovigilance is proposed.

Risk minimisation activities

Routine risk minimisation measures through the Product Information have been proposed by the sponsor for all ongoing safety concerns.

Reconciliation of issues outlined in the RMP report

Table 9 summarises the RMP evaluator's first round evaluation of the RMP, the sponsor's responses to issues raised and the RMP evaluator's evaluation of the sponsor's responses.

Table 9. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated request for information and/or the nonclinical and clinical evaluation reports	All safety considerations raised by the nonclinical and clinical evaluators, including requests made to the RMP, have been addressed in the framework of the responses to the consolidated request for information. The RMP response document clearly	The sponsor's response is satisfactory.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	stipulates where the issue raised will have a future impact on the EU RMP and/or ASA. Moreover, any safety concerns that have an impact on the RMP will be addressed in the EU RMP and/or ASA, according to the timelines specified below: The EU-RMP will be updated in June 2015 as soon as the currently ongoing EU evaluation procedures are completed, and the final opinion is adopted by the CHMP. An updated ASA will be provided to the TGA after the final PI negotiations for this evaluation have taken place (anticipated June/July 2015), and/or after the EU RMP is updated to the next version in June 2015.	
Subject to the evaluation outcomes of the nonclinical and clinical aspects of the safety specification, it is recommended that the identified class effects of 'QT/QTc interval prolongation' and 'anaphylaxis, anaphylactic/anaphylactic reaction and shock' be upgraded to 'important identified risks' in the ASA.	The spectrum of the most severe forms of drug induced hypersensitivity reactions, which includes potentially life threatening conditions such as anaphylaxis, naphylactic/anaphylactoid reactions and shock, represents a major concern. The occurrence of these reactions after intravenous palonosetron exposure is very limited; postmarketing data collected show that spontaneous cases of severe hypersensitivity reactions have been reported to happen very rarely following palonosetron administration. No event of severe hypersensitivity reaction, including anaphylaxis or similar reactions (anaphylactic/anaphylactoid reactions and shock) occurred in the netupitant/palonosetron FDC clinical development phase. However, the potential risk of severe reactions due to its use in the post-marketing setting cannot be ruled out. The safety concern relating to the	The sponsor's response is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	onset of such severe hypersensitivity reactions has been considered in the RMP of Akynzeo as an 'important potential risk'; however Helsinn, the originator of the FDC, concurs with TGA recommendation to upgrade the aforementioned severe reactions to 'important identified risks'. This update is expected to be implemented in the EU RMP post approval in Europe (June 2015), and the ASA will be updated accordingly at that time. Regarding the safety issue of 'QT/QTc prolongation': for the 5-HT_3 RAs, prolongation of the QT interval appears to be a class effect. Results of the ICH E14 compliant Thorough QTc study in healthy subjects receiving palonosetron escalating IV doses up to 2.25 mg (9 fold higher than the marketed dosage of 0.25 mg), demonstrated no 'clinically relevant prolongation of the QTc interval' These results are reflected in the Aloxi PI approved by TGA. Furthermore, a total of 3 individual spontaneous case reports of QT interval prolongation were notified to the sponsor over a period of more than 10 years of use, namely starting from September 2003, the date of palonosetron commercialisation, up to 24 July 2014 (the data lock point of the last Periodic Safety Update Report (PSUR)/Periodic Benefit-Risk Evaluation Report (PBRER). Two of these cases were considered possibly related to palonosetron (mainly due to timing of event), while the remaining case could not be thoroughly assessed due to the limited available information. Nevertheless, all the cases are confounded by factors such as concomitant treatment with chemotherapy or anaesthetics. Concerning the fixed dose combination, a Thorough ICH E14 study (NETU 07-20) conducted in 200 adult male and female healthy	

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	volunteers on netupitant (200 and 600 mg) orally administered with palonosetron (0.5 and 1.5 mg) demonstrated that Akynzeo had no clinically important effects on ECG parameters. The ECG data analyses including a pharmacodynamic-pharmacokinetic (PD-PK) analysis showed no effects on cardiac repolarization. In conformity with the submitted EU RMP for Akynzeo, the sponsor proposes to maintain 'QT/QTc prolongation' as an important potential risk at this time. Additional data from individual spontaneous case reports will further elucidate this potential safety concern and will be reviewed to establish whether this categorisation needs to be changed.	
Serotonin syndrome should be added as a potential risk.	In Europe, the EMA Pharmacovigilance Risk Assessment Committee (PRAC) considered that serotonin syndrome is a potential risk for the pharmacological class of 5-HT_3 RAs when drugs pertaining to this class are administered in combination with other serotonergic agents. The use of these antiemetics may increase the systemic availability of serotonin and may lead to the stimulation of other serotonin receptor subtypes by endogenous serotonin. Since this safety concern is a labelled effect for some 5-HT_3 RAs, it was recommended to add a wording about this class effect in the EU SmPC also for palonosetron. The recommendation was endorsed by the European Commission (EC) (EC final opinion on 23rd April 2014). The PI of Aloxi in Australia was recently amended to include the safety concern of serotonin syndrome (PI version 8 July 2014). The PI for Akynzeo submitted has been updated to reflect the same	The sponsor's response is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	wording in the 'Precautions' and 'Interactions' sections. Based on this recommendation, the EU RMP for Akynzeo will also be updated to include serotonin syndrome as an important potential risk for the fixed dose combination. This update is expected to be implemented in the EU RMP in Europe post-approval (June 2015), and the ASA will be updated accordingly at that time.	
Leucocytosis and neutropaenia should be added as potential risks, as they were reported as treatment-related AE s.	In the clinical development programme carried out with Akynzeo six out of 1,442 patients (0.4%) exposed to netupitant and palonosetron in combination (regardless of the dosage) experienced leucocytosis and 2 out of 1442 patients (0.1%) had neutropenia; both events were considered related to the investigational medicinal treatment by the investigator. A similar incidence of reactions (leucocytosis) was observed in the active comparator groups, namely in the palonosetron active comparator group 3 out of 1600 (0.2%) patients had leucocytosis assessed as adverse drug reaction (ADR) and 1 in 238 (0.4%) in the aprepitant plus a 5-HT_3 RA group). No patient in the aprepitant comparator group and one palonosetron treated patient had neutropenia as ADR. Leucocytosis occurred in two patients treated with netupitant 100 mg + palonosetron 0.50 mg, in 1 patient treated with netupitant 200 mg + palonosetron 0.50 mg and in 3 patients treated with the highest dose of netupitant (300 mg) combined with palonosetron 0.50 mg. All patients but one, were enrolled in the Phase II Study NETU 07-07. None of the related events of leucocytosis was serious and of severe intensity.	The sponsor's response is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	Interestingly most of patients (N = 6) with leucocytosis judged as related to study treatments, either netupitant/palonosetron combination or comparators, were recruited at the same study site; therefore it can be assumed that a site effect is likely to occur. Worthy of note, all these patients received dexamethasone, which is known to induce leucocytosis upon its initiation[17]. A study[18] concluded that a single dose of dexamethasone causes a granulocytosis primarily by a shift of PMNs from the marginated to the circulating pool, with a minor contribution from marrow release. Some solid tumours (most commonly described in carcinoma of the lung and in undifferentiated carcinoma) cause leukocytosis by the tumour cells called paraneoplastic leukemoid reaction. This is rare in children, but has been well described in adult patients. The presumed mechanism is production of cytokines, such as granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage colony-stimulating factor (GM-CSF), by tumour cells or metastatic cells. Neutropenia as ADR was reported in the Phase III Study NETU-08-18 for three patients, two of them received netupitant/palonosetron combination and one patient palonosetron as single agent. All patients were recruited at the same study site. A concise narrative of each patient is provided underneath. NETU/PALO FDC (N = 2) Patient [Information redacted] was a 65 years old male with infiltrating ductal carcinoma of the breast first treated with netupitant/palonosetron	

[17] Abramson N and Melton B. Leukocytosis: Basics of clinical assessment. *Am Fam Physician*. 2000; 62: 2053-2060.
[18] Nakagawa M et al. Glucocorticoid-Induced Granulocytosis. Contribution Of Marrow Release And Demargination Of Intravascular Granulocytes. *Circulation* 1998; 98: 2307-2313.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	and scheduled chemotherapy (cyclophopshamide, epirubicin and 5-FU) on May 3rd 2012. He developed neutropenia on 21 May. The event was non-serious, of severe intensity and resolved after specific therapy on 19 June. The sponsor believes that neutropenia is more likely attributable to the known cytotoxic effect of the chemotherapy with a nadir approximately two weeks after treatment. Patient [Information redacted] was a 34 years old female with infiltrating ductal breast cancer on prophylaxis with netupitant/palonosetron and treated with cyclophopshamide, epirubicin and 5-FU on July 18, 2012. Neutropenia was detected on August 2; it was non-serious, of moderate intensity and resolved without treatment on August 7. Also in this patient it is apparent that neutropenia was induced by the aggressiveness of the chemotherapy considering the time lag between its occurrence and the chemotherapy course. Palonosetron (N = 1) Patient [Information redacted] was a 50 years old female with infiltrating ductal breast carcinoma first treated with cyclophosphamide, epirubicin and 5-FU on May 30, 2012 who had neutropenia on June 11. The non-serious event was moderate in intensity and patient fully recovered from it approximately one week later. The low level of white blood cells detected approximately ten days after chemotherapy can be plausibly explained by the bone marrow depression triggered by the antineoplastic agents. Overall conclusion; Leucocytosis and neutropenia are listed in the Akynzeo PI as uncommon reactions (≥ 0.1% to < 1%), since these events occurred in at least two cancer patients. Because both alternate etiologies	

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	could explain the very limited number of reactions of leucocytosis and neutropenia, and in absence of clinically remarkable events (no SAEs), the sponsor does not agree to include these reactions as important potential risks for Akynzeo in the EU RMP or the ASA.	
It is noted that 6 and 12 geriatric participants were included in the two studies (NETU-08-12 and NETU-10-12) respectively. The small sample size means that the evidence collected is very limited. Considering that geriatric patients could form a significant proportion of the target population, it is recommended that 'use in the elderly' be added to the ongoing safety concern list as missing information in the ASA.	Both NETU 08-12 and NETU 10-12 are studies essentially designed to evaluate the effect of age on the PK of Akynzeo. Generally PK studies are descriptive, include moderate sample size; powered to detect a minimum difference based on expected population variability, to characterise basic PK parameters for parent drug and measure active metabolites only. To provide an accurate overview of the elderly cancer patients participating in the clinical development programme, additional data analyses were conducted on the Phase III multicycle studies, that consisted of cancer patients aged 65 years or older, who are considered geriatric population as per the guideline.[19] This guidance notes that for drugs with significant use in the elderly, the inclusion in clinical trials of a minimum of 100 patients aged 65 years or older 'would usually allow detection of clinically important differences' in drug responses compared with younger patients. The sponsor provided a table that displays the age subgroup of the population of the Phase III multicycle Studies (NETU 08-18 and NETU 10-29) carried out with Akynzeo. The Phase III studies included more patients with < 65 years (1,519 out of 1862, 81.6%) than patients with ≥ 65 years (343 out of 1,862, 18.4%). The most frequent neoplasms were breast	The sponsor's response is acceptable.

[19] ICH E7(R1): Studies in Support of Special Populations: Geriatrics.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	and lung/respiratory cancers. The percentage of patients with at least 1 TEAE during any cycle was comparable in these subgroups of patients overall (89.3%, 1356 out of 1,519 patients and 91.5%, 314 out of 343 patients, respectively) and in the netupitant-palonosetron group (89.3%, 749 out of 839 patients versus 94.8%, 184 out of 194 patients, respectively), with the most commonly reported TEAEs in each of the 2 age subgroups reflecting those in the overall safety population. At the preferred term (PT) level, the most commonly reported TEAEs in both overall age groups (< 65 years and ≥ 65 years) generally reflected those observed in the overall safety population: alopecia (49.6% and 43.1%, respectively), neutropenia (39.3% and 40.5%), leukopenia (21.7% and 27.4%, respectively), asthenia (13.1% and 12.2%, respectively), anaemia (10.6% and 14.6%, respectively) and headache (11.1% and 12.0%, respectively). These events occurred in a slightly higher percentage in the ≥ 65 years group, with the exception of alopecia and asthenia. As expected, AEs were most commonly reported in body systems (systems organ class) (SOC)) that are most often involved with the cytotoxic effects of chemotherapy administration, with the exception of headache, which is a known effect of the antiemetic treatment. Considering that TEAEs were counted only in the cycle in which they were first reported, the percentage of patients who underwent at least 6 consecutive cycles of treatment who reported TEAEs decreased with each additional cycle of treatment for both age subgroups in the netupitant-palonosetron group, ranging from 68.9% (184 out of 267 patients) at Cycle 1 to 31.8% (85 out of 267	

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	patients) at Cycle 6 in patients < 65 years of age and from 72.0% (36 out of 50 patients) at Cycle 1 to 36.0% (18 out of 50 patients) at Cycle 6 in patients ≥ 65 years of age. At each cycle, similar percentages of patients in the 2 age subgroups reported at least 1 TEAE in the netupitant-palonosetron group. Among patients who had at least 6 consecutive cycles of treatment, SAEs were reported in < 2% of patients in either age subgroup, with the exception of Cycle 5 in the < 65 years of age, where 6 (2.2%) patients reported SAEs. Overall, it can be assumed that there is no significant unknown safety concern in the population aged more than 65 years compared to that observed in cancer patients aged less than 65 years. Moreover the safety profile of Akynzeo is similar in both age categories, considering the type and frequency of the reported TEAEs. Taking into account the above data, the sponsor proposes to not include 'use in the elderly' in the ongoing safety concern list as 'missing information'.	
In a different pharmacokinetic study (NETU-10-10), the sponsor reported increases in exposure to netupitant in participants with mild and moderate hepatic impairment 'presumably due to reduced hepatic metabolism' and 'the effect appeared to increase with the degree of hepatic impairment'. A high variability amongst the participants was also observed. In addition, the small sample size of two participants with severely impaired hepatic function	The mentioned Study NETU-10-10 was conducted to assess the PK of a single dose of Akynzeo in patients with different stages of hepatic impairment in comparison to healthy volunteers. A total of 36 subjects were enrolled: 18 subjects with hepatic impairment classified by Child-Pugh scoring system as mild (N = 8 Child-Pugh 5 to 6), moderate (N = 8 Child Pugh 7 to 9) and severe (N = 2 Child Pugh 10 to 15) and 18 healthy subjects matched to the subjects with hepatic impairment by age, weight and gender. In 8 subjects with mild hepatic impairment, exposure to netupitant was slightly higher compared to	The sponsor's response is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
precluded a definitive conclusion in this group. Given that netupitant is 'eliminated mainly by hepatic metabolism' ('interactions with other medicines', proposed PI), 'use in moderate to severe hepatic impairment' should be added to the safety concern list as missing information in the ASA.	matching healthy subjects; while in subjects with moderate hepatic impairment exposure to netupitant was significantly higher compared to healthy subjects. Mildly hepatic impaired patients (N = 8) showed a C_{max} of palonosetron slightly higher compared to control with an increase of 14% for C_{max}. However, the increase was not statistically significant. In patients with moderate hepatic impairment, C_{max} of palonosetron was similar to that of matching healthy subjects. A wide variability of calculated half-lives of netupitant was observed both, in moderately impaired subjects and in healthy subjects as well as of the C_{max}/AUC values across all the subject groups for netupitant. The mean exposure values for the moderate matched healthy subjects were lower than the mild matched subjects, while the exposure mean values for mild and moderate impaired subjects were actually similar. The statistical significance of the moderately impaired group could be largely due to the comparison with the specific matched healthy subjects, and the absolute difference between mild and moderate impaired subjects was small. Therefore no dose adjustment was deemed needed for mildly or moderately hepatic impaired patients. The small sample size of severely impaired subjects (N = 2) was scarce, a trend toward increased exposure is likely to exist; however the variability in the data precluded a definitive conclusion. Based on these results, the sponsor believes that only the use in patients with severe liver impairment should be considered missing information to be included in the EU RMP. This update is expected to be completed in the EU RMP in Europe post-approval (June 2015), and the ASA will be updated accordingly at that time.	

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	The PI for Akynzeo submitted has been updated to advise caution in patients with severe hepatic impairment. The sponsor believes that no additional warnings or precautions are required.	
The pharmacovigilance section of the ASA should be updated accordingly to provide plans for managing the aforementioned safety issues. The sponsor should propose relevant new additional pharmacovigilance activities or assign these ongoing safety concerns to existing activities.	The EU RMP will be updated in June 2015 as soon as the EU evaluation procedures that are currently ongoing are completed and the final opinion is adopted by the CHMP. The ASA will be updated accordingly at that time and/or when the final PI negotiations for this evaluation have taken place.	The sponsor's response is acceptable.
The safety review conducted by Health Canada on serotonin blocking drugs led to the request for manufacturers to incorporate serotonin syndrome into the product labelling.[20] The TGA also published a safety alert on 22 September 2014 against the risk of serotonin syndrome. It is understood that requests for updating relevant sections of the PI and CMI are underway.[21] It is recommended to the Delegate that warnings against serotonin syndrome are added to the PI and CMI of Akynzeo.	As stated above, the Aloxi PI in Australia has been recently amended to include the safety concern of serotonin syndrome (PI updated version 8 July 2014). The PI for Akynzeo submitted has been updated to reflect the same wording in the 'precautions' and 'interactions' section. The CMI for Akynzeo will be aligned with the PI after final PI negotiations have taken place.	The sponsor's response is acceptable.
'Interaction with CYP3A4 inhibitors and inducers' is listed as an important	The sponsor does not agree to include a contraindication for concomitant use of Akynzeo and drugs that are	The recommendation remains, awaiting

[20] http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/review-examen/serotonin-eng.php
[21] http://tga.gov.au/safety/alerts-medicine-serotonin-140922.htm#.VCIx0PmSx8E

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
potential risk for Akynzeo. Patients scheduled to receive any strong or moderate inhibitor of CYP3A4 and patients scheduled to receive any of the CYP3A4 substrates including terfenadine, cisapride, astemizole and pimozide were excluded from clinical trials (Section SIV.2, EU-RMP). The approved PI for aprepitant, another substance P/neurokinin 1 antagonist contains the following wording under 'contraindication': should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Dose dependent inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions.' It is recommended that the Delegate considers whether a similar contraindication should apply to Akynzeo. Furthermore, the PI should list representative examples of CYP3A4 inhibitors and inducers, in particular chemotherapeutic agents.	substrates for CYP3A4. The proposed PI already submitted to the TGA describes this metabolic interaction in the section 'interactions with other medicines', however this wording has been strengthened and now also includes examples of chemotherapeutic agents that are known to be metabolised by CYP3A.	consideration by the Delegate.[22]
Available trial data on geriatric patients and patients with moderate to severe hepatic impairment is limited. It is recommended to the Delegate that wording on data limitation is added in the PI.	Please refer to responses above. Regarding the elderly, the PI states that no dosage adjustment is necessary for elderly patients. Regarding hepatic impairment, the PI already states that: 'hepatic impairment does not significantly affect total body clearance of palonosetron compared to the healthy	The sponsor's response is acceptable.

[22] The Delegate did not subsequently request for this recommendation to be implemented

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	subjects. No dosage adjustment of Akynzeo is necessary for patients with mild or moderate hepatic impairment (Child-Pugh score 5 to 8). Limited data exist in patients with severe hepatic impairment (Child Pugh score ≥ 9).' However, in agreement with the TGA recommendations, the following statement has been added to the PI that is submitted: 'Therefore Akynzeo should be used with caution in these patients.'	

Summary of recommendations

Outstanding issues

Issues in relation to the RMP

Details on the following outstanding issue are in Table 8. 'Reconciliation of issues outlined in the RMP report'.

The recommendation(s) on the draft PI remain, awaiting consideration by the Delegate.

Additional recommendations

The RMP evaluator supports the recommendations made by the nonclinical evaluator. The content of nonclinical part of the safety specification and the table of ongoing safety concerns should be revised as recommended.

Suggested wording for conditions of registration

RMP

Implement EU-RMP version 1.0 (undated; data lock point 31 August 2013) with the Australian Specific Annex version 1.0 (dated 28 February 2014) and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

Based on the quality evaluation report, there are no major issues with the pharmaceutical chemistry data evaluation.

Nonclinical

The nonclinical evaluation report draws attention to high concentrations of netupitant affecting cardiac conduction ('probably by binding to the L-type Ca^{2+} channel and inhibiting the hERG channel'). The report notes that there is a potential for additive effects on cardiac conduction with concomitant palonosetron.

There was reference to significant hypotension and bradycardia in rabbits exposed to palonosetron and netupitant. The nonclinical evaluator also notes that netupitant, M1 and M3 accumulate in heart tissue, in at least two species, but there was no major histopathology identified.

A pregnancy category of B3 was proposed by the evaluator (the sponsor proposed B2).

Clinical

Table 10. Overview of clinical data

Name	Type	Description
NETU-08-18	efficacy and safety pivotal in MEC*	oral FDC (netupitant 300 mg/palonosetron 0.5 mg) versus oral palonosetron MEC* (*see discussion); single and multiple chemo cycles
NETU-07-07	dose finding for netupitant pivotal in HEC	oral netupitant palonosetron 100/0.5 versus 200/0.5 versus 300/0.5 versus - /0.5 mg (primarily); FDC not used HEC; single cycle
NETU-10-29	Safety supportive for efficacy	oral FDC (netupitant 300 mg/palonosetron 0.5 mg) versus aprepitant + palonosetron MEC and HEC; multiple cycles
PALO-10-01	Efficacy bridging	palonosetron 0.5 mg versus 1 dose IV palonosetron 0.25 mg HEC; single cycle
PALO-03-13	dose finding bridging	oral palonosetron 0.25 versus 0.5 versus 0.75 mg versus IV 0.25 mg MEC; single cycle
PALO-03-14	efficacy and safety bridging	oral palonosetron 0.75 mg MEC; multiple cycles
Misc	other indications	NETU-08-03 (netupitant in overactive bladder) NETU-09-11 (netupitant/palonosetron FDC in acute pain) not evaluated in CER
Misc	IV palonosetron	PALO-99-03, PALO-99-04, PALO-99-05 (IV palonosetron versus other 5-HT_3R antagonists) not evaluated in CER

Name	Type	Description
Misc	pharmacology	23 clinical pharmacology studies (20 with PK data; 4 with PD data) 1 population PK/PD analysis

There were no paediatric data.

Formulation

Akynzeo is a hard gelatin capsule (containing 3 times 100 mg netupitant immediate release tablets and one 0.5 mg palonosetron soft gelatin capsule), that is, a fixed dose combination.

The outer capsule is described as Size 0, which indicates a largish tablet with 'locked length' 21.7 mm and external diameter 7.65 mm. The large size might be problematic in patients with dysphagia, or upper gastrointestinal (GI) mucositis from earlier cycles of chemotherapy; no data indicate this was a practical problem in the reported clinical trials, but this aspect may not be well reported.

Pharmacokinetics

The clinical evaluation report discusses PK and summarises PK studies; the evaluator's views about PK issues (limitations of the PK characterisation of Akynzeo) are discussed under the heading evaluator's conclusions on pharmacokinetics.

Netupitant

Key PK characteristics of netupitant are:

- molecular weight is 332.87
- T_{max} is 5 hours in healthy subjects (from NETU-11-02); the median T_{max} in PopPK Study NETU-10-02 in patients was 3.6 hours
- half-life in healthy subjects is 77 hours (from NETU-11-02); 88 hours was estimated in cancer patients (NETU-10-02, PopPK analysis)
- absolute bioavailability is estimated to be > 60%, up to approximately 87%
- exposure is higher in the fed state (C_{max} higher by 18 to 89% depending on study; $AUC_{0-\infty}$ higher by 16 to 53% depending on study); Study NETU-10-12 analysed 22 subjects and used the final FDC formulation, and in that study C_{max} was 18% and $AUC_{0-\infty}$ 16% higher in the fed state
- apparent volume of distribution is high, suggesting widespread tissue distribution
- netupitant is highly bound to plasma proteins, with only 0.33% of drug being free drug
- clearance is predominantly hepatic/biliary (for example, NETU-09-21 showed that by 696 hours, 71% of radioactivity was recovered in faeces; < 5% was recovered in urine)
- CYP3A4 produces 3 metabolites (M1, M2, M3, all active to an extent); M4 has also been detected at lower levels
- Intersubject PK variability was high in NETU-07-20 (42 to 47% for AUC_{0-t} and 48 to 56% for C_{max}); variability was higher again in patients with hepatic impairment
- Exposure was modestly higher with mild hepatic impairment (11% higher for C_{max}; 19% higher for $AUC_{0-\infty}$); exposure was significantly higher with moderate hepatic impairment (70% higher for C_{max}; 143% higher for $AUC_{0-\infty}$); only 2 subjects with severe hepatic impairment were studied

- In NETU-10-12, there was evidence older subjects (≥ 65 years) had higher exposure to netupitant (36% higher C_{max}; 25% higher $AUC_{0-\infty}$) than younger subjects (18 to 45 years); this was not confirmed in the PopPK report but the clinical evaluator was not convinced about the design of the PopPK study
- Netupitant exposure increased (by 140% for $AUC_{0-\infty}$) with concomitant ketoconazole (a strong inhibitor of CYP3A4), and decreased (by 62% for C_{max} and 83% for $AUC_{0-\infty}$) with concomitant rifampicin
- Exposure to midazolam (a CYP3A4 substrate) was increased with concomitant 150 mg netupitant (144% increase, that is, 2.4 fold higher, for $AUC_{0-\infty}$); likewise, exposure to erythromycin rose
- Co-administration with palonosetron (0.75 mg) did not affect netupitant (450 mg) exposure, but increased palonosetron exposure modestly (15% for C_{max} and 10% for $AUC_{0-\infty}$)
- Co-administration with dexamethasone (a CYP3A4 substrate) resulted in increased dexamethasone exposure (by 70% for AUC_{0-24h} at 300 mg netupitant dosing on Day 1, and by 140% on Day 2; C_{max} was affected to a lesser extent but C_{min} was affected to a greater extent). See next section for more details
- Cross study comparison suggested a reduction in netupitant exposure with co-administration of dexamethasone but a study has not been conducted to confirm this. Also, NP16603 studied only 4 subjects per arm, making this cross study comparison unreliable
- Netupitant appears to increase exposure to docetaxel (by 49% for C_{max}, 35% for $AUC_{0-\infty}$), and to a lesser extent etoposide and cyclophosphamide. In the case of docetaxel, this increase is clinically significant (for example, the Taxotere PI states: 'a dose of 100 mg/m^2 has been shown to result in a moderate increase in response rates compared with 75 mg/m^2 but is associated with greater toxicity').

NETU-06-07

The interaction study with dexamethasone (NETU-06-07) is expanded upon here since its interpretation is important in the assessment of the FDC's clinical efficacy. The key outcomes are copied below (numbers indicate the point estimate of the geometric mean ratio of test/reference, as a percentage where 100 would indicate no change from test to reference) in Table 10.

Table 11. Key outcomes

Dexamethasone+Netu 300 mg vs Dexamethasone alone	AUC_{0-24} (h*mcg/L)	171.62
	AUC_{24-36} (h*mcg/L)	243.02
	AUC_{84-108} (h*mcg/L)	238.17
	AUC_{84-inf} (h*mcg/L)	243.21
	$C_{max\ (0-24h)}$ (mcg/L)	111.01
	$C_{max\ (24-36h)}$ (mcg/L)	166.33
	$C_{max\ (84-108h)}$ (mcg/L)	174.90
	$C_{min\ (24-36h)}$ (mcg/L)	487.10
	$C_{min\ (36-48h)}$ (mcg/L)	416.89
	$C_{min\ (48-60h)}$ (mcg/L)	512.66
	$C_{min\ (60-72h)}$ (mcg/L)	388.73
	$C_{min\ (72-84h)}$ (mcg/L)	348.02

There are no data beyond 4 days although an ongoing effect appears likely.

The cellular mechanisms of the anti-emetic action of dexamethasone against vomiting have been reviewed recently.[23] Multiple broad pathways are implicated in dexamethasone's efficacy in CINV.

A review of the PK and PD of systemically administered glucocorticoids[24] states that PK parameters such as elimination half-life and PD parameters such as the concentration producing half-maximal effect determine duration and intensity of glucocorticoid effects.

In the Delegate's opinion it is likely that AUC or, potentially, C_{min}, are more closely correlated with anti-emetic efficacy of dexamethasone than C_{max} (given that in some settings, it is given as a single dose yet exerts an effect for days). Of AUC and C_{min}, C_{min} is more strongly influenced by netupitant's inhibition of dexamethasone metabolism.

The clinical study report also notes that 'the smaller effect on C_{max} compared to AUC and the prolonged t½z of dexamethasone may indicate that the major part of the inhibition is related to systemic clearance and that the effect on first-pass is minor'.

Palonosetron

Key PK characteristics of palonosetron are:

- molecular weight is 578.61
- T_{max} is 3 hours in healthy subjects (from NETU-11-02); the median T_{max} in Population PK Study NETU-10-02 in patients was 2.3 hours
- half-life in healthy subjects is 37 hours (from NETU-11-02)
- absolute bioavailability is 97%
- exposure does not vary in fed versus fasting states
- the Aloxi PI indicates that CYP2D6 and, to a lesser extent, CYP3A and CYP1A2 are involved in metabolism
- the PI also indicates that in a mass balance study, 80% of the administered dose of radioactivity is recovered within 144 hours in urine, with palonosetron representing 40% of the dose
- inter-subject variability is not high, at approximately 20 to 30% across AUC_{0-t} and C_{max} (NETU-07-20)
- Exposure was moderately higher with mild hepatic impairment (14% higher for C_{max}; 33% higher for $AUC_{0-\infty}$); exposure was significantly higher with moderate hepatic impairment (little difference for C_{max} but 62% higher for $AUC_{0-\infty}$); only 2 subjects with severe hepatic impairment were studied
- The Aloxi PI states that hepatic impairment does not significantly affect total body clearance of palonosetron
- the Aloxi PI states that mild to moderate renal impairment does not affect palonosetron PK parameters, while total systemic exposure increased by 28% in severe renal impairment relative to healthy subjects
- In NETU-10-12, there was evidence that older subjects (≥ 65 years) had higher exposure to palonosetron (10% higher C_{max}; 37% higher $AUC_{0-\infty}$) than younger subjects (18 to 45 years); this was not confirmed in the PopPK report

[23] Chin-Chen Chu et al. The cellular mechanisms of the antiemetic action of dexamethasone and related glucocorticoids against vomiting, *European Journal of Pharmacology*, 2014; 722:48–54.
[24] Czock et al. Pharmacokinetics and Pharmacodynamics of Systemically Administered Glucocorticoids. *Clin Pharmacokinet* 2005; 44: 61-98.

- Palonosetron exposure was not much affected by concomitant ketoconazole, although $AUC_{0-\infty}$ declined 19% with concomitant rifampicin.

Other findings

Bioequivalence was established in NETU-11-02 between the FDC formulation used in 'late Phase I and Phase III studies' and the commercial formulation.

Conclusions about pharmacokinetics

Key limitations of the PK characterisation of Akynzeo are:

- the PopPK study was primarily in females
- too few subjects were studied to understand the influence of severe hepatic impairment on PK of either netupitant or palonosetron
- no studies examined variation in netupitant exposure with renal impairment (based on the low excretion of netupitant into urine in the mass balance study, an effect of impaired renal function may be less likely; however, chronic renal failure reduces the non-renal clearance and alters bioavailability of drugs mainly metabolised by the liver and intestine).

Key PK issues are:

- there is hepatic metabolism via CYP3A4 with netupitant, with attendant drug-drug interaction effects (some quite pronounced)
- netupitant is also a moderate inhibitor of CYP3A4 (that is, substrate and inhibitor)
- there is a significant effect of moderate hepatic impairment on netupitant exposure (and severe hepatic impairment is inadequately characterised)
- the effect of renal impairment on netupitant exposure is unknown.

Pharmacodynamics

The clinical evaluation report describes pharmacodynamics (PD) studies. Study NETU-07-20 (QT interval) is considered under 'Safety' below. Study NP16603 (mood/sedation) is considered under 'Safety'.

Study NETU-06-08 gathered information on NK-1 receptor occupancy of netupitant, using positron emission tomography (PET) scanning. The information is not pivotal in nature.

Dose selection

The sponsor's approach to dose selection was reasonable for the palonosetron component (for example, outcomes of PALO-03-13) and the netupitant component (for example, outcomes of NETU-07-07), although the overall approach assumes no synergy between the two components (hypothetically, palonosetron targets acute CINV and netupitant targets delayed CINV, but there was some suggestion from NET-07-07 that 300 mg netupitant contributes to efficacy in prevention of acute CINV.

Clinical efficacy

NETU-08-18

NETU-08-18 was a pivotal study. It was a randomised, double blind, double dummy study of netupitant / palonosetron (FDC, 300 mg/.5 mg) versus oral palonosetron (0.5 mg) for prevention of nausea and vomiting in patients receiving MEC. In both arms, patients also received oral dexamethasone; the FDC arm received 12 mg, the palonosetron arm received 20 mg. Treatments were given 60 minutes prior to start of chemotherapy on Day 1, except dexamethasone (30 minutes prior to chemotherapy).

The imbalance in dexamethasone dosage (12 mg versus 20 mg) was to adjust for expected drug-drug interactions. This is a fairly standard approach in clinical studies of NK1 R inhibitors in CINV. Dexamethasone (4 mg) tablets had a matching placebo.

Patients were adults, and not previously treated with cytotoxic chemotherapy; those with symptomatic CNS malignancy were excluded. They were to receive an anthracycline and cyclophosphamide regimen to treat a malignant solid tumour. In the multiple cycle extension phase, cycles of chemotherapy had to be ≥ 21 days apart.

There were 177 study sites in 15 countries; the study was conducted from April 2011 to November 2012.

Complete response was defined as no emesis and no use of rescue medications. The primary endpoint was complete response in the 25 to 120 hours (delayed) phase at Cycle 1. The primary endpoint was tested in the full analysis set (FAS), resembling an intention-to-treat population. The study was designed as a superiority study.

Some 1,455 patients were randomised: 726 to the FDC group, 729 to the palonosetron group. Some 1,438 patients completed Cycle 1; 907 patients completed the multiple cycle extension (the maximum number of treatment cycles was 8, completed by 5 patients).

Some 98% of subjects were female (protocol specified chemotherapy was mostly indicated for breast cancer); approximately 80% were White. Mean age was approximately 54 years. Other details of baseline characteristics are described in the CER (Attachment 2). 97 to 98% of patients had breast cancer and in 16% cancer was metastatic. Almost all patients received cyclophosphamide; in about two thirds, doxorubicin was given, and in one third, epirubicin.

The percentage of patients with CR over 25 to 120 hours after start of MEC in Cycle 1 was 76.9% (FDC) versus 69.5% (palonosetron); p = 0.001. The odds ratio in favour of FDC was 1.48 (95% CI 1.16 to 1.87).

Results of key secondary endpoints are discussed in the CER (Attachment 2). Efficacy in suppression of nausea (distinct from vomiting) was adequately investigated (for example, within composite endpoints such as 'complete protection' or 'total protection').

There was a slight advantage of the FDC in prevention of acute phase CINV (CR 88.4% versus 85.0%), though the statistical significance of this effect was not evident in per protocol analysis. The number needed to treat to prevent one additional case of acute CINV, relative to the control arm, approaches 30.

There was some suggestion that most efficacy beyond that of palonosetron was seen in younger patients. This is despite moderate signals from PK studies that exposure is higher for both netupitant and palonosetron in older subjects.

Discussion of dexamethasone exposure as a confounder

The overall impression is that efficacy of the FDC is modestly improved over that of oral palonosetron, and that most of the improvement is in prevention of delayed phase CINV (but even here, the effect size relative to palonosetron was not great).

Dexamethasone exposure in the FDC arm (where patients were given 12 mg) may in fact be higher than in the palonosetron arm (where patients were given 20 mg).

Patients on 12 mg dexamethasone receiving netupitant would have about twice as high a trough concentration of dexamethasone as patients on 20 mg not receiving netupitant.

If C_{min} is correlated with an anti-emetic effect of dexamethasone, this level of increased exposure might, potentially, account for the additive efficacy seen in the FDC arm.

There is evidence from one study for a dose response with dexamethasone,[25] although the evidence from another is in conflict.[26]

The sponsor's population PK/PD analysis did not consider variation across individuals in exposure to dexamethasone.

Other issues arising from NETU-08-18

The choice of comparator is not strictly appropriate in Australia, as palonosetron is only registered for IV use here (but in comparable markets oral palonosetron is registered). The sponsor provided studies that aimed to bridge evidence of benefit for parenteral and oral palonosetron.

In updated American Society of Clinical Oncology (ASCO) antiemetic guidelines, combined anthracycline and cyclophosphamide regimens have been reclassified as highly emetic.[27] This approach is endorsed by EviQ,[28] which states that IV cyclophosphamide with anthracycline in breast cancer is HEC.

There is also a role for the maintenance of glucocorticoid dosing after Day 1, but this was not implemented in NETU-08-18.

Up-to-date[25] describe the following benefit of combining other NK1 R antagonists with a 5-HT_3 receptor (5-HT_3R) antagonist plus a glucocorticoid:

> Efficacy; The benefit of combining an NK1 R antagonist (aprepitant, fosaprepitant, or casopitant) with an 5-HT_3 receptor antagonist plus a glucocorticoid for the prevention of acute CINV was addressed in a meta-analysis of 17 trials, totaling 8740 patients who were receiving highly or moderately emetogenic chemotherapy. The addition of a NK1 R antagonist to standard antiemetic therapy significantly improved the rate of complete response (CR, absence of emesis and no need for rescue antiemetics) in both the overall phase (during the first 120 hours of chemotherapy, 72 versus 54 percent, odds ratio [OR] 0.51, 95% CI 0.46-0.57) and in the acute (first 24 hours, OR 0.56, 95% CI 0.48-0.65) as well as delayed phase (OR 0.48, 95% CI 0.42-0.56).

CR in the overall phase in NETU-08-18 was 74.3% (FDC) versus 66.6% (palonosetron arm), and the difference narrowed in the acute phase, so the additive efficacy of netupitant in this study appears relatively low.

NETU-07-07

This study was a randomised, double blind, double dummy study of different doses of netupitant or placebo, given with palonosetron and dexamethasone, to prevent CINV in patients receiving HEC. There was also an active comparator arm, included for 'exploratory purposes'. Patients were randomised 1:1:1:1:1 into five arms, with the

[25] http://www.uptodate.com/contents/prevention-and-treatment-of-chemotherapy-induced-nausea-and-vomiting: The impact of glucocorticoid dose was explored in a double-blind trial that randomly assigned 531 patients receiving cisplatin ≥ 50 mg/m^2 to one of four intravenous doses of dexamethasone administered by a 15 minute infusion prior to cisplatin administration*. All patients received 8 mg of ondansetron as well. At doses of 20, 12, 8, and 4 mg, complete protection from vomiting was achieved in 83, 79, 69, and 69 percent of patients, respectively, and nausea was prevented in 71, 67, 61, and 61 percent.
*Italian Group for Antiemetic Research. Double-blind, dose-finding study of four intravenous doses of dexamethasone in the prevention of cisplatin-induced acute emesis. *J Clin Oncol* 1998; 16: 2937–2942.
[26] Italian Group for Antiemetic Research. Randomised, double-blind, dose-finding study of dexamethasone in preventing acute emesis induced by anthracyclines, carboplatin, or cyclophosphamide. *J Clin Oncol* 2004; 22: 725–729.
[27] Basch E et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *JCO* 2011; 29: 4189
[28] An online service of the Cancer Institute of NSW (Australia)

following interventions (oral unless specified; and FDC formulations were not used, that is separate tablets were given concomitantly).

Table 12. Study design NETU-07-07

Arm	NK1R antagonist	5-HT_3R antagonist	Dexamethasone
1	nil (placebo arm)	palonosetron 0.5 mg, Day 1	20 mg on Day 1, 8 mg BD on Days 2 to 4
2	netupitant 100 mg, Day 1	palonosetron 0.5 mg, Day 1	12 mg on day 1, 8 mg daily on Days 2 to 4
3	netupitant 200 mg, Day 1	palonosetron 0.5 mg, Day 1	12 mg on day 1, 8 mg daily on Days 2 to 4
4	netupitant 300 mg, Day 1	palonosetron 0.5 mg, Day 1	12 mg on day 1, 8 mg daily on Days 2 to 4
5	aprepitant 125 mg on day 1, 80 mg on Days 2 to 3	IV ondansetron, 32 mg on Day 1	12 mg on day 1, 8 mg daily on Days 2 to 4

The double dummy arrangement extended to using placebo ampoules of saline (0.9% sodium chloride (NaCl)), for IV infusion (since in Arm 5, ondansetron was given IV).

The study was conducted at 44 sites in 2 countries (Russia, Ukraine), from February to November 2008. Alcohol abuse is well-recognised as protective against CINV. Alcohol consumption was recorded as a baseline characteristic: 54 to 59% of subjects reported no alcohol consumption, 34 to 40% reported rare alcohol consumption and 4 to 8% reported occasional alcohol consumption. Current evidence of alcohol abuse was an exclusion criterion. It is possible this exclusion criterion skewed enrolment towards relatively light drinkers. It is also possible that actual alcohol consumption was not well documented.

Patients were adult, chemotherapy naïve, had a malignant solid tumour and were to receive cisplatin (≥ 50 mg/m^2 over 1 to 4 hours) on Day 1, ± other chemotherapy.

The primary efficacy endpoint was the proportion of patients with complete response (no emesis, no rescue medications) in the overall phase (0 to 120 hours after start of HEC). Efficacy analyses were based on the full analysis set (those randomised who received at least one dose of study treatment) excluding Arm 5.

The Food and Drug Administration (FDA) mandated a post-hoc analysis where the primary efficacy endpoint became CR in the delayed phase.

Some 694 patients were randomised (135 to 143 per arm). Baseline characteristics were comparable across arms; 56 to 58% of subjects were male; mean age was 54 to 55 years; virtually all patients were White. 63 to 65% of subjects were from Russia. About half of subjects had metastatic disease.

With respect to complete response rate in Arms 1 to 4, Arm 4 had the best outcomes. In comparison of 300 mg netupitant, palonosetron and dexamethasone versus placebo, palonosetron and dexamethasone, the netupitant-containing arm performed better in prevention of both acute and delayed CINV. Arms 4 and 5 had comparable outcomes (the numerical advantage was with Arm 4).

Outcomes of subgroup analyses by gender and country revealed some differences, for example, there was a fairly pronounced difference in CR in Arm 1 between male and female patients. Males had better outcomes than females in Arm 4.

NETU-10-29

This study was a randomised, double blind, double dummy study of two treatment regimens;

- netupitant and palonosetron as an FDC (300 mg/0.5 mg) on Day 1, with oral dexamethasone (12 mg on Day 1, then, in HEC patients only, 8 mg on Days 2 to 4)
- aprepitant (125 mg on Day 1, then 80 mg on Days 2 to 3), palonosetron (0.50 mg on Day 1) and dexamethasone (regimen as above).

Patients were adult, chemotherapy naïve, and scheduled to receive repeated course HEC or MEC for treatment of a malignant tumour. Efficacy assessment was secondary to that of safety.

The study was conducted at 72 sites across 10 countries, from July 2011 to September 2012.

Some 413 patients were randomised: 309 to the FDC arm, 104 to the aprepitant-containing arm. Three quarters of patients received MEC in Cycle 1, and a quarter HEC. There was no large contribution of 'anthracycline + cyclophosphamide' to the MEC subgroup, so reclassification of this regimen as HEC has little effect. 40% of subjects completed Cycle 6. Baseline demographics were comparable across arms; half of subjects were male, 84% were White, mean age was 57 years. There were imbalances in primary cancer diagnosis and in the fraction of patients with metastases (higher in the FDC arm, 52% versus 43%).

The proportion of patients with a CR in Cycle 1 was 83.2% (FDC) versus 77.7% (aprepitant) in the delayed phase, and 92.9% versus 94.2% respectively in the acute phase. This pattern continued in Cycles 2 to 6, with a tendency for differences across arms to be fairly minimal in the acute phase.

Results were comparable in subgroup analysis by MEC versus HEC status; there was a much lower delayed phase CR rate in the small HEC subgroup in the aprepitant arm, for Cycle 1, but this was not apparent in the acute phase; nor was it seen in the delayed phase for the MEC subgroup.

There was a numerical advantage in males for CR, although not for 'no nausea'.

Other studies

Other studies are described in the CER (Attachment 2) and are of indirect relevance, and support the use of palonosetron 0.50 mg oral formulation in pivotal studies.

Safety

Safety of Akynzeo is described in the CER (Attachment 2).

Exposure

In NETU-08-18, there were 724 patients in the FDC group, and the median number of days on study drug was 4 (about a quarter of patients received 6 doses). In NETU-10-29, a further 308 patients were exposed to the FDC and the median number of days on FDC was 5. Other large studies did not use the FDC.

Adverse event (AE) profile

In general, patients were receiving toxic chemotherapies and many AEs are attributable to chemo rather than anti-emetic therapy.

Study NETU-08-18's design is able to isolate the toxicity of netupitant. Severe AEs were more common with FDC than with palonosetron (13.0% versus 9.1%) in Cycle 1, although the difference narrowed in the multiple cycle extension phase; (15.4% versus 14.6%). Also, a similar trend was not apparent in NETU-07-07.

Patients in the FDC arm reported more serious neutropenia / febrile neutropenia (for example, Cycle 1, febrile neutropenia SAEs: 0.6% for FDC versus 0.4% for palonosetron; extension phase, febrile neutropenia: 0.9% versus 0.6%; extension phase, neutropenia: 0.9% versus 0.2%). However, neutropenia per se was not reported more often in the FDC arm, and there was no major imbalance in Grade 3 to 4 neutropenia (that is, analysis of lab results). Effects on neutrophil function were not studied.

There was an imbalance in reporting of infections in the extension phase of NETU-08-18 (11.2% for FDC, 7.8% for palonosetron), but there was no major imbalance in reporting of serious AEs of infection in the extension phase. NK1R antagonists have been linked to an increased risk of severe infection, via increased dexamethasone exposure, increased chemotherapy drug exposure and / or intrinsic effects on immunity.[29] The magnitude of increased risk suggested by dos Santos et al[29] was not seen in NETU-08-18.

8 FDC patients in NETU-08-18 reported anticholinergic AEs, versus 4 in the palonosetron arm, although most AEs were not considered study drug related.

7 FDC patients versus 3 palonosetron patients in NETU-08-18 reported AEs implicated in neuroleptic malignant syndrome; only 1 (blood myoglobin increased) was considered study drug related.

2 FDC patients (and no palonosetron patients) in NETU-08-18 reported extrapyramidal syndrome-linked AEs; no AE was considered study drug related.

There was an indication from NETU-10-29 that netupitant may have a side effect profile that differs from aprepitant. Drug related AEs were reported in 10.1% in the FDC group, but 5.8% in the aprepitant group. There were 16 deaths in the FDC group (5.2%), versus 1 death in the aprepitant group (1.0%). None of the deaths was considered study drug related. The incidence of SAEs was comparable (16.2% for FDC; 18.3% for aprepitant). The incidence of febrile neutropenia SAEs was 1.9% (FDC) versus 1.0% (aprepitant). Also, the rates of discontinuation were similar across arms (9.1% for FDC; 12.5% for aprepitant).

QT interval

Study NETU-07-20 examined effects of netupitant and palonosetron on the QT interval. The main identified effect was a non dose related reduction in heart rate of 4 bpm. ECG results were also analysed in NETU-08-18; in both arms, the mean QTcF increase was around 13 ms in Cycle 1 at 5 hours post dose. There was no strong indication that netupitant caused any cardiac conduction problems.

Mood and sedation

Study NP16603 assessed impact of netupitant (450 mg) on mood and sedation in healthy males. There was some suggestion of an impact on performance as assessed by tests of digit vigilance, numeric working memory, self rated alertness and word recall/recognition. This was attributed to outlying effects in two subjects, but only 4 subjects were studied.

One patient in NETU-08-18 reported 'mood alteration' in Cycle 2, which resolved after 13 days without treatment; it was considered possibly study drug related.

One patient in NETU-10-29 experienced acute psychosis, which was attributed to the FDC although dexamethasone was also being given.

[29] dos Santos et al.: Neurokinin-1 receptor antagonists for chemotherapy-induced nausea and vomiting: a systematic review, *J Natl Cancer Inst.* 2012; 104:1280-1292.

The sponsor has integrated data relating to mood changes. This did suggest a possible effect of netupitant on sleep (for example, more insomnia was reported with the FDC than with palonosetron). Dexamethasone may cause insomnia; netupitant may increase exposure to dexamethasone.

Clinical evaluator's recommendation

The clinical evaluator recommended that the application for registration of Akynzeo for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic and moderately emetogenic cancer chemotherapy be approved.

Risk management plan

The following RMP was reviewed:

Akynzeo EU-RMP version 1.0 (undated; data lock point 31 August 2013) with the Australian Specific Annex version 1.0 (dated 28 February 2014)

ACSOM advice was not sought for the submission.

A proposed condition of registration was:

> Implement EU-RMP version 1.0 (undated; data lock point 31 August 2013) with the Australian Specific Annex version 1.0 (dated 28 February 2014) and any future updates as a condition of registration.

The RMP evaluator draws attention to the PI for aprepitant having a contraindication related to concomitant use of certain CYP3A4 substrates (since inhibition of CYP3A4 by aprepitant could lead to elevated plasma concentrations and serious reactions). The contraindication is as follows:

> *Emend should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Dose-dependent inhibition of cytochrome P450 isoenzyme 3A4 (CYP3A4) by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions.*

This is not a contraindication that is always applied for moderate CYP3A4 inhibitors.

Risk-benefit analysis

Benefit/risk balance

Some benefits of Akynzeo are its potential convenience as a single tablet; and a modest gain in efficacy with the addition of netupitant, relative to oral palonosetron.

Some uncertainties associated with these benefits are that:

- 'convenience' is assumed rather than demonstrated
- the mechanism by which netupitant adds to efficacy is unclear
- bridging is required from the chosen comparator (oral palonosetron) to establish its relevance in Australia.

Some risks of Akynzeo (other than those linked to the uncertainties outlined above) are that:

- there may be pharmacokinetic interactions between netupitant and other CYP3A4 substrates

- netupitant may be linked to an increased risk of infection, whether directly or indirectly.

Delegate's considerations

Evidence for netupitant efficacy

Netupitant is an NK1 R antagonist and, with its different mechanism of action, is expected to provide additive anti-emetic prophylactic efficacy when used alongside a 5-HT_3 RA and dexamethasone. This expectation aligns with the additive anti-emetic efficacy of other NK1R antagonists such as aprepitant and also with nonclinical evidence of netupitant's efficacy.

In clinical studies in this submission, the additive anti-emetic efficacy of netupitant was modest, even for delayed phase CINV (this was more so in the more robust NETU-08-18 study than the smaller NETU-07-07 study).

Study NETU-06-07 provides evidence of an interaction between netupitant (acting as a CYP3A4 inhibitor) and dexamethasone (acting as a CYP3A4 substrate), such that with concomitant use of netupitant, exposure to dexamethasone is considerably increased.

This resulted in the strategy of reducing the dexamethasone dose in arms that included netupitant, for example, in NETU-06-18 the arm without netupitant used 20 mg dexamethasone, while the netupitant arm used 12 mg. The same approach has been used in studies of other NK1R antagonists.

The concern is that by most measures (for example, C_{max} after Day 1; AUC; C_{min}), the exposure to dexamethasone in the FDC arm (12 mg dexamethasone) should be considerably higher than in the palonosetron arm (20 mg dexamethasone).

There is some evidence of a dose response for dexamethasone and anti-emetic effect.

Therefore, imbalance across arms in exposure to dexamethasone is a confounder in the assessment of netupitant's contribution to efficacy.

Thus there is doubt about the mechanism by which addition of netupitant to a backbone of palonosetron and dexamethasone results in a (modest) efficacy gain. The proposed mechanism is NK1R antagonism; but it might be via pharmacokinetic potentiation of the role of dexamethasone.

This drug-drug interaction also increases the risk of dexamethasone related AEs. More broadly, netupitant's CYP3A4 inhibition may impact on exposure to other drugs, for example, chemotherapy. Because Akynzeo is presented as a single fixed dose combination, there is no possibility of dose adjustment (except by moving to alternative treatments).

Evidence in MEC

The anthracycline + cyclophosphamide regimen used in NETU-08-18 is now considered highly emetogenic. Accordingly, this study provides evidence for use in HEC. The evidence for use in MEC is therefore from NETU-10-29, and by extrapolation from HEC. This evidence base is in the Delegate's opinion sufficient to allow conclusions to be drawn about use in prevention of MEC induced nausea and vomiting.

Drug interactions

Netupitant is at least a moderate inhibitor of CYP3A4. In addition to increased exposure to dexamethasone, there may be other clinically relevant consequences, for example, increased exposure to docetaxel. Docetaxel has low emetogenicity, but MEC / HEC status is based on the drug within any combination regime with greatest emetic risk, so docetaxel may be used in regimes where Akynzeo is used for prevention of CINV.

Hepatic impairment

Exposure to netupitant was higher in moderate hepatic impairment, by 143% for AUC. There is no potential for dose adjustment with Akynzeo, since there is only one dose strength and only one dose is given per cycle. The possible consequences of a more than doubling of exposure include exacerbation of drug-drug interaction issues (for example, a more pronounced increase in exposure to dexamethasone; yet there is already advice in the Dexmethsone PI to 'use with caution in patients with impaired hepatic function, a reduction of dosage may be necessary') and increased risk of netupitant specific AEs.

Proposed action

The Delegate is not in a position to say, at this time, that the application for Akynzeo should be approved for registration because the Delegate would like to receive advice from the ACPM, about issues discussed in the Delegate's overview.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Does the ACPM consider that the anti-emetic efficacy of netupitant is confounded by the pharmacokinetic interaction with dexamethasone?
2. If so, how; if at all, does this impact on the assessment of Akynzeo's benefit/risk profile?
3. Does the ACPM consider there is sufficient evidence of use in MEC?
4. Should there be advice in the Akynzeo PI not to use the product in patients with moderate and / or severe hepatic impairment?
5. Does the ACPM object to the name Akynzeo (for example, is it too close to Akineton?)
6. Does the ACPM consider that Akynzeo has a positive benefit / risk balance?
7. What indication in prevention of CINV does the ACPM consider is supported by the evidence for Akynzeo?
8. Does the ACPM have any comments or suggestions about the Akynzeo PI or CMI?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Delegate's request to alter the proposed indication

The sponsor proposes to retain the indication submitted with the original application.

The sponsor does not agree with the Delegate's statement 'there is concern that netupitant is at least partially providing efficacy via potentiating the effect of dexamethasone, this should be reflected in the indication'.

The sponsor acknowledges the role of dexamethasone as the backbone of preventative therapy as adopted by EviQ in the Australian clinical setting. The sponsor proposes to add reference to the use of dexamethasone within the dosage and administration section of the PI.

Evidence for netupitant efficacy and its relationship to concomitant use of dexamethasone

The sponsor does not agree with the Delegate's statement that '*the overall impression is that efficacy of the FDC is modestly improved over that of oral palonosetron, and that most of*

the improvement is in prevention of delayed phase CINV (but even here, the effect size relative to palonosetron was not great)' and the subsequent link to the proposed changes to the indication.

The adjustment of dexamethasone dose in the three Akynzeo pivotal efficacy and safety studies NETU-07-07, NETU-08-18 and NETU-10-29 was based on the results of the randomised, open, 3 period crossover drug – drug interaction Study NETU-06-07, which investigated the effects of 3 different doses of oral netupitant (100mg, 300 mg and 450 mg) on the pharmacokinetics of dexamethasone in healthy male and female subjects receiving the standard dexamethasone antiemetic regimen administered using a 5-HT_3 RA inhibitor alone. The reduction in dexamethasone dose on Day 1 adopted in Akynzeo clinical trials was consistent with a 1.7 fold increase in exposure (AUC_{0-24}) for the 300 mg netupitant dose level (12 mg times 1.7 fold increase is approximately 20 mg) observed in NETU-06-07; on Days 2 to 4, in patients receiving HEC in Study NETU-07-07 and NETU-10-29 the daily dexamethasone dose was halved from 8 mg twice daily (BD) to 8 mg once daily (QD) again consistently with the 2 fold increase in exposure observed in healthy volunteers. Information on concurrent dexamethasone dosages used in clinical studies is included in the PI.

Of note, this dexamethasone dose adjustment scheme was fully consistent with the one adopted in the clinical development of the 3-day oral aprepitant (Emend) regimen (125 mg on Day 1 and 80 mg on Day 2 and 3), which is also reflected in the Australian Emend Product Information, Dosage And Administration. The recommended dexamethasone dose is 12 mg on Day 1 and 8 mg QD on Days 2 to 4 for the prevention of CINV associated with HEC and 12 mg on Day 1only for the prevention of CINV associated with MEC. The dose adjustment was based on the 2.2 fold increase of dexamethasone AUC observed in a drug-drug interaction study conducted in healthy volunteers receiving the 3 day oral aprepitant regimen and the dexamethasone antiemetic regimen administered using a 5-HT_3 RA inhibitor alone.

Moreover, the Delegate's statement that C_{min} may be correlated with an anti-emetic effect of dexamethasone is purely speculative and, to the sponsor's knowledge, is not substantiated by published literature. The outdated Italian multicentre study[30] was conducted in the mid 1990's when neither palonosetron nor aprepitant were available on the market and ondansetron was used as 5-HT_3 receptor antagonist of reference.

The highest of the four dexamethasone doses tested in this study was 20 mg, which represents the currently recommended dose. Three out of the four doses tested would be considered suboptimal by today's standards. Since doses higher than 20 mg were not tested, this study is intrinsically unable to address whether increased dexamethasone exposure after doses higher than 20 mg could lead to an improved response rate. Although the study showed that the highest dose (20 mg) of dexamethasone had greater efficacy than the lower doses (4 and 8 mg) in preventing vomiting in the acute phase, this advantage was less clear in patients receiving an intermediate dose (12 mg). The greater efficacy of the 20 mg dose of dexamethasone was limited to patients who received lower doses of cisplatin and no dose response was observed in patients receiving the highest doses of cisplatin. Importantly, no dose effect was observed on the number of vomiting episodes, nausea incidence and severity. Finally, no data on the prevention of nausea and vomiting in the delayed phase are available from this study, limiting the relevance of these data.

The same Italian collaborative group published six years later the results of a multicenter study in chemotherapy-naive patients scheduled to receive cyclophosphamide 600 to 1,000 mg/m^2, doxorubicin > 50 mg/m^2, epirubicin > 75 mg/m^2, or carboplatin

[30] Italian Group for Antiemetic Research. Double-blind, dose-finding study of four intravenous doses of dexamethasone in the prevention of cisplatin-induced acute emesis J Clin Oncol 1998; 16: 2937-2942

> 300 mg/m^2: Patients were randomised to receive one of the following dexamethasone scheme: Arm A: one dose of 8 mg IV 30 minutes before chemotherapy and four oral doses of 4 mg every 6 h; Arm B 24 mg IV 30 minutes before chemotherapy; Arm C 8 mg IV 30 minutes before chemotherapy.

All patients received ondansetron 8 mg IV 15 minutes before chemotherapy on day 1 and oral dexamethasone 4 mg every 12 hours on Days 2 to 5. During the acute phase, the rate of protection from vomiting and nausea was comparable among the three groups.

Remarkably both these Italian studies used the first generation 5-HT_3 RA ondansetron as a reference. Two recent studies[31] [32]consistently showed that when palonosetron is included in a CINV preventative regimen, comparable emesis and nausea control can be achieved with dexamethasone given on 1 day only, without additional dexamethasone on Days 2 and 3. A double blind, multicentre, non-inferiority study was conducted in chemotherapy naive breast cancer patients receiving 0.25 mg palonosetron and 8 mg dexamethasone on Day 1, randomly assigned to receive placebo (n = 151) or 4 mg twice daily (BD) dexamethasone (n = 149) on Days 2 and 3. Complete response rate was similar in the two groups both in the acute and in the delayed phase. In the second study enrolling patients receiving 0.25 mg palonosetron prior to either anthracycline cyclophosphamide (AC) or other common MEC regimens, the single-day dexamethasone regimen produced overall complete response rate comparable to the 3 day dexamethasone schedule.

The unique pharmacodynamics and pharmacokinetics characteristic of palonosetron substantiate the prolonged antiemetic protection observed in the delayed phase, without the need for multiple days of dexamethasone. In comparison with the first generation 5-HT_3 RA, palonosetron exhibits a higher potency, a significantly longer half-life and a different molecular interaction with 5-HT_3 receptors. Its 5-HT_3 receptor binding affinity is at least 30 fold higher than other 5-HT_3 receptorantagonists. Based on the clinical efficacy studies results, palonosetron has been recommended as the preferred 5-HT_3 receptor antagonist by multiple international antiemetic guidelines for the prevention of acute nausea and vomiting associated with initial and repeat courses of MEC and HEC and for the prevention of delayed nausea and vomiting associated with initial and repeat courses of MEC.

It is therefore particularly relevant that the efficacy of Akynzeo has been established by showing superiority to palonosetron. The selected superiority study design, including the dexamethasone dose adjustment, comparing netupitant/palonosetron combination to palonosetron in the two efficacy studies NETU-07-07 and NETU-08-18 is fully adequate to isolate the therapeutic effect of the netupitant component within the fixed combination and allows a robust interpretation of the anti-emetic clinical effect of each component of Akynzeo.

It is the sponsor's opinion that clinical relevance and statistical significance of the therapeutic benefits of the netupitant component is at least as meaningful as those reported with aprepitant in global registration studies. Both NETU-08-18 and NETU-07-07 provided compelling statistically significant results for primary efficacy endpoint ($p = 0.001$ in NETU-08-18 and $p = 0.004$ in NETU-07-07). This statistical evidence is considerably stronger than the usually required threshold of $p < 0.050$. The differences in CR between arms for the primary endpoints were of the order of 7.4% and 13.2% for NETU-08-18 and NETU-07-07 respectively, which are considered clinically meaningful.

[31]Aapro M, et al. Double-blind, randomised, controlled study of the efficacy and tolerability of palonosetron plus dexamethasone for 1 day with or without dexamethasone on days 2 and 3 in the prevention of nausea and vomiting induced by moderately emetogenic chemotherapy. *Ann Oncol*. 2010; 21:1083-1088.
[32] Celio L, et al Italian Trials in Medical Oncology Group. Palonosetron in combination with 1-day versus 3-day dexamethasone for prevention of nausea and vomiting following moderately emetogenic chemotherapy: a randomised, multicenter, phase III trial. *Support Care Cancer*. 2011; 19:1217-1225.

Table 13 below displays the OR for absence of complete response in the overall phase (0 to 120 h) in the FDC pivotal HEC Study NETU-07-07 and in the MEC Study NETU-08-18, contrasted with aprepitant HEC Studies 052 and 054 and the MEC 071 study, respectively. Odds ratio reduction was similar and numerically larger in FDC pivotal studies compared to aprepitant studies. Analysis of CR in the acute and delayed phase provides consistent results.

Table 13. Results for odds ratio for absence of response in the overall phase in comparator studies

Study	Comparator	Active n/N	Control n/N	Unadjusted OR (point estimate and 95% CI)	
HEC setting					
NETU-07-07	Palonosetron	14/135	32/136	0.376	0.190-0.743
HEC study 052*	Ondansetron	71/260	124/261	0.415	0.288-0.598
HEC study 054**	Ondansetron	97/261	149/263	0.453	0.319-0.642
MEC setting					
NETU-08-18	Palonosetron	186/724	242/725	0.690	0.550-0.866
MEC study 071***	Ondansetron	213/433	244/424	0.714	0.546-0.935

*Hesketh P. et al, JCO 2003[33]; **Poli Bigelli S. et al, Cancer 2003[34]; ***Warr D. et al, JCO 2005[35]

Moreover studies NETU-10-29 and NETU-07-07 provided efficacy data with Akynzeo compared to a combination of the 3-day oral aprepitant regimen and a 5-HT_3 RA. In NETU-10-29 CR rate at Cycle 1 was numerically higher with Akynzeo than in the aprepitant+palonosetron group in the delayed and overall phases, and were similar in the acute phase. In Study NETU-07-07, a post-hoc analysis was performed to compare the efficacy of Akynzeo versus the aprepitant/ondansetron combination. The percentage of responders was numerically higher in the Akynzeo arm for all primary and secondary efficacy endpoints in the overall, acute and delayed phase.

Evidence in MEC

The sponsor acknowledges the recent reclassification of anthracycline-cyclophosphamide chemotherapy to HEC adopted in the US by the ASCO and subsequently endorsed by EviQ in Australia.

The sponsor proposes to include the following sentence in section 'clinical studies' of the proposed PI: 'At the time of the study, anthracycline-cyclophosphamide (AC) containing chemotherapy regimens were considered to be moderately emetogenic. Recent guidance has updated these regimens to highly emetogenic.'

'Moreover, the sponsor proposes to amend the 'adverse effects' section of the PI as follows':

> *'The safety profile of Akynzeo was evaluated in 1169 cancer patients, including 782 exposed to Akynzeo for at least 4 cycles and 321 exposed for at least 6 cycles, up to a maximum of 12 cycles of chemotherapy.'*

[33] Hesketh P. et al, The Oral Neurokinin-1 Antagonist Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting: A Multinational, Randomized, Double-Blind, Placebo-Controlled Trial in Patients Receiving High-Dose Cisplatin—The Aprepitant Protocol 052 Study Group. *JCO* 2003; 21: 4112-4119.
[34] Poli Bigelli S. et alAddition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. , *Cancer* 2003; 97 : 3090-3098
[35] Warr D. et al. Efficacy and Tolerability of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting in Patients With Breast Cancer After Moderately Emetogenic Chemotherapy. *JCO* 2005;23: 2822-2830.

However it is the sponsor's opinion that whilst these guidelines on MEC have recently changed it is not fully accurate to conclude that the indication sought for Akynzeo is only supported in the HEC setting.

At global and European level, Multinational Association of Supportive Care in Cancer (MASCC)/European Society for Medical Oncology (ESMO) guidelines still categorise AC chemotherapy as MEC. In the MEC setting, MASCC/ESMO clinical antiemetic guidelines have given special consideration to patient related risk factors contributing to the emetogenic potential for patients receiving AC based chemotherapy. While historically guidance has been based solely on the emetogenicity of the chemotherapy, committees have acknowledged that the young age and female gender of the population typically receiving AC based chemotherapy puts this group at a higher risk for CINV.

From a regulatory view point, since the development of oral ondansetron up to the recent registration of Emend and Aloxi, AC chemotherapy has served as the 'worst case' emetogenicity representative for MEC chemotherapy: the AC regimen has represented the gold standard of the MEC regimen in antiemetic efficacy pivotal trials and this model is familiar to clinicians for use to prevent CINV induced by MEC. The patient population of the MEC registration Study 071 with Emend, was represented almost exclusively by patients scheduled to receive AC. Also the US and EU MEC registration of oral palonosetron 0.50 mg (Aloxi), was founded on Study PALO-03-13, which predominantly enrolled patients scheduled to receive AC based chemotherapy.

It is the sponsor's opinion the role of NETU-08-18 as the pivotal study supporting the efficacy of Akynzeo in preventing CINV induced by MEC, represents the worst case scenario in the MEC setting and supports the indication proposed in MEC.

Hepatic Impairment

It is the sponsor's opinion that increased exposures to netupitant in moderate hepatic impairment observed in Study NETU-10-12 should not be considered clinically relevant. The sponsor refers the ACPM to further comments regarding this point leading to the conclusion that moderate hepatic impairment does not necessitate any dose reduction and no specific cautionary statement for use in these patients should be included in the PI.

Regarding severe hepatic impairment, limited data (n = 2) do not allow drawing conclusions for this population. Lack of specific data does not constitute per se a reason for contraindication, consistently with the case for Emend. Although no data were available with Emend in patients with severe hepatic impairment, the product has not been contraindicated and no cautionary statement has been included in its PI, which includes the following statement: 'There are no clinical or pharmacokinetic data (with Emend) in patients with severe hepatic insufficiency (Child-Pugh score > 9)'.

Therefore the sponsor considers that the current sentence in the Akynzeo PI: 'No dosage adjustment is necessary for patients with mild or moderate hepatic impairment (Child-Pugh score5 to 8). Limited data exist in patients with severe hepatic impairment (Child Pugh score ≥ 9). ThereforeAkynzeo should be used with caution in these patients.'is adequate.

Safety concerns linked to the pharmacokinetic interactions between netupitant and other CYP3A4 substrates and potential increased risk of infections.

Data analysis on the subpopulation of cancer patients from the four Phase II/III clinical studies was performed to investigate the potential of safety concerns related to the concomitant administration of the chemotherapeutic agents; docetaxel, etoposide and cyclophosphamide metabolised by CYP3A4, and Akynzeo. Serious events suggestive of hematological toxicities and of diarrhoea and any event with the preferred term (PT) within the system organ class (SOC) "infections and infestations" were considered.

In Tables 14 to 16 the numbers of patients by chemotherapy treatment and by study were presented. A total of 1,765 (53.8%) out of 3,280 patients received cyclophosphamide, 311 (9.5%) etoposide and 106 (3.2%) docetaxel. The percentage of patients experiencing at least one SAE was 3.8% (67 out of 1,765) among patients administered cyclophosphamide, 8.0% (25 out of 311) among patients administered etoposide and 18.9% (20 out of 106) of patients administered docetaxel. A summary of patients with SAEs and any selected TEAE for cyclophosphamide, or etoposide or docetaxel subpopulation for palonosetron 0.25 IV, oral palonosetron 0.5, the Akynzeo and aprepitant/palonosetron groups was presented.

Table 14. Cyclophosphamide population

Study Identifier	Treatment							
Frequency (%)	**Palo I.V. 0.25 mg**	**Oral Palo 0.50 mg**	**Netu/Palo 100/0.50 mg**	**Netu/Palo 200/0.50 mg**	**Netu/Palo FDC 300/0.50 mg**	**Aprepitant plus Onda**	**Aprepitant plus Palo**	**Total**
NETU-07-07	0 0.00	40 5.06	49 100.00	37 100.00	46 5.71	39 100.00	0 0.00	211
NETU-08-18	0 0.00	725 91.77	0 0.00	0 0.00	725 89.95	0 0.00	0 0.00	1450
NETU-10-29	0 0.00	0 0.00	0 0.00	0 0.00	35 4.34	0 0.00	14 100.00	49
PALO-10-01	30 100.00	25 3.16	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	55
Total patients	30	790	49	37	806	39	14	1765
Total exposure (Cycles)	**30**	**3051**	**49**	**37**	**3178**	**39**	**75**	**6459**

Table 15. Etoposide subpopulation

Study Identifier	Treatment							
Frequency (%)	**Palo I.V. 0.25 mg**	**Oral Palo 0.50 mg**	**Netu/Palo 100/0.50 mg**	**Netu/Palo 200/0.50 mg**	**Netu/Palo FDC 300/0.50 mg**	**Aprepitant plus Onda**	**Aprepitant plus Palo**	**Total**
NETU-07-07	0 0.00	33 38.82	26 100.00	29 100.00	28 31.46	25 100.00	0 0.00	141
NETU-08-18	0 0.00	3 3.53	0 0.00	0 0.00	5 5.62	0 0.00	0 0.00	8
NETU-10-29	0 0.00	0 0.00	0 0.00	0 0.00	56 62.92	0 0.00	12 100.00	68
PALO-10-01	45 100.00	49 57.65	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	94
Total patients	45	85	26	29	89	25	12	311
Total exposure (Cycles)	**45**	**88**	**26**	**29**	**300**	**25**	**53**	**566**

Table 16. Docetaxel subpopulation

Study Identifier	Treatment							
Frequency (%)	**Palo I.V. 0.25 mg**	**Oral Palo 0.50 mg**	**Netu/Palo 100/0.50 mg**	**Netu/Palo 200/0.50 mg**	**Netu/Palo FDC 300/0.50 mg**	**Aprepitant plus Onda**	**Aprepitant plus Palo**	**Total**
NETU-07-07	0 0.00	0 0.00	1 100.00	0 0.00	0 0.00	1 100.00	0 0.00	2
NETU-08-18	0 0.00	13 35.14	0 0.00	0 0.00	19 38.78	0 0.00	0 0.00	32
NETU-10-29	0 0.00	0 0.00	0 0.00	0 0.00	30 61.22	0 0.00	5 100.00	35
PALO-10-01	13 100.00	24 64.86	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	37
Total	13	37	1	0	49	1	5	106
Total exposure (Cycles)	**13**	**77**	**1**	**0**	**196**	**1**	**21**	**309**

Cyclophosphamide subpopulation

Four patients died, 2 (0.3%) patients in the oral palonosetron 0.50 mg and 2 (0.2%) in the Akynzeo groups, respectively. The percentage of patients with at least one SAE ranged from 3.3% in both palonosetron groups to 7.1% in the aprepitant plus palonosetron group. In the Akynzeo group, the rate was 4.8%. No serious events of diarrhoea were reported to occur in any treatment group. The very limited number of patients and cycles in the aprepitant group and palonosetron 0.25 mg IV. do not allow a meaningful comparison with the other treatments for the events of hematological aetiology.

Etoposide subpopulation

Eight patients died, 3 (6.7%) patients in the palonosetron 0.25 mg IV, 1 (1.2%) patient in the oral palonosetron 0.50 mg and 4 (4.5%) in the Akynzeo groups, respectively. The frequency of patients with SAE ranged from 9% in the Akynzeo group to 25% in the aprepitant plus palonosetron group. No serious events of diarrhoea occurred in any treatment group.

Docetaxel subpopulation

Five patients died, 3 (23.1%) patients in the palonosetron 0.25 mg IV, 1 (2.7%) in the oral palonosetron 0.50 mg and 1 (2%) in the Akynzeo group. The rate of patients with SAE ranged from 13.5% in the oral palonosetron 0.50 mg group to 30.8% in the palonosetron 0.25 mg IV group. In the Akynzeo group, SAEs occurred in 10 patients (20.4%). The frequency of patients with at least one SAE and of patients with any selected TEAE in this subpopulation across treatment groups is higher compared to the subpopulation who received other chemotherapeutic agents. This is probably attributable to docetaxel specific toxicity (myelosuppression) and other confounders such as patients' demographics, cancer diagnosis and stage, concomitant chemotherapeutic agents. Therefore, the increased frequency of patients with TEAEs observed in the Akynzeo group might be reasonably explained by the repeated exposure to chemotherapy cycles with this antineoplastic agent.

Chemotherapy regimen dose adjustment

Listings with details of chemotherapy over cycles, including the doses, were provided. Decreases in chemotherapy actual dose are observed in a very limited number of patients, in all treatment groups and are small adjustments in nature. Often a concomitant decrease in body weight is observed in these patients. It is sponsor's opinion that most of these chemotherapy dose changes are not to be considered dose adjustments due to safety reasons.

Netupitant and risk of infections

Integrated Summary Safety tables of all cycles for the Phase II/III cancer patients were reviewed to evaluate the incidence of TEAEs and Serious TEAEs in the SOC 'infections and infestations'. The present analysis considers either the total number of patients exposed to netupitant plus palonosetron, regardless of dosage (n = 1,442) or the patients exposed to the active comparators, palonosetron (n = 1,600) and aprepitant plus a 5-HT_3 RA (n = 238). All these patients concomitantly received dexamethasone.

In the SOC 'infections and infestations' a total of 154 (10.7%) patients reported any type of infections in the netupitant/palonosetron group, 94 (5.9%) in the palonosetron group and 20 (8.4%) in the aprepitant treated patients. At the preferred term level the percentage of patients with events was very low and does not exceed 1.5% and 0.5% for nasopharyngitis in the netupitant group and palonosetron group, respectively, while for aprepitant group the highest rate (1.7%) was found for patients with cystitis.

The frequency of serious TEAEs was 1% in 15 patients in the netupitant and palonosetron group. The type of reported SAEs is attributable to complications commonly observed in

the setting of cancer patients such as catheter site infection, device related infection, pneumonia or respiratory tract infection in lung cancer. A similar picture was observed for palonosetron treated group where 0.6% (10 patients) had serious TEAEs. Again pneumonia was the most frequent reported event accounting for 5 patients (0.3%). In the aprepitant group a total of 4 patients (1.7%) reported serious TEAEs. These results are not suggestive of any increased risk of infection associated with netupitant.

In summary, for any of the above mentioned chemotherapeutic agents, there is no evidence of an increased frequency in SAEs (including death) and selected TEAEs in the Akynzeo group compared to the other treatment groups. This is consistent with the pharmacological consideration that the netupitant component of Akynzeo may qualify as a mild inhibitor of CYP3A4 when considering these chemotherapeutic agents. Overall, the sparse events of infections supports the sponsor opinion that netupitant has implicated neither directly nor indirectly in their development, rather multiple factors may predispose patients to the risk of opportunistic infection or facilitate the infectious process.

Similarity of Akynzeo Tradename to iconazole or Akineton

The sponsor requests that Akynzeo be retained as an appropriate proposed proprietary name. Reasons are summarised below:

Trade/Brand Name

- Akynzeo is the global brand name for the netupitant/palonosetron combination under evaluation by regulatory agencies worldwide. No other trade name can be used currently. To identify and trademark an alternative name would take at least two years.
- The US FDA has approved the netupitant/palonosetron combination with Akynzeo as the product brand name, even though Akineton is also available in the US market. A similar query has been successfully addressed with EU authorities.
- Akynzeo has been used as the product name in the Pharmaceutical Benefits Scheme (PBS) submission currently under evaluation by the Pharmaceutical Benefits Advisory Committee (PBAC) and no objection has been received to date.
- Akineton has been available commercially in Australia since 2008, that is, before the trademark application for Akynzeo was submitted. Akynzeo has been granted global trademarking (including Australia), with no objections/oppositions/challenges being received by trademark offices or third parties. Likewise, no objections were raised by the manufacturers of Akineton, with the implication that they do not consider the trademarks to be confusingly similar.

Medication Errors

Akynzeo and Akineton share a common route of administration, however, the product profile differences are significant with respect to posology, frequency of administration, usual dose, strength type, dosage strength and form, and indications, and would minimise any concern of medication errors between the two products.

Other

Iconazole is not included in the ARTG as an active ingredient in any registered medicine. It is unclear why the Delegate has requested ACPM's advice on the similarity between Akynzeo and iconazole.

Advisory Committee Considerations

The submission seeks to register a new chemical entity and a fixed dose combination.

The ACPM, taking into account the submitted evidence of pharmaceutical quality, safety and efficacy advised that Akynzeo hard gelatin capsule, containing 3 x 100 mg netupitant immediate release tablets and 1 x 0.5 mg palonosetron soft gelatin capsule, has an overall positive benefit–risk profile for the following indication:

> *Akynzeo is indicated in adult patients for:*
> *Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.*
> *Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.*

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information and Consumer Medicine Information amendments

The ACPM specifically advised on the inclusion of the following in the PI:

- Provision of very clear information regarding the interaction of Akynzeo with dexamethasone and other drugs.
- Include under 'precautions', information about use in combination with docetaxel and in patients with liver impairment.
- The ACPM did not agree that the addition of 'in combination with dexamethasone' was necessary to be included in the indication for Akynzeo.

Specific advice

The ACPM advised the following in response to the specific Delegate's questions on this submission:

1. *Does the ACPM consider that the anti-emetic efficacy of netupitant is confounded by the pharmacokinetic interaction with dexamethasone? If so, how if at all does this impact on the assessment of Akynzeo's benefit / risk profile?*

The ACPM considered it was theoretically possible that concurrent dexamethasone had an impact on Akynzeo efficacy but the extent of the interaction on efficacy would be difficult to ascertain with any certainty. In addition, the ACPM noted that the current standard of care includes use of 5-HT_3 antagonists in combination with NK1 R antagonists and therefore it would be difficult to conduct a clinical trial without using dexamethasone. The ACPM agreed with the sponsor's pre ACPM response which stated that there is no evidence in the literature to support that the C_{min} of Akynzeo is correlated with an anti-emetic effect of dexamethasone.

2. *Does the ACPM consider there is sufficient evidence of use in MEC?*

The ACPM noted the sponsor's pre ACPM response with regards to the re-categorisation of combination AC (doxorubicin/cyclophosphamide) chemotherapy from MEC to HEC. The ACPM advised that the extrapolation of the data for AC regimen for use in MEC is reasonable.

3. *Should there be advice in the Akynzeo PI not to use the product in patients with moderate and/or severe hepatic impairment?*

The ACPM advised that information regarding the risk of use in patients with severe hepatic impairment should be included in the 'precautions' section of the PI.

4. *Does the ACPM object to the name Akynzeo (for example, is it too close to Akineton?)*

The ACPM had no objections to the product name, Akynzeo.

5. *Does the ACPM consider that Akynzeo has a positive benefit-risk balance?*

The ACPM advised that the evidence submitted support a positive benefit-risk balance Akynzeo. In addition, the advantages of a single oral dose compared to IV administration for the patient and for nursing staff in convenience and time are clear. The ACPM noted that compliance with administration of parenteral anti-emetics is not generally a major issue; however, the committee further noted that the capsule was rather large and may be difficult to swallow for some patients.

6. *What indication in prevention of CINV does the ACPM consider is supported by the evidence for Akynzeo?*

The ACPM considered that Akynzeo will most likely be used in combination with dexamethasone but noted that neither Emend (aprepitant) nor Aloxi (palonosetron) specify use with dexamethasone in the indication. The ACPM noted that there are a few paediatric cancers where dexamethasone is contraindicated for use for the treatment of nausea, noting; however that Akynzeo will be limited to use in the adult population. The ACPM therefore advised that the indication for Akynzeo need not specify use in combination with dexamethasone.

7. *Does the ACPM have any comments or suggestions about the Akynzeo PI or CMI?*

The ACPM considered that information regarding Akynzeo use in patients with liver impairment and use in combination with docetaxel should be included under 'precautions' to highlight the risk of liver toxicity. The PI should also clearly explain the interaction of Akynzeo with dexamethasone and other drugs.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Akynzeo netupitant/palonosetron (as hydrochloride) 300 mg/0.5 mg capsule blister pack indicated for:

> *Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.*
>
> *Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.*

Specific conditions of registration applying to these goods

The Akynzeo (netupitant/palonosetron) Risk Management Plan (RMP), EU-RMP version 1.0 (undated; datalock point 31 August 2013) with the Australian Specific Annex version 1.0 (dated 28 February 2014) and any future updates as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Akynzeo approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au