Taiwan Food and Drug Administration

Assessment Report

Trade Name：嘔可舒注射液 /
Akynzeo Concentrate for solution for infusion

Active Ingredient：Fosnetupitant/Palonosetron

License Number：MOHW-PI-028832

Applicant：和聯生技藥業股份有限公司

Approval Date：2024/12/26

Indication：
預防起始及反覆癌症化學療法(不僅限於高致吐性化學療法)引起之急性及延遲性噁心和嘔吐。

Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy (not limited to highly emetogenic cancer chemotherapy) .

Background Information

Trade Name	嘔可舒注射液 / Akynzeo Concentrate for solution for infusion
Active Ingredient(s)	Fosnetupitant/Palonosetron
Applicant	和聯生技藥業股份有限公司
Dosage Form & Strengths	注射液劑 235/0.25mg
Indication	預防起始及反覆癌症化學療法(不僅限於高致吐性化學療法)引起之急性及延遲性噁心和嘔吐。
Posology	fosnetupitant/palonosetron 235 mg/0.25 mg (一小瓶濃縮液的含量，稀釋使用)，在每個化療週期開始前約 30 分鐘開始投予，以輸注輸注超過 30 分鐘。
Pharmacological Category **ATC Code**	None / A04AA55

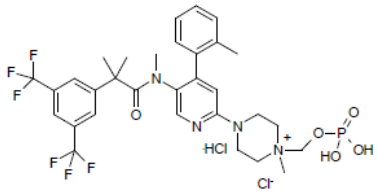
2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Fosnetupitant

The drug substance, fosnetupitant chloride hydrochloride, is chemically designated as 2-(3,5-bis-trifluoromethylphenyl)-*N*-methyl-*N*-[6-(4-methyl-4-*O*-methylene-phosphatepiperazinium-1-yl)-4-o-tolyl-pyridin-3-yl]- isobutyramide chloride hydrochloride and has the following structure:



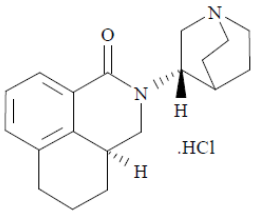
It is a white to off-white to yellowish solid. The molecular formula and the relative molecular mass for fosnetupitant are $C_{31}H_{36}F_6N_4O_5P$•Cl•HCl and 761.53g mol-1 respectively.

Adequate information of characterization of the drug substance has been provided. The molecular structure of fosnetupitant has been confirmed by IR spectrum, nuclear magnetic resonance (NMR) spectroscopy, mass spectrum and elemental analysis.

Adequate specification has been presented for the drug substance and the test items include appearance, identification, water content, chloride content, assay, related substance, genotoxic impurities, residual solvents, *N*,*N*-diisopropylethylamine, iodide content, chloromethyl chlorosulphate content, ammonium content and microbiology. Batch analysis data from commercial scale batches of the drug substance are provided and the test results are within the specifications.

Palonosetron

The drug substance, palonosetron hydrochloride, is chemically designated as (3*aS*)-2-[(*S*)-1-Azabicyclo[*2.2.2*]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*-benz[de] isoquinoline hydrochloride and has the following structure:



It is a white to off-white crystalline powder. The molecular formula and the relative molecular mass for fosnetupitant are $C_{19}H_{24}N_2O$•HCl and 332.87g mol-1 respectively. Adequate information of characterization of the drug substance has been provided. The molecular structure of fosnetupitant has been confirmed by elemental analysis, IR spectrum, nuclear magnetic resonance (NMR) spectroscopy and mass spectrum. Stereochemistry is determined by single crystal X-ray diffraction analysis.
Adequate specification has been presented for the drug substance and the test items include appearance, identification, clarity of solution, optical rotation, loss on drying, sulphated ash, heavy metals, related substances, assay, chloride content, residual solvents, bioburden, bacteria endotoxins and Yeast and Molds. Batch analysis data from commercial scale batches of the drug substance are provided and the test results are within the specifications.

2.1.2 Drug product

The drug product is supplied for dilution and parenteral administration as clear, colorless to slightly yellow solution containing 235 mg fosnetupitant (equivalent to 260 mg fosnetupitant chloride hydrochloride) and 0.25 mg palonosetron (equivalent to 0.28 mg palonosetron hydrochloride). The specifications for excipients used in the solution formulation are adequate.

Adequate specification has been presented for the solution and the test items include appearance, visible particles, container appearance, fosnetupitant identification, fosnetupitant assay, fosnetupitant impurities, palonosetron identification, palonosetron assay, palonosetron impurities, volume in container, uniformity of dosage units, pH, sub-visible particulate, sterility and bacterial endotoxins. Batch analysis data from representative batches of the solution are provided and the test results are within the specifications. Analytical methods are described well and validated.
Stability studies of the solution under long term condition (25°C/60% RH) and accelerated condition (40°C/75% RH) have been carried out. Up to 60 months of long-term and 6 months of accelerated stability data are submitted. Based on available stability data, the shelf life of the solution can be granted for 36 months under the storage condition of 25°C.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Fosnetupitant is a prodrug of netupitant, a selective antagonist of human substance P/NK-1 receptors. Fosnetupitant and netupitant had similar in vitro binding profiles and bioactivity. In vivo pharmacological comparison showed that fosnetupitant and netupitant exhibit a similar efficacy and potency in the SBL (scratching, biting, and licking) test in substance P-treated mice.

In rats, no significant changes in safety endpoints for the respiratory system were noted up to the highest dose examined (79.2 mg/kg). No neurological changes in the Irwin test and pro-convolusion test were noted at 39.5 mg/kg in rats. No anti-convulsant effects were noted up to the highest dose examined (79 mg/kg) in rats. No QT prolongation potential was noted up to 30 μM in an in vitro hERG assay or up to the highest dose examined (13.12 mg/kg) in dogs. In dogs treated with the fosnetupitant/palonosetron combination, QT prolongation was observed at the highest dose examined; a NOAEL was 3.95/3 mg/kg. The QT prolongation was also seen in the netupitant/palonosetron combination. Some renal and gastrointestinal tract effects were observed; the clinical relevance is considered low. No abuse liability potential was identified in baboon studies.

2.2.2 Toxicological Studies

In rats, two in the fosnetupitant high dose (39.47 mg/kg/day) group were found dead with no clear cause of death; mortality increased in the fosnetupitant/palonosetron combination groups [4 in the high dose (39.47/10 mg/kg/day) group and one in the mid-dose (13.16/3 mg/kg/day) group]. In dogs, no significant changes were noted up to the highest dose (13.16 mg/kg/day) of fosnetupitant examined. QT prolongation and inflammation at injection sites were observed for fosnetupitant/palonosetron combination in dogs; a NOAEL was 1.316/1 mg/kg/day. Phospholipidosis/ phospholipidosis signs were observed for the approved oral netupitant/palonosetron combination but not for the IV fosnetupitant/palonosetron combination (rat: up to 39.47 mg/kg/day; dog: up to 13.16 mg/kg/day).

No genotoxicity was noted for fosnetupitant in an in vitro Ames test, an in vitro chromosomal aberration study, or an in vivo rat micronucleus assay. It is acceptable that no carcinogenicity studies are conducted. In rats, no significant changes in fertility were noted up to the highest dose examined (39.47 mg/kg/day). On the other hand, embryofetal toxicities were observed in both rats and rabbits. In rats, 1 dead fetus, 1 fetus with malformation, and 6 fetuses with no ossification of pubis were observed; a

NOAEL was 13.16 mg/kg/day. In rabbits, a slight increase in intrauterine deaths was observed in the mid- and high-dose groups; a NOAEL was 3.13 mg/kg/day. In the pre- and postnatal development study, rats (both F0 and F1 generation) in the high dose group had reduced body weight; a NOAEL was 13.16 mg/kg/day. No significant changes in the reproductive performance were noted in the F1 generation. A delay in the pre-weaning development test for F2 generation was noted in the high-dose group. A good tolerability of fosnetupitant and the IV fosnetupitant/ palonosetron combination was demonstrated. No antigenic potential was detected in guinea pigs. Fosnetupitant is considered phototoxic by the latest criteria for the classification of phototoxicity (OECD guideline 432). The results for fosnetupitant and netupitant were very similar; netupitant was classed as non-phototoxic using previous criteria.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Akynzeo Concentrate for solution for infusion is an intravenous (IV) infusion solution and contained two active substances, fosnetupitant and palonosetron. It is used for the prevention of chemotherapy-induced nausea and vomiting (CINV). Fosnetupitant, a phosphorylated prodrug of netupitant, is a novel molecule and developed to provide another choice for patients who are not able to tolerate an oral formulation (i.e. Akynzeo® capsule). Since the basic pharmacokinetic characteristic of netupitant is already known, the objective of Akynzeo Concentrate for solution for infusion is to provide comparable exposure with Akynzeo® capsule.

According to the dosing finding study, it proved that the IV dose of 260 mg fosnetupitant chloride hydrochloride can provide comparable exposure (AUC) to that of oral 300 mg netupitant. As expected, the C_{max} was higher, T_{max} was achieved earlierly for fosnetupitant (IV infusion) than that in Akynzeo® capsule (0.5 hrs vs. 4 hrs). Following IV administration of fosnetupitant/palonosetron (260 mg/0.25 mg) to cancer patients receiving a single cycle of highly emetogenic chemotherapy, it can see that unchanged fosnetupitant disappeared rapidly from the systemic circulation, and netupitant formed quickly, maintained for a while, and declined with a long halt-life ($T_{1/2}$=143.73 hrs). The mean C_{max} and AUC_{inf} of fosnetupitant in patients were lower than that in healthy subjects, but netupitant and its metabolites (M1, M2 and M3) were comparable.

The average human plasma protein binding of fosnetupitant was 93.5%, and blood to plasma concentration ratio in humans was 0.4 - 0.6, regardless of concentration. Primary elimination route for fosnetupitant is metabolism. Fosnetupitant is rapidly and

completely hydrolyzed to netupitant by non-CYP450 hydrolytic enzymes (e.g., phosphatases).

2.3.2 Interaction Studies

Since netupitant is a moderate CYP3A4 inhibitor, the exposure (AUC) of dexamethasone (a CYP 3A4 substrate) was increased by 50% on Day 1, by 142% on Day 4 in healthy subjects, when dexamethasone combined with fosnetupitant (IV infusion). Thus, the dose of dexamethasone should be adjusted to 12 mg on Day 1 and 8 mg once a day on Day 2-4 when Akynzeo Concentrate for solution for infusion are indicated in combination with dexamethasone in target patients.

2.3.3 Special Populations

No new intrinsic factors analysis was conducted for fosnetupitant, considering it disappeared quickly in systemic circulation and completely formed netupitant; thus, the dose adjustment recommendation for Akynzeo Concentrate for solution for infusion in special population can be adopted from Akynzeo® capsule.

Overall, the pharmacokinetic studies conducted were satisfactory met the minimum requirements to support the marketing authorization of Akynzeo Concentrate for solution for infusion. It is recommended to approve the NDA of Akynzeo Concentrate for solution for infusion from the PK/PD perspective.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

In this submission, one pivotal study ([PALO-15-17]) and two supportive studies ([NEPA-15-18] and [NEPA-17-05]) are provided to support the efficacy of Akynzeo®. Akynzeo® is indicated in combination with dexamethasone in adults for the prevention of nausea and delayed nausea and vomiting associated with initial and repeat course of highly emetogenic cancer chemotherapy. The key efficacy findings of the three studies are summarized below:

[PALO-15-17] was a Phase III, randomized, double-blind, double-dummy, multi-national, multi-center, active-controlled study to evaluate the efficacy of a single dose of palonosetron 0.25 mg administered as a 30-minute IV infusion versus a single dose of palonosetron 0.25 mg administered as a 30-second IV bolus, each administered with oral dexamethasone prior to highly emetogenic chemotherapy (HEC).

The primary efficacy endpoint of [PALO-15-17] was CR in the acute phase, which was 82.7% in the 30-min infusion group versus 86.5% in the 30-sec bolus group, with a

difference in proportion of -3.8% (99% CI: -12.2%, 4.7%). As the lower limit was greater than the pre-defined non-inferiority margin of -15%, the non-inferiority of palonosetron 30-min infusion vs. 30-sec bolus was demonstrated for FAS. In addition, the non-inferiority was also demonstration in the PP population. Therefore, the primary noninferiority objective of this study was achieved.

Study [NEPA-15-18] and [NEPA-17-05] were phase 3, multinational, multicenter, randomized, double-blind, double-dummy, active-controlled study comparing intravenous fosnetupitant/palonosetron 235 mg/0.25 mg combination (IV NEPA FDC) and oral netupitant/palonosetron 300 mg/0.5 mg combination (oral NEPA FDC). The primary objective was to evaluate the safety and tolerability of IV NEPA FDC, and the secondary objective was to describe the efficacy of IV NEPA FDC versus oral NEPA FDC. Study [NEPA-15-18] enrolled subjects with malignant solid tumors who were chemotherapy naïve and scheduled to receive at least 4 consecutive cycles of HEC. Study [NEPA17-05] enrolled female subjects with breast cancer who were naïve to moderately or highly emetogenic antineoplastic agents and scheduled to receive at least 4 consecutive cycles of anthracycline-cyclophosphamide chemotherapy. The efficacy results, including CR rate, proportion of subjects with no emetic episodes or proportion of subjects with no rescue medication, were comparable between the two groups in both studies.

In summary, results of the pivotal study ([PALO-15-17]) and the two supportive studies ([NEPA-15-18] and [NEPA-17-05]) have been provided sufficient evidence to support the efficacy of Akynzeo for the claimed indication.

2.4.2 Safety Results

In Study NEPA-15-18 and NEPA-17-05, the incidence and severity of treatment-emergent adverse events (TEAEs) were comparable between the intravenous fosnetupitant/palonosetron 235 mg/0.25 mg combination (IV NEPA FDC) group and the oral netupitant/palonosetron 300 mg/0.5 mg combination (oral NEPA FDC) group.

As expected in the cancer population receiving cytotoxic treatments, the most frequently (≥ 10%) reported TEAEs included alopecia, neutropenia, anemia, leukopenia, and fatigue. The most frequently (≥ 1%) reported serious TEAEs were neutropenia and pneumonia. The incidence of the above TEAEs or serious TEAEs were all similar in the IV NEPA FDC and the oral NEPA FDC groups.

Based on the pharmacokinetic evaluation and safety data from Japanese subjects, the

bridging study of AKYNZEO concentration for solution for infusion has been waived.

2.6 Conclusion

Based on the above multidiscipline review, CDE review team leader recommends approval of AKYNZEO concentration for solution for infusion.

1. Recommended Indication: Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of chemotherapy (not limited to highly emetogenic cancer chemotherapy).
2. The recommended dose is fosnetupitant/palonosetron 235 mg/0.25 mg (1 vial of AKYNZEO). Infuse over 30 minutes starting 30 minutes before chemotherapy.
3. The shelf life of the solution can be granted for 36 months under the storage condition of 25°C.

3. Post-Marketing Requirements

Nil