TGA Approves AKYNZEO® (netupitant/palonosetron) for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV)

First New Fixed Combination Targeting Two Critical Pathways Involved in CINV

Lugano, Switzerland and Melbourne, Australia, May 8, 2015 – Helsinn, the Swiss Group focused on building quality cancer care, and Australian biopharmaceutical company Specialised Therapeutics Australia (STA), announce that the Therapeutic Goods Administration (TGA) has approved AKYNZEO® for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy[1].

AKYNZEO® is the first approved fixed dose combination oral agent that targets two critical signalling pathways associated with CINV by combining netupitant, an NK_1 receptor antagonist, and palonosetron, a 5-HT_3 receptor antagonist, in a single capsule for the prevention of CINV.[1]

"Cancer patients are burdened with having to take multiple drugs, often several times per day and certainly multiple times per cycle of chemotherapy, to reduce unwanted side effects. With every increased drug/schedule there is an increased risk of mistakes and/or non-compliance," said Professor Dorothy Keefe, Clinical Ambassador, Transforming Health and Professor of Cancer Medicine, University of Adelaide. "The availability of this combination of drugs, in a single capsule, allows 'once per cycle' dosing (which is even better than once per day dosing) for the benefit of the patient."

The approval of AKYNZEO® was based on the submission of Phase 2 and Phase 3 trials with AKYNZEO® in patients undergoing treatment with moderately and highly emetogenic chemotherapy regimens for a variety of tumour types. The most common adverse reactions reported by ≥ 1% of patients treated with AKYNZEO® for one or more cycles were headache, constipation and fatigue.[1]

STA Chief Executive Officer Mr Carlo Montagner said "AKYNZEO® was a valuable addition to STA's Oncology Supportive Care portfolio, providing patients with access to an effective and convenient antiemetic therapy. We look forward to making this drug available to cancer patients around the country, for improved management of some of the most common side effects of chemotherapy, which can severely diminish a patient's quality of life. STA will now seek to have AKYNZEO® listed on the Pharmaceutical Benefits Scheme for reimbursement."

"This approval paves the way for Australian patients to have access to a new treatment option for CINV," said Riccardo Braglia, Helsinn Group Chief Executive Officer. "Helsinn is delighted

that the TGA has approved AKYNZEO® and we look forward to a successful launch in Australia, and to working alongside Specialised Therapeutics Australia, with whom we have a long-standing relationship," said Riccardo Braglia, Helsinn's Group Chief Executive Officer. "This approval offers patients access to a new treatment option for CINV prevention that is effective in preventing both nausea and vomiting, particularly in the delayed phase, following emetogenic chemotherapy regimens."

CINV is one of the most common and troublesome side effects of chemotherapy.[2] Its management has been refined over the past several decades, but despite the availability of effective treatments and clear antiemetic guidelines, many patients still suffer from CINV, particularly during the delayed phase after chemotherapy.[3] Studies show that patients often receive antiemetic drug regimens that are inconsistent with CINV treatment guidelines, which call for multiple-pathway targeted antiemetic prophylaxis. [3]

AKYNZEO® provides cancer care teams with two antiemetics in a single oral fixed dose combination capsule. A combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist and dexamethasone meets guideline recommendations for optimal antiemetic therapy following highly emetogenic chemotherapy. [4]

About AKYNZEO® (netupitant/palonosetron)

AKYNZEO® is an oral, fixed combination of an NK_1 receptor antagonist, netupitant, and a 5-HT_3 receptor antagonist, palonosetron, in a single capsule, that targets two critical signalling pathways associated with chemotherapy-induced nausea and vomiting (CINV).[1]

AKYNZEO® was approved on October 10th 2014 by the US Food and Drug Administration (FDA), 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.

On January 22, 2014, the European Medicines Agency (EMA) started to review the submission of Helsinn's Marketing Authorisation Application for netupitant/palonosetron fixed dose combination for the prevention of acute and delayed CINV.

Additional regulatory submissions for netupitant/palonosetron fixed dose combination are underway worldwide.

HELSINN
Building quality cancer care together

About Specialised Therapeutics Australia

Specialised Therapeutics Australia Pty Ltd (STA) is a biopharmaceutical company dedicated to working with leading international pharmaceutical and diagnostic companies to provide patient access to innovative healthcare solutions.

With the highest professional and ethical standards, we commercialise therapies and technologies that uniquely fulfil the unmet medical needs of our community. The STA therapeutic portfolio and pipeline at present encompass oncology, haematology, urology and ophthalmology.

Additional information can be found at www.specialisedtherapeutics.com.au

About Helsinn Group

Helsinn is a family run, privately owned pharmaceutical group focused on building quality cancer care with a large portfolio of products. Founded in 1976 with headquarters in Lugano, Switzerland, Helsinn also has operating subsidiaries in Ireland, the U.S. and a representative office in China. Helsinn's business model is focused on the licensing of pharmaceuticals, medical devices and nutritional supplement products in the therapeutic area of cancer care.

Helsinn Group in-licenses early-to-late stage new chemical entities, completing their development by performing preclinical and clinical studies and associated manufacturing activities. Helsinn then prepares necessary regulatory filings in order to achieve marketing approvals worldwide. Helsinn's products are out-licensed to its global network of marketing and commercial partners that have been selected for their local market knowledge. Helsinn supports these partners by providing a full range of product and scientific management services, including commercial, regulatory, and medical marketing advice. In March 2013, Helsinn established a new commercial organization within its subsidiary, Helsinn Therapeutics (U.S.), Inc., in order to conduct direct sales and marketing activities within the U.S. market. Helsinn's products are manufactured according to the highest quality, safety, and environmental standards at Helsinn's GMP facilities in Switzerland and Ireland from where they are then supplied worldwide to customers. Further information on Helsinn Group is available at www.helsinn.com

HELSINN
Building quality cancer care together

About the AKYNZEO® (netupitant/palonosetron) Pivotal Clinical Trials

The efficacy of AKYNZEO® was established in a pivotal, Phase 2, randomised, double-blind, dose ranging study in 694 patients undergoing cisplatin-based chemotherapy for a variety of tumor types. The efficacy of AKYNZEO® was assessed in 135 chemotherapy-naïve patients who received AKYNZEO® (netupitant 300 mg/palonosetron 0.5 mg), and 136 patients who received oral palonosetron 0.5 mg. For the key efficacy endpoints of complete response (CR), defined as no emetic episode and no use of rescue medication, for the delayed phase (25-120 hour interval), the acute phase (0-24 hour interval), and the overall phase (0-120 hours) after the start of chemotherapy administration. AKYNZEO® showed significantly higher CR rates compared with oral palonosetron in the delayed, acute and overall phases (90.4% versus 80.1%; P=0.018; 98.5% versus 89.7%; P=0.007; 89.6% versus 76.5%; P=0.004, respectively).[1,5]

The clinical efficacy profile was further established in a multinational, randomised, double-blind, parallel-group, Phase 3 study in 1455 chemotherapy-naïve patients receiving anthracycline and cyclophosphamide-based chemotherapy. Patients were randomized to receive a single oral dose of either AKYNZEO® plus dexamethasone or palonosetron plus dexamethasone prior to chemotherapy. The percentage of patients who met the primary endpoint of CR in the delayed phase was significantly higher in the AKYNZEO® group compared to the oral palonosetron group (76.9% versus 69.5%; P = 0.001), which was also seen in the overall (74.3% versus 66.6%; P = 0.001) and acute (88.4% versus 85.0%; P = 0.047) phases post chemotherapy. In this study, AKYNZEO® was generally well tolerated with a safety profile similar to that of palonosetron.[6]

In a separate study, 309 patients undergoing initial and repeat cycles of chemotherapy (including carboplatin, cisplatin, oxaliplatin, and doxorubicin regimens) received AKYNZEO®; efficacy was maintained throughout all cycles.[7]

AKYNZEO® Important Safety Information

Warning and Precautions[1]

- Hypersensitivity reactions to palonosetron may occur in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists.
- Patients with a history of constipation or signs of subacute intestinal obstruction should be monitored following administration.

- Since AKYNZEO® contains a 5-HT_3 receptor antagonist caution should be exercised in the concomitant use of AKYNZEO® with medicinal products that increase the QT interval or in patients who have or are likely to develop prolongation of the QT interval.
- Serotonin syndrome has been reported with the use of 5-HT_3 receptor antagonists either alone or in combination with other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs).
- Systemic exposure to chemotherapy agents and other medicines metabolised by CYP3A4 may increase when administered with or after AKYNZEO®. Patients should be closely monitored for adverse reactions that may arise from this additional exposure to relevant chemotherapies and other medicines.
- AKYNZEO® should not be used during pregnancy unless the clinical condition of the woman requires treatment with palonosetron and netupitant (Category B3).
- Breastfeeding should be discontinued during treatment with AKYNZEO®.

Use in Specific Populations[1]

- Avoid use of AKYNZEO® in patients with severe hepatic impairment, severe renal impairment, or end stage renal disease.

Drug Interactions[1]

- When AKYNZEO® is used concomitantly with medications that induce CYP3A4 activity, netupitant plasma concentrations could be reduced and this may result in decreased efficacy of AKYNZEO®. AKYNZEO® can increase plasma concentrations of concomitantly administered medications that are metabolised via CYP3A4. The inhibitory effect on CYP3A4 can last for multiple days.
    - Dexamethasone doses should be reduced when given with AKYNZEO®.
    - Consider the potential effects of increased plasma concentrations of erythromycin, midazolam or other benzodiazepines metabolised via CYP3A4 (alprazolam, triazolam) when administering with AKYNZEO®.
    - Caution and monitoring for chemotherapy-related adverse events are advised in patients receiving chemotherapy agents metabolised primarily by CYP3A4, including docetaxel, paclitaxel, etoposide, irinotecan, cyclophosphamide, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine.

- Avoid concomitant use of AKYNZEO® in patients on chronic use of a strong CYP3A4 inducer such as rifampicin as this may decrease the efficacy of AKYNZEO®.

Adverse Reactions [1]

- Most common adverse reactions (≥1% in patients receiving AKYNZEO®): headache, fatigue, and constipation.

AKYNZEO® is available by prescription only.

Please review AKYNZEO® Product Information before prescribing at www.specialisedtherapeutics.com.au

AKYNZEO® is under license from Helsinn Group, Switzerland.

For more information about AKYNZEO®, visit www.AKYNZEO.com

References:

1. AKYNZEO® Approved Product Information.

2. Roscoe JA, Morrow GR, Hickok JT, Stern RM. Nausea and vomiting remain a significant clinical problem: Trends over time in controlling chemotherapy-induced nausea and vomiting in 1413 patients treated in community clinical practices. J Pain and Symptom Management. 2000;20(2):113-121.

3. Aapro M, Molassiotis A, Dicato M et al. The effect of guideline-consistent antiemetic therapy on chemotherapy-induced nausea and vomiting (CINV): the Pan European Emesis Registry (PEER). *Ann Oncol* 2012; 23(8): 1986–92.

4. National Cancer Comprehensive Network (NCCN). Clinical Practice Guidelines in Oncology. Antiemesis. v 2.2014. www.nccn.org. Accessed August, 2014.

5. Hesketh PJ, et al. Efficacy and safety of NEPA, an oral combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy: a randomized dose-ranging pivotal study *Ann Oncol*. 2014 Jul;25(7):1340-6.

6. Aapro,M, et al. A randomized phase III study evaluating the efficacy and safety of NEPA, a fixed dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced

nausea and vomiting following moderately emetogenic chemotherapy. *Ann Oncol*. 2014 Jul:25(7):1328-33.
7. Gralla, RJ, et al. A phase III study evaluating the safety and efficacy of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting over repeated cycles of chemotherapy. *Ann Oncol*. 2014 Jul;25(7):1333-9.

For more information, please contact:

Helsinn Group
Paola Bonvicini
Head of Communication & Press Office
Tel: +41 91-985-21-21
info-hhc@helsinn.com