

PALONOSETRON: THE LONG-LASTING ANTIEMETIC ACTION FINDS ITS BASIS

New data on the mechanism of action of the second generation 5-HT₃ antagonist palonosetron presented today at the 33rd ESMO Congress in Stockholm, Sweden

Stockholm, September 12, 2008 – New data presented today at the 33rd ESMO (European Society of Medical Oncology) Congress in Stockholm may contribute to explain the reason why palonosetron, a second generation 5-HT₃ receptor antagonist, demonstrates in clinical trials and clinical practice a unique long-lasting action in the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients with cancer. A single intravenous dose of palonosetron (0.25 mg) provides better protection from CINV than first-generation 5-HT₃ receptor antagonists, such as ondansetron and granisetron, throughout a 5-day post-chemotherapy period*. This means that a single administration of palonosetron also grants protection during the delayed phase of CINV*.

Compared to other 5-HT₃ receptor antagonists, palonosetron has a unique chemical structure and exhibits high binding affinity for the 5-HT₃ receptor. Since the beginning its structural differences have been investigated to understand whether they may lead to a different interaction of the compound with the 5-HT₃ receptor.

All 5-HT₃ receptor antagonists bind to the same site as serotonin, thus preventing the neurotransmitter from causing emesis. Palonosetron exhibits allosteric binding and positive cooperativity, unlike granisetron and ondansetron which exhibit simple bimolecular binding and no cooperativity. This suggests that palonosetron interacts with the 5-HT₃ receptor at sites distinct to granisetron and ondansetron and induces a conformational change in the receptor.

“The binding mode and the high receptor affinity of palonosetron make it a more efficient receptor antagonist compared to agents such as ondansetron and granisetron, as palonosetron may be less likely to be displaced by serotonin”, said Dr. Matti Aapro, Dean of the Multidisciplinary Oncology Institute, Genolier, Switzerland. “However, the efficacy of palonosetron during the delayed phase of CINV* cannot be explained solely by this higher affinity and its longer half-life”, he added.

Some *in vitro* studies have shown that palonosetron exhibits a long-lasting inhibition of 5-HT₃ receptor function. Thus, it has been hypothesized that the drug’s mechanism of action may also be associated to a decrease in the number of overall receptor sites available to serotonin.

Actually, the findings presented today by Dr. Aapro at the ESMO conference visualize, via a special microscopy investigation (confocal fluorescence microscopy), that the binding of palonosetron is also associated to another conformational change of the receptor, which is internalized into the cell and therefore “hidden” to serotonin.

“The receptor internalization is a differentiating pharmacological feature which may account for the effect of palonosetron, persisting beyond its binding to the 5-HT₃ receptor”, Dr. Aapro commented.

Chemotherapy-induced nausea and vomiting (CINV) is among the most dreaded side effects following therapy in patients with cancer. Despite prophylaxis, on the day of chemotherapy, up to 30-45 percent of patients experience nausea or vomiting or require rescue therapy following administration of certain types of emetogenic chemotherapy.

The 5-HT₃ receptor plays a pivotal role in the process of emesis, and agents that antagonise these receptor subtypes are the basis for control of this effect. Following the development of the first generation 5-HT₃ receptor antagonists, such as ondansetron and granisetron, in the late '80s and early '90s, in the recent years new compounds have been made available for preventing CINV, including palonosetron.

Palonosetron has been developed by Helsinn Healthcare SA of Switzerland and today it is marketed in more than 40 countries world-wide as Aloxi[®], Onicit[®], and Paloxi[®]. According to the IMS rank of the Top New Chemical Entities registered world-wide in the years 2003-2007, palonosetron is the 25th best selling compound, accounting for over 300 million dollars in audited world sales in 2007. Palonosetron, marketed as Aloxi[®], is the leading brand in the USA within the CINV Day of Chemo segment, and it is steadily growing in the European markets. Its approval in Japan is expected during 2009.

“This result of palonosetron, a compound indicated in a ‘niche’ market, is an outstanding one and demonstrates the commitment of our company and all our partners in highlighting palonosetron intrinsic value”, commented Dr. Riccardo Braglia, CEO of Helsinn Healthcare. “We expect soon more key achievement for palonosetron, to further provide important benefits to the medical community and cancer patients”, he said.

About Palonosetron (Aloxi[®], Onicit[®], Paloxi[®])

Palonosetron (palonosetron hydrochloride) is a selective 5-HT₃-receptor antagonist, developed for the prevention of CINV, with a long half-life of 40 hours and at least 30 times higher receptor binding affinity than currently available compounds. Several clinical trials demonstrated that palonosetron covers up to 5 days following chemotherapy in comparison with single doses of other competitor products*. Since its availability in USA in September



2003, there have been over 7 million administrations of palonosetron. The product has shown to be effective in preventing both acute and delayed CINV in patients receiving moderately emetogenic chemotherapies.

Palonosetron 0.075 mg IV is also approved by FDA as a single intravenous dose administered immediately before the induction of anaesthesia for the prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery.

Palonosetron is contraindicated in patients known to have hypersensitivity to the drug or any of its components. The most commonly reported adverse reactions (incidence $\geq 2\%$) in CINV trials with palonosetron were headache (9 %) and constipation (5 %), and they were similar to the comparators. In PONV trials, the most commonly reported adverse reactions were QT prolongation (5 %), bradycardia (4 %), headache (3 %), and constipation (2 %), similar to placebo

For more information about palonosetron, please visit the website: www.aloxi.com.

About Helsinn Healthcare

Helsinn Healthcare is a privately owned pharmaceutical group with headquarters in Switzerland and is the worldwide licensor of palonosetron. Helsinn's core business is the licensing of pharmaceuticals in therapeutic niche areas. The company's business strategy is to in-license early stage new chemical entities and complete their development from the performance of pre-clinical/clinical studies and CMC development to the attainment of market approvals in U.S. and Europe. Helsinn's products are eventually out-licensed to its marketing partners for distribution. The active pharmaceutical ingredients and the finished dosage forms are manufactured at Helsinn's cGMP facilities and supplied worldwide to its customers.

*These sentences refer to Moderately Emetogenic Chemotherapy (MEC) setting

For more information about Helsinn Healthcare, please visit the company's website at www.helsinn.com.

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