Novel Formulations to Improve the Control of Emesis

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Reformulation is a key strategy for product development and helps address the challenges of the current market, such as longer new chemical entity (NCE) development timelines, fewer new drug approvals, increasing costs, looming patent expirations and the threat of generic erosion. Today, offering convenience in dosing or administration alone is no longer a sufficient product differentiator in the marketplace, but must be included as part of the overall product formulation strategy. Other parts of the formulation strategy might include improving solubility/bioavailability to enhance efficacy, reducing side effects, or taste masking.

Addressing Unmet Needs

Drug reformulation can help address the unmet needs of patients and prescribers by improving patient acceptance of and adherence to prescribed treatment regimens. In the treatment of emesis, improved efficacy and extended delivery of antiemetic therapy are desirable therapeutic improvements over many current treatments in the antiemetic category. These improvements may also help ease patients’ nausea and vomiting-related fears as they undergo difficult, but beneficial, treatments or procedures (e.g. chemotherapy or radiotherapy), thereby helping them maintain their willingness to continue with such treatments.

Tapping into the 5-HT3 Receptor Antagonist (5-HT3 RA) Market Opportunity: Ondansetron

Antiemetics are used to control nausea and vomiting across a broad range of therapeutic indications and in a variety of risk settings (e.g. high, moderate, low emetogenic risk). This category of drugs has seen recent new product entries. Specifically, companies are tapping into the large market opportunity in the 5-HT3 RA class of antiemetics, a current market size of approximately $705 million and the current mainstay of antiemetic therapy.

In the U.S. antiemetic category, ondansetron dominates the solid oral 5-HT3 RA segment. Ondansetron is marketed in both generic and branded form. It has several therapeutic indications, including prevention of postoperative nausea and vomiting (PONV) as well as chemotherapy- or radiation-induced nausea and vomiting (CINV and RINV, respectively) in a variety of risk settings. Current oral formulations of ondansetron (liquid, tablet, and orally dissolving tablet [ODT]) are indicated for administration in multiple daily doses, potentially over a series of days. This is due to the pharmacokinetic profile of ondansetron, which has a half-life of approximately 3–6 hours in adults, with a time to peak plasma levels of approximately 2 hours.

Long-Acting Formulations Needed

The requirement for multi-dosing can negatively affect efficacy and treatment adherence as well as heighten emesis-related patient anxiety, particularly for patients who have difficulty taking pills within physician-recommended timeframes. In the postsurgical setting, at-risk patients experience deep fear and anxiety about nausea and vomiting, generally viewing it as more troubling than even pain. Not surprisingly then, in a post-operative survey, patients revealed they are willing to spend as much as $100 out of pocket for an effective antiemetic. In the setting of cancer chemotherapy, the experience of nausea and vomiting is one of the most common and distressing side effects of cancer treatment and has been associated with noncompliance with receiving chemotherapy, particularly in the era prior to the availability of current prophylactic drugs.

By complicating or preventing administration of planned therapies, CINV can lead to poor treatment outcomes and decrease quality of life for patients that have to interrupt or discontinue planned treatment. Similarly, the lengthy duration of radiotherapy—sometimes lasting 6 to 8 weeks—can result in prolonged symptoms of nausea and vomiting that can negatively impact patients’ quality of life and contribute to noncompliance with planned radiotherapy treatments.

Although there have been advances with the introduction of combination antiemetic treatment, there is still a need for sustained protection, particularly when patients are faced with prolonged or
recurrent treatment during which they are at risk of CIN V or RIN V, as well as the risk of nausea and vomiting for up to five days after chemotherapy administration and for several days after completion of radiotherapy. Improved adherence to antiemetic regimens and development of extended-release antiemetic drug formulations have been identified as a way to improve patient outcomes.

1025-ONDANSETRON ER, An Extended-Release Formulation of Ondansetron

Responding to this need, we are developing 1025-ONDANSETRON ER, a novel, once-daily, oral formulation of ondansetron that is designed for improved efficacy and increased patient compliance across the many therapeutic indications and risk settings related to nausea and vomiting. 1025-ONDANSETRON ER combines immediate-release (IR) and extended-release (ER) components in one capsule.

Although oral dosage forms are preferred by patients, developing an ER formulation of oral antiemetic market leader ondansetron has challenged drug makers. This is because ondansetron is only freely soluble in the acidic pH of the stomach. Using our Diffucaps® customized release technology (Figure 1), 1025-ONDANSETRON ER will potentially be the first once-daily, ER oral ondansetron formulation.

In pivotal pharmacokinetic (PK) studies, 1025-ONDANSETRON ER provides 24 hours of coverage, eliminating the peaks and troughs in plasma concentration associated with twice- or thrice-daily ondansetron formulations. The improved PK profile is designed to provide more consistent control of nausea and vomiting, reducing the probability of breakthrough emesis that can occur between IR doses. This, and the fact that it is a single dose, may promote higher patient compliance as well as reduce emesis-related anxiety.

**Bioavailability Enhancement Using Diffucaps®**

This enhanced formulation of ondansetron was developed using our proprietary Diffucaps® customized drug release technology, which improves the bioavailability of drugs that exhibit extreme pH-dependent solubility profiles. In this formulation challenge, the Diffucaps technology was optimized to address the specific solubility issues for ondansetron, resulting in improved bioavailability and, thus, once-daily dosing.

The development of 1025-ONDANSETRON ER is representative of our R&D excellence in oral delivery formulation development. With a broad portfolio of technologies, the company has had six partnered and proprietary products approved by the FDA since 2001 and has developed more than 40 products for commercialization by partners worldwide. The company is actively seeking partners to market 1025-ONDANSETRON ER in the U.S. Visit the company’s website at www.AptalisPharmaceuticalTechnologies.com/contact.html to learn more.

**REFERENCES:**


**Anthony Recupero,** Ph.D., is currently Senior Director, Licensing at Aptalis Pharmaceutical Technologies where he is responsible for new business development and licensing for North America.

*Aptalis Pharmaceutical Technologies (formerly Eurand Pharmaceutical Technologies) develops and manufactures enhanced oral pharmaceutical products based on its broad range of proprietary technologies which include bioavailability enhancement of poorly soluble drugs, custom release profiles and taste-masking formulations for a variety of dosage forms including orally disintegrating tablets.*