

## Skewering Pain at Javelin Pharmaceuticals

By Alissa Poh

Oct. 15, 2008 | There will be some 73 million surgical procedures in the US this year, to say nothing of 110 million admissions to the emergency room. And along the way, nearly half of those patients will also have to deal with insufficient pain management.

"There's a significant need in the acute moderate-to-severe pain medication segment," says Martin Driscoll, Javelin Pharmaceuticals' CEO, of the \$30-billion global pain market, which has an annual growth rate of six to seven percent. Pharmaceutical companies occupying this pain space, such as Cephalon, King, and Alpharma, have concentrated on reformulating opioid drugs to make them less prone to abuse. But 150-strong Javelin, headquartered in Cambridge, Mass., has a different focus: developing new and proprietary administration routes for well-characterized molecules of the non-opioid category, with an eye on the hospital marketplace.

"Physicians are still trying to reduce the amount of opioid use, particularly in the acute care setting," Driscoll says. "They'd like to get patients out of the hospital sooner, since many surgeries today are less interventional. But the more opioids a clinician has to use in the surgical or post-surgical environment, the greater the chance that a patient will be in the hospital longer, since [opioid] side effects are dose-dependent."

In other words, there's a real effort toward opioid sparing through multimodal therapy, where opioids are used in combination with other effective, safer analgesics. This, says Driscoll, plays very well for Javelin's portfolio of three late-stage product candidates, one of which was approved for sale in the UK last year.

### UK Approved

Dyloject, the UK-approved drug, is an improved version of diclofenac, a non-steroidal anti-inflammatory drug (NSAID) long marketed by Novartis as Voltaren (oral), or Voltarol (slow-infusion). By adding a specific cyclodextrin to its formulation, Javelin has succeeded in producing a more soluble drug that can be delivered as a bolus injection, providing rapid action with a better safety profile.

Currently, ketorolac – marketed as Toradol, by Roche – is the only approved injectable NSAID in the US. But traditional concerns with NSAIDs aside, this analgesic has had several black-box warnings slapped on it over the years, due to effects on bleeding, as well as cardiovascular and liver problems. It's also been forced off the market in Germany and France, for toxicity reasons. However, Toradol is still available in the US and widely used (35 million units/year). "It works," Driscoll says, "but it has safety issues. Physicians are also instructed not to use it prior to, or during, surgery, which reduces flexibility."

So Dyloject's benefits in this regard – when compared to ketorolac – are four-fold, according to Driscoll. Not only does diclofenac have the highest intrinsic efficacy among NSAIDs, its opioid-sparing capabilities are also clearer. And while the use of ketorolac (either IV or oral) is limited to five days due to toxicity concerns, Driscoll doesn't anticipate such restrictions for Dyloject, as it has produced no significant safety signal during its 10 months in the UK market. Physicians should thus find it easier to wean their patients off injectable Dyloject to an oral form of the drug.

As well, adds Rick Pierce, Javelin's vice-president of investor relations, Dyloject is neither COX1- nor COX2-preferential in its mode of action, and should have none of the bleeding side effects associated with COX1 inhibitors (like Toradol), or the cardiac implications of COX2 inhibitors (namely, Vioxx). "[Dyloject] fills a great void that was the result of the whole COX2 debacle," says Pierce.

### The Right Dose

Javelin's second non-opioid product is Ereska, an intranasal form of ketamine formulated with an additional preservative, and developed as a unique bi-spray device for single use, where a squirt up each nostril represents one dose of ketamine. As such, it can be delivered at one-tenth the usual dose of this anesthetic agent, providing immediate relief for acute pain in ER and trauma settings. Javelin has, in the past, received two Dept. of Defense grants for the development of intranasal ketamine, and Driscoll sees the US military as yet another market for this particular product.

"Opioids affect sympathetic tone – for instance, reducing blood pressure," Driscoll explains, "but ketamine [a glutamate (NMDA) receptor antagonist] has a different mechanism where neither ventilation nor cardiovascular function are affected. What the military found was that even after administering opioids to wounded soldiers out on the battlefield, they could still lose them before transferring them to the field hospital, due to dramatic decreases in blood pressure. So they're very interested in Ereska, which could be given directly to soldiers on the field, before stabilizing them with opioids."

Rylomine is Javelin's third product – another intranasal formulation, albeit of morphine, where chitosan has been added for better adherence to the nasal mucosa, allowing for improved absorption characteristics, says Pierce. But while Javelin is on pace to file two NDAs with the FDA – one for Dyloject, the other for Ereska – Rylomine has been assigned, at least temporarily, to the back burner. "We believe it will have good value in the market, but not as great commercial appeal as our other two products," Driscoll says.

In the meantime, Driscoll will concentrate on Javelin's scheduled NDA filings, and on acquiring broader European territory approvals for Dyloject. Engaging in "multiple robust commercial partnerships" is also another priority. "We're pretty close to out-licensing the commercial rights to Dyloject throughout Europe," Driscoll says, "and we're in advanced discussions with US partners interested in commercializing either Dyloject or Ereska; we'll then build our own commercial capability around the other product."

Does Javelin have plans for expanding its line of vision, or its target market? "I come from the world of 'never say never,'" Driscoll says, "but I'm also a big believer in focus. Today, our strength lies in pain compounds for acute care in the hospital setting, so I'd like to leverage that."

After all, promotional costs of any product tend to balloon exponentially with an increase in market size. And given the fierce competition that characterizes much of pharma and biotech, not to mention the woeful state of the economy these days, maintaining focus is probably wise. Watch this space as Javelin attempts to address the limitations of existing prescription pain medications in non-opioid fashion, skewering acute pain in the gut and turning this particular segment of health care on its head.