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Regulatory worries dampen enthusiasm for Map's Levadex deal

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If Map Pharmaceuticals' investors were looking for a big deal to signal validation of its Levadex anti-migraine therapy, and the inhalation technology that supports it, the co-promotion agreement with Allergan probably is not it. Shares have remained mostly flat since the deal was announced Monday, signalling that investors are not that impressed with a deal that pitches one of the biggest unpartnered late-stage assets only to neurologists and pain specialists (*Partnering opportunities abound in oncology, CNS and infectious diseases, October 21, 2010*).

The modest $60m upfront fee and failure so far to hook a partner with wider reach into the primary-care market likely signals a reluctance to take a chance with an inhalation product outside the respiratory space. If Levadex passes muster with the FDA, it would be the only major non-respiratory inhalation drug approved by the regulator; the Exubera debacle and recent struggles of MannKind's insulin Afrezza and Alexza Pharmaceuticals' anti-psychotic AZ-004 do not portend well (*Alexza investors right to be agitated over FDA rebuff, October 13, 2010*).

Partnering

For $60m upfront, Allergan agreed to a co-promotion deal that would see its representatives include Levadex in their kit bags during migraine-related sales calls to specialists for Botox. As a strategic proposition, it appears to make sense: Botox is indicated for prevention of chronic migraines, while Levadex, a reformulation of an old hospital injection drug, dihydroergotamine mesylate, is for acute treatment. It contains the same active ingredient as Migranal, a nasal spray marketed by Valeant Pharmaceuticals International.

Map is committing 50 sales representatives to the effort, at an estimated cost of $10-$12m a year for a company that so far has been developmental stage. For Allergan, it was not necessarily a difficult decision: it was sitting on $3.1bn in cash as of September 30, so $60m to secure a phase III product with estimated sales of $224m in 2016 may seem a reasonable bet.

The deal leaves the larger primary-care market, where 75-80% of migraine patients are treated, and global markets open to partnership deals. From Map's perspective, this gives Levadex potential to become the "pipeline in a product" that many drug developers dream of (*Stick to plan for FIPCO success, Ironwood says, October 11, 2010*).

But without a major dilutive fundraising, Map cannot hope to do the primary-care market on its own – analysts from Leerink Swann estimate such an effort would require 600 sales reps, a huge ask of a company with $41.8m cash on September 30. Map last raised money with a $47.1m share offering at the end of September.

Thus, another deal will almost certainly be necessary, and the Leerink Swann analysts reckon that would be more likely to be a straight royalty deal, rather than a co-promotion.

The look forward

In a call with investors, Map chief executive described partnership negotiations as "competitive" with strong interest in Levadex, but would not say when to expect any more deals. Filing Levadex with the regulators will come in the first half of 2011, which will trigger a portion of the $97m in regulatory milestones as part of the Allergan deal.

It is that regulatory review that probably has many investors and partners waiting on the sidelines. The FDA has been a friend in that it has required only a single phase III efficacy study with a long-term safety follow-up for Levadex (*FDA clears course for MAP, January 12, 2010*).

However, the inhalation delivery route is proving ever-tougher for products outside the respiratory space, as demonstrated by the complete lack of such products on the market today. The withdrawal of inhaled insulin Exubera was a key moment in the field, but regulators have even raised concerns about certain common

inhaled respiratory drugs (*New LABA warnings unlikely to make big players pause for breath, June 3, 2010*).

While the Exubera affair did not faze MannKind or its founder Alfred Mann, Afrezza has been stiff-armed twice by the regulator on bio-equivalence concerns, and the company has signalled it will continue trials in the hopes of getting it on the market someday (*Another major setback for MannKind's inhaled insulin, January 20, 2011*).

It is a luxury that only can be afforded by a company backed by a billionaire; Alexza lost a partner in Valeant when AZ-004 received a complete response letter.

Given that Map's platform rests on inhalational technology, there might be reasons to worry – although it does have a combined long-acting beta agonist/corticosteroid for chronic obstructive pulmonary disease on the shelf in the event the inhalational route is completely shut down for all non-respiratory products.

The omens suggest now is not a good time to be developing an inhalational product in any space but respiratory, explaining why a broader deal on Levadex was not in the offing. It could surprise on especially clean safety data and efficacy at least the equal of Migranal. But in the absence of a major safety U-turn on the part of the regulator, an unlikely scenario, the hurdles will be high.