New IGF drug stirs competition in growth factor segment

An important molecule for growth recently received approval in the US. This approval heralds the first medical application of insulin-like growth factor 1 (IGF-1) as a drug to promote growth in a rare group of very small children. But to be commercially successful, makers of IGF-1 will have to expand that market. That means either competing with growth hormone, an established drug for most short-stature children, or finding uses outside of the growth market. Either way, it's a tall order.

Robert Duyvskirt

The newly approved IGF-1 drug could help children of short stature get closer to the average height of their friends

Biotech companies have long been interested in IGF-1 because it is the principal mediator of both cartilage and bone growth in the body. Growth hormone signals the production of IGF-1 in the pituitary gland. A deficiency in IGF-1 results in impaired growth and is associated with metabolic abnormalities including insulin resistance, increased adiposity and delayed wound healing.

On August 31, the US Food and Drug Administration (FDA) approved Tercica's Increlex (mecasermin) recombinant human IGF-1 as a long-term treatment for children with severe primary IGF-1 deficiency (IGFD). S. San Francisco, California-based Tercica estimates the US patient population of such children at around 6,000. But for broad use as a short-stature drug, the burden of proof will be on the IGF-1 manufacturers to show the drug is as safe and effective as growth hormone. "It'll be an uphill battle," suggests Ron Rosenfeld of the Oregon Health and Science University in Portland, a physician who has worked with IGF-1 for 25 years. "Growth hormone has been available for 40 years, and hundreds of thousands of patients have been treated."

Tercica CEO John Scarlett believes the availability of IGF-1 could stimulate its broader development. "It could lead to a second wave of physiologic interest in the molecule," including other areas of growth and carbohydrate metabolism. "Some of the most interested parties are preclinical scientists who have received a shot in the arm knowing that with the approval, some of the roadblocks to the molecule have been cleared." Tercica expects to begin selling Increlex at the start of 2006.

By then, FDA will likely have decided the fate of a second IGF-1 drug candidate: Insmed's Somatokine, which is IGF-1 bound to IGF-1 binding protein 3 (IGF-1BP3). Insmed, located in Glen Allen, Virginia, is developing the combination product because in circulation, IGF-1 is bound to IGF-1BP3, buffering it. The firm believes Somatokine will therefore have a longer half-life and improved safety profile over IGF-1 alone.

In an unusual and apparently fruitless competitive tactic, Insmed recently filed a Citizen's Petition with FDA challenging the adequacy of the data Tercica had submitted for approval. That challenge has apparently been put to rest. "Our understanding is that it's been denied," Scarlett said on the analyst conference call discussing Increlex's approval.

But FDA still has to wrestle with potentially dueling Orphan Drug designations on IGF-1. Tercica received an Orphan Drug designation on Increlex for its now-approved use, whereas Insmed has Orphan Drug Status on Somatokine to treat growth hormone insensitivity syndrome (GHIS), which encompasses patients who aren't growing well on growth hormone, a considerably larger patient population than that for which Increlex is now approved. Indeed, Tercica itself estimates that 20,000 children in the US are GHIS.

Tercica expects clarification of the potentially competing Orphan drug claims by October 3, 2005—Insmed's Prescription Drug User Fee Act date, by which FDA has to take action on its application for marketing approval of Somatokine in GHIS. Although the FDA Orphan Products division has already said that the two compounds are similar, because Increlex is given twice a day and Somatokine may be given once a day, some FDA watchers believe their orphan claims could be differentiated on the basis of dosing frequency.

Irrespective of what happens with Somatokine, in terms of finally beginning to explore the potential for IGF-1 therapy, the Increlex approval can be seen as letting the camel's nose under the tent. "Think about almost any chronic disease—cystic fibrosis, rheumatoid disease, irritable bowel disease—in which a child is not growing," imagines Edward Reiter, professor at Tufts University's Baystate Medical Center in Springfield, Massachussetts. "There is the potential for that child to be relatively nonresponsive to growth hormone and possibly respond to an IGF-1 treatment modality. That's a huge universe of potential patients."

Indeed, IGF-1's history encompasses much more than its development in growth indications. But the previous hopes of companies for wider use of IGF-1 have been dashed. Genentech, for example, which licensed rights to IGF-1 to Tercica in 2002, tested it as a broad-based therapy for type 1 & 2 diabetes, reaching phase 3 studies in 1997 before halting the program over side effects, including diabetic retinopathy. Cephalon of West Chester, Pennsylvania, was the other major developer of IGF-1: it received an approvable letter from FDA in 1998 requesting additional study of its Myotrophin recombinant IGF-1 in amyotrophic lateral sclerosis (ALS), and stopped development of the drug in 2001. Pharmacia developed and received a few approvals for IGF-1 in Europe in the 1990s for GHIS, but never marketed the drug, and later licensed its GHIS-oriented regulatory files to Insmed.

Beyond GHIS, Insmed is currently testing Somatokine in diabetes types 1 & 2, as well as severe burn injury and hip fractures, all in phase 2. Tercica has initiated a phase 3b study in less severe IGFD patients, in hopes of expanding the Increlex label. It is downplaying the opportunities for development of Increlex in diabetes, however. "We're trying to identify people with abnormal levels of biological action of IGF-1," explains Scarlett, which, he says, could include diabetics who are also IGF-1 deficient and where IGF-1 replacement therapy "could make sense."

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