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Shire needs Firazyr to stand out in HAE crowd

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Hereditary angioedema (HAE) represents a tiny market of a few thousand patients, yet a remarkable five products have been developed to treat it in the last couple of years. Three have made it to the US market and only this week the fourth candidate, Shire's Firazyr, was re-filed with the FDA as the final contender's application, Pharming and Santarus' Rhucin, was rejected.

Despite the seemingly crowded space these companies clearly see commercial opportunity. But this is only going to get harder to capitalise on as competition heats up and patients become harder to find. Dyax's Kalbitor, the latest to launch in the US, has disappointed so far and Shire will have to work hard to carve its own space in the market - winning an important differentiator from the FDA will be crucial.

Differentiation needed

The products that have reached the market have been approved to treat different aspects of HAE – an inherited condition characterised by attacks of sometimes very dangerous swelling, which can occur in the abdomen, face and throat.

For example ViroPharma's Cinryze, an enzyme replacement therapy, is infused a couple of times a week to prevent attacks from happening. The others have been approved in an acute setting, subcutaneous injection Kalbitor to treat all attacks whereas CSL's Berinert, another infused product, is not indicated to treat the life-threatening laryngeal episodes.

Shire is seeking approval to treat all types of attacks but the key differentiator for Firazyr could be self-administration - another important advantage being it can be stored at room temperature.

The drug, a bradykinin inhibitor, was issued with a complete response letter a couple of years ago when it was being developed by Jerini. Shire acquired Jerini for $455m soon after and has now re-filed with data from another pivotal trial and evidence from a self-administration study.

European regulators gave a green light to self-administration in January, how that impacts uptake this year will be watched with interest. Should the FDA grant approval in self-administration straight off Shire will be handed a valuable advantage over rivals, although it remains to be seen if the cautious US regulator will be comfortable with this.

Competition

Should it reach the market the company's most direct competitor in terms of product offering will be Dyax with Kalbitor, the only other small molecule, subcutaneous therapy available (*Dyax finally wins US approval for HAE treatment Kalbitor, December 2, 2009*).

Sales of Kalbitor, which reached the market in February 2010, missed expectations by a couple of million dollars in the fourth quarter of last year, coming in at $3m, and the company issued much lower-than-expected guidance for this year.

Dyax now anticipates sales of $20-24m this year; consensus from *EvaluatePharma*compiled before that guidance was issued indicates on average analysts were expecting $35m.

Consensus is now likely to head south - Needham has already slashed forecasts in half for the next three years, and is now expecting sales of $21m this year rising to $62 by 2013. Peak US sales may reach $200m-$300m, the analysts believe.

The company believes sales could reach $110-$125m by 2016; a number which some believe is ambitious. Leerink Swann analysts reckon that would imply the recruitment of an additional 1,800-2,100 patients in the US, or 300-340 each year, to Dyax's access programme. Given the presence of two other products on the market and a third on the way, all fighting for an estimated 7,000-8,000 US patients, the goal does look optimistic.

Boxed warnings

Uptake was probably never going to be swift for Kalbitor, largely because of the risk evaluation and mitigation strategy (REMS) that has been implemented. Anaphylaxis was seen in clinical trials and the drug carries a boxed warning of the risk of these attacks. As a result the drug is highly unlikely to win approval for self administration as medical professionals need to be present when it is used.

But demand is growing: by the end of 2010 the company had 650 patients enrolled in its access programme, 342 of which had completed processing with the drug available at their designated treatment sites. This number expanded 50% on the end of September, an encouraging sign, analysts believe.

According to a survey conducted by Leerink Swann, HAE doctors are increasingly prescribing all three products. At the beginning of 2011, doctors treating around a third of the estimated 3,000 known US HAE patients had 324 patients on Cinryze, 262 patients on Kalbitor and 262 patients on Berinert.

ViroPharma's Cinryze, launched in 2009, generated $175m last year. CSL does not disclose figures for Berinert.

The launch of a self-administered therapy has the potential to significantly change the dynamics of the market, although Shire will face the disadvantage of being fourth to the US market. Sales forecasts below so far suggest analysts are cautiously optimistic, leaving a lot riding on the FDA's review of Firazyr, for Shire and the other contenders.

Hereditary Angioedema Candidates

						Annual Sales WW ($m			
	Product	**Company**	**Pharmacological Class**	**Key Markets**	**First Launch**	**2008**	**2010**	**2012**	**2014**
Marketed	Cinryze	ViroPharma	C1 esterase inhibitor	US	US - Jan 2009	-	175	328	434
	Firazyr	Shire	Bradykinin B2 antagonist	WW	EU - Sep 2008	1	11	56	117
	Kalbitor	Dyax	Kallikrein inhibitor	US	US - Feb 2010	-	9	62	91
	Ruconest	Swedish Orphan Biovitrum	C1 esterase inhibitor (recombinant)	EU	EU - Dec 2010	-	-	-	-
	Cetor	Sanquin Blood Supply Foundation	C1 esterase inhibitor	Certain EU	EU - 1997	-	-	-	-
	Rhucin	Pharming	C1 esterase inhibitor (recombinant)	Royalties	EU - Dec 2010	-	-	-	-
	Berinert P	CSL	C1 esterase inhibitor	WW	EU - <20 years US - May 2010	-	-	-	-
Filed	Rhucin	Santarus	C1 esterase inhibitor (recombinant)	US	-	-	-	-	20
	Kalbitor	Sigma-Tau Group	Kallikrein inhibitor	EU	-	-	-	-	-
					Total	1	195	446	662

Source: EvaluatePharma