

Therapeutic Focus - Thin Cushing pipeline loses lead candidate



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Novartis' announcement that it has withdrawn its application for Cushing's syndrome treatment SOM230 will be a disappointment to patients and specialists who treat this rare disease that causes weight gain, skin dysfunction and abnormal hair growth. With only one drug on the market, and only available in Japan, there was hope that as many as two new treatments might be on the market next year to combat the hormonal imbalances that cause Cushing's.

The FDA is due to decide on Corcept Therapeutics' Corlux by February 17, 2012, and if approved it will be the only treatment in the US specifically indicated for the endogenous form of the disease, in which a pituitary tumour leads to excess production of the steroid cortisol. Behind the Corcept and Novartis candidates is a thin pipeline, however, suggesting Corlux would have a significant lock on the market if the regulators give it a thumbs-up (see table).

Hormone imbalance

Cushing's syndrome has two principal causes - use of corticosteroids or malfunctioning endocrine glands. The iatrogenic form is usually treated by reducing dosages of corticosteroids, such as prednisone, which can be used to treat inflammatory or autoimmune conditions, or withdrawing them altogether.

However, treating the disease when it has endocrine origins is more complicated. A benign tumour in the pituitary causes the gland to pump out excess adrenocorticotropin hormone, which in turn stimulates the adrenal glands to release excess cortisol.

A response to stress, cortisol is important to controlling blood pressure, inflammatory response and other key metabolic functions. Too much of it, however, can lead to such symptoms as weight gain, thinning of the skin, excess hair growth, fatigue, and elevated blood pressure and blood sugar. Corcept says 20,000 Americans have it and 3,000 new cases are diagnosed each year.

Typical treatment protocols have included surgical removal and radiotherapeutic destruction of the tumour. However, in cases where those treatments are inappropriate or unsuccessful, few therapeutic options are available. For example, the antifungal Nizoral, which has been found to block cortisol production, and Metopirone, an inhibitor of cortisol used to test adrenocorticotropin hormone function, are used off-label.

Opeprim, launched in 1984, is marketed in Japan by Yakult Honsha to treat the disease. It, too, suppresses the production of cortisol by the adrenal glands.

New hope

Thus specialists and patients are putting some hope in Corlux, a repurposing of the pregnancy termination drug mifepristone. Rather than suppressing cortisol, it blocks the cortisol receptor, disrupting dysfunctional metabolic functions.

Although composition of matter patents have expired on the compound, the California company has licensed method of use patents in the Cushing's syndrome setting, and Corlux has also been granted an orphan drug designation.

In a sign that Corcept's intellectual property might not be strong enough to prevent others from launching similar products, France's HRA Pharma also is testing a mifepristone product called Mifedren. However, clinicaltrials.gov lists only one active trial of Mifedren, a National Institutes of Health-led study that began in 2006 and that is not expected to conclude until 2013.

Novartis' role

The other late-stage product is Novartis' SOM230, the US application for which the company said this week had

been withdrawn because of a chemistry, manufacturing and control issue, which also delayed its European application. Novartis plans to resubmit the US application and expects a European Union decision in 2012.

The Swiss group also has a long-acting formulation in phase III, which is a monthly treatment as compared to the twice daily treatment of the standard formulation.

Beyond that the pipeline is fairly dry. In phase II Novartis again has LCI699, which is in a 10-week safety study expected to conclude in early 2012.

Thus, whilst Cushing's syndrome patients may have as many as two new options in the near future, the pharma industry is not yet racing to fill this apparent void, as it has other orphan indications. The use of off-label generic drugs likely discourages new research and development investment. However, an opportunity awaits for a medication that could attack some of the underlying causes of the condition.

Cushing's syndrome pipeline						Annual Sales WW (\$m)		
	Product	Generic Name	Company	Pharmacological Class	Proprietary Level 2	2012	2014	2016
Filed	Corlux	mifepristone	Corcept Therapeutics	Selective glucocorticoid receptor (GR-II) antagonist	NDA (Patented Compound)	31	108	327
	SOM230	pasireotide	Novartis	Somatostatin analogue	New Derivative	67	178	235
Phase III	Mifedren	mifepristone	HRA Pharma	Glucocorticoid receptor antagonist	NDA + Proprietary Drug Delivery	-	-	-
	SOM230 LAR	pasireotide	Novartis	Somatostatin analogue	New Derivative	-	-	-
Phase II	LCI699	-	Novartis	Aldosterone synthase inhibitor	NME (Patented Compound)	-	-	-
					Total	97	348	726