

Therapeutic focus - COPD market looking for the daily dose



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Estimated to be worth \$9bn a year and growing fast, the COPD market is already well served by a number of big blockbuster drugs like GlaxoSmithKline's Advair and Boehringer Ingelheim's Spiriva. Longer acting and more potent than first generation products, these newer treatments have certainly improved the lives of sufferers through their greater efficacy and more convenient dosing schedules.

However there is still much room for improvement, and there are a huge amount of products in development seeking to both treat the symptoms of the disease, which is mainly brought on by smoking, and target the underlying mechanisms (see tables below). With a substantial licensing deal between Nycomed and Forest Laboratories over novel COPD treatment Daxas announced earlier this week and the approaching European Respiratory Society conference, which will yield interesting data on a number of promising new treatments, the field is likely to receive a fair amount of attention in the coming months.

Because most COPD drugs are also prescribed for asthma, and companies do not separate sales by indication, it is hard to gauge precise revenues generated in the area. The table below lists the top five products, including sales across all indications. With Boehringer Ingelheim's products Spiriva and Atrovent solely sold for COPD, an idea can be gained of how significant the field is.

COAD/COPD market (Including Aggregated Product Sales across ALL INDICATIONS)					Annual Sales WW		
Rank	Product	Company	Pharmacological Class	Indication Summary	2008	2010	2012
1	Seretide/Advair	GlaxoSmithKline	Beta 2 agonist & corticosteroid	Asthma [Marketed]; COAD/COPD [Marketed]	7,658	8,253	7,545
2	Spiriva	Boehringer Ingelheim	Muscarinic antagonist	COAD/COPD [Marketed]	3,042	3,741	4,693
3	Symbicort	AstraZeneca	Beta 2 agonist & corticosteroid	Asthma [Marketed]; COAD/COPD [Marketed]	2,004	2,544	2,456
4	Flixotide/Flovent	GlaxoSmithKline	Corticosteroid	Asthma [Marketed]; COAD/COPD [Marketed]	1,253	1,122	920
5	Foradil	Novartis/Chiesi/Schering-Plough/AstraZeneca	Beta 2 agonist	Asthma [Marketed]; COAD/COPD [Marketed]	689	638	622
6	Combivent	Boehringer Ingelheim	Muscarinic antagonist & beta 2 agonist	Bronchitis, chronic [Marketed]; COAD/COPD [Marketed]	813	711	669
7	Atrovent HFA	Boehringer Ingelheim	Muscarinic antagonist	COAD/COPD [Marketed]	428	440	487
8	Pulmicort	AstraZeneca	Corticosteroid	Asthma [Marketed]; Bronchitis, chronic [Marketed]; COAD/COPD [Marketed]	1,495	647	476
9	Serevent	GlaxoSmithKline	Beta 2 agonist	Asthma [Marketed]; COAD/COPD [Marketed]	487	355	281
10	Proventil	Schering-Plough	Beta 2 agonist	COAD/COPD [Marketed]	190	188	187

COPD patients are gradually given more treatments as their disease progresses; severely ill people can be on several different products. Short-acting bronchodilators are used first as a monotherapy, although are gradually being taken over by the more convenient longer acting agents (LABAs) such as Novartis' Foradil and Glaxo's Serevent or long-acting muscarinic antagonists (LAMAs) such as Boehringer's Spiriva. Inhaled corticosteroids (ICS) are added when symptoms worsen and exacerbations, or attacks, occur. This is when combination products like Glaxo's Advair and more recently Astra's Symbicort are used.

As well as a rising incidence of the disease the introduction of products that have to be used less frequently - Advair is twice daily and Spiriva only once daily, compared with four times daily for Atrovent - has contributed to growth in the market, and this trend is seen continuing. With the short acting bronchodilators coming or already at the end of their patented lives, and the longer acting agents not having long before generics can enter, new products will have to show better efficacy and convenience to compete.

Nearest the market

The two products awaiting news on regulatory approval appear to fit that bill.

Most novel is Nycomed's Daxas, which would be the first oral treatment for the disease. A phosphodiesterase 4 (PDE4) enzyme inhibitor, Daxas acts on the underlying mechanism of the disease and would probably be used alongside inhaled products that help lessen symptoms. With regulatory filings complete and Forest signed up as US marketing partner, the next key event for Daxas is the release of full data from the pivotal trial programme on September 12, at the European Respiratory Society meeting ([*Forest takes another punt on COPD with Nycomed's Daxas, August 10, 2009*](#)).

The other product that has been submitted for approval is Novartis' indacaterol, the most advanced once-daily LABA. It was filed in the US and EU at the end of 2008 on the back of impressive phase III data, which demonstrated a long lasting improvement in lung function and five-minute onset of action.

COAD/COPD late-stage pipeline

	Product	Generic Name	Pharmacological Class	Indication Summary	Company
Filed	Indacaterol (QAB149)	indacaterol	Beta 2 agonist	COAD/COPD [Filed]; Asthma [Phase III]	Novartis
	Daxas	roflumilast	Phosphodiesterase IV inhibitor	COAD/COPD [Filed]; Asthma [Phase III]	Nycomed
Phase III	Avamys/Veramyst	fluticasone furoate	Corticosteroid	Rhinitis, seasonal allergic/Hay fever [Marketed]; Asthma [Phase III]; COAD/COPD [Phase III]	GlaxoSmithKline
	Flutiform	formoterol & fluticasone propionate	Beta 2 agonist & corticosteroid	Asthma [Filed]; COAD/COPD [Phase III]	Abbott Laboratories/Purdue Pharma/SkyePharma
	MFF258	formoterol & mometasone furoate	Beta 2 agonist & corticosteroid	Asthma [Phase III]; COAD/COPD [Phase III]	Schering-Plough
	LAS 34273	aclidinium	Muscarinic M3 antagonist	Bronchitis, chronic [Phase III]; COAD/COPD [Phase III]; Asthma [Phase II]	Forest Laboratories/Laboratorios Almirall
	NVA237	glycopyrrolate	Muscarinic antagonist	COAD/COPD [Phase III]	Novartis/Vectura/Sosei
	Zyflo CR	zileuton	5-lipoxygenase inhibitor	Asthma [Marketed]; COAD/COPD [Phase III]	Cornerstone Therapeutics/Mylan
	CHF 5188	carmoterol & budesonide	Beta 2 agonist & corticosteroid	Asthma [Phase III]; COAD/COPD [Phase III]	Chiesi/Mitsubishi Tanabe Pharma
	Foster	formoterol & beclomethasone dipropionate	Beta 2 agonist & corticosteroid	Asthma [Marketed]; COAD/COPD [Phase III]	Chiesi
	BI 1744	-	Beta agonist	COAD/COPD [Phase III]	Boehringer Ingelheim

Indacaterol largely forms the backbone of Novartis' move into the respiratory world, where the Swiss pharma

giant has been investing a huge amount into building a franchise, both branded and generic. As well as novel compounds, the group's Sandoz division is thought to be working on the most advanced generic versions of Advair and Symbicort.

Combination potential

Whilst indacaterol has the potential to be a big product on its own, a number of combinations are also in development. One is with NVA237, a new once-a-day LAMA, the same class as Spiriva.

Phase II results laid out the hopes for NVA237 as a similarly efficacious treatment to Spiriva, but with fewer side effects, principally dry mouth, and possibly faster onset of action. Confirmatory phase III studies started a couple of months ago, and Novartis has guided to regulatory filings in the US and EU in 2011.

The combination of NVA237 and indacaterol, referred to as QVA149, is a product with considerable potential in terms of potency and convenient once-daily dosing. If successful, it would be the first combination of a LABA and LAMA on the market.

Important phase II data from QVA149 is due to be announced at the European Respiratory Society meeting in September and will be watched with interest, particularly by followers of the smaller partner involved in the product, Vectura. Phase III trials are pencilled in to start in the final quarter of this year, which would trigger a \$7.5m milestone for the British respiratory specialist. Hopes are high for the product, and analysts believe it has blockbuster potential. Citi estimates peak sales of \$1.28bn, with the product capturing 6% of the global COPD market.

Whilst QVA149 would probably target patients that do not respond to monotherapies like Spiriva or indacaterol, another potential combination, indacaterol with the ICS mometasone, would be used in more severe cases. That product, called QMF149, is also in phase II trials.

Boehringer Ingelheim is of course working to protect its valuable Spiriva franchise, beyond the drug's patent expiry in 2015. Phase III trials of a new beta agonist BI 1744 have recently commenced, whilst a pivotal trial of the product in combination with Spiriva is expected to start this year. This could well be equally or more effective as indacaterol, but the private company has released little information on the product to date.

The phase II pipeline is expansive, and incorporates many more drugs that attempt to act on the underlying disease mechanisms, such as Novartis' antibody approach Ilaris and Osiris with a stem cell approach, Prochymal. However, there are also many new LABAs and LAMAs, which will need to demonstrate huge improvements in efficacy and safety to compete.

By the time they reach the market, the more advanced once-daily treatments should already have made it, as well as a swathe of generics. How the COPD market evolves with the release of these more potent agents remains to be seen. However one thing that seems likely is that differentiation will, like in many crowded markets, be crucial.

Efforts to establish a survival benefit, like Glaxo tried a few years ago with Advair in the large Torch trial, and only narrowly failing, might be needed. The first drug to demonstrate this would be in a very strong position.

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