

## RESPIRATORY AND INFLAMMATION (R&I) MEDICINES

### MARKETED PRODUCTS

**Symbicort Turbuhaler** (budesonide/formoterol in a dry powder inhaler) is a combination of an inhaled corticosteroid and a fast onset, long-acting bronchodilator for the treatment of asthma and COPD. *Symbicort Turbuhaler* is also available as *Symbicort SMART*.

**Symbicort pMDI** (budesonide/formoterol in a pressurised metered-dose inhaler) for the treatment of asthma.

**Pulmicort** (budesonide) is a corticosteroid anti-inflammatory inhalation drug that helps prevent symptoms and improves the control of asthma.

**Pulmicort Respules** (budesonide inhalation suspension) is the first and only nebulised corticosteroid in the US for the treatment of asthma in children as young as 12 months.

**Rhinocort** (budesonide) is a nasal steroid treatment for allergic rhinitis (hay fever), perennial rhinitis and nasal polyps.

**Oxis** (formoterol) is a fast onset, long-acting beta-agonist therapy for treating asthma and COPD.

**Accolate** (zafirlukast) is an oral leukotriene receptor antagonist for the treatment of asthma.

### 2007 IN BRIEF

- > **Symbicort sales of \$1.6 billion, up 22%.**
- > **Symbicort pMDI for long-term maintenance treatment of asthma launched in the US to specialists and primary care physicians.**
- > **Outside the US, Symbicort SMART now launched in over 40 countries.**
- > **Pulmicort continued to grow with sales of over \$1 billion, up 10%.**
- > **Acquisition of MedImmune strengthened the R&I portfolio.**
- > **Acquisition of Verus Pharmaceuticals' paediatric asthma business in North America.**
- > **European Patent Office revoked the European combination patent for Symbicort for use in asthma. Other patent property and data exclusivity for Symbicort not affected by the decision.**

### PERFORMANCE

	2007			2006			2005	2007 compared to 2006		2006 compared to 2005	
	Sales \$m	Growth underlying \$m	exchange effects \$m	Sales \$m	Growth underlying \$m	exchange effects \$m		Growth underlying %	Growth reported %	Growth underlying %	Growth reported %
<i>Symbicort</i>	1,575	265	126	1,184	182	(4)	1,006	22	33	18	18
<i>Pulmicort</i>	1,454	128	34	1,292	132	(2)	1,162	10	13	11	11
<i>Rhinocort</i>	354	(16)	10	360	(27)	-	387	(4)	(2)	(7)	(7)
<i>Oxis</i>	86	(9)	7	88	(3)	-	91	(10)	(2)	(3)	(3)
<i>Accolate</i>	76	(6)	1	81	9	-	72	(7)	(6)	13	13
Other	166	7	13	146	(9)	-	155	5	14	(6)	(6)
<b>Total</b>	<b>3,711</b>	<b>369</b>	<b>191</b>	<b>3,151</b>	<b>284</b>	<b>(6)</b>	<b>2,873</b>	<b>12</b>	<b>18</b>	<b>10</b>	<b>10</b>

### PIPELINE

Compound	Mechanism	Areas under investigation	Phase			Estimated filing date		
			I	II	III	Europe	US	
<b>NCEs</b>								
AZD9056	ion channel blocker (P2X7)	rheumatoid arthritis	■	■			2012	2012
AZD1981	prostaglandin receptor antagonist	asthma	■	■				
AZD5672	chemokine antagonist (CCR5)	rheumatoid arthritis	■	■			2012	2012
MEDI-528	anti-IL-9 antibody	asthma	■	■				
AZD4818	CCR1 antagonist	COPD	■					
CAT-354	anti-IL-13 antibody	asthma	■					
AZD5904	MPO inhibitor	COPD	■					
AZD1744	dual CCR3/H1 receptor antagonist	COPD	■					
AZD1236	matrix metalloproteinase inhibition	COPD	■					
AZD9668	neutrophil elastase inhibitor	COPD	■					
MEDI-563	anti-IL-5R antibody	asthma	■					
MEDI-545	anti-IFN $\alpha$ antibody	SLE, myositis	■					
Pneumococcal vaccine <sup>1</sup>	pneumococcal vaccine	streptococcus pneumoniae	■					
AZD3199	iLABA	asthma/COPD	■					
CAM-3001	anti-GM-CSFR antibody	rheumatoid arthritis	■					
<b>Line extensions</b>								
<i>Symbicort pMDI</i>	inhaled steroid/fast onset, long-acting $\beta_2$ agonist	asthma	■	■	■		Filed <sup>2</sup>	Launched <sup>3</sup>
<i>Symbicort pMDI</i>	inhaled steroid/fast onset, long-acting $\beta_2$ agonist	COPD	■	■	■		Filed <sup>2</sup>	2Q 2008

<sup>1</sup> Partnered product.

<sup>2</sup> To be supplemented in 2008 with data supporting two additional strengths.

<sup>3</sup> US approval based on 12 years and above.

For discontinued projects see page 30.

## WE AIM TO BUILD ON OUR STRONG POSITION IN ASTHMA TREATMENT THROUGH THE GROWTH OF KEY PRODUCTS, PARTICULARLY *SYMBICORT*, NEW INDICATIONS AND MARKET LAUNCHES AND THE SUCCESSFUL INTRODUCTION OF NOVEL APPROACHES TO OTHER AREAS OF INFLAMMATORY DISEASE SUCH AS SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) AND RHEUMATOLOGY.

### PRODUCTS

*Symbicort Turbuhaler* provides rapid, effective control of asthma and effective reduction of exacerbations, improving symptoms and providing a clinically important improvement in the health of patients with severe COPD.

*Symbicort pMDI*, approved for the long-term maintenance treatment of asthma in patients 12 years of age and older, was launched in the US in June 2007 to specialists and in July 2007 to primary care physicians. There has been a good uptake of *Symbicort* in the US, most notably with specialist asthma physicians. Further information about the progress of *Symbicort* since its launch in the US is set out on page 69 (Geographical Review).

In October 2007, the US Food and Drug Administration (FDA) approved the actuation counter for the *pMDI* and plans are in place for launch in the US in the second half of 2008. The paediatric and COPD trials for *Symbicort pMDI* are on track to support the US supplementary new drug applications planned in the second quarter of 2008.

Outside the US, *Symbicort* for the treatment of asthma is marketed in the *Turbuhaler* dry powder inhaler and is approved in over 100 countries and launched in more than 70. *Symbicort Turbuhaler* is also approved in many countries for use in patients with severe COPD, where trial data in two pivotal studies have shown that it reduces exacerbation rates compared to a long-acting bronchodilator alone, and rapidly improves symptoms compared to its mono-components and placebo, providing clinically important improvement in health status.

Following its approval in October 2006, *Symbicort SMART*, a new approach to managing adult asthma, has been launched in over 40 countries. This treatment concept represents a change from current medical practice. *Symbicort* contains formoterol, a bronchodilator which is both rapid-acting and long-lasting, coupled with the corticosteroid budesonide, to provide an important anti-inflammatory effect. This approach

provides increased asthma control and simplifies asthma management because patients only need one inhaler for both maintenance and relief of asthma symptoms. The *Symbicort SMART* approach is also a cost-effective treatment option for many healthcare payers. At the end of 2006, *Symbicort SMART* was endorsed by the Global Initiative for Asthma.

The COMPASS and AHEAD studies, the results of which were published in 2007 and involved over 3,000 and 2,000 patients respectively, along with the COMPASS health economic analysis paper, confirmed that the *Symbicort SMART* treatment concept is more clinically effective, and more cost-effective compared with the best treatment approach provided by salmeterol/fluticasone (Seretide™) at any dose plus 'as needed' short-acting reliever therapy.

In October 2007, following an appeal by a group of generic manufacturers, the European Patent Office (EPO) Technical Board of Appeal revoked the European combination patent for *Symbicort* for use in asthma. The EPO decision is not expected to have an immediate impact in the EU or any impact on the US and Japanese patents. *Symbicort* has data exclusivity until at least August 2010 in most major European markets, which means that generics are unlikely to enter the market until some time after this date. In addition, the *Turbuhaler* device, preferred by many prescribers and patients, has multi-component patent protection until 2019. In the EU, *Symbicort Turbuhaler* is also protected by two COPD use patents (under appeal and opposition, respectively), which expire in 2018 and an 'as needed' (*Symbicort SMART*) use patent, which expires in 2019.

*Pulmicort* remains one of the world's leading asthma medicines and is available in several forms, including the *Turbuhaler* dry powder inhaler, a pressurised metered dose inhaler and *Pulmicort Respules* suspension for the treatment of children and infants 12 months and older. In the US, the *Pulmicort Turbuhaler* has been technically modified to improve

dosing properties (especially dose uniformity) and to introduce an enhanced dose indicator. The enhanced version was launched as *Pulmicort Flexhaler* in April 2007. European approvals for the more environmentally friendly HFA-based *Pulmicort pMDI* were extended in 2007 to cover additional countries, including Spain. *Pulmicort Respules* is the first and only nebulised corticosteroid in the US for children as young as 12 months. Sales have grown strongly as a result of high medical need in the age group combined with the product's beneficial profile, which together have strengthened the product's position as the inhaled corticosteroid of choice for the treatment of children under five with asthma.

Information about our continuing patent infringement action against IVAX in the US, which began in October 2005, in relation to IVAX's abbreviated new drug application (ANDA) for a budesonide inhalation suspension is set out in Note 27 to the Financial Statements on page 158.

*Oxis* is a formoterol beta-agonist therapy with a fast onset and long-acting clinical effect for the relief of asthma symptoms. *Oxis* is added to the treatment regime when corticosteroid treatment alone is not adequate. *Oxis* is also indicated for symptom relief in COPD.

*Rhinocort* is a treatment for allergic rhinitis (hay fever). It combines powerful efficacy with rapid onset of action and minimal side effects and is available as a once-daily treatment in the *Rhinocort Aqua* (nasal spray) and the *Turbuhaler* dry powder inhaler forms.

In September 2007, we received a letter from Apotex Inc. stating that Apotex had submitted an ANDA for a budesonide nasal spray (32 mcg spray) and that it intended to engage in the commercial manufacture, use and sale of a generic version of *Rhinocort Aqua* budesonide nasal spray before the expiration of our US FDA Orange Book patents covering *Rhinocort Aqua*. After investigating the allegations in Apotex's letter, we decided not to file a patent infringement suit against Apotex. We will not maintain or enforce the patents referred to in the letter and have requested their de-listing from the US FDA Orange Book.

### PIPELINE

Our pipeline includes life cycle management initiatives for the approved products mentioned above, as well as development compounds across the whole discovery and development spectrum. We focus on developing new therapies for currently unmet medical needs in COPD, asthma and rheumatology.

The development of *Symbicort pMDI* for COPD and paediatric asthma in the US is on track, with regulatory submissions for both indications scheduled for the second quarter of 2008. Our existing regulatory filings for *Symbicort pMDI* in the EU for asthma and COPD are scheduled to be supplemented with data supporting two additional strengths in the second half of 2008.

A regulatory submission in Japan for *Symbicort* for the treatment of asthma in adults and adolescents (from 16 years and above) was filed in May 2007.

Our three-year partnership with Dynavax Technologies Corporation, which began in 2006, continues to pursue opportunities in the field of toll-like receptor 9 (TLR 9) for use in asthma and COPD. Dynavax has unique competence in generating immunostimulatory DNA sequences that activate TLR 9. The alliance should enable us to expand our portfolio of small molecule and biological drugs to treat asthma and COPD.

In February 2007, we announced a major discovery alliance with Argenta Discovery Limited aimed at identifying improved bronchodilators to treat COPD. A team of scientists from each company will collaborate in order to identify long-acting muscarinic antagonist (LAMA) and dual-acting muscarinic antagonist- $\beta_2$  agonist (MABA) candidate drugs.

In May 2007, we agreed to acquire the paediatric asthma business of Verus Pharmaceuticals, Inc., which includes the North American rights to CyDex Captisol™ enabled budesonide solution and a proprietary albuterol formulation. This deal also includes the North American rights to the agreement Verus Pharmaceuticals has with PARI, the German medical device company that makes eFlow™, a novel nebuliser. The transaction will potentially allow us to provide patients and carers with new products that may be administered with a smaller, more portable nebuliser that could administer the medicine in less time than the current therapy, thereby improving treatment adherence in paediatric asthma patients.

In July 2007, we established an R&D collaboration with Silence Therapeutics plc, primarily in the respiratory field. The three-year collaboration is intended to discover and develop proprietary siRNA molecules against up to five specific targets provided by AstraZeneca. Silence Therapeutics and AstraZeneca will jointly collaborate in the early phase of identification and optimisation of novel siRNA molecules. We will retain full responsibility for clinical development and commercialisation.

Our early R&I small molecule pipeline includes novel compounds that target high unmet medical needs with a focus on COPD, but also asthma and musculoskeletal diseases. Compounds are in development for both oral administration and inhalation.

#### MedImmune

Multiple programmes are being pursued by MedImmune to develop targeted treatments for a variety of R&I diseases. An important area of focus is the potential control of asthma symptoms. MedImmune programmes targeting asthma include a phase II trial studying CAT-354, a fully human monoclonal antibody (MAb) targeting interleukin-13 (IL-13) in patients with severe asthma, continuing trials studying MAbs targeting the interleukin-5 receptor (IL-5R) (MEDI-563) and interleukin-9 (IL-9) (MEDI-528), in phase I and II respectively; and an early-stage clinical trial being led by researchers at Yale University studying the role of a chitinase-like protein (YKL-40) as a potential new biomarker for determining asthma severity, and its role in the pathobiology of the disease.

MedImmune is also carrying out a phase I study assessing the safety and efficacy of an anti-interferon-alpha treatment (MEDI-545), which has shown consistent evidence of clinical activity across multiple measures of disease in patients with mild-to-moderate systemic lupus erythematosus.

The first phase I study of CAM-3001 has been initiated to evaluate the safety and tolerability of single doses in patients with rheumatoid arthritis. CAM-3001 is a MAb targeting the alpha sub-unit of the granulocyte-macrophage colony stimulating factor receptor (GM-CSFR). The phase I study is the first clinical trial in which a MAb targeting GM-CSFR is being investigated in this population. During 2007, MedImmune acquired exclusive development rights to the CAM-3001 programme from CSL Limited.

#### PERFORMANCE 2007

##### Reported performance

Continued growth from *Symbicort* drove the increase in reported sales for Respiratory and Inflammation, which grew by 18% from \$3,151 million in 2006 to \$3,711 million in 2007.

##### Underlying performance

On a constant exchange rate basis, sales in Respiratory and Inflammation increased by 12%.

*Symbicort* sales for the full year were up 22% to \$1,575 million. Sales in Western Europe were up 16%, with market share up another point in the last 12 months, aided by the

rollout of the *Symbicort SMART* regime and growth from use in COPD. Good growth for the year was achieved in Canada (up 25%) and in Emerging Markets (up 26%). Sales in the US were \$50 million since launch at the end of June 2007. Specialist physicians have rapidly adopted the product; nearly 75% of allergists and more than 60% of pulmonary specialists in our target audience have prescribed *Symbicort*. Share of new prescriptions for fixed combination products was 5.8% in the week ending 18 January 2008; market share of patients newly starting combination therapy is over 11.5%.

*Pulmicort* sales increased by 10% to \$1,454 million. US sales increased 15% for the full year to \$964 million. *Pulmicort Respules* sales in the US were up by more than 20% for the full year, on estimated volume growth of 15%. Of the approximately six million children under the age of eight who are treated for asthma, more than one million benefit from treatment with *Pulmicort Respules*. Sales in other markets were unchanged for the year.

*Rhinocort* sales fell by 4% to \$354 million, with a 9% decline in the US being compensated by small gains elsewhere.

#### PERFORMANCE 2006

##### Reported performance

Sales in the R&I therapeutic area grew by 10% from \$2,873 million in 2005 to \$3,151 million in 2006. *Pulmicort* and *Symbicort* were the major contributors to this growth.

##### Underlying performance

On a constant exchange rate basis, sales in R&I increased by 10%.

Sales of *Symbicort* increased by 18% to \$1,184 million on continued market growth and share gains in Europe, where sales were \$1,018 million. Sales in other markets reached \$166 million.

Worldwide sales of *Pulmicort* were up 11% to \$1,292 million. Once again, the primary driver for growth was *Pulmicort Respules* in the US, where sales were up 24%. Volume growth in the US was approximately 10%, with price changes, managed care rebate adjustments and inventory movements also contributing to the sales growth. *Pulmicort* sales in the rest of the world were \$457 million.

*Rhinocort* sales were down 7% to \$360 million, chiefly on sales of *Rhinocort Aqua* in the US market (down 9%).