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COMMERCIAL SERIES

Pipeline and Commercial Insight: Allergic Rhinitis

Immunotherapy growth surpassed by generic erosion

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OVERVIEW

Catalyst

Key patent expiries are forecast to shrink the allergic rhinitis market over the next ten years. The only class forecast to grow is immunotherapy. With significant change seen in clinical development, immunotherapy is attracting increasing attention, and is the center of innovation in allergic rhinitis.

Summary

- Datamonitor estimates that the allergic rhinitis market reached $5 billion in the seven major markets in 2009, and forecasts that it will drop to $4 billion by 2019, with patent expiries having the greatest impact on the market;
- The role of immunotherapy in allergic rhinitis is increasing as new regulations drive development. With numerous products in the pipeline the immunotherapy market is set to experience significant growth, and Datamonitor forecasts two key late-stage sublingual immunotherapy tablets;
- Datamonitor identified two nasal antihistamine/corticosteroid combinations in late-stage development for allergic rhinitis, the first of which, Meda Pharma's azelastine/fluticasone, is forecast to reach the US market in 2012 and the EU in 2013, introducing a new treatment option for severe patients;
- Coverage: Seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK).

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Datamonitor Healthcare provides a total business solution to the pharmaceutical and healthcare industries. Its services reflect its expertise in therapeutic, strategic and eHealth market analysis and competitive intelligence. For more details of Datamonitor Healthcare's syndicated and customized products and services, please refer to the Appendix or contact:

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About the Immunology & Inflammation pharmaceutical analysis team

Datamonitor's therapeutic area studies comprise the following features:

- clinical opinion leader intelligence and best-in-class case studies, leading to actionable recommendations;
- R&D pipeline and unmet need analysis;
- scenario-based revenue and epidemiology forecasting;
- a slide pack and a data pack.

The Immunology & Inflammation team is headed by Clare Davies (MEng). Clare has experience in the field of market research in a range of autoimmune and inflammatory disease areas, and holds a Masters degree in Biochemical Engineering from University College London. Clare can be contacted on +44 (0)20 7551 9023 and at cdavies@datamonitor.com.

EXECUTIVE SUMMARY

Strategic scoping and focus

The allergic rhinitis market is well established, but remains dynamic with significant changes forecast over the next ten years. Patent expiries will have the greatest impact on market size, with different drug classes expected to experience differing levels of generic erosion. Datamonitor provides a discussion of the commercial opportunity that remains in this market, and analyzes life cycle management strategies that have been utilized by key companies. Trending forward current sales and accounting for events that will impact the market, Datamonitor provides a 10-year forecast of key classes and brands in the allergic rhinitis market, split by specific indication use estimates.

With changing regulations there is a strong focus on immunotherapy in the allergic rhinitis market, and this niche market is explored extensively within this report. A patient based analysis is used to forecast three novel immunotherapy products, with patient potential determined on the basis of epidemiology, discussion with key opinion leaders, and analysis of the market.

The total allergic rhinitis market is estimated at $5 billion in 2009 in the seven major markets (US, Japan, France, Italy, Spain, and the UK). Datamonitor calculates that allergic rhinitis accounted for an average of 37% of the total sales of drugs in the classes analyzed, which reached $13.5 billion in the same year for all their respective indications.

Datamonitor insight into the allergic rhinitis market

In the course of its research and analysis for *Pipeline and Commercial and Insight: Allergic Rhinitis*, Datamonitor identified the following key conclusions:

- **Generic erosion to change the market over the next ten years** - Datamonitor estimates allergic rhinitis sales in the seven major markets at $5 billion in 2009. This is estimated to drop to $4 billion in 2019, driven by the entrance of cheap generics following patent expiries, most notably in the US. Datamonitor has observed a high level of generic erosion of oral antihistamines, compared to nasal corticosteroids, and forecast future patent expires based on these analogues. This trend is attributed to the device used with nasal corticosteroids, which holds a separate patent and can create brand loyalty.
- **Unmet needs in a small subset of patients are driving development -** allergic rhinitis is well treated in the majority of patients and unmet needs remain minimal, but subsets of patients with severe uncontrolled disease do require alternative treatment options. Datamonitor's analysis of the pipeline for allergic rhinitis revealed that Phase III drug candidates consist of immunotherapies, and a nasal antihistamine/nasal corticosteroid combination. Both of these classes aim to offer an improved treatment option for patients poorly controlled on symptomatic treatments, such that unmet needs appear to be driving development.

- **Life cycle management strategies involve franchise expansion -** in the antihistamine class, a prominent life cycle management strategy that has been observed for key brands is the reformulation of molecules and/or combinations with decongestants. This strategy helps to maintain sales and strengthen brand recognition following patent expiry of the primary molecule. However, its success relies heavily on timing of new launches relative to generic entry. Merck's Clarinex (desloratadine) suffered as a result of launching after its predecessor Claritin's (loratadine) patent expired, which was demonstrated by it reaching only a quarter of Claritin's peak sales in 2009. Meda Pharma, on the other hand, has seen successful patient switching from once to twice-daily azelastine having launched prior to patent expiry, and is developing an azelastine/fluticasone combination that is expected to further strengthen its franchise.
- **The changing market for immunotherapy will create growth -** changing regulations and increasing guidelines for immunotherapy are driving development in that class, with the first large-scale development programs seen in recent years. Immunotherapy is becoming an evidence based pharmaceutical class, having previously been given on a named patient basis with little regulation. Immunotherapy is expected to remain a niche market with cost being the greatest constraint, but innovation is expected to create significant growth. Two sublingual grass tablets, Grazax (ALK-Abelló) and Oralair (Stallergènes) are forecast to have sales of $264m in the US and five major EU markets by 2019.

The basis for these conclusions, along with supporting data is provided in the accompanying PowerPoint presentation. Forecasts for the seven major markets are provided in the accompanying Excel file of this document.

N.B. This report is produced in three parts:

- **Word document:** contains key conclusions and a summary of the current market and future opportunities and threats, outlines the assumptions and events utilized in forecasting the market assesses strategic case studies to provide insight into potential market strategies;
- **Excel document**: contains forecasts on a country-by-country basis for the seven major markets. Volume and value forecasts are presented in this file for each of the following levels: country/region, class, molecule and product;
- **PowerPoint executive presentation:** shares Datamonitor's key insight into the market with supporting data and recommendations.

Related reports

Datamonitor (2009) *Pipeline Insight: Asthma & COPD – Simplified treatments to split the market,* December 2009, DMHC2569

Datamonitor (2009) *Commercial Insight: Asthma & COPD – On the verge of generic entry,* June 2009, DMHC2520

Upcoming related reports

Datamonitor (2010) *Forecast Insight: Asthma & COPD,* September 2010, DMHC2658

Datamonitor (2010) *Stakeholder Insight: COPD in Emerging Markets*, November 2010, DMHC2633

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1. PATIENT AND MARKET OVERVIEW

Key findings

- Datamonitor estimates that there are approximately 181m people living with allergic rhinitis in the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK). This is based on self-reported questionnaires, such that this is a maximum estimate including both diagnosed and undiagnosed disease. These patients can be segmented by severity, with approximately 81% having either moderate/severe intermittent or moderate/severe persistent allergic rhinitis.
- Key drug classes used to treat allergic rhinitis are estimated to have been worth a total of $13.5 billion in 2009 in the seven major markets. Using IMS Prescribing Insights data to split individual products by indication, Datamonitor estimates that 37% of this, roughly $5 billion, was attributed to allergic rhinitis specifically.
- While the volume of drug sales is seen to be increasing slightly by an estimated CAGR of 0.5% from 2009-2019, value is decreasing, owing to increased generic erosion. This is expected to continue over the next ten years, with the expiries of key patents.
- Opportunities and threats in the allergic rhinitis market have been identified across the seven major markets. A key opportunity is the shift to over-the-counter status. The potential for this is greatest in the US and EU, although new regulations are increasing opportunity in Japan as well. The greatest threat to the market is generic erosion. While this will have the greatest impact in the US, increasing focus on cost containment in the EU and Japan is expected to impact generic uptake.
- While generally considered well treated, some unmet needs remain in allergic rhinitis. A subset of patients, estimated to represent 15-20% of the patient population, continue to suffer symptoms despite the use of symptomatic treatments. Furthermore, compliance remains a key issue in treating the disease.
- Clinical trial design in allergic rhinitis has seen a shift in recent years. While traditional symptom scores continue to be widely used as primary endpoints, a new approach, which adjusts symptom scores for the use of rescue medication, is gaining popularity. This approach has been most widely used in the recent development of immunotherapy, and was first advocated in the European Medicine Agency's (EMA) guidelines on the clinical development of products for specific immunotherapy for the treatment of allergic diseases (EMA, 2008; http://www.ema.europa.eu).

Market definition for this report

The market analysis and forecasts in this report uses both IMS Health data and patient-based forecasts to size the market. The following Anatomical Therapeutic Classification (ATC) drug classes are used to define the current allergic rhinitis market:

- R1A1: nasal corticosteroids;
- R1A6: nasal anti-allergic agents;
- R1A7: nasal decongestants;
- R1B0: systemic nasal preparations;
- R6A0: systemic antihistamines;
- R3J2: antileukotrienes;
- V1A0: allergens.

For the purposes of this report, Datamonitor has split sales by indication using IMS Prescribing Insights data, and we have defined allergic rhinitis as comprising the following International Classification of Diseases, version 10 (ICD-10) diagnoses:

- J301: allergic rhinitis – pollen;
- J302: other seasonal allergic rhinitis;
- J303: other allergic rhinitis;
- J304: allergic rhinitis unspecified;
- J310: chronic allergic rhinitis.

Throughout this report, the term 'seven major markets' (or 7MM) refers to the major pharmaceutical markets, comprising the US, Japan, France, Germany, Italy, Spain and the UK.

For a detailed methodology regarding market definition, please see the section entitled Data definitions, limitations and assumptions in Appendix A.

Sales split by indication

For this report Datamonitor analyzed sales of key classes and brands in allergic rhinitis by considering total sales, and our estimate of sales by indication. To do so, data from MIDAS Prescribing Insights was utilized, applying the percentage of sales prescribed for each indication. MIDAS Prescribing Insights data is collected from physician diary information. Differing numbers of specialists are sampled in each country, which can impact the validity of the data. Table 1 shows physician coverage by country of relevant specialties. The panel size represents the number of physicians surveyed, while country total gives the total number of physicians of each specialty within each country. It is clear that for some countries, such as the US and Germany, coverage is greater than, for instance, Spain and the UK. As a result, data is considered more robust for these countries, and at times Datamonitor has, for example, used Germany as a proxy for other European countries. Total brand sales are shown as well as sales split by indication in the excel deliverable accompanying this report, in order to put all sales in context.

Table 1: MIDAS Prescribing Insights Physician Coverage, 2010

Specialties Covered	Panel Size	Country total	% represented
USA			
Allergy	150	3315	5%
General Practice	108	5632	2%
Pulmonary Diseases	108	4741	2%
Japan			
Internal Medicine & Gastroenterology	299	52,438	1%
France			
General Practitioners	400	60,392	1%
Pulmology	20	1141	2%
Germany			
General Practitioner + Internists	900	63,111	1%
ENT-doctors	150	4050	4%
Pneumologists	60	775	7.7%
Italy			
General Medicine	667	46,894	1%
Pneumologists	50	3,213	1.6%
Spain			
General Medicine	160	24,389	1%
Respiratory System	30	2039	1%
UK			
General Practitioner	500	42,086	1%

Source: Prescribing Insights, IMS Health, March 2010, Copyright ©, reprinted with permission.

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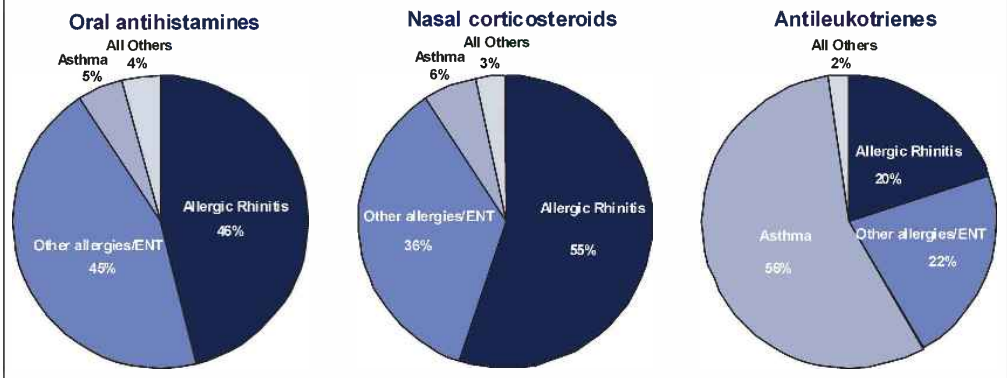
Using Prescribing Insights data, Datamonitor split sales by indication. The proportion of sales attributable to different indications varies by drug class. For oral antihistamines and nasal corticosteroids, allergic rhinitis makes up roughly half of all sales, while for antileukotrienes, allergic rhinitis accounts for just 20% of sales, with the majority attributable to asthma. The indication split for these classes is shown in Figure 1.

Figure 1: Key classes in allergic rhinitis split by indication, 2009



Source: MIDAS Sales Data and Prescribing Insight, IMS Health, March 2010, Copyright ©, reprinted with permission

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Sales forecasts of key brands are provided at both the total brand level, and by indication, in the excel deliverable that accompanies this report.

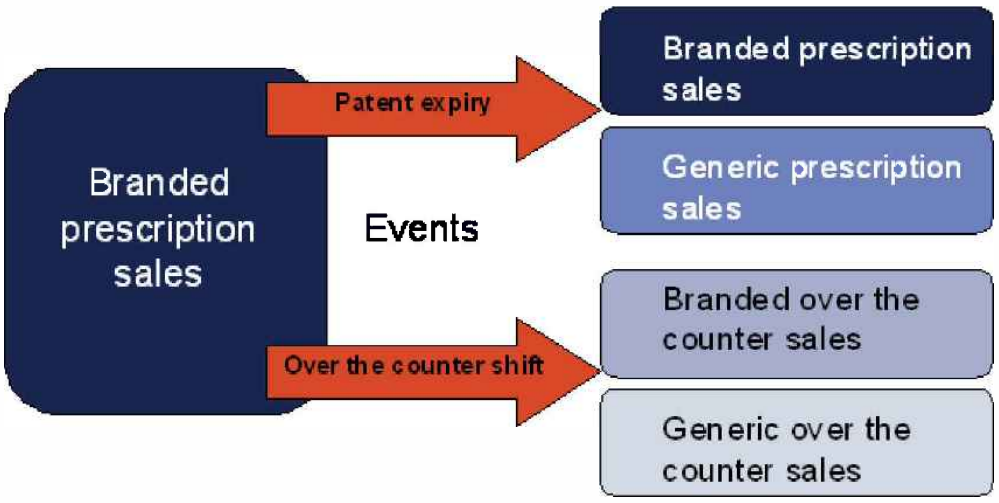
Over- the-counter market impact

Several companies in the allergic rhinitis market have shifted their products to over-the-counter (OTC) status, most commonly in the oral antihistamine class. This can help to reduce the loss of patients to generics, as OTC products are generally cheaper than prescription brands, and direct-to-consumer advertising is extensively used to create brand recognition and loyalty.

Datamonitor's forecast is based on IMS MIDAS sales data, which primarily represents prescription sales, with minimal OTC sales captured. In forecasting generic erosion, Datamonitor assumes that products will remain only on the prescription market, such that the potential impact of an OTC switch is not represented. In the case that a product does move OTC, this would overestimate the uptake of generics.

Figure 2 depicts the way that patent expiries and a shift to OTC can impact branded prescription sales. With a patent expiry, branded prescription sales are split with generic prescription sales. In the case that a brand moves OTC, branded prescription sales are split between branded OTC sales, and when the product is off-patent, generic OTC sales.

Figure 2: The impact of patent expiries and over-the-counter shifts on branded prescription sales, 2010



Source: Datamonitor

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Patient potential

Disease definition

Allergic rhinitis is a disease characterized by symptoms such as sneezing, watery nasal discharge, nasal obstruction and itching, associated with inflammation. The most likely cause of allergic rhinitis is underdevelopment of the immune system in childhood, while the most significant risk factors include a personal and family history of asthma and other allergies, such as eczema and hives. Heredity is a major factor in atopy which predisposes an individual to allergic disease.

Initial contact with an allergen sensitizes the immune system and leads to the production of immunoglobulin E (IgE), which can then bind to the surface of mast cells. On re-exposure, allergens bind and cross-link IgE molecules on the surface of mast cells beneath the mucosal surfaces of the throat and nose (Walls *et al.,* 2005). This interaction between the antigen and IgE molecule causes the subsequent release of mediators, including histamine, which results in the symptoms of allergic rhinitis in the nose, throat and eyes within minutes of allergen exposure (early-phase response) (Naclerio, 1999). This is followed several hours later by the late-phase response, involving the infiltration of inflammatory cells and the release of mediators into the nasal mucosa. The symptoms are essentially the same as in the early-phase response, but congestion predominates.

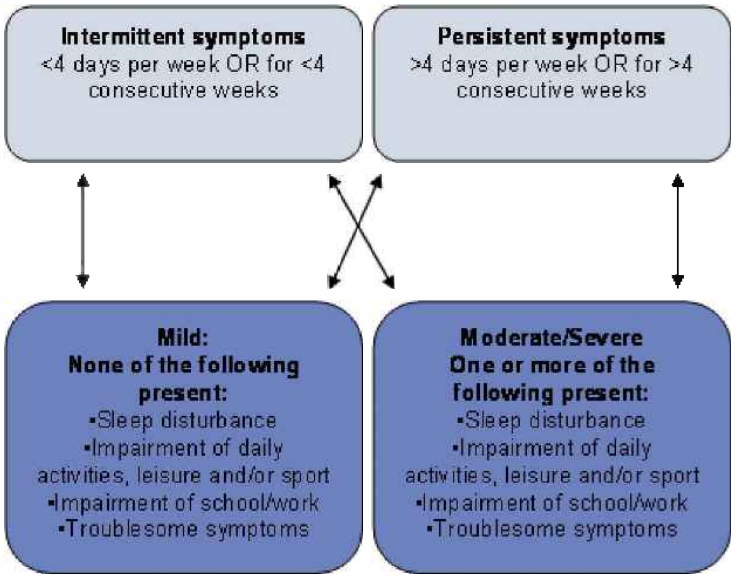
Minimal persistent inflammation is an important concept in the etiology of allergic rhinitis. Accumulating evidence suggests that allergic rhinitis is a chronic inflammatory disease instead of a disease of acute symptoms (Storms, 2003). In patients with persistent allergic rhinitis, allergen exposure varies throughout the year and there are periods where contact is minimal (ARIA, 2008). A study performed by Ricca *et al.* (2000) shows that subjects with seasonal allergic rhinitis had a significant inflammatory reaction throughout the pollen season, even during periods with a low pollen count, but that symptoms were low or absent (Storms, 2003).

Patient segmentation

Allergic rhinitis has traditionally been categorized as either 'seasonal', where pollen or moulds are the usual triggers, or 'perennial', in which case house dust mites or pet dander allergens are typically responsible. Sometimes the category 'occupational allergic rhinitis' is used, although this is not standard and is difficult to differentiate from other subsets of rhinitis. This set of subdivisions was regarded as unsatisfactory, and a new system of classification for allergic rhinitis was proposed by Allergic Rhinitis and its impact on Asthma (ARIA) guidelines in 2001, with an update in 2008, which:

- uses symptom-based and quality of life parameters;
- is based on duration, and is subdivided into 'intermittent' and 'persistent' disease;
- is based on severity, and has subsets for 'mild' and 'moderate/severe' depending on symptoms and quality of life.

Figure 3: Allergic rhinitis and its impact on asthma (ARIA) classification, 2008



Source: Datamonitor adapted from ARIA, 2008

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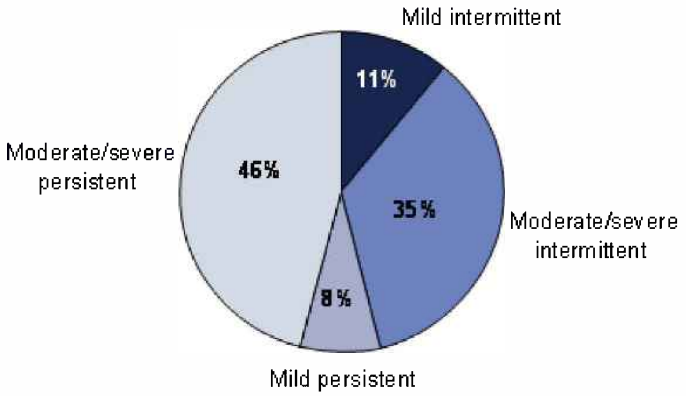
"I tend to use the ARIA classification, mild, moderate, severe, and intermittent versus persistent."

UK key opinion leader

Bousquet *et al.* (2006) studied the effect of allergic rhinitis using the new classification as proposed by ARIA. Out of a total of 3,052 patients consulting general practitioners for this disease, mild intermittent rhinitis was diagnosed in 11% of the patients, moderate/severe intermittent rhinitis in 35%, mild persistent rhinitis in 8%, and moderate/severe persistent rhinitis in 46% of the patients.

Figure 4: Distribution of severity of diagnosed allergic rhinitis patients



Source: Bousquet *et al* ., 2006

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Based on these results, over 80% of patients had a moderate/severe form of allergic rhinitis, however, it must be noted that this study over-represents more severe patients, as patients with milder symptoms are less motivated to visit their doctor and may prefer to self-medicate. This over-representation of more severe cases was confirmed in discussions with key opinion leaders, and distinguishes allergic rhinitis from diseases such as asthma, in which patients with more severe symptoms are the minority.

> *"I would say with the bias of my practice, it is not quite like asthma where you have a lesser percentage* [of moderate to severe patients], *I think you might have 60% falling into the moderate to severe category, in the ARIA guidelines."*
>
> US key opinion leader

Seven major markets

Figure 5 shows the allergic rhinitis populations in the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK) for 2010. Datamonitor estimates that the allergic rhinitis population totals 181 million across these countries. This is based on self-reported questionnaires, such that the sum includes both diagnosed and undiagnosed disease. The largest population (80 million) is seen in the US, and the smallest (6 million), in Spain. The differences between countries are largely attributable to total population sizes, with an impact from variations in local allergens as well. Furthermore, within each country, the prevalence rates can change as pollen seasons differ.

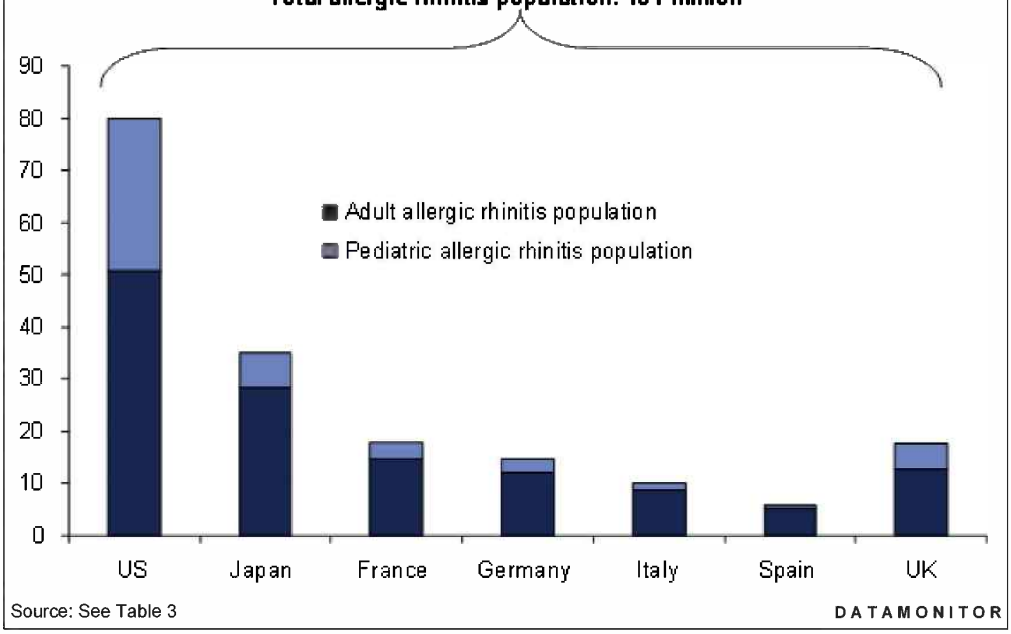
"In our region we demonstrated that there was an increase of pollen [over 27 years] *and there was also an increase in the number of days* [in a pollen season]."

EU key opinion leader

"There is the perspective that in 2020, one out of every two pediatric patients will have allergic rhinitis."

EU key opinion leader

Figure 5: Allergic rhinitis prevalent population in the seven major markets, 2010



Source: See Table 3

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Surveys exploring prevalence rates of allergic rhinitis can vary considerably according to their location and timing, or with their definition of allergic rhinitis, for example, physician-diagnosed versus self-reported disease. In examining prevalence rates for each of the seven major markets, emphasis was placed on comparability across countries, and sample size. Datamonitor selected surveys using population based questionnaires, therefore including both diagnosed and undiagnosed self-reported allergic rhinitis. As many patients never consult a physician, instead using one of the many symptomatic treatments available over-the-counter (OTC), using physician-diagnosed allergic rhinitis prevalence rates would provide an underestimation, although should be considered when analyzing prescription only therapies.

In order to estimate the allergic rhinitis populations across the seven major markets, 2010 population projections were calculated from the UN World Population Prospects: 2008 revision. Child and adult prevalence rates were considered separately, as it is generally believed that children are more prone to allergic rhinitis with frequency lessening with age (ARIA, 2008).

Table 2 provides an overview of the prevalence rates used and the resultant allergic rhinitis populations.

Table 2: Adult and pediatric allergic rhinitis prevalent populations in the seven major markets, 2010

Country	2010 Population (million) aged 20 years and above*	Adult allergic rhinitis prevalence	Adult allergic rhinitis population (000s)	Reference
US	231,003	22.00%	50,821	Nathan *et al.* , 2008
Japan	104,205	27.40%	28,552	Kusunoki *et al.* , 2009
France	47,396	30.75%	14,574	Burney *et al.* , 1996
Germany	66,843	18.20%	12,165	Burney *et al.* , 1996
Italy	48,678	18.30%	8,908	Verlato, *et al.* , 2003
Spain	36,345	14.05%	5,106	Burney *et al.* , 1996
UK	47,186	26.95%	12,717	Burney *et al.* , 1996
Adult total			**132,844**	

Country	2010 Population (million) aged 0–19 years*	Pediatric allergic rhinitis prevalence	Pediatric allergic rhinitis population (000s)	Reference
US	86,640	33.6%	29,111	ISAAC, 1998
Japan	22,795	27.95%	6,371	ISAAC, 1998
France	15,239	19.05%	2,903	ISAAC, 1998
Germany	15,214	16.40%	2,495	ISAAC, 1998
Italy	11,420	10.40%	1,188	ISAAC, 1998
Spain	8,973	9.50%	852	ISAAC, 1998
UK	14,713	32.90%	4,841	ISAAC, 1998
Child Total			**47,761**	

Note: totals may not sum due to rounding.

Source: Various (see above); *UN World Population Prospects: 2008 revision DATAMONITOR

A number of epidemiological studies are available regarding the prevalence of allergic rhinitis in countries around the world. However, while several more recent studies are available, the most comprehensive European survey of adults remains the European Community Respiratory Health Survey (ECRHS) (Burney *et al.* 1996). For this survey, 48 centers, predominantly in Western Europe, were asked to identify a suitable population of at least 150,000. Random samples of at least 1,500 men and 1,500 women aged 20–44 were then selected from each group. The survey involved a screening questionnaire that was mailed to the selected individuals, which included seven questions relating to the prevalence of respiratory symptoms. One of these questions was 'Do you have any nasal allergies including hay fever?' The responses to this question can be used to estimate the prevalence of allergic rhinitis. Reported prevalence rates can differ markedly because of variations in disease definition, diagnosis criteria and the type of population studied. The ECRHS study is therefore highly valuable in that it includes large populations from various centers within each included country, and, where available, Datamonitor used the ECRHS study to estimate the prevalent population aged 20 and above.

For children, the International Survey for Asthma and Allergies in Children (ISAAC) is the most comprehensive survey. This worldwide study included a written questionnaire directed at two age groups, 13–14 years and 6–7 years. The questionnaire was completed in 156 collaborating centers in 56 countries with a total of 721,601 children participating. For each of the seven major markets, Datamonitor used the self-reported response to 'Have you ever had hay fever?,' from the 13–14 age group to estimate the prevalent population for children aged 0–19.

The results from these and other surveys identified by Datamonitor are summarized in Table 3.

Table 3: Allergic rhinitis prevalence literature review, 2010

Country	Criteria	Study	Sample Size	Age (years)	Prevalence (%)	Source
US	Self-reported hay fever ever	ISAAC	2,330	13–14	34	ISAAC, 1998
US	% of respondents told they have hay fever in the last 12 months	The National Health Interview Survey, 2004	31,326	18+	8.6	CDC, 2005
US	Various	Review	n/a	n/a	15–28	Sly, 1999
US	Self-reported, physician-diagnosed seasonal or perennial allergic rhinitis symptoms on >=7 days in past year	Burden of Rhinitis survey	19,657	n/a	22	Nathan, *et al* ., 2008
Japan	Self-reported hay fever ever	ISAAC	7,297	13–14	28	ISAAC, 1998
Japan	Japanese cedar pollinosis; self-evaluation questionnaire	n/a	5,624	n/a	19.4	Okuda, 2003
Japan	Perennial allergic rhinitis, definition unknown	n/a	17,301	n/a	19.8	Nakamura *et al* ., 2002
Japan	n/a	n/a	13,250	7–15	20.3 (1996); 27.4 (2006)	Kusunoki, *et al* ., 2009
France	Self-reported hay fever ever	ISAAC	6,878	13–14	19.05	ISAAC, 1998
France	Do you have any nasal allergies including hay fever?	ECRHS	12,589*	20–44	30.75**	Burney *et al* ., 1996
France	Physician diagnosis	n/a	1,606	Adults	24.5	Bauchau and Durham, 2004
Germany	Self-reported hay fever ever	ISAAC	7,172	13–14	16.4	ISAAC, 1998
Germany	Do you have any nasal allergies including hay fever?	ECRHS	6,584*	20–44	18.2**	Burney *et al* ., 1996
Germany	Physician diagnosis	n/a	1,613	Adults	20.6	Bauchau and Durham, 2004
Italy	Self-reported hay fever ever	ISAAC	5,531	13–14	10.4	ISAAC, 1998
Italy	n/a	ECRHS	6,876	20–44	18.3	Verlato, *et al* ., 2003
Italy	Self-reported allergic rhinitis	ECRHS	6,031	20–44	15.9 (Phase I); 18.5(Phase II)	Olivieri *et al* ., 2002
Italy	Do you have any nasal allergies including hay fever?	ECRHS	6,034*	20–44	15**	Burney *et al* ., 1996
Italy	Physician diagnosis	n/a	1,600	Adults	16.9	Bauchau and Durham, 2004
Spain	Self-reported hay fever ever	ISAAC	7,082	13–14	9.5	ISAAC
Spain	Do you have any	ECRHS	16,469*	20–44	14.05**	Burney *et al* .,

Table 3: Allergic rhinitis prevalence literature review, 2010

Country	Criteria	Study	Sample Size	Age (years)	Prevalence (%)	Source
Spain	nasal allergies including hay fever? Physician diagnosis	n/a	1,600	Adults	21.5	1996 Bauchau and Durham, 2004
UK	Self-reported hay fever ever	ISAAC	6,795	13–14	32.9	ISAAC
UK	Do you have any nasal allergies including hay fever?	ECRHS	11,451*	20–44	26.95**	Burney *et al* ., 1996
UK	Physician diagnosis	n/a	1,625	Adults	26	Bauchau and Durham, 2004

*Sum of country sites

**Average of country sites

CDC = Center for Disease Control; ECRHS = European Community Respiratory Health Survey; ISAAC = International Survey for Asthma and Allergies in Children

Source: Various, see above

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The methodology for selecting prevalence rates from the literature review is highlighted below.

- **US:** for adults the prevalence rate of 22% from Nathan (2008) was used for the US as this study is the most recent available and includes a large sample size (n=19,657). The result is also supported by the fact that it falls into the prevalence range of 15–28% reported by Sly (1999). While the CDC (2005) used a larger sample (n=31,326), a much lower prevalence rate of 8.6% was found, likely resulting from the criteria of physician-diagnosed, rather than self-reported allergic rhinitis. Using the self-reported diagnosis rate from Nathan (2008) allows for greater comparability across countries, where a similar definition was used. Furthermore, a physician diagnosis is not necessary for all patients receiving treatment, as patients are in many cases able to self-medicate with over the counter options. For children, the International Survey for Asthma and Allergies in Children (ISAAC) result of 34% for 13–14 year olds was applied.
- **Japan:** two surveys looking at the prevalence of allergic rhinitis in Japan, Nakamura *et al.* (2002) and Okuda (2003), found prevalence of about 20%. However, these surveys focused on single subsets of allergic rhinitis, Japanese cedar pollinosis and perennial allergic rhinitis, respectively, therefore underestimating the total prevalence. A third survey Kusunoki *et al.* (2009) was therefore selected, which found a higher prevalence rate of 27.4%. This survey is also preferable as it is the most recent identified. Although this study included children aged 7–15 years, it was used to estimate the adult prevalence rate. For children, the ISAAC result of 28% was applied.
- **France:** for adults, the average prevalence from the five ECRHS centers in France is 30.75%. A second study, Bauchau and Durham (2004), found a prevalence rate of 24.5%, however, a smaller sample size was used, and the criterion was physician diagnosis such that the result is of less use for comparisons across countries. For children, the ISAAC result of 19.05% was applied.

- **Germany:** for adults, the prevalence rate of 18.2% based on the ECRHS centers in Germany was used. This study has a large sample size and is comparable to other countries. Using the result from the same study as other EU countries ensures consistent methodology. While another more recent study, Bauchau and Durham (2004), also looks at prevalence, it is less appealing in terms of comparability as it focuses on physician-diagnosed allergic rhinitis. For children, the ISAAC result of 16.4% was applied.
- **Italy:** for adults, the three Italian ECRHS centers in Italy found an average prevalence rate of 15%. Verlato *et al.*, (2003) revisited these data, and determined a prevalence rate of 18.3%. As this is a more recent result but retains methodology consistent with the previous ECRHS study, Datamonitor has selected it to estimate the Italian prevalent population. This is furthermore supported by the finding of Olivieri *et al.*, (2002), which is very comparable at 18.5%. For children, the ISAAC result of 10.4% was applied.
- **Spain**: an average prevalence of 14.05% was found from the six Spanish ECRHS samples. While Bauchau and Durham (2004) found a higher rate of 20.5% when looking at physician-diagnosed allergic rhinitis, that survey used a significantly smaller sample size, and therefore the ECRHS study is preferred. For children, the ISAAC result of 9.5% was applied.
- **UK**: the four ECRHS centers in the UK reported an average prevalence rate of 26.95% which was used to estimate adult allergic rhinitis prevalence in the UK. This is very comparable to the result of Bauchau and Durham (2004), which looked at physician-diagnosed allergic rhinitis, and found a prevalence of 26%. For children, the ISAAC result of 32.9% was applied. A UK key opinion leader validated these results, and emphasized that prevalence is significantly higher in patients with asthma.

  "We are talking about 30% of the population potentially, and that will be higher in some subgroups like people with asthma for instance, where it may be as high – well certainly a minimum of 65% – and it may be as high as 90%."

  UK key opinion leader

Rest of World

While limited epidemiological data exist regarding allergic rhinitis in the rest of the world, Datamonitor believes there is likely to be a large patient potential outside of the seven major markets. Applying results from the ECRHS survey, as a proxy for country specific studies, Datamonitor estimates that the total allergic rhinitis prevalent population in the BRIC (Brazil, Russia, India and China) countries could reach 313 million.

Table 4: BRIC nations allergic rhinitis population, 2010

Country	2010 Population (million)*	Allergic rhinitis prevalence (%)	Allergic rhinitis population (million)	Reference
Brazil	195.4	14.05	27	Burney *et al* ., 1996
Russia	140.4	18.20	26	Burney *et al* ., 1996
India	1,214.5	10.10	123	Burney *et al* ., 1996
China	1,354.1	10.10	137	Burney *et al* ., 1996
Total			**313**	

Source: Various (see above); *=UN World Population Prospects: 2008 revision

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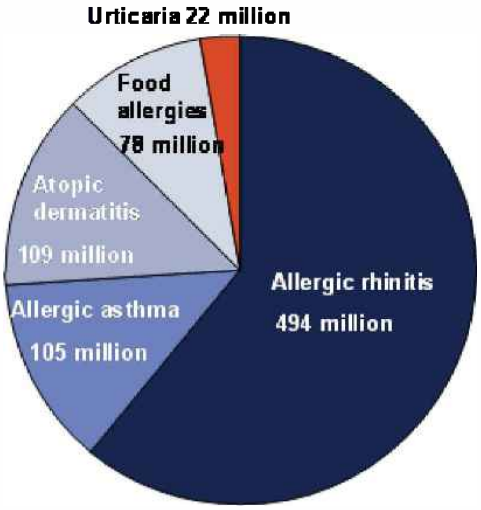
For this estimate, the Spanish prevalence rate was used for Brazil, while for Russia, German prevalence was applied. India's prevalence was reported from an ECRHS study center in Mumbai (formerly known as Bombay) and this figure was also applied to China.

Prevalence of key allergic diseases

Allergic rhinitis is the most prevalent allergic disease in the seven major markets and BRIC nations. However, antihistamines in particular, are also used for other allergic conditions, and Figure 6 shows the prevalent population of allergic rhinitis compared to other key allergies. The allergic rhinitis population exceeds the combined prevalent populations of allergic asthma, atopic dermatitis, food allergies, and urticaria.

Figure 6: Prevalent populations of key allergic diseases in the seven major markets and BRIC nations, 2010



Seven major markets = US, Japan, France, Germany, Italy, Spain and the UK

BRIC = Brazil, Russia, India and China

Source: See APPENDIX B – ALLERGIES PREVALENCE SOURCES

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Allergens

Allergic rhinitis can be triggered by a number of different sources. According to a presentation by ALK-Abelló, the typical patient with an allergic disease has an allergy to 2.3 substances. The following table summarizes the most prominent triggers.

Table 5: Most common allergens in the US and EU

Trigger	US % of allergic population	EU % of allergic population
Grasses	56	52
House dust mites	45	49
Ragweed	49	n/a
Birch	23	14
Cats	39	30
Weeds	n/a	27
Japanese Cedar	10	n/a
Dogs	19	n/a
Food	10	11
Venom	13	13

n/a = not available

Source: ALK-Abelló, 2008b, http://www.alk-abello.com

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While the symptoms experienced on exposure to various allergens can be largely similar, the prevalence rates for each type become particularly relevant when discussing the potential for immunotherapy. It is also important to note that within countries, the allergen profile can differ widely between regions.

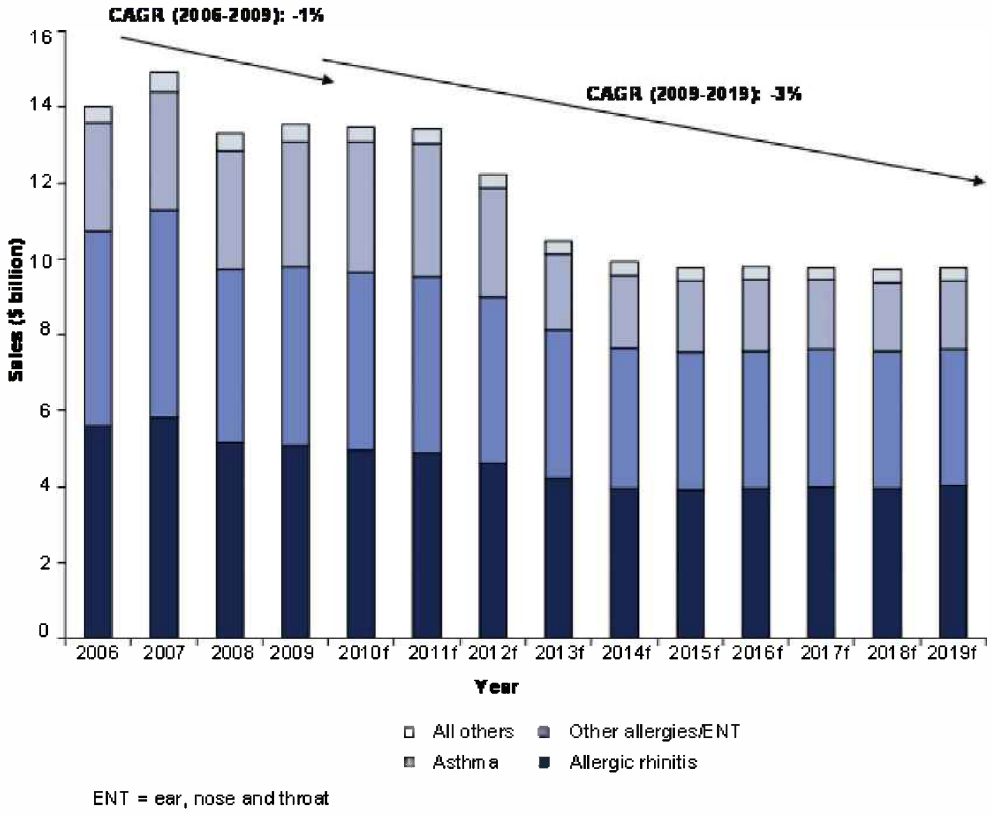
> *"In Italy, there are very different pollens depending on the regions … if you go to the Northern region, grass is the most important one. On the coast olive is a very important allergen too, and there are new emerging ones such as cypress."*
>
> EU key opinion leader

Market overview

In 2009, Datamonitor calculates that the allergic rhinitis market reached $5 billion in the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK). This was determined using total brand sales and applying the percentage estimated to be for allergic rhinitis only. Allergic rhinitis accounted for 37% of the total sales, which reached $13.5 billion in the same year, but this sum includes sales for other allergic disorders such as urticaria and allergic asthma (please see the section: Market definition for this report for a breakdown of the drug classes included in this calculation).

Figure 7 breaks down the products used to define this market by indication, detailing the proportion considered to be for allergic rhinitis alone. A sharp decline is seen from 2007 to 2008, and this is attributed to exchange rate fluctuations. In trending forward sales, Datamonitor uses a constant exchange rate to smooth the effect of such fluctuations (see Appendix for more details on Datamonitor's methodology). Datamonitor forecasts an increased decline in the market, with a compound annual growth rate (CAGR) of -3% for 2009–2019, as the result of a number of key patent expiries. In addition it should be noted that these data are predominantly for prescription only sales.

Figure 7: Total branded sales for all allergic rhinitis drug classes in the seven major markets by indication ($ billion), 2006–2019



ENT = ear, nose and throat

Source: 2010–2019 forecast = Datamonitor; 2006–09 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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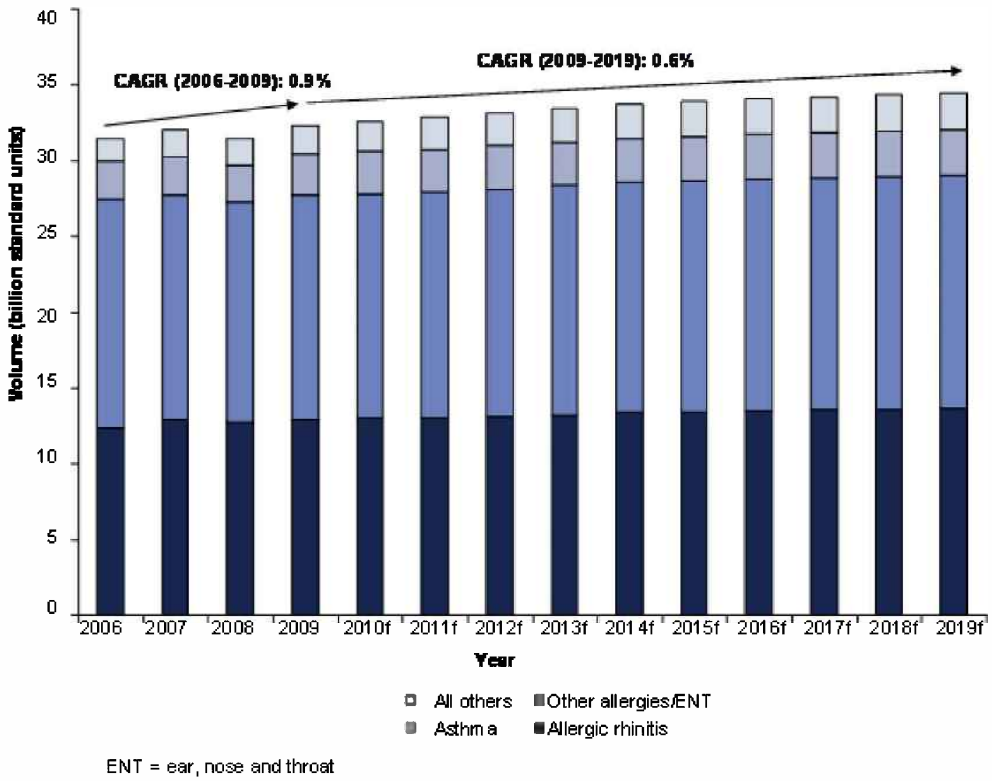
Figure 8 shows a small positive trend in standard unit sales from 2006 to 2009 in the seven major markets. This is expected to continue, with standard units increasing until the forecast ends in 2019, and a CAGR of 0.6% from 2009 to 2019. Cheaper generics are expected to enter the market during that time, explaining the decrease in market value seen, despite the slow increase in volume sales.

Figure 8: Total brand volume for all allergic rhinitis drug classes in the seven major markets by indication (standard units), 2006–2019



ENT = ear, nose and throat

Source: 2010–2019 forecast = Datamonitor; 2006–09 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010,

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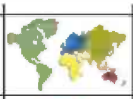
Opportunities and threats

This section outlines the environmental factors that will facilitate or threaten growth in the allergic rhinitis market. The success of any individual brand or company in the allergic rhinitis market will be defined by its relative strengths and weaknesses in either maximizing the opportunities or managing the threats outlined below.

Figure 9: Opportunities and threats in the allergic rhinitis market, 2010

Opportunities		Threats
• OTC may extend revenue after patent expiry • Increasing awareness of allergic rhinitis • Longer and more intense allergy seasons		• Governments reducing healthcare spending • Key patent expiries looming
• OTC is becoming more important • DTC advertising of prescription medicine		• Reimbursement controls dominate P&R • High generic erosion
• New regulations on OTC drugs • No gatekeeper system		• Generic influence to grow • Long approval process
• Generic markets less developed than in US • Changing regulations for immunotherapy leading to registration as pharmaceuticals		• Cost containment policies • Restrictive reimbursement

DTC = direct-to-consumer; P&R = pricing and reimbursement; OTC = over-the-counter

Source: Datamonitor

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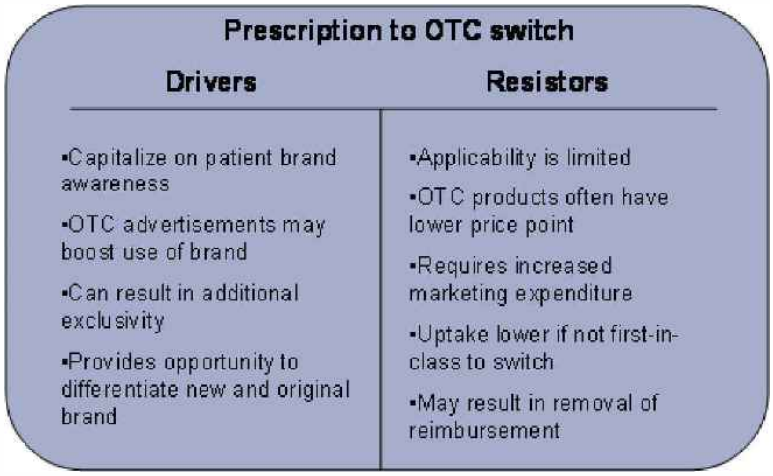
Seven major market opportunities and threats

Opportunity 1 – over-the-counter (OTC) status may extend revenue after patent expiry

Increasing numbers of prescription drugs are being made available over-the-counter (OTC) worldwide, and there are several reasons why this number may increase in the future (Brass, 2001; Marwick, 1997; Harrington & Shepherd, 2002). After years of use, some prescription drugs have the proven safety record needed to secure OTC status (Harrington & Shepherd, 2002) and patients are increasingly interested and involved in the management of their own health, making OTC drugs more viable. This is largely facilitated by the internet, which allows patients greater access than ever before to healthcare information. Furthermore, the escalating economic burden of providing insurance coverage for pharmaceutical products has prompted payers to shift costs to patients (The Kaiser Family Foundation, 2002). In 2001, BlueCross of California, a US healthcare insurer, initiated a citizens' petition to the US Food and Drug Administration (FDA) to request the OTC sale of second-generation antihistamines. This was the first time that a health insurer had initiated a request to transfer prescription drugs to OTC status. Cohen *et al.* (2005) conducted a survey of 12 leading managed care organizations (MCOs) regarding their responses to drugs being switched to OTC status. They found a strong tendency to remove switched drugs from the formulary and to raise copayments for prescription drugs in the same class, which provides patients with a financial incentive to take the OTC drug. For example, all 12 organizations removed loratadine from their formularies when it received OTC status and increased copayments for prescription antihistamines, while a third of the MCOs took all second-generation antihistamines off their formularies (Cohen *et al* ., 2005).

For the pharmaceutical industry, the switch from prescription to OTC provides a means of sustaining revenues from branded products. However, for drugs that are still patent protected, there is little or no commercial incentive to seek a change of status. Having dual status for a drug may be of benefit, as this would allow a prescription and OTC product with the same brand name to appear on the market simultaneously. Both drugs would be under patent protection, with the OTC version available in a lower dose and only the prescription drug would be reimbursed by insurers.

Figure 10: Drivers and resistors of prescription to OTC switch, 2010



Source: Datamonitor DATAMONITOR

Different markets have distinct processes and regulations regarding the switch from prescription to OTC, which can affect the attractiveness of the option. In some European countries, for example, there is an extra classification in addition to prescription and OTC; a class of drugs that is generally kept behind the counter (BTC) at pharmacists, and may be requested by consumers or recommended by pharmacists without a physician's prescription. When prescription drugs switch in Europe they often go into this BTC class.

Forced prescription-to-OTC switches are a new phenomenon, although there have been very few such occurrences to date. Forced switches occur in the absence of a manufacturer's request, but are allowed as part of many regulators' OTC drug review processes. The most high profile forced switch was that of Claritin (loratadine) in the US, which was initiated by several health management organizations (HMOs) rather than by Schering-Plough, which eventually gave its approval for the switch in 2002.

Opportunity 2 – increasing awareness of allergic rhinitis

According to the National Pollen and Aerobiology Research Unit (NPARU), allergic rhinitis was unknown before 1800, and has only become widespread over the last 100 years. While the first case dates back to 1819, the causes of allergic rhinitis were not identified until 1873. Throughout the 1900s, the number of people affected by the disease has risen. Furthermore, in countries where the disease was previously unknown it has become prevalent, such as in Japan where 40 years ago it had not been identified. This increasing prevalence rate is attributed both to a real increase and also to improving recognition and treatment of the disease (NPARU, 2010; http://www.worc.ac.uk).

The prevalence of allergic rhinitis has increased considerably since the beginning of the 21st century (World Health Organization fact sheet, 2003; Jarvis & Burney, 1998). Urban air pollution has been commonly identified as one of the potential causative or precipitating agents. Other suggested causal factors in the growing prevalence of hay fever include greater sensitivity in some ethnic groups, social class, family size and maternal smoking (World Health Organization fact sheet, 2003).

"The prevalence of allergic disease is increasing and the main reason is the Western lifestyle, but there are several reasons, it is not just one reason."

EU key opinion leader

The International Survey for Asthma and Allergies in Children (ISAAC) Phase Three study reviewed three studies that assessed time trends in hay fever or allergic rhinitis in school-aged children, and are summarized in Table 9. The studies in the UK and Finland show a slight increase in prevalence, whereas in Germany it is substantial. The latter may present an increase in allergic rhinitis diagnosis instead of an actual change in allergic rhinitis prevalence. With the growing awareness of allergic rhinitis in both the general public and primary care physicians, diagnosis of the disease has been on the rise.

Table 6: Time trends in hay fever or allergic rhinitis in school-age children in the UK, Finland, and Germany, 1973–1996

Location	Baseline – year	Comparison – year	Annual change
Wales, UK[1]	9% – 1973	15% – 1988	3.5%
Finland[2]	9% – 1977	14.9% – 1991	3.7%
Leipzig, Germany[3]	2.3% – 1991/92	5.1% – 1995/6	22.0%

Source: [1] Burr, *et al.* , 1989; [2] Rimpela, *et al.* , 1995 ; [3] Von Mutius, *et al.* , 1998 DATAMONITOR

"There is the perspective that in 2020, one out of every two pediatric patients will have allergic rhinitis."

EU key opinion leader

Opportunity 3 – allergy seasons start earlier, last longer and are more intense

More severe and longer lasting allergy seasons have been widely reported in recent history. According to the World Health Organization (WHO), the last 30 years have seen an expansion in the pollen season by an average of 10–11 days (WHO, 2010a; http://www.euro.who.int). In a statement regarding climate change, the WHO also stated that ground-level ozone can increase as a result of higher temperatures, which in turn hastens the onset of the pollen season (WHO, 2008; http://www.who.int).

> *"In our region we demonstrated that there was an increase of pollen* [over 27 years] *and there was also an increase in the number of days* [in a pollen season]."
>
> EU key opinion leader

With the vast majority of allergic rhinitis treatments used for symptomatic relief during the pollen season, this trend translates into a direct increase in market potential, representing an opportunity for all classes of drugs.

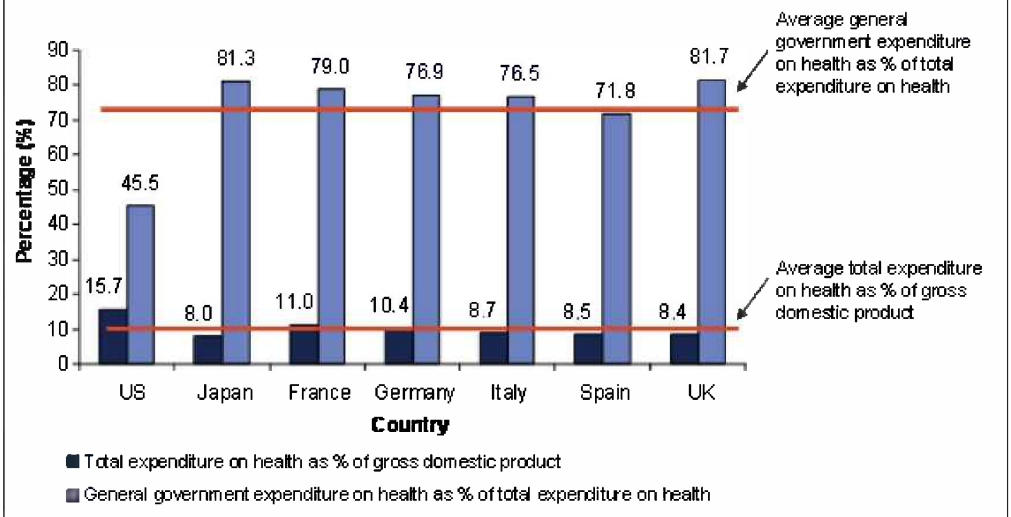
Threat 1: governments reductions in healthcare expenditure through controlling pricing and reimbursement

In all seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK), healthcare is becoming increasingly expensive. The reasons for the overall growth in healthcare spending include the aging population, the shift towards newer and more expensive drugs, the higher prevalence of lifestyle drugs and the greater number of diseases that are now treatable.

Private and public payers have a number of options for reducing healthcare spending and establishing cost-containment strategies. These cost-containment options include regulating drug prices, reducing the length of hospital stays and transferring the cost of healthcare to the private sector. Of these, drug prices are a high-visibility target and in all seven major markets, the focus on pricing and reimbursement (P&R) is consequently intensifying. The ability of a drug to launch at a favorable price and secure reimbursement is often based on a cost-effectiveness analysis. To secure a high price and reimbursement level, many P&R bodies are increasingly turning to pharmacoeconomics (PE) and budget impact analysis to support decisions. Therefore, P&R teams in pharmaceutical companies play an increasingly prominent role in demonstrating a drug's cost effectiveness to ensure a strong return on the company's drugs. With immunotherapy for allergic rhinitis—which is significantly more expensive than traditional treatments—making its way through the pipeline and onto the market, pharmacoeconomics will have a growing role in the allergic rhinitis market. Indeed, a cost-effectiveness study of Grazax (pollen, ALK-Abelló) was published in 2007 (Bachert *et al.*, 2007), and Datamonitor expects additional studies will be seen for that drug class.

Data from World Health Statistics 2010 (WHO, 2010b; http://www.who.int) reveal that in 2007, the average total expenditure on health as a percentage of gross domestic product was significantly higher in the US than in the other six major markets, at 15.7% compared to the average of 10.15% in the seven major markets. When looking at government expenditure on health as a percentage of a country's total health expenditure, an opposite trend is seen, with the US considerably lower, with 45.5% compared to the average of 73.2%. It is therefore clear that while excessive healthcare spending is an issue in each of the major markets, different issues need to be addressed within individual countries. In the US, which is the largest drug market, both public and private payers are implementing cost-containment measures across a wide range of healthcare expenses to reduce the burden. In Europe and Japan, governments are the most exposed to high healthcare costs and drug spending and therefore constitute powerful drug purchasers with significant leverage. The ways in which each country is addressing these issues are outlined in the country-specific opportunities and threats sections.

Figure 11: Healthcare spending in the seven major markets, 2007



Source: WHO, 2010b; http://www.who.int

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Threat 2: key patent expires will change the allergic rhinitis market

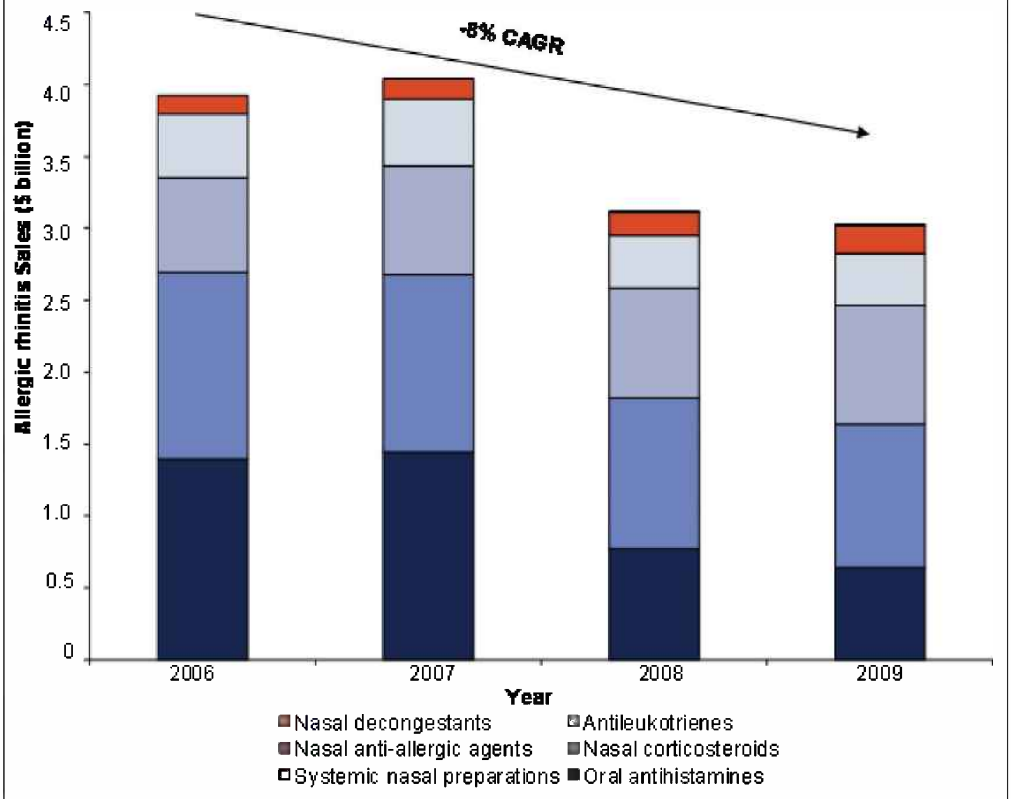
Several key patents are set to expire over the next few years which will alter the allergic rhinitis market. The impact of these is expected to vary greatly depending by market and by drug class, with the greatest effect expected in the US. Within the EU, generic impact also differs depending on the maturity of the local generic market, with countries such as the UK being most affected by generic entry, while less mature generic markets are seen in Italy and Spain. This is expected to change over the coming years as cost-cutting measures begin to strengthen the influence of the generic markets. This is discussed in greater detail when looking at the individual regions below, and also in the Case Study chapter at the end of this report.

US: opportunities and threats

Allergic rhinitis market overview

The allergic rhinitis market in the US in 2009 totaled around $3 billion and has decreased between 2006 and 2009 with a compound annual growth rate (CAGR) of -8%. However, there has not been a consistent decline year-on-year, and the variable sales pattern is influenced strongly by variations in pollen seasons. In addition Datamonitor speculate that the recession may have had an impact of patients' willingness to pay for allergic rhinitis treatments, especially those with mild to moderate symptoms.

Figure 12: US: total sales for allergic rhinitis by class ($ billion), 2006–09



Source: Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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US formulary tier status for leading brands

Tiering negotiations are becoming a central component of new branded drug launch strategies because this has a direct impact on patient access. In general, generics and lower priced agents are placed in the more desirable lower tiers and more expensive agents are placed in higher tiers. This is particularly relevant in the allergic rhinitis market, where symptomatic treatments vary from relatively cheap oral antihistamines to nasal corticosteroids which are generally more expensive and therefore less accessible to patients. Furthermore, with many products available over the counter, their prescription counterparts have lost reimbursement.

Table 7 includes the formulary status of the leading branded agents used to treat allergic rhinitis. Formularies were chosen as a representative sample from the top national players in the employer-sponsored insurance companies and from the top Medicare Part D players according to number of lives covered or enrolled in pharmacy benefit plans. This list is not meant to be a comprehensive analysis.

Table 7: US formulary tier status for leading brands in allergic rhinitis, 2010

Brand	Aetna	Humana 3-Tier	Humana 4-Tier	UnitedHealth California
Antihistamine + decongestant				
Allegra-D 12 Hour	Tier 3-Prior authorization	Tier 3-Quantity limit	Tier 3; High copay	Not Covered
Allegra-D 24 Hour	Tier 3-Prior authorization	Tier 3-Quantity limit	Tier 3; High copay	Not Covered
Clarinex-D 24 Hour	Tier 3-Prior authorization	Tier 3-Quantity limit	Tier 3; High copay	Not Covered
fexofenadine/ pseudoephedrine	Tier 1; Low copay	Tier 1; Low copay	Tier 3; High copay	No status assigned
Zyrtec-D	Not Covered	Tier 3-Quantity limit	Tier 3; High copay	Tier 2-Quantity limit
Clarinex-D 12 Hour	Tier 3-Prior authorization	Tier 3-Step therapy	Tier 3-Step therapy	Not Covered
Oral antihistamine				
fexofenadine	Tier 1-Prior authorization	Tier 1; Low copay	Tier 2; Intermediate copay	Tier 3; High copay
Allegra	Tier 3-Prior authorization	Tier 3-Quantity limit	Tier 3; High copay	Not covered
cetirizine	Not covered	Tier 1; Low copay	Tier 3; High copay	OTC
Clarinex RediTabs	Tier 3-Prior authorization	Tier 3-Quantity limit	Tier 3; High copay	Not covered
Xyzal	Tier 3-Prior authorization	Tier 3; High copay	Tier 3; High copay	Tier 3-Quantity limit
Zyrtec Allergy	Not covered	Tier 3-Quantity limit	Tier 3; High copay	Tier 2-Quantity limit
Clarinex	Tier 3-Prior authorization	Tier 3-Quantity limit	Tier 3-Quantity limit	Not covered
Children's Claritin	OTC	OTC	OTC	OTC
Children's Zyrtec Allergy	OTC	OTC	OTC	OTC
Claritin	Not covered	OTC	OTC	OTC
Claritin RediTabs	Not covered	OTC	OTC	OTC
loratadine	Not covered	OTC	OTC	OTC
Nasal corticosteroid				
fluticasone propionate nasal	Tier 1; Low copay	Tier 1; Low copay	Tier 2; Intermediate copay	Tier 1-Quantity limit
Nasonex	Tier 2; Intermediate copay	Tier 2; Intermediate copay	Tier 2; Intermediate copay	Tier 2-Quantity limit
Flonase	Tier 3; High copay	Tier 3; High copay	Tier 2-Prior authorization	Tier 3-Quantity limit
Omnaris	Tier 3; High copay	Tier 3; High copay	Tier 3; High copay	No status assigned
Rhinocort Aqua	Tier 3-Step therapy	Tier 3-Step therapy	Tier 3; High copay	Tier 3-Quantity limit
Beconase AQ	Tier 3; High copay	Tier 3; High copay	Tier 3-Prior authorization	Tier 3-Quantity limit
Nasacort AQ	Tier 3-Step therapy	Tier 3-Step therapy	Tier 3-Prior authorization	Tier 3; High copay
Nasarel	Tier 3; High copay	Tier 3; High copay	Tier 3-Prior authorization	Tier 3-Quantity limit
Veramyst	Tier 2; Intermediate copay	Tier 2; Intermediate copay	Tier 3-Prior authorization	Not covered
Nasal antihistamine				
Astelin	Tier 2; Intermediate copay	Tier 2; Intermediate copay	Tier 2; Intermediate copay	Tier 2-Quantity limit
Astepro	Tier 2; Intermediate copay	Tier 2; Intermediate copay	Tier 2; Intermediate copay	No status assigned
Patanase	Tier 3; High copay	Tier 3; High copay	Tier 3; High copay	No status assigned

OTC = over the counter

Source: Epocrates® Online, 2010

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The reimbursement of allergic rhinitis products is largely restricted, leaving patients to pay for products themselves, and likely hampering product use. Branded antihistamine plus decongestant combinations are seen to have high copays because of generic availability. This is a significant disadvantage for branded products and is reflected in the relatively low sales seen for these brands. Several oral antihistamines are available over-the-counter (OTC), which restricts their reimbursement. This furthermore creates a challenge when assessing the allergic rhinitis market, as OTC sales are generally not captured by IMS MIDAS sales data.

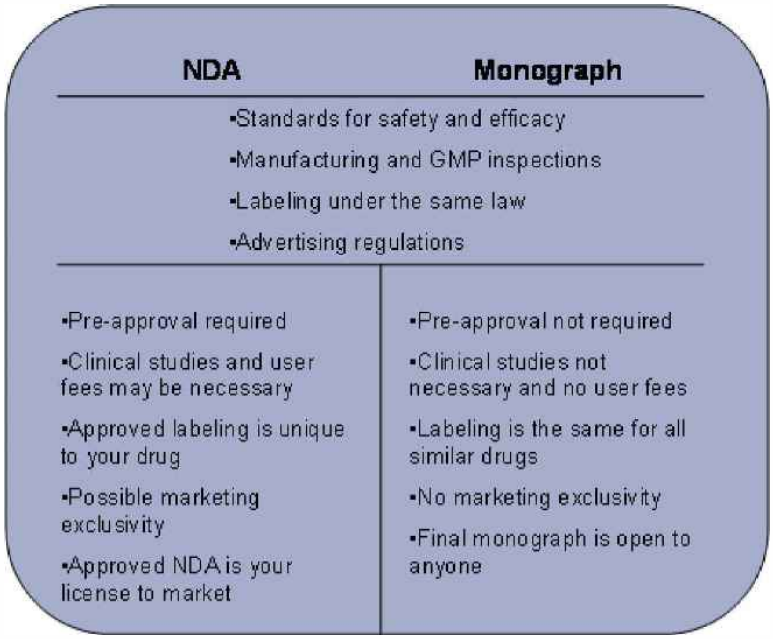
Branded nasal corticosteroids are either Tier-2 or Tier-3 under most plans. The only generic available in the US, fluticasone propionate, is Tier-1, which has led to generic erosion of the brand (Flonase), despite the fact that in other countries generic erosion has been minimal due to the product's device. It is therefore clear that reimbursement plays an important role in the allergic rhinitis market, and is a key factor in brand choice and patient access.

Opportunities

Opportunity 1 – the OTC market is becoming more important in the US

Over-the-counter (OTC) drugs play an increasingly vital role in the US healthcare system by providing easy access to certain drugs that can be used safely without the help of a healthcare practitioner. The US Food and Drug Administration (FDA) usually evaluates OTC products as part of the OTC Drug Review Program. The goal of this program is to establish OTC drug monographs for each class of product. In the US, such monographs exist for antihistamines and nasal decongestants. Products conforming to a monograph may be marketed without FDA pre-approval, while those that do not must undergo a separate review and approval through the New Drug Application (NDA) process, which is also used for new ingredients entering the OTC marketplace (FDA, n.d.; http://www.fda.gov). Direct-to-consumer advertising (DTC) in the US has led to high brand recognition of certain products which facilitates the uptake of drugs that have switched to OTC status.

Figure 13: New Drug Applications versus monographs



GMP = Good Manufacturing Practices; NDA = new drug application

Source: FDA, http://www.fda.gov , 2007

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An example of an allergy therapy available OTC in the US is Merck's Claritin (loratadine). The FDA approved Claritin as an OTC product in December 2002, after which insurance companies changed their policies with regard to non-sedating antihistamines. More recently, in December 2009, Sanofi-Aventis announced that it was to acquire Chattem, a leading manufacturer of branded consumer healthcare products, in order to facilitate the conversion of Telfast/Allegra to an OTC product (Sanofi-Aventis, 2009; http://en.sanofi-aventis.com/).

Opportunity 2 – direct-to-consumer (DTC) advertising of prescription medicines highly influential in the US

The US is one of only two countries in which direct-to-consumer (DTC) advertising of prescription drugs is legal, the other country being New Zealand. Promotional spending by pharmaceutical manufacturers has been increasing rapidly, more than doubling from $9.2 billion in 1996 to $19.1 billion in 2001 (The Kaiser Family Foundation, 2003). DTC advertising accounted for 14% of this spending, including advertisements targeted toward consumers through magazines, newspapers, television, radio, and outdoor advertising. In a review of a number of studies, the US General Accounting Office concluded that, on the whole, advertising increases both drug utilization and sales (US General Accounting Office, 2002).

Some critics of DTC advertising are concerned that it diverts patients from treatment with cheaper but equally effective generic drugs. Other criticisms of DTC advertising are based on concerns that much of the advertising aims to play on consumers' anxieties about their health. Furthermore, DTC advertisement is often used to seduce people, rather than to inform them. A study performed by Woloshin *et al.* (2001) concluded that of the 67 magazine advertisements evaluated, 67% used emotional appeals, 39% encouraged consumers to consider medical causes for their experiences and 87% described the benefit of medication in vague, qualitative terms instead of relying on data. Additionally, DTC advertising is limited to drugs with the greatest potential to generate revenue from such activity—mostly expensive, new drugs for long-term use in common indications. Such advertising increases premature rapid uptake and overuse of new drugs before flaws, including safety problems, have been discovered and communicated to health professionals (Gilbody *et al* ., 2005; Topol, 2004; Lasser *et al* ., 2002).

On the other hand, it is argued that DTC advertisements may induce a placebo effect that could increase the clinical effectiveness of the advertised drugs. Patients who take the advertised medication may be conditioned to elicit the positive feelings that were portrayed in the advertisement, which should thereby enhance the drug's clinical effect (Almasi *et al.*, 2006). Through the placebo effect, patients' positive expectations from DTC advertising may potentially reduce the amount of treatment requested or required (Walach & Maidhof, 1999). An enhanced placebo response could furthermore improve patient adherence and outcomes.

Threats

Threat 1 – reimbursement controls reduce healthcare expenditure in the US

In the US, private healthcare plays the leading role in healthcare provision. The US government is less involved in influencing healthcare markets and drug pricing and reimbursement than European governments tend to be, since there is no centralized government scheme providing access to healthcare for the entire US population. Furthermore, the US healthcare system is highly complex, and there are a wide range of stakeholders that influence pricing and reimbursement.

Of the seven major markets, the US has the least restrictive pricing controls, and as a result, drug prices are 18–67% lower in other Organization for Economic Co-operation and Development (OECD) countries compared to the US (International Trade Administration (ITA), 2004). Reimbursement is more of an issue in the US than price controls, and plays a considerable role in the allergic rhinitis market. In many cases, where a drug is available OTC, it no longer qualifies for reimbursement. An overview of reimbursement for key allergic rhinitis products in the US can be found in the section: US formulary tier status for leading brands.

Threat 2 – generic entry to shrink the allergic rhinitis market

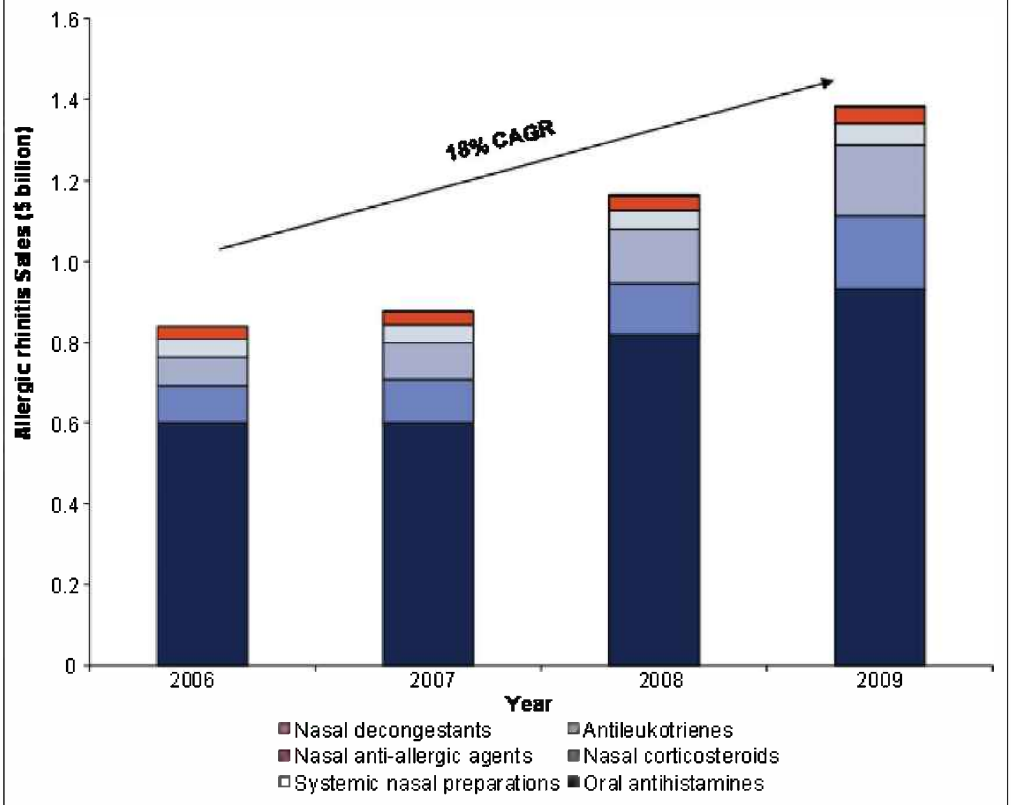
The US generic market is more mature than that of any other major market. Patent expiry is associated with immediate generic entry and substantial sales erosion. Over the next 10 years, Datamonitor expects the US to seem market entry of generic versions of Allegra-D 24 hour (fexofenadine/pseudoephedrine; Sanofi-Aventis), Aerius/Clarinex (desloratadine; Schering-Plough), Xyzal (levocetirizine, UCB/Sepracor), Singulair (montelukast, Merck), Nasonex (mometasone, Merck); Rhinocort (budesonide; AstraZeneca), Omnair/Omnaris (ciclesonide, Nycomed), and Patanase (olopatadine; Alcon). The impact of these patent expiries will be substantial in the US, with Datamonitor forecasting that the US allergic rhinitis market will decline from $3 billion in 2009 to $1.9 billion in 2019.

Japan: opportunities and threats

Allergic rhinitis market overview

Sales for allergic rhinitis in Japan for 2009 are estimated at $1.4 billion, having experienced significant year-on-year growth since 2006, with a compound annual growth rate (CAGR) of 21%. This was largely driven by an increase in oral antihistamine sales, attributable to the increasing severity of pollen seasons. Substantial growth was also seen in the antileukotriene class, linked to the success of Singulair (montelukast, Merck), after it secured approval for allergic rhinitis in 2008, as well as the launch of new formulations. Less off-label prescribing is recorded in Japan, meaning that allergic rhinitis appeared to account for almost 50% of the anti-allergy drug sales investigated for this report.

Figure 14: Japan: total sales for allergic rhinitis by class ($ billion), 2006–09



Source: Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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Opportunity 1 – new regulation of OTC drugs

New regulations covering over-the-counter (OTC) drugs could provide a considerable opportunity within the allergic rhinitis market (MHLW, 2009; http://www.mhlw.go.jp). In June 2009 the Japanese government implemented new, more lenient rules on OTC drugs with the aim of reducing costs. Drugs are now classified into three groups depending on risk:

- Class 1: Highest risk – relatively new to over-the-counter sales (e.g. H2 blocker, diclofenac sodium);
- Class 2: Moderate risk – rarely cause side effects requiring inpatient care (e.g. aspirin, diphenhydramine);
- Class 3: Relatively low risk – may cause slight discomfort (e.g. isothipendyl hydrochloride, acriflavine).

Sales requirements by class are as follows:

- Class 1: can only be purchased when a pharmacist is available to provide necessary information on the medicine with written material(s) for proper use of the drug;
- Class 2: recommended to be sold when either a pharmacist or registered sales clerk are available to provide necessary information on proper use of the drug;
- Class 3: no specific guideline for this class.

Datamonitor believes that these new regulations will increase the market potential for allergic rhinitis drug manufacturers, enabling expansion into the OTC arena as has been the case in the US and EU. There is the possibility that a switch to OTC could also be a threat as drug prices would likely decrease, but Datamonitor believes the increased availability of drugs would have a net positive effect on the market.

Opportunity 2 – no gatekeeper system

Japan does not have a 'gatekeeper' or primary care system, instead allowing patients to seek care directly from a specialist. For allergic rhinitis this is important as it means that patients can go directly to an allergist, thus increasing their chances of receiving optimal treatment. With optimal treatment, patients are more likely to see positive results, which may improve adherence and extend length of treatment. This, in turn, leads to higher sales for allergic rhinitis drug manufacturers.

Threat 1 – generic influence to grow

While the Japanese pharmaceutical market has traditionally seen little impact from generics, this is set to change as the government pushes for wider generic use in order to cut costs. From 2007 to 2008 the generic share of the pharmaceutical market was 17% based on volume, and just 6% based on value. In October 2007 the Japanese government set a target for generics to account for 30% of the market volume by 2012 (MHLW, 2009; http://www.mhlw.go.jp).

Foreign companies have reacted by entering the Japanese market with the expectation of sales growth; key generics manufacturer Teva set up a company with Kowa in 2008 with the aim of achieving 10% market volume share by 2015 (Teva, 2008; http://www.teva.jp). With significant patent expiries anticipated in the Japanese allergic rhinitis market over the next 10 years, this change is highly relevant and is expected to have a direct influence on the market in the long run.

Threat 2 – long approval process dampens access to Japanese market

Historically, the process of gaining approval and securing a price and reimbursement level has been slow in Japan relative to other major markets. This is particularly true for new drugs that were originated outside of Japan, in part because of problems using clinical trial data generated with non-Japanese patients. It has been argued that there are genetic differences between Japanese and other ethnic groups, which must be addressed in clinical trials before drug approval in Japan. This issue gains significance because late-stage clinical trials are between two and four times more expensive in Japan than abroad, reducing the incentive to carry out bridging studies and launch in Japan (US Department of Commerce, International Trade Administration, 2004).

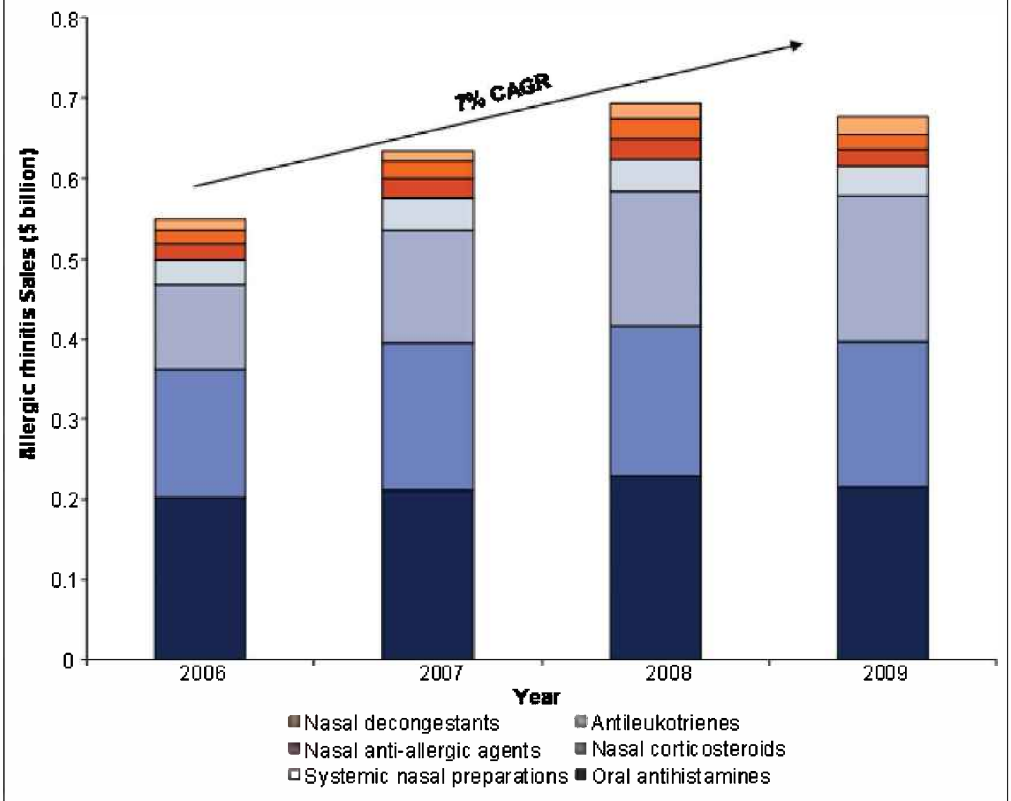
Although there are relatively few allergic rhinitis treatments in development in comparison to other diseases such as asthma, the slow regulatory process has also been an issue in this market. GlaxoSmithKline, which holds the rights to Xyzal (levocetirizine) in Japan, filed the drug in December 2008 and, as of Q2 2010, has not received a final response (Thomson Pharma, May 2010, Copyright Thomson Scientific).

EU: opportunities and threats

Allergic rhinitis market overview

Allergic rhinitis sales in the five major European markets (France, Germany, Italy, Spain, and the UK) totaled around $680m in 2009. Over the period 2006–09 a positive compound annual growth rate (CAGR) of 7% was observed. Across the five major EU markets, allergic rhinitis accounted for a smaller proportion of total brand sales compared to the US and Japan. For example, based on IMS Prescribing Insights physician diary information Datamonitor estimates that only approximately 30% of total branded sales for the oral antihistamines class are for allergic rhinitis, with other indications such as sinusitis, urticaria and other allergies being stated more often as the use for which the products are prescribed.

Figure 15: Five major EU markets: total sales for allergic rhinitis market by class ($ billion), 2006–09



Source: MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission

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Opportunity 1 – generic markets less developed than in the US

The EU markets are characterized by relatively low levels of generic penetration compared to the US. There is large variation between the EU countries in terms of the extent of generic erosion following patent expiry. While some countries do have mature generics markets, including the UK and Germany, and therefore experience relatively quick erosion, a number of EU countries see minimal impact from generic entry, such as Italy and Spain.

> *"Usually the Italian customers are very, very keen to have the brand."*
>
> EU key opinion leader

In these countries the opportunity remains for brands to enjoy strong sales for years after patent expiry. However, this benefit is threatened by cost containment plans aimed at reducing this trend, as discussed below.

Threat 1 – cost containment policies to impact drug prices

Throughout the EU, concern is growing over rising healthcare costs, and governments are taking action. In early June 2010 plans to reduce healthcare spending were announced in both France and Italy. The main focus of the plans is to cut drug prices. Italy plans to cut off-patent generic drug prices by 12.5% by the end of 2010, and France aims to reduce drug prices by $122m during the year. Italy's reimbursement of generics is also expected to change from 2011, limiting reimbursement to the least expensive medicine within four therapeutic categories (FirstWordPlus, 2010; http://www.firstwordplus.com).

For the allergic rhinitis market, the greatest impact from cost containment is expected to come from price cuts. These can reduce brand sales both through reductions in drug prices, but also by encouraging generic sales thereby eroding brand volume. As numerous generics are already available in the EU, the impact of these reforms is expected to shift volume sales from branded to cheaper generic drugs, reducing the allergic rhinitis market potential.

Threat 2 – reimbursement policies impact allergic rhinitis drug classes

In a market where products span over-the-counter, branded and prescription medications, reimbursement has a considerable role to play in allergic rhinitis. Discussions with key opinion leaders revealed the role that reimbursement can play, not only with patients, but also with healthcare providers influenced by policies.

> *"There are problems in Italy concerning the reimbursement, because the only reimbursed drugs are the antihistamines for allergic rhinitis, and for instance nasal steroids are not reimbursed.* [Therefore] *they are used but not as much as they potentially could be."*
>
> EU key opinion leader

"Adherence to treatment … is decreasing when someone is not reimbursed. So, there is a direct influence from reimbursement."

EU key opinion leader

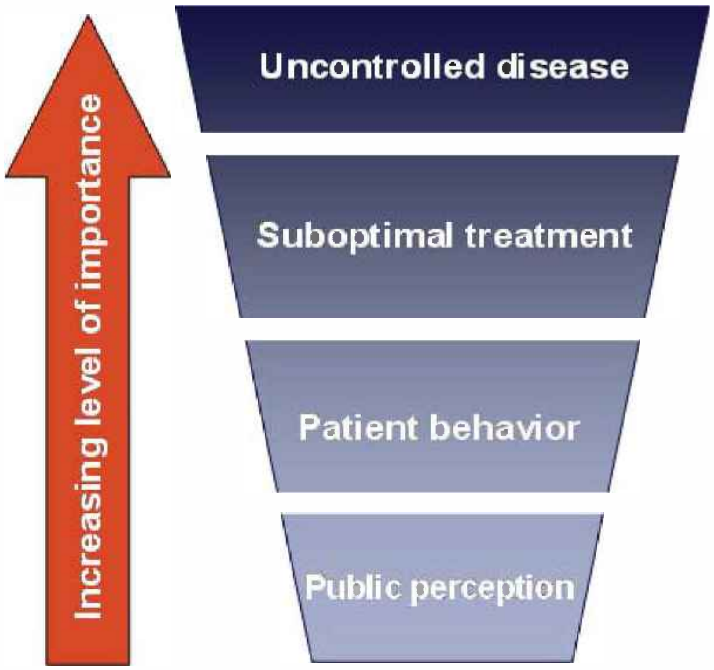
"If you look at the prescribing patterns, what you tend to see is that for nasal steroids used throughout the year, the branded products tend to be slightly more common, and then during the hay fever season, you see a more substantial increase in the beclometasone and the fluticasone propionate, and the GPs [general practitioners] *are trying to save some money there."*

UK key opinion leader

Unmet needs

A key unmet need in allergic rhinitis is the lack of a cure; patients experience symptoms and are required to take medication throughout their lives. Furthermore, although allergic rhinitis is generally considered to be well controlled with numerous available therapies, this perception is in itself an unmet need. While there is relatively little public attention paid to this non-life threatening disease, many patients experience troublesome symptoms despite regular treatment, and as a result face disruption to their daily activities and a poor quality of life. In addition, a large number of patients never seek treatment, or experience symptoms for several years before seeking treatment. The following figure provides an overview of the main unmet needs in allergic rhinitis.

Figure 16: Unmet needs in allergic rhinitis, 2010



Source: Datamonitor

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Clinical unmet needs

Lack of a cure

One of the most important unmet needs in allergic rhinitis, as in many diseases, is the lack of a cure. Allergic rhinitis is largely treated from a symptom perspective, while the underlying disease is only partially understood. A drug that targeted the underlying disease pathology would be a major step forward in the treatment of allergic rhinitis. However, as long as the exact pathology of this disease and its relation to other diseases like asthma remains unclear, it will be difficult to develop a drug that targets this basis.

It is suggested that immunotherapy could be the first step towards a cure for allergic rhinitis, while also offering a preventative treatment for asthma. In 2009 Grazax became the first immunotherapy in Europe to gain approval as a 'disease modifying treatment,' representing a significant step towards the possibility of a cure (ALK-Abelló, 2009; https://newsclient.omxgroup.com). While it is still too soon to proclaim that a cure is indeed possible for allergic rhinitis, it is clear that development is actively moving in that direction and the industry is therefore closer than ever before.

Uncontrolled disease

A subgroup of allergic rhinitis patients are poorly controlled with nasal corticosteroids and other standard-of-care medications. Consequently, these patients can experience frequent exacerbations and continual symptoms, limiting their activity and often resulting in a poor quality of life.

At the 2010 European Academy of Allergy and Clinical Immunology (EAACI) Annual Congress, Peter Howarth spoke at a Stallergènes sponsored symposium. He asserted that 15–20% of patients with allergic rhinitis remain uncontrolled despite the use of symptomatic medications, representing a significant unmet need. With new developments in immunotherapy it may be possible to address this unmet need.

Suboptimal therapy

Of those patients on current therapies, whose symptoms are considered to be controlled, many continue to experience breakthrough symptoms, or require multiple treatments to treat different types of symptoms (e.g. nose, eyes, etc.). At a press conference at the 2010 EAACI Annual Congress Peter Howarth discussed the need to focus on finding better treatments, noting that no single therapy is fully effective. This view was echoed by key opinion leaders interviewed by Datamonitor.

> *"Up until now antihistamines and also nasal steroids are demonstrated to be quite effective… still, there is a lot of margin for improvement, that is my personal feeling."*
>
> EU key opinion leader

"We still have people breaking through with our nasal steroids and our antihistamines and our other medications, so even though they are effective, I do not think they by any means take away the symptoms entirely."

US key opinion leader

Environmental unmet needs

Patient behavior

There are two main unmet needs in terms of patient behavior, first, many patients do not seek treatment for allergic rhinitis, and second, compliance is relatively low. At the 2010 EAACI Annual Congress Randolf Brehler reported the results of a study that showed allergic rhinitis patients experience symptoms for an average of 4–5 years before seeking care from an allergy specialist. Because of the many treatments available over-the-counter (OTC), a low proportion of patients with allergic rhinitis ever seek treatment from a healthcare professional.

"It is difficult to be sure because so much treatment is over the counter in the UK…but it is probably around 10–15% of the population that gets treated by their GP for their allergic rhinitis."

Compliance is essential to achieve optimal medical management. Issues such as failure to take, and improper use of, medications as prescribed can lead to dissatisfaction in their control of symptoms. A survey performed by the Asthma and Allergy Foundation of America found that 60% of the patients suffering from allergic rhinitis are 'very interested' in finding a new medication and 25% are 'constantly' trying different medications to find one that 'works' (Marple *et al* ., 2007). Those who were dissatisfied also said their healthcare provider does not understand their allergy treatment needs and did not take their allergy symptoms seriously. This dissatisfaction can in turn lead to reduced compliance and an increased reliance on multiple agents and OTC products. A lack of effective communication between healthcare provider and patient can furthermore lead to noncompliance and unhappiness in a significant portion of patients. An additional difficulty with steroid treatment is that patients often dislike the idea of continuous treatment due to a perceived risk of side effects. On the other hand, patients can also overmedicate when experiencing more intense allergic rhinitis symptoms or when they have a cold. This can increase side effects which, especially in nasal corticosteroids, can be problematic.

Cost can also lead to noncompliance, with patients unable or unwilling to pay for treatments. As many treatments for allergic rhinitis are either only available OTC, or not reimbursed, this is a key factor that is difficult to address.

"Adherence to treatment … is decreasing when someone is not reimbursed. So, there is a direct influence from reimbursement."

EU key opinion leader

"Whilst getting nasal congestion under control may be an aspiration of guidelines and may be important to the patient, they are not prepared to bear the cost of either the impact of using a nasal steroid or the hassle factor of seeing a physician."

UK key opinion leader

Compliance issues in allergic rhinitis are compounded when complex treatment regimens are necessary. This problem is often exacerbated in elderly patients, where the number of concomitant therapies can increase confusion and reduce convenience. Improved dosing regimens should be the key focus for companies looking to improve compliance in these patient groups. Several combinations of nasal antihistamines and nasal corticosteroids are in development, and, should they reach the market, these could help to address this need.

The costs of noncompliance are two-fold: the patient experiences a reduced quality of life, and healthcare systems are put under pressure by noncompliant patients, whose conditions have worsened, thus requiring more costly acute medical interventions. Stern *et al.* (2006) examined the association between medication compliance and exacerbation in asthma patients. This study showed that more compliant patients were significantly less likely to experience exacerbations than less compliant patients were.

Lack of public attention

Allergic rhinitis causes a significant loss of productivity, creating a huge economic burden. Many patients lose work/school days and are unable to continue their normal daily activities. This was highlighted at a press conference at the 2010 EAACI Annual Congress. Jan Cotvall discussed the need for a dialogue with authorities regarding diseases that impact quality of life, whereas the current focus is often directed towards deadly diseases. There is a widespread belief that allergy is not a 'disease,' but rather something that you just live with. But, in reality, allergic rhinitis has a large impact on quality of life, and therefore needs to be taken seriously with increased recognition.

"There is a sort of attitude in some GPs' hands, that rhinitis is not a significant condition. Patients can buy virtually everything they need over the counter; you can buy an antihistamine, you can buy short cortisone nasal steroids … [GPs think] *patients can get most things they need or they put them on repeat prescription and then they are left to their own devices."*

UK key opinion leader

Clinical trial design in allergic rhinitis

New trends in endpoints

Allergic rhinitis treatments are traditionally evaluated on the basis of reported symptoms. The US Food and Drug Administration (FDA) published draft guidance in 2000, which recommends the use of patient-reported instantaneous and reflective composite symptom scores (FDA, 2000; http://www.fda.gov). Rhinorrhea, nasal congestion, nasal itching and sneezing are generally included in clinical trials, and rated on a scale of 0–3 where:

- 0 = absent symptoms (no signs/symptoms present);
- 1 = mild symptoms (signs/symptoms clearly present, but minimal awareness; easily tolerated);
- 2 = moderate symptoms (definite awareness of signs/symptoms that are bothersome but tolerable);
- 3 = severe symptoms (signs/symptoms that are hard to tolerate; causes interference with the activities of daily living and/or sleeping).

Additional non-nasal symptoms may be included in the composite score and should be discussed with the FDA on a case-by-case basis. The FDA further notes that both patient-rated symptom scores and physician-rated symptom scores may be measured, but the patient scores are preferred for use as a primary endpoint. Additionally, given the subjectivity of endpoints in allergic rhinitis clinical trials, blinding is of critical importance and should be carefully described in the study protocol.

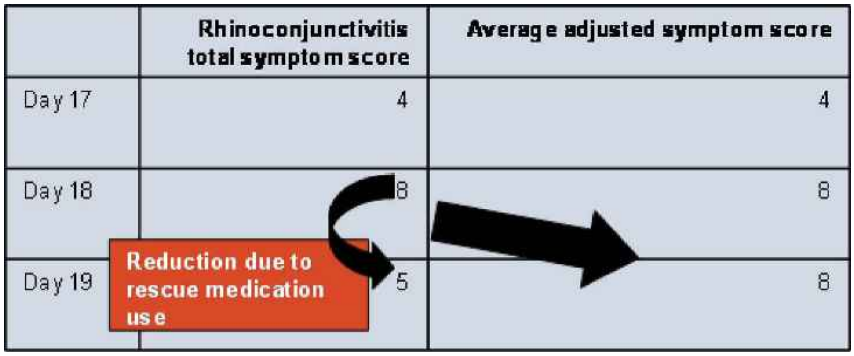
A recent development has seen a movement towards the use of an adjusted symptom score, which takes into account rescue medication use over the duration of a trial. Such a score corrects for the way that rescue medication impacts symptoms, allowing for a greater understanding of the efficacy of the treatment being investigated.

> *"The rationale for* [a combined score] *is that if your symptoms go down but your medication use goes up, that is not necessarily a significant improvement."*
>
> US key opinion leader

This approach has been most widely used in the recent development of immunotherapy, and was first advocated in the European Medicine Agency's (EMA) guidelines on the clinical development of products for specific immunotherapy for the treatment of allergic diseases (EMA, 2008; http://www.ema.europa.eu). The guidelines list the same 0–3 symptom scale mentioned above, but further note that the use of rescue medication has an impact on symptoms, and therefore both symptoms and rescue medication usage must be incorporated in the primary endpoint.

At the 2010 Annual Congress the European Academy of Allergy and Clinical Immunology (EAACI) held in London, the topic of adjusted symptom scores was extensively discussed. During the Stallergènes company-sponsored symposium Pascal Demoly discussed the fact that the impact of rescue medication will be greater in the placebo group, as their symptoms are expected to be more severe prior to treatment, which led to the use of an adjusted symptom score and its acceptance by the EMA. Demoly illustrated the difference that medication use can make by considering a case using both the Rhinoconjunctivitis Total Symptom Score (RTSS) and the Average Adjusted Symptom Score (AASS), this is depicted in Figure 17. In this example, the reduction in the RTSS seen from Day 18 to Day 19, is attributable to rescue medication, so that for the AASS, this reduction is not included, and instead the symptom score from Day 18 is carried over to Day 19.

Figure 17: Average adjusted symptom score example



Source: Datamonitor adapted from Pascal Demoly, presented at EAACI 2010

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The impact of allergic rhinitis is not fully captured by looking at symptom scores alone, as quality of life can be substantially diminished with many patients missing work/school days and experiencing sleep disturbance. To capture these and other disease-specific heath-related quality of life (QoL) aspects, questionnaires such as the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) have been developed and validated for clinical trial use. The incorporation of health-related QoL questionnaires into clinical trials broadens the information obtained regarding the effect of the therapeutic intervention and helps to focus on those issues relevant to the individual patient. The use of the RQLQ has been seen as a secondary endpoint in trials for immunotherapy including Grazax (ALK-Abelló) and Oralair Grasses (Stallergènes).

Challenges with seasonality of disease

Time constraints typically apply to trials in allergic rhinitis. If perennial allergic rhinitis (PAR) is being studied, then seasonal allergies could influence the results. It is therefore necessary to time trials carefully with a sufficient margin to avoid the major pollen season. In contrast, it is crucial to hit the relevant season when studying seasonal allergic rhinitis (SAR).

A further difficulty is that pollen seasons fluctuate in both duration and severity, with a direct impact on clinical trial outcomes. Without a sufficiently high pollen level, and corresponding symptoms, it can be difficult to reach statistical significance in a trial. On the other hand, during particularly severe seasons, efficacy may be exaggerated.

One potential way to address seasonal variations is the use of pollen chambers and allergen challenges. Both the EMA and FDA address the possible use of challenges in their guidelines. The EMA states that the Conjunctival Allergen Challenge (CAC; also known as the Conjunctival Provocation Test) is a validated model for the study of allergic conjunctivitis. With it, quantifiable symptoms, such as redness and itching are reproducible. The guidelines further state that the use of CAC and other provocation tests used to evaluate the response to an allergen challenge, may be used as supporting evidence for efficacy and to establish optimal dosing, under the condition that the test be thoroughly justified. Other potential models for pharmacodynamic studies include the Nasal Allergen Challenge, and the Environmental Exposure Unit (EEU), with the validity of these models requiring justification (EMA, 2004; http://www.ema.europa.eu). FDA guidelines also emphasize the supporting nature of challenge tests, stating that if EEU and/or park studies demonstrate a shorter onset of action than is seen in Phase III trials, the results must be replicated. This stems from the shorter duration of EEU and/or park studies, and their restricted setting. Furthermore, onset of action data from Phase III trials must be included in package inserts, to reflect the real world setting (FDA, 2000; http://www.fda.gov). It is therefore clear that neither agency would accept evidence from challenge tests in isolation, such that while they are useful, they cannot entirely solve the issues surrounding the variability of symptoms.

> *"I know some studies are trying to look at challenge chambers and then using that as a surrogate for efficacy. There are not many challenge chambers the world, that is one problem and the other is whether the FDA is willing to accept that, and at this point in time I do not think they are…if you have a bad pollen year or something goes wrong, you have lost a whole year of the study."*
>
> US key opinion leader

Study populations

Given the variability between seasons and therefore of the symptoms experienced by patients with allergic rhinitis, it is essential to include patients with a sustained history of the disease. For seasonal allergic rhinitis (SAR) trials, the FDA's inclusion criteria includes a history of SAR for a minimum of 2 years prior to study entry, with documented sensitivity proven by positive skin testing or by validated *in vitro* tests for immunoglobulin E (IgE) specific to the relevant seasonal allergen within the study's geographic area and not more than 12 months before enrollment. The same documented sensitivity requirement pertains to perennial allergic rhinitis (PAR) effectiveness trials. An additional requirement for both SAR and PAR trials is that patients should meet or exceed a minimum level for specific symptoms at the time of enrollment, which should then be included in the primary endpoint, and patients should also have at least moderate severity for the majority of individual symptoms. The FDA further recommends exclusion criteria, such as patients with asthma (except for mild intermittent asthma), chronic or intermittent use of corticosteroids, and patients using long-acting antihistamines (FDA, 2000; http://www.fda.gov). The EMA inclusion criteria echoes that of the FDA, however, its guidelines provide less information regarding who should be excluded, stating only that patients who received anti-allergy immunotherapy over the previous 2 years should not be eligible (EMA, 2004; http://www.ema.europa.eu).

While adherence to these guidelines should help to ensure appropriate patient selection, the fact that patients are selected for clinical trials based on their history of symptoms, which is not necessarily representative of what they will experience during future seasons, remains a challenge to clinical trial design.

Comparator drugs

Comparator drugs are traditionally not seen in allergic rhinitis trials. With many companies' lifecycle management strategies involving the launch of follow-on products, the use of head-to-head trials could help to promote the advantages of second and third generation products, however, this is rarely seen in practice.

Without head-to-head trials it is difficult to convince physicians that a follow-on product offers an improvement, which could explain why some companies have failed to see substantial patient switching, particularly in the oral antihistamine class.

On the other hand, Meda Pharma has successfully moved patients in the US from its twice-daily nasal antihistamine Astelin (azelastine), to its reformulated once-daily follow-on product Astepro (azelastine). While the primary improvement of the follow-on product is its once-daily dosing, Astepro's Phase III program included over 1,000 patients in placebo-controlled head-to-head trials of Astepro and Astelin. In total, fewer reports of bitter taste and nasal discomfort occurred with Astepro compared to Astelin. Patients also described better symptom relief with the follow-on product (Meda, 2009c; http://feed.ne.cision.com; Meda, 2008; http://feed.ne.cision.com). By comparing the two drugs in the Phase III program, Meda Pharma was able to clearly demonstrate the advantages of the follow-on product, which contributed to its success in the market.

Guidelines in immunotherapy

In 2008 the EMA issued guidelines on the development of allergen immunotherapy for the first time. These guidelines were extensively discussed at the European Academy of Allergy and Clinical Immunology (EAACI) Annual Congress held in London in June 2010. The guidelines were of particular interest because they are currently driving the development of future immunotherapy, with large-scale trials seen in recent years.

The guidelines have been developed to improve the assessment and comparability of study results, and they note the previously wide variation across all aspects of study design. The guidelines highlight the differing claims that can be made from immunotherapy studies, noting that the main aim of specific immunotherapy is a persistent effect due to changes in the immune system. Such an outcome can only be demonstrated in long-term studies, while efficacy may be demonstrated over a single pollen season for allergic rhinitis/rhinoconjunctivitis or over one or two control periods for perennial allergies. Four possible claims are given, including:

- treatment of allergic symptoms: short-term clinical trials conducted to demonstrate efficacy in the first pollen season after the start of a specific immunotherapy or to show efficacy in perennial allergies after some months of treatment;
- sustained clinical effect: the maintenance of significant and clinically relevant efficacy during 2–3 treatment years;
- long-term efficacy and disease modifying effect: sustained significant and clinically relevant efficacy in post treatment years;
- curing allergy: the sustained absence of allergic symptoms in post treatment years (EMA, 2008; http://www.ema.europa.eu).

The guidelines also recommend endpoints, suggesting that the primary endpoint should reflect both symptom severity and the intake of rescue medication. However, it is acknowledged that, to date, no validated system for balancing symptom scores and medication use exists, and different approaches to combining these factors are possible. The guidelines therefore encourage the establishment of a validated scoring system.

The EAACI 2010 conference also considered possible amendments to the regulatory procedures for allergen immunotherapy. At the Stallergènes company-sponsored symposium, Randolf Brehler discussed these changes, noting that EU national regulations are converging. Allergy vaccines have for years been prescribed on a 'named patient basis', under which they were not registered pharmaceuticals, but rather used under the responsibility of the prescribing physician, and produced and supplied directly to a named patient. However, this is set to change as a number of EU countries are updating their regulations, including Germany, the Netherlands, Spain, Italy and France. Before 2012, allergen immunotherapy will be available on a named patient basis, for which marketing authorization is not required. However, after 2013 named patient products will only include treatments for rare allergies, excluding such allergens as grass, mites, and venom. Companies developing such products must therefore follow the EMA guidelines in order to seek full marketing approval, as with other pharmaceutical products.

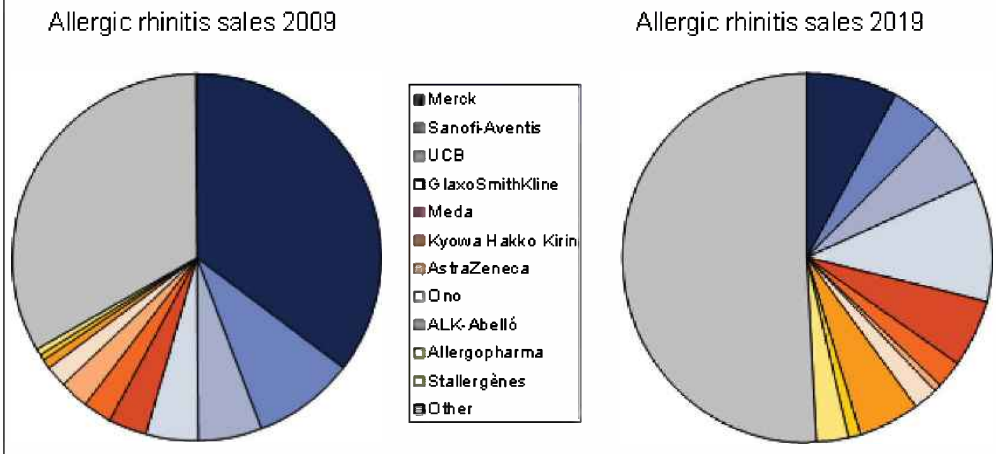
ALK-Abelló's 2009 Annual Report provides an overview of these regulatory changes, and the impact they will have on the industry. France was the first to update its system, with documentation for approving named patients' products produced in 2004/05. In the Netherlands, the relevant regulatory changes pertain to reimbursement, negatively impacting unregistered products. In Germany, future significant allergen based products will have to be registered and gain marketing approval. Spain and Italy have indicated that increased clinical documentation on allergens will be required in the future, but no official requirements have yet been announced. These changes will negatively impact the vast majority of allergen products currently in use, and are the driving force behind the new trend towards allergen immunotherapy, with large-scale evidence-based development programs seen for the first time (ALK-Abelló, 2009; http://nozebra.ipapercms.dk/alk/uk/aarsrapport09uk/).

As of June 2010 the FDA has not published guidance for industry on allergen immunotherapy.

Key companies involved in the allergic rhinitis market

Numerous treatment options are available for allergic rhinitis, with the overall market fragmented between a number of key players. Figure 18 shows market share for allergic rhinitis sales by company for the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK) for 2009 and 2019.

Figure 18: Allergic rhinitis-specific market share by company in the seven major markets, 2009 and 2019



Seven major markets = US, Japan, France, Germany, Italy, Spain, and the UK

Source: 2019 forecast = Datamonitor; 2009 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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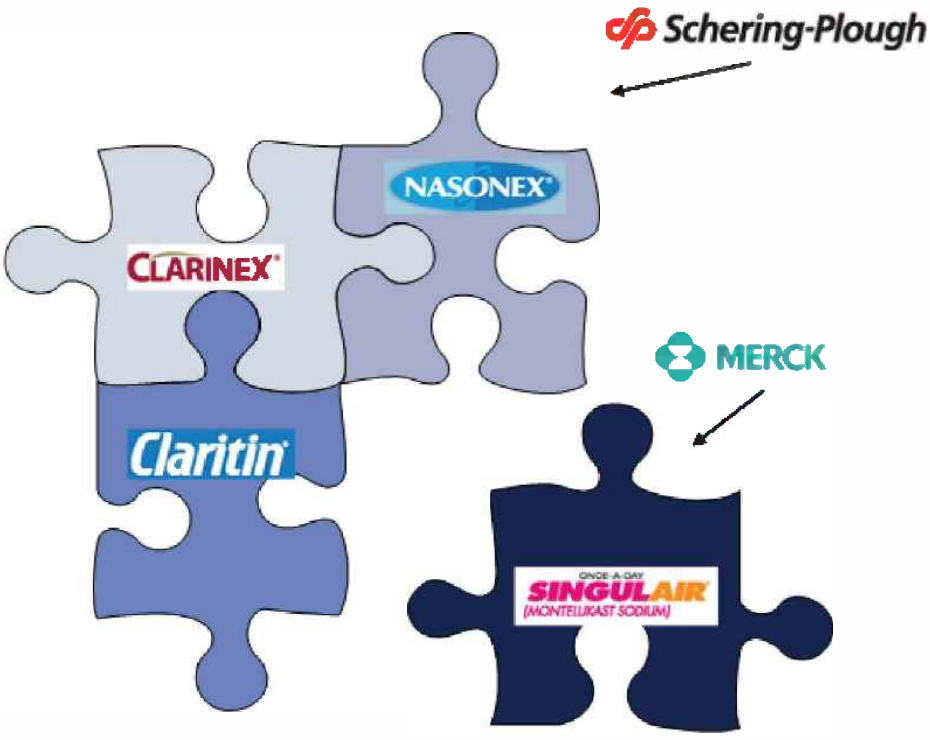
With its acquisition of Schering-Plough, Merck has obtained a number of products that strengthen its respiratory franchise, which already contained the blockbuster Singulair (montelukast). Merck has established its position as the company with the largest presence in this mature market, accounting for a third of all allergic rhinitis sales in the seven major markets in 2009. This significantly surpasses the second largest company, Sanofi-Aventis, with allergic rhinitis sales of just 9% of the market.

Merck's respiratory franchise now consists of four key products, spanning oral antihistamines, nasal corticosteroids, and antileukotrienes. The company's product offering is therefore diversified, with the products complementing, rather than competing, with each other. These are shown in Figure 19.

Figure 19: Merck's respiratory franchise, 2010



Source: Datamonitor

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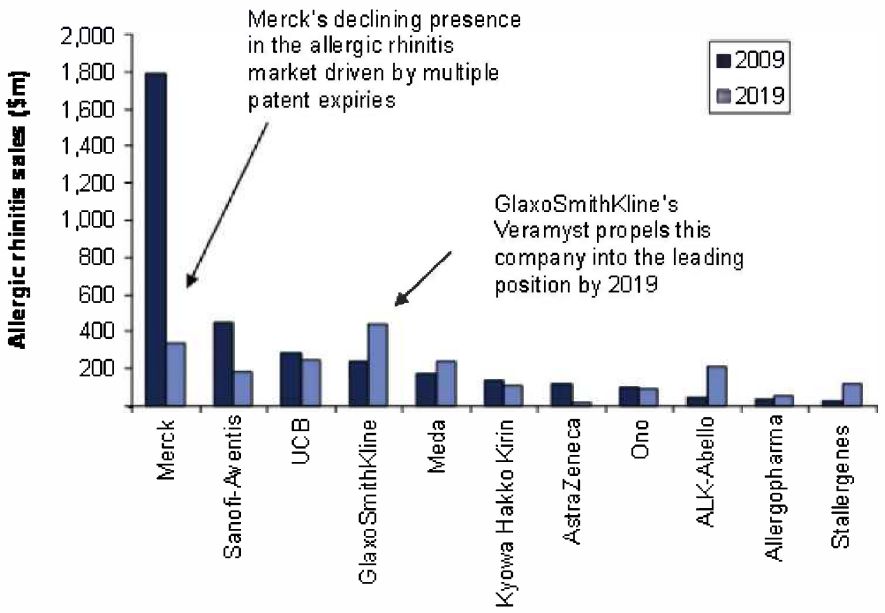
The next 10 years are expected to bring significant change to the composition of the allergic rhinitis market, with key patent expiries causing further fragmentation of the market, as generic companies increase their presence. By 2019 Merck's share of the market is forecast to drop to just 8%, making it the second largest company in the market, after GlaxoSmithKline which will see its share grow from 5% to 11% by 2019.

Merck's share will shrink as Nasonex (mometasone), Clarinex (desloratadine), and Singulair (montelukast) all go off-patent by 2019. GlaxoSmithKline's growth, on the other hand, will come from increased sales of Veramyst (fluticasone furoate), which will help to regain a portion of its previous sales of Flixonase/Flonase (fluticasone propionate), which were largely lost to generics. However, even as the market leader, the company will not see sales on a par with what it once had, before Flixonase/Flonase going off-patent.

With market dynamics varying by country, Japanese companies are expected to see the least impact from patent expiries, as the degree and speed of generic erosion is significantly less in Japan compared to the US and EU. This is reflected in only marginal decreases the Japanese companies Kyowa Hakko Kirin and Ono have seen in sales, and maintaining steady market shares of 3% and 2%, respectively, over the period 2009–2019.

Figure 20 shows sales achieved by the major allergic rhinitis companies in 2009 and 2019, demonstrating these dynamics.

Figure 20: Allergic rhinitis sales in the seven major markets, 2009 and 2019



Source: 2019 forecast = Datamonitor; 2009 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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Immunotherapy companies are expected to gain market share over the next 10 years, as sublingual immunotherapy drugs increase the exposure of this class. ALK-Abelló and Stallergènes are forecast to increase their sales four-fold by 2019, with market share increasing from 1% each to 5% for ALK-Abelló and 3% for Stallergènes by 2019.

2. ORAL ANTIHISTAMINE FRANCHISES

Key findings

- The oral antihistamine class accounts for 36% of all allergic rhinitis sales in the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK), making it the most valuable class, with allergic rhinitis sales of $1.8 billion in 2009. Numerous generic products already exist within the class, and with the additional patent expiries of Aerius/Clarinex (desloratadine) in the EU, Xyzal (levocetirizine) in the US and EU, the class is forecast to reduce in sales to $1.7 billion by 2019, counter balanced slightly by Xyzal's forecast launch in Japan.
- In the oral antihistamine class, key companies have developed franchises in order to retain patients post-patent. Several products have been combined with decongestants, and follow-on products have been introduced with reformulations of original molecules. However, with little differentiation between products, and minimal improvements identified, companies have failed to maintain the sales seen from their original antihistamine product. An example of this is Merck's Aerius/Clarinex (desloratadine), which reached total brand sales of $457m in the seven major markets in 2009, only a fraction of what its predecessor, Claritin's (loratadine) sales of $1.9 billion in 2002 prior to patent expiry.
- Several key companies have strengthened their franchises by combining their oral antihistamines with a decongestant. These combinations form a large part of the systemic nasal preparation class, and are significantly more common in the US than in other major markets. In 2009, the systemic nasal preparations class reached allergic rhinitis sales of about $450m in the seven major markets, roughly a quarter of sales seen for oral antihistamines. However, this represents primarily prescription sales, and oral antihistamine/decongestant combinations are widely sold over the counter.

Overview of oral antihistamines

Oral antihistamines are the largest class in the allergic rhinitis market, comprising 36% of sales in the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK) in 2009. Sales of oral antihistamines for allergic rhinitis in those markets totaled nearly $1.8 billion in 2009, and are forecast to remain strong with only a slight drop to $1.7 billion in 2019. With numerous generics available, this class is characterized by high volume with low and decreasing prices.

While first generation antihistamines suffered from sedating effects, second and third generation antihistamines are now available and are considered both safe and effective. With numerous products available, there is little to clinically differentiate antihistamines from one another, making marketing a particularly important factor for this class.

> *"Well, the first thing is not to use a first generation oral antihistamine, a sedating antihistamine, and that is the most important thing because we know that impacts on people that either study or work. Beyond that really, they are much of a muchness, I mean there may be minor differences but there really is not much."*
>
> UK key opinion leader

"To be honest, I find it very difficult to differentiate. I mean some patients get on well with one, some patients get on well with another. I have no specific brand loyalty. "

UK key opinion leader

Oral antihistamines are considered a first-line treatment for milder symptoms of allergic rhinitis, and patients can often self-treat with the many molecules now available over the counter (OTC), but they are not thought of as effective for treating more severe forms of the disease.

"Antihistamines are not considered effective for patients with more severe disease."

EU key opinion leader

"The vast majority of people I see have got significant disease, and an antihistamine is not going to be adequate for them."

UK key opinion leader

A pivotal trend that has been observed in the oral antihistamine class is the strengthening of 'franchises'. Several major brands have been strengthened either through the development of additional formulations, thus appealing to various patient populations, or through the introduction of new brands based on adaptations of the central molecule. This lifecycle management strategy can help to extend a franchise's profitability post-patent expiry, and, in particular, its strength in the OTC sector where patient loyalty is a crucial factor. However, it is less successful in the prescription market as physicians tend to switch to a different molecule entirely when patients require an alternative, rather than prescribing a supposedly improved version.

"In the United States, most are not being covered by insurances, because a fair number have been made over the counter. Fewer and fewer are prescribed."

US key opinion leader

Oral antihistamines have also been combined with decongestants as part of a franchise strategy. The use of oral antihistamines combined with decongestants is primarily over the counter in the EU, with physicians hesitant to prescribe such drugs.

"The sales [of antihistamines plus decongestants] *are quite good but they are not prescribed by the specialists, I mean as OTC drugs these are effective and of course having the pseudoephedrine, this is very well perceived by the patients, but usually as specialists we are against the use of ephedrine, at least in Europe."*

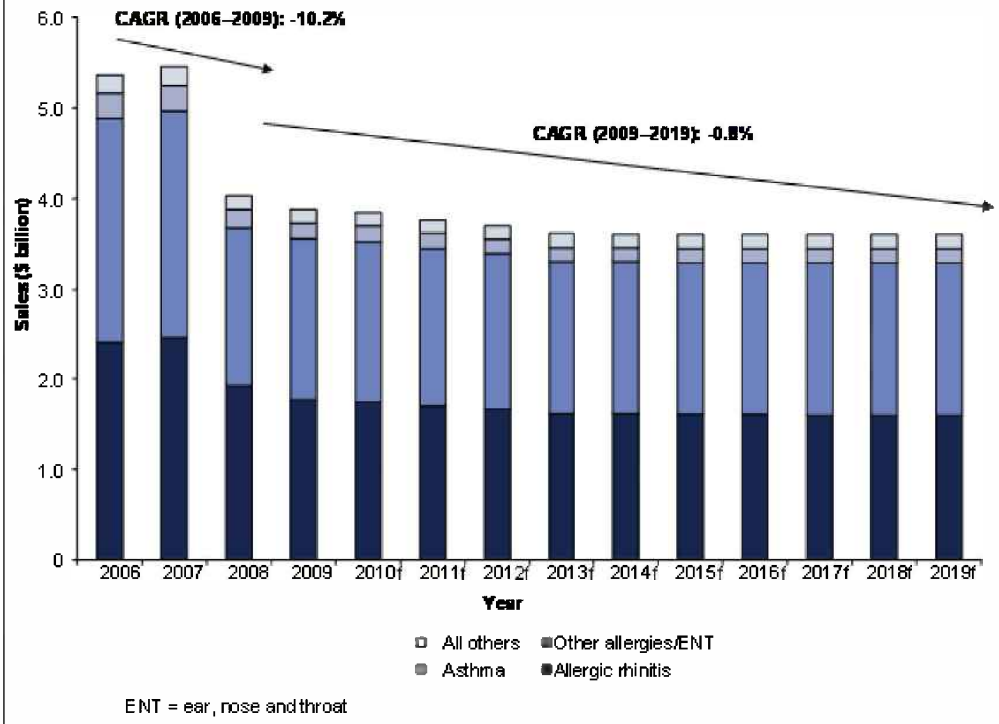
EU key opinion leader

Diagnosis value data from MIDAS Prescribing Insights revealed a wide variation in year-on-year indication splits of antihistamines combined with decongestants in the EU, and Datamonitor believes this is due to the minimal sales captured by IMS, which are primarily prescription based, thus excluding the over the counter element of the market. To correct for this variation, Datamonitor has applied the diagnosis value split from the US to the EU as well, as it is believed to be the most robust.

Oral antihistamine market size

The oral antihistamine market is lucrative, with sales across the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK) of nearly $4 billion in 2009. However, this was down from $5.5 billion in 2007, as generics continue to increase their presence in the market. Specifically this time period was impacted by the expiry of Zyrtec (fexofenadine) (see the Chapter 8 Case Study for detail of this impact). With several additional key patent expiries expected over the next 10 years, Datamonitor forecasts the oral antihistamine market will continue to decline, with an overall compound annual growth rate (CAGR) of -0.8% from 2009 to 2019.

Figure 21: Oral antihistamine sales in the seven major markets by indication ($ billion), 2006–2019



ENT = ear, nose and throat

Source: 2010–2019 forecast = Datamonitor; 2006–09 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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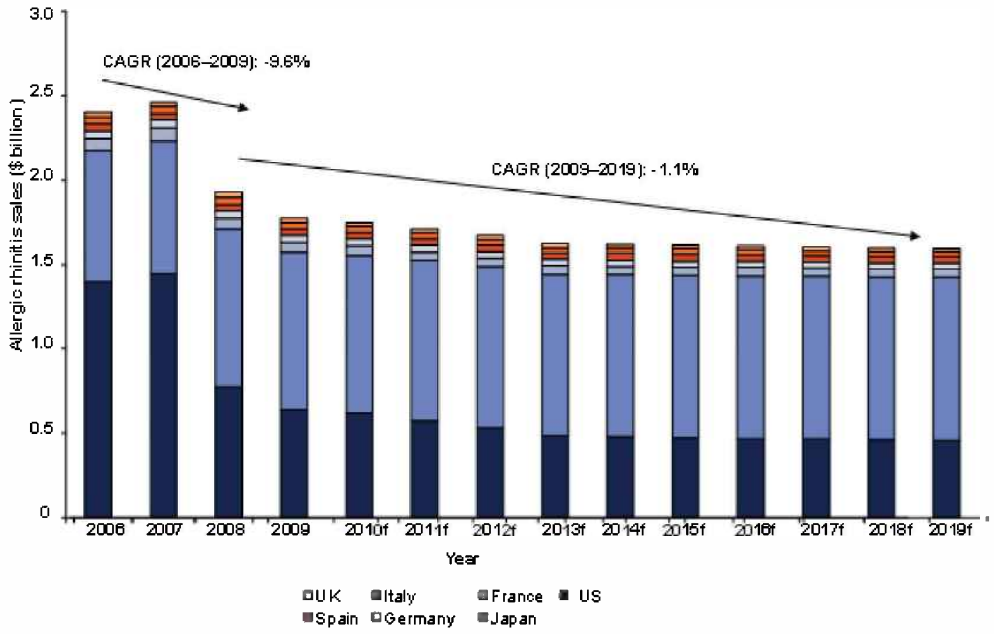
Allergic rhinitis sales made up $1.7 billion of oral antihistamine sales in the seven major markets in 2009. Allergic rhinitis sales by country are shown in Figure 22. As with the class as a whole, allergic rhinitis sales are forecast to experience a steady decline over the next 10 years, with indication-specific sales of $1.6 billion in 2019.

Figure 22: Allergic rhinitis sales of oral antihistamines in the seven major markets by country ($ billion), 2009–2019



Source: 2010–2019 forecast = Datamonitor; 2006–09 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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Allegra/Allegra-D franchise (fexofenadine, Sanofi-Aventis)

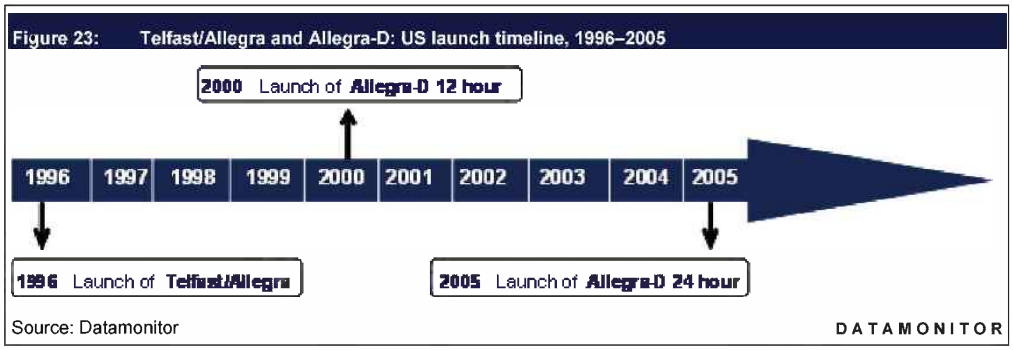
Summary takeaways:

- **Franchise products:** Telfast/Allegra (fexofenadine); Allegra-D (fexofenadine/pseudoephedrine);
- **2009 sales:** Telfast/Allegra: total brand: $538m, allergic rhinitis: $262m; Allegra-D: total brand: $419m, allergic rhinitis: $191m;
- **2019 forecast sales:** Telfast/Allegra: total brand: $384m, allergic rhinitis: $183m; Allegra-D: total brand: $5m, allergic rhinitis: $2.4m.

Sanofi-Aventis developed and launched Telfast/Allegra (fexofenadine), an oral antihistamine that is available in 12- and 24-hour formulations. Hoechst Marion Roussel (now Sanofi-Aventis) inlicensed fexofenadine from Sepracor in 1993 and launched Telfast/Allegra in the US in late 1996. This was followed by launches in the EU in 1997, and Japan in 2000 (Thomson Pharma, April 2010, Copyright Thomson Scientific). The product is indicated for the relief of symptoms of seasonal allergic rhinitis (SAR) in patients 2 years of age and older and has a further indication for the treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in patients 6 months of age or older (Sanofi-Aventis, 2007). In October 2006, an oral suspension of the drug was approved for children aged 6 months to 11 years in the US, and was launched in March 2007. This was followed in February 2008 by the introduction of orally disintegrating tablets in the US for children aged 6–11 years. Furthermore, a pediatric formulation was launched in Japan in 2007 (Thomson Pharma, April 2010, Copyright Thomson Scientific), and Sanofi-Aventis has filed for approval of orally disintegrating tablets in Japan as well (Sanofi-Aventis, 2009; http://en.sanofi-aventis.com/). Telfast/Allegra's key product patent expired in the US in 2005, and has since expired across the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK).

Sanofi-Aventis has also developed Allegra-D (fexofenadine/pseudoephedrine), a combination oral antihistamine and decongestant. Allegra-D was the first such combination to launch, entering the US market as a twice-daily product in 2000. By the end of 2000, Sanofi-Aventis (then Aventis) licensed AAIPharma to develop a once-daily formulation of the product. That collaboration resulted in US Food and Drug Administration (FDA) approval of a 24-hour formulation in October 2004, leading to a one-off payment to AAIPharma. A US launch followed in July 2005 (Thomson Pharma, April 2010, Copyright Thomson Scientific). Both the once-daily and twice-daily formulations of Allegra-D are approved for the relief of symptoms associated with SAR in adults and children 12 years of age and older (Sanofi-Aventis, 2006).

Figure 23 shows the timeline for the launches of the branded fexofenadine products in the US.



Franchise profile

Table 8: Telfast/Allegra and Allegra-D – franchise profile, 2010

Telfast/Allegra and Allegra-D	
Molecule	Telfast/Allegra – fexofenadine;
	Allegra-D – fexofenadine/pseudoephedrine
Mechanism of action	Telfast/Allegra – Antihistamine
	Allegra-D – Antihistamine plus decongestant
Originator	Sanofi-Aventis
Marketing company	Sanofi-Aventis
Primary indication	Telfast/Allegra – Relief of symptoms associated with seasonal allergic rhinitis in patients aged 2 years and older; treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in patients aged 6 months and older;
	Allegra-D – Relief of symptoms associated with seasonal allergic rhinitis in patients aged 12 years and older.
Formulation	Tablet, (pediatric forms: syrup, orally disintegrating tablet)
Dosing frequency	Telfast/Allegra – once- or twice-daily
	Allegra-D –once- or twice-daily
Reimbursement status	Telfast/Allegra –High copay in US or not covered as generic available.
	Allegra-D – High copay
First launch date	Telfast/Allegra - July 1996 (US); May 1997 (France, Italy, Spain and the UK); November 2000 (Japan, Germany); March 2007 (syrup – US)
	Allegra-D – Twice-daily: June 2000 (US), Once-daily: July 2005 (US)
Primary patent expiry	Telfast/Allegra – Expired (US/EU); 2014 (Japan)
	Allegra-D – Expired (US)
2009 sales, 7MM	Telfast/Allegra: total brand: $538m, allergic rhinitis: $262m
	Allegra-D: total brand: $419m, allergic rhinitis: $191m
2019 sales, 7MM	Telfast/Allegra: total brand: $384m, allergic rhinitis: $183m
	Allegra-D: total brand: $5m, allergic rhinitis: $2.4m

7MM = seven major markets (US, Japan, France, Germany, Italy, Spain, UK)

Source: Datamonitor, Thomson Pharma; Allegra prescribing information;

Allegra-D prescribing information; MIDAS sales data, IMS Health, March 2010,

Product positioning

Telfast/Allegra (fexofenadine; Sanofi-Aventis)

Telfast/Allegra is considered to be an effective antihistamine and has a history of impressive sales, particularly in the US.

> *"It is a very active, very good antihistamine."*
>
> UK key opinion leader

However, the introduction of generic fexofenadine to the US and EU markets, starting in the US in 2005 has eroded the total brand sales of Telfast/Allegra in the seven major markets, which peaked at $1.7 billion in 2003, before dropping to $398m in 2006. In the US, despite the launch of new formulations in 2007 and 2008, sales have continued to drop, with a compound annual growth rate (CAGR) from 2006 to 2009 of -31%, and total brand sales in 2009 of just $57m. Sales of generic fexofenadine in the US reached $450m in the same year. Of the total US brand sales in 2009, $31m was attributed to allergic rhinitis (Total brand source IMS MIDAS sales data; allergic rhinitis sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010).

Telfast/Allegra sees marginal sales in the five major EU markets (France, Germany, Italy, Spain, and the UK) as well, with just $29m attributed to the brand in 2009. However, subsequent sales growth has been the result of increased uptake in Japan, with the Japanese market accounting for 84% of the $539m total brand sales in 2009 in the seven major markets.

The Japanese market is expected to see further growth with the introduction of orally disintegrating tablets forecast to launch in 2010. This growth will continue until 2014, when the Japanese patent, which has been extended to February 2014, will expire and generic erosion will begin (Dolphin, May 2010, Copyright Thomson Scientific).

A citizen's petition has been filed with the FDA to switch Telfast/Allegra to over-the-counter (OTC) status, and in May 2001 an FDA advisory committee recommended this change be implemented (Thomson Pharma, April 2010, Copyright Thomson Scientific). In December 2009 Sanofi-Aventis announced that it was to acquire Chattem, a leading manufacturer of branded consumer healthcare products, and further that it planned to use this acquisition to facilitate the conversion of Telfast/Allegra to an OTC product (Sanofi-Aventis, 2009; http://en.sanofi-aventis.com/). This move will lead the product down the same path seen for Claritin (loratadine, Merck) and Zyrtec (cetirizine, Pfizer), and could help the company to regain a portion of the sales lost to generics, as brand recognition is influential in the OTC setting.

Allegra-D (fexofenadine/pseudoephedrine; Sanofi-Aventis)

Both the once-daily and twice-daily formulations of Allegra-D are approved for the relief of symptoms associated with SAR in adults and children 12 years of age and older. Although this is a fairly limiting indication compared with Zyrtec-D's indication of SAR and perennial allergic rhinitis in patients 2 years and older, its first-to-market position has made this product the highest-selling combination in the US. The development of Allegra-D has therefore proven successful for Sanofi-Aventis, although the drug did not reach the level of sales achieved by Telfast/Allegra. Sales peaked at $479m in the US in 2007, but with the entrance of generic fexofenadine/pseudoephedrine combinations, which started in 2009, they are forecast to fall to just $5m in the US by 2019, half of which will be attributed to allergic rhinitis (Total brand source IMS MIDAS sales data; allergic rhinitis sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010).

An Abbreviated New Drug Application (ANDA) for Allegra-D was submitted by Dr Reddy's Laboratories in October 2003 and in February 2004 Impax Laboratories was granted tentative approval for its ANDA for generic Allegra-D. Tentative approvals were also received by Mylan in May 2004 and by Barr in July 2004. Barr believed it was the first company to file a Paragraph IV challenge on all but one of the patents related to this product and in February 2005 Barr filed a suit against the FDA, challenging its policy of awarding generic exclusivity on a patent-by-patent basis rather than solely to the first company to submit an application containing a Paragraph IV certification to a listed patent. The company believed that this policy is contrary to the Hatch-Waxman Act and that it is entitled to sole exclusivity for its generic Allegra-D tablet product. Impax filed a motion to intervene as a defendant in this lawsuit, as it related to Impax's tentative approval for Allegra-D. In April 2005, after the FDA granted it 180 days exclusivity and Barr withdrew its lawsuit (Thomson Pharma, April 2010, Copyright Thomson Scientific).

Teva's generic version of 12-hour Allegra-D first entered the market in Q4 2009. This followed Teva's acquisition of Barr, which in November 2008 signed a Settlement and License Agreement settling outstanding patent litigation, giving the company permission to launch the generic in November 2009 under the condition that it would pay Sanofi-Aventis a royalty (Thomson Pharma, April 2010, Copyright Thomson Scientific).

Dr Reddy's Laboratories was previously expected to be the first to market a 24-hour generic version of Allegra-D, with a launch planned for Q1 2011, following FDA approval of its product in March 2010. However, the same month, Albany Molecular Research and Sanofi-Aventis filed a motion for a preliminary injunction to prevent the launch in the US (Thomson Pharma, April 2010, Copyright Thomson Scientific). In June 2010 a US court granted the injunction (Reuters, 2010; http://www.reuters.com). While Dr. Reddy's plans to appeal, Datamonitor assumes that the generic entry will be blocked, and that generic Allegra-D 24-hour will not reach the US market until November 2012, at which point the pediatric extension on the patent on the oral tablet formulation of fexofenadine plus pseudoephedrine will expire (Dolphin, June 2010, Copyright Thomson Scientific).

SWOT analysis

The following figure highlights the strengths, weaknesses, opportunities and threats (SWOT) of Sanofi-Aventis's allergic rhinitis franchise.

Figure 24: Sanofi-Aventis Allegra/Allegra-D franchise – SWOT analysis, 2010

Strengths	Weaknesses
Telfast/Allegra: ▪ Oral 12 and 24 hour formulations ▪ Available in all seven major markets ▪ Oral suspension version launched in US in 2007 ▪ Orally disintegrating tablets launched in US in 2008 ▪ Pediatric formulation launched in Japan in 2007 **Allegra-D:** ▪ Oral 12 and 24 hour formulations ▪ Was the first oral antihistamine/ decongestant combination product to launch leading to class dominance ▪ Highest selling oral antihistamine/ decongestant combination	**Telfast/Allegra:** ▪ Lack of PAR indication ▪ Generics have eroded sales in the US and EU **Allegra-D:** ▪ Lack of PAR indication
Opportunities	**Threats**
Telfast/Allegra: ▪ Promote new formulations in additional markets e.g. Japan where orally disintegrating tablets have been filed ▪ Use acquisition of Chattem to facilitate OTC switch	**Telfast/Allegra:** ▪ Generic erosion will begin in 2014 in Japan after patent expiry **Allegra-D:** ▪ Competitor Zyrtec-D (cetirizine/pseudoephedrine; UCB) has an additional indication for PAR ▪ Generic erosion of 12-hour formulation began in 2009 ▪ First 24 hour generic expected in the US in 2012

Seven major markets = US, Japan, France, Italy, Spain, and the UK

OTC = over-the-counter; PAR = perennial allergic rhinitis

Source: Datamonitor

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Brand forecast to 2019

Datamonitor makes the following assumptions in its forecasts for Telfast/Allegra and Allegra-D.

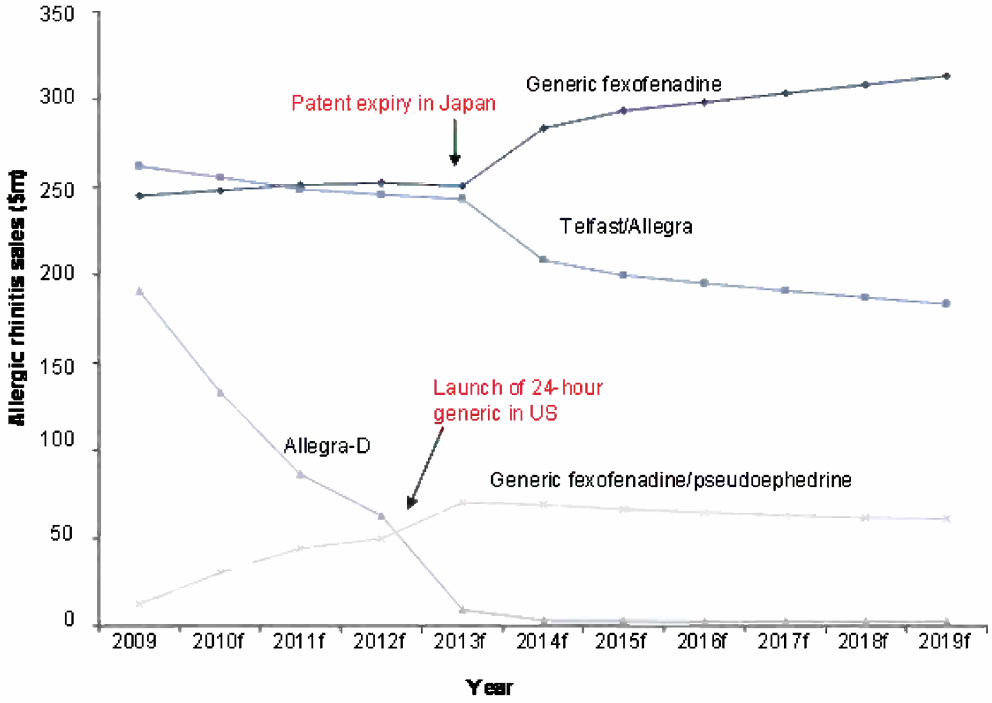
Telfast/Allegra forecast assumptions

- Total sales are expected to continue their downward trend in the US and the five major EU markets resulting from generic erosion;
- the launch of Xyzal (levocetirizine, UCB) in 2010 in Japan will reduce brand sales marginally, taking 3% of the brand's volume over 5 years;
- growth is expected to continue in Japan until patent expiry in 2014, when 30% of its current share is forecast to be lost to generic fexofenadine over 10 years;
- historical and forecasted sales are presumed to be prescription only, as IMS MIDAS sales data do not generally capture over-the-counter sales.

Allegra-D forecast assumptions

- As discussed at the start of this chapter, Datamonitor has applied the sales split by indication for antihistamine/decongestant combinations in the US (based on diagnosis value data from MIDAS Prescribing Insights), to the EU for robustness;
- Allegra-D is not currently launched in Japan and Europe and Datamonitor does not forecast its introduction to these markets as Sanofi-Aventis shows no development activity for Allegra-D in these markets;
- uptake of generic Allegra-D 12-hour will continue rapidly in the US with an additional 40% of branded volume to be lost in 2010;
- the launch of generic Allegra-D 24-hour is expected in 2012. Total brand sales are forecast to drop by 90% with generics priced at approximately 25% of the brand price;
- historical and forecasted sales are presumed to be prescription only, as IMS MIDAS sales data do not generally capture over–the-counter sales.

Figure 25: Telfast/Allegra and Allegra-D allergic rhinitis sales in the seven major markets ($m), 2009–2019



Seven major markets = US, Japan, France, Germany, Italy, Spain, and the UK

Source: 2010–2019 forecast = Datamonitor; 2009 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission. DATAMONITOR

Table 9: Sales forecasts for Telfast/Allegra, Allegra-D in allergic rhinitis in the seven major markets ($ 000), 2009–2019						
	2009	2011f	2013f	2015f	2017f	2019f
Zyrtec						
US	314	189	128	107	99	96
Japan	155,290	147,489	147,890	148,667	150,498	151,918
France	500	180	68	12	0	0
Germany	891	844	836	831	828	825
Italy	6,886	5,485	4,709	4,177	3,814	3,562
Spain	1,228	1,153	1,034	941	868	812
UK	1,275	1,220	1,138	1,090	1,053	1,024
Zyrtec total	**166,384**	**156,560**	**155,803**	**155,825**	**157,160**	**158,237**
Xyzal						
US	85,633	7,690	8,792	9,633	10,212	10,944
Japan	0	33,169	46,515	53,305	53,518	53,682
France	8,832	3,431	2,168	1,416	953	657
Germany	5,289	1,760	1,238	871	563	292
Italy	5,590	4,551	4,229	4,073	3,987	3,932
Spain	4,763	3,459	2,917	2,398	1,901	1,421
UK	894	199	111	64	37	21
Xyzal total	**111,001**	**54,259**	**65,970**	**71,760**	**71,171**	**70,949**
Zyrtec-D						
US	25	20	21	21	21	22
France	570	789	898	985	1,058	1,116
Germany	2,150	1,887	1,679	1,508	1,374	1,270
Italy	5,715	6,941	7,870	8,605	9,192	9,654
Spain	2,656	2,526	2,440	2,371	2,318	2,277
Zyrtec-D total	**11,116**	**12,163**	**12,908**	**13,490**	**13,963**	**14,339**
Franchise total	**288,501**	**222,982**	**234,681**	**241,075**	**242,294**	**243,525**

Source: 2010–2019 forecast = Datamonitor; 2009 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission. DATAMONITOR

The 10-year market forecast for Telfast/Allegra and Allegra-D, for both allergic rhinitis and other indications, is outlined separately in the accompanying forecast tool, a downloadable Excel spreadsheet that details the forecast for this drug in the seven major markets.

Zyrtec/Zyrtec-D/Xyzal franchise (levocetirizine, UCB/Sepracor/Sanofi-Aventis)

Summary takeaways:

- **Franchise products:** Zyrtec (cetirizine); Xyzal (levocetirizine); Zyrtec-D (cetirizine/pseudoephedrine);
- **2009 sales:** Zyrtec: total brand: $230m, allergic rhinitis: $166m; Xyzal: total brand: $298m, allergic rhinitis: $111m; Zyrtec-D: total brand: $17m, allergic rhinitis: $15m;
- **2019 forecast sales:** Zyrtec: total brand: $208m, allergic rhinitis: $158m; Xyzal: total brand: $121m, allergic rhinitis: $71m; Zyrtec-D: total brand: $20m, allergic rhinitis: $10m.

Zyrtec (cetirizine) is an oral, once-daily antihistamine developed by UCB. UCB has a complex marketing structure for Zyrtec, involving a number of small and large companies with a strong presence in their respective countries. Several companies (including GlaxoSmithKline, Abbott Laboratories, Sanofi-Aventis and Pfizer) have entered into sales agreements with UCB, allowing Zyrtec to reach all major markets.

Available in tablet and syrup formulations, Zyrtec is approved for the treatment of both seasonal allergic rhinitis (SAR) in patients 2 years of age and older, and perennial allergic rhinitis (PAR) and chronic idiopathic urticaria in patients aged 6 months and older (UCB, 2006). Following its patent expiry in the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK) in 2007, Zyrtec gained approval for over the counter (OTC) sale in January 2008, with Johnson & Johnson holding the rights to the OTC product (Thomson Pharma, April 2010, Copyright Thomson Scientific).

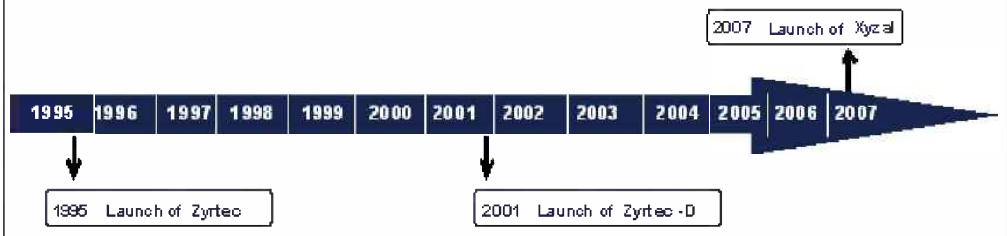
UCB and Pfizer have developed and launched the extended release treatment Zyrtec-D, a combination of cetirizine and pseudoephedrine. Pfizer holds US and Canadian rights for this drug while, as with Zyrtec, a number of other companies including GlaxoSmithKline, Abbott and Sanofi-Aventis are involved in agreements with UCB to market and distribute the drug worldwide (Thomson Pharma, April 2010, Copyright Thomson Scientific).

Zyrtec-D is approved for the relief of nasal and non-nasal symptoms associated with SAR or PAR in adults and children over 12 years of age (Pfizer, 2003). Furthermore, the US Food and Drug Administration (FDA) approved chewable tablets for the treatment of SAR and PAR and for chronic urticaria in children aged 2 years and older in March 2004 (Thomson Pharma, April 2010, Copyright Thomson Scientific).

UCB and Sepracor co-developed Xyzal (levocetirizine) as a follow-on product for Zyrtec and launched this once-daily product to Europe in 2001 (Thomson Pharma, April 2010, Copyright Thomson Scientific). Filing in the US was held up by the need to strike a deal with Sepracor — Sepracor has a method-of-use patent covering levocetirizine while UCB has a manufacturing patent, which meant that neither could launch in this market without the agreement of the other. Under the agreement between the two companies, UCB has exclusive rights to all of Sepracor's patents in the US regarding levocetirizine, and royalties will be payable to Sepracor on the US sales of levocetirizine products (UCB, 2006; http://www.ucb.com). The drug was filed in the US in July 2006, and in September 2006 UCB and Sanofi-Aventis entered into an agreement to co-market Xyzal in the US (UCB, 2007; http://www.ucb.com). This was followed by FDA approval in May 2007 and launch in October 2007. In February 2008 the FDA approved an oral solution formulation, which was launched in May 2008 (Thomson Pharma, April 2010, Copyright Thomson Scientific). Xyzal was originally approved for the relief of perennial allergic rhinitis (PAR) and for the treatment of uncomplicated skin manifestations of chronic idiopathic urticaria (CIU) for patients aged 6 years and older, and for the symptomatic treatment of seasonal allergic rhinitis (SAR) in patients 2 years and older. In August 2009 the FDA approved the use Xyzal for the treatment of PAR and CIU for patients aged 6 months and older, and for SAR in patients 2 years and older (UCB, 2009; Red Orbit, 2009; http://www.redorbit.com).

Figure 26 shows the launch timeline of this franchise in the US.

Figure 26: Zyrtec, Zyrtec-D and Xyzal: US launch timeline, 1996–2007



Source: Datamonitor

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Franchise profile

Table 10: Zyrtec/Zyrtec-D/Xyzal (levocetirizine; UCB) – franchise profile, 2010

Zyrtec/Zyrtec-D/Xyzal	
Molecule	Zyrtec (cetirizine),
	Xyzal (levocetirizine),
	Zyrtec-D (cetirizine/pseudoephedrine)
Mechanism of action	Antihistamine (Zyrtec-D plus decongestant)
Originator	UCB
Marketing/partner company	Zyrtec: UCB
	Xyzal UCB, Sepracor, Sanofi-Aventis
	Zyrtec-D: UCB, Pfizer
Indications	Zyrtec: Relief of symptoms associated with seasonal or perennial allergic rhinitis; treatment of uncomplicated skin manifestations of chronic idiopathic urticaria
	Xyzal: Relief of symptoms associated with seasonal or perennial allergic rhinitis; treatment of uncomplicated skin manifestations of chronic idiopathic urticaria
	Zyrtec D (12 and 24 hour): Relief of nasal and non-nasal symptoms associated with seasonal or perennial allergic rhinitis.
Formulation	Zyrtec: Tablet; syrup
	Xyzal: Tablet; liquid solution
	Zyrtec-D: 12 and 24 hour, tablet, chewable tablet
Dosing frequency	Zyrtec: Ages 6+: 5–10mg/Day; Ages 6 months–5 years: 2.5mg syrup/day
	Xyzal: Ages 12+: 5mg/day; Ages 6–11 years: 2.5mg/day: Ages 6months–5 years: 1.25mg/day
	Zyrtec-D: once- and twice-daily
Reimbursement status	Zyrtec: Available OTC- not covered/high copay under most plans
	Xyzal: High copay
	Zyrtec-D: Available OTC- not covered/high copay under most plans
First launch date	Zyrtec: 1989 (France, Italy and the UK); 1990 (Spain, Germany); 1995 (US); September 1998 (Japan)
	Xyzal: February 2001 (Germany), October 2001 (UK), rest of EU after 2001, June 2007 (US), NDA filed 2008 (Japan)
	Zyrtec-D: September 2001 (US); June 2001 (Japan); not launched in EU. Launched OTC in Jan 2008
Primary patent expiry	Zyrtec: December 2004 (France); February 2007 (Germany, UK); April 2007 (Italy); June 2007 (Japan); December 2007 (US); April 2009 (Spain)
	Xyzal: September 2012 (US), September 2013 (France, Germany), January 2016 (Italy, Spain, the UK)
	Zyrtec-D: Expired (7MM)
Alternative brand names	Zyrtec: Reactine (France, Germany, Italy, Spain), Virlix (Germany, Spain, Japan, France), Vividrin Akut (Germany); Piritize (UK, Japan); Formistin (Italy, Spain)
	Xyzal: Xusal, Xyzall
	Zyrtec-D: Virlix-D (Spain), Reactine Duo (Germany), Reactine (Italy, Spain), Cirrus (Japan, Italy, Spain)
2009 sales, 7MM	Zyrtec: total brand: $230m, allergic rhinitis: $166m
	Xyzal: total brand: $298m, allergic rhinitis: $111m
	Zyrtec-D: total brand: $17m, allergic rhinitis: $15m
2019 sales, 7MM	Zyrtec: total brand: $208m, allergic rhinitis: $158m
	Xyzal: total brand: $121m, allergic rhinitis: $71m
	Zyrtec-D: total brand: $20m, allergic rhinitis: $10m

7MM = seven major markets (US, Japan, France, Germany, Italy, Spain, UK)

OTC = over the counter

Table 10: Zyrtec/Zyrtec-D/Xyzal (levocetirizine; UCB) – franchise profile, 2010
Source: Datamonitor, Thomson Pharma; Zyrtec, Xyzal and Zyrtec-D prescribing information; MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission. DATAMONITOR

Product positioning

Zyrtec (cetirizine; UCB)

While Zyrtec was the first prescription-only antihistamine to be approved for seasonal allergic rhinitis, perennial allergic rhinitis, and chronic idiopathic urticaria in the US, several other products now boast the same indications, including Zyrtec's follow-on product Xyzal (levocetirizine; UCB/Sepracor). Furthermore, Zyrtec is disadvantaged by its safety profile, as it causes sedation, and these side effects are often dose-dependant.

> *"If I am worried about sedation, then I am a bit more nervous about cetirizine, it probably does cause a little bit more in clinical practice than loratadine or desloratadine."*
>
> UK key opinion leader

> *"It tends to be a bit more potent, but it tends to have a bit more drowsiness as a side effect. Further up the dose response curve, so you tend to see more efficacy and more side effects."*
>
> UK key opinion leader

Prior to its US patent expiry in 2007, Zyrtec dominated the prescription antihistamine market in the US with sales of almost $1.7 billion in 2007, compared to the second-highest selling drug in its class, Schering-Plough's Aerius/Clarinex which had total brand sales of $540m in the same year. However, from 2007 to 2008 sales of Zyrtec fell by 87% owing to generic entry, and in 2009 the total prescription sales of Zyrtec in the US were just $716,000, of which $314,000 are attributed to allergic rhinitis.

In Europe sales of Zyrtec have been low for years, due to its over the counter status, generic competition and the conversion to Zyrtec's follow-on product Xyzal (levocetirizine), which launched in 2001 (UCB, 2005; http://www.ucb.com). In 2009 sales of Zyrtec in the five major EU markets (France, Germany, Italy, Spain, and the UK) were $35m according to IMS Health.

Zyrtec was launched in Japan in 1998, and, although competition from generics began in 2007, causing a small dip in sales from 2006 to 2007, sales have continued to grow over the last few years. Japan remains the strongest market for prescription sales of Zyrtec, reaching $194m in 2009, of which, $155m were for allergic rhinitis.

In the seven major markets, total sales of the drug were $230m in 2009, of which, $166m came from allergic rhinitis (Total brand source IMS MIDAS; Allergic rhinitis sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010).

Zyrtec-D (cetirizine/pseudoephedrine; UCB/Pfizer)

Zyrtec-D's product patent has expired in each of the seven major markets. The biggest impact on sales came from patent expiry in the US in 2007. In February 2008 the US Food and Drug Administration (FDA) approved Teva's Abbreviated New Drug Application (ANDA) for a generic version of Zyrtec-D, and, with the introduction of generics, total prescription brand sales dropped in the US from $166m in 2007, to $12m in 2008, and then to just $45,000 in 2009. In January 2008 Zyrtec-D became available over-the-counter (OTC) in the US (Thomson Pharma, April 2010, Copyright Thomson Scientific).

Zyrtec-D is available OTC and is not prescribed by physicians in a number of markets. There are no prescription sales of Zyrtec-D in the UK, and prescription sales captured by IMS Health in France, Spain, Germany and Italy have been low, as with all oral antihistamine/decongestant combination products, with total brand sales of $18m. Datamonitor reports IMS Health sales data, which tend to cover prescription sales only, although this is somewhat dependant on the variable data collection methods by country, and therefore the OTC component is not captured.

> *"Well, it is used in Italy, so the sales are quite good but they are not prescribed by the specialists, I mean as OTC drugs these are effective and of course having the pseudoephedrine, this is very well perceived by the patients, but usually as specialists we are against the use of ephedrine, at least in Europe, because of the side effects."*
>
> EU key opinion leader

Xyzal (levocetirizine; UCB and Sepracor)

Xyzal contains only the r-isomer of cetirizine, which has twice the binding affinity compared to cetirizine, presumably making Xyzal more effective with fewer side effects than its predecessor (Chen, 2008). However, Xyzal has the same disadvantage of Zyrtec in terms of a sedation effect, and key opinion leaders interviewed by Datamonitor suggest that the differences between the two drugs may be minimal.

> *"There was never a head–to-head study designed, so it depends on the susceptibility of each patient. As an impression, apparently there are not that many differences."*
>
> EU key opinion leader

> *"I will use it – I mean it may be a little bit better tolerated, but if I am having a sedation problem with cetirizine, I will switch* [patients] *to a different one entirely."*
>
> UK key opinion leader

"I do not see a big difference between Zyrtec and Xyzal… I rarely switch between them looking for better efficacy."

US key opinion leader

The launch of Xyzal in the US in 2007 boosted worldwide sales of the brand, with the majority (68%) of Xyzal's 2009 total sales coming from the US region. Only marginal sales have been reached in the EU, where it was launched in 2001. In December 2008 GlaxoSmithKline, which holds the rights to the drug in Japan, filed a New Drug Application (NDA) (Thomson Pharma, April 2010, Copyright Thomson Scientific), and Datamonitor forecasts the drug will gain approval and launch in Q4 2010.

Xyzal was covered by new product data exclusivity in the US until May 2010, ensuring its place in the market for 3 years after approval. The FDA Orange Book also lists a method-of-use patent for the treatment of allergic rhinitis that runs until September 2012, with a pediatric extension to March 2013 (FDA Orange Book, 2010; http://www.accessdata.fda.gov/). However, Barr Pharmaceuticals, Synthon, L Perrigo, Teva, and PLIVA, are listed as patent opponents or infringers by Dolphin (Dolphin, June 2010, Copyright Thomson Scientific), and the FDA lists two Paragraph IV patent certificates pertaining to levocetirizine: one for an oral solution dated January 2009, and one for tablets dated December 2007 (FDA, 2010; http://www.fda.gov/). Both of these were based on ANDAs filed by Synthon (Synthon, 2009; http://www.synthon.com) and UCB and Sepracor have filed a lawsuit against Synthon alleging patent infringement (Thomson Pharma April 2010, Copyright Thomson Scientific).

It is not clear when generic versions of Xyzal will be available in the US and the timing will depend on the outcome of these lawsuits, or the decision to launch 'at risk.' As of June 2010 there is no indication that a generic product has entered the market. However, Datamonitor believes the method of use patent will not be sufficient to withhold generic entry, resulting in the loss of exclusivity, as generics enter the market later in 2010.

In Europe, Xyzal had a 'new use' patent which was set to expire in 2013 in Germany and France and in 2016 in Italy, Spain, and the UK. However, in June 2007, Teva filed a claim against this patent, which was declared invalid and revoked in March 2008 (Dolphin, June 2010, Copyright Thomson Scientific). As a result, Teva launched its generic in both Spain and France in 2009, and Datamonitor expects the company to expand into additional EU markets in 2010.

Total brand sales reached $305m in the US and the five major EU markets in 2009, of which, $113m came from allergic rhinitis sales (Total brand source IMS MIDAS sales data; Allergic rhinitis sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010). Despite an anticipated Japanese launch for 2010, Datamonitor forecasts brand sales to drop year-on-year starting in 2010 as generics erode sales throughout the US and EU. By 2019, total brand sales in the seven major markets are forecast to reach just $150m, roughly half of its peak.

SWOT analysis

The following figure highlights the strengths, weaknesses, opportunities and threats (SWOT) of UCB's franchise for allergic rhinitis.

Figure 27: UCB Zyrtec/Zyrtec-D/Xyzal franchise – SWOT analysis for allergic rhinitis, 2010

Strengths

Zyrtec:
- Oral 24 hour formulations
- Indicated for adults and pediatrics for both SAR and PAR
- Strong marketing capabilities from various collaborations

Zyrtec-D:
- Oral formulations
- Indicated for adults and pediatrics for both SAR and PAR
- Strong marketing capabilities from various collaborations
- Chewable tablets available for children

Xyzal:
- Oral 24 hour formulations
- Gained pediatric approval in 2009

Weaknesses

Zyrtec:
- Note regarding somnolence in prescribing information
- Patent expiry in all major markets has led to generic erosion of sales

Zyrtec-D:
- Low uptake in EU; not launched in UK and France
- Twice-daily formulation
- Patent expiry in all major markets has led to generic erosion of sales

Xyzal:
- Delayed launch in US lessened switch from Zyrtec
- Note regarding somnolence in prescribing information

Opportunities

Zyrtec:
- Gained approval for OTC status in 2008

Zyrtec-D:
- Only major antihistamine/decongestant combination to have an indication for PAR

Xyzal:
- Filed in Japan in 2008
- Promote as more effective and better tolerated follow-on to Zyrtec

Threats

Xyzal:
- Generic erosion will continue in the EU
- Generic erosion expected in the US from 2010

OTC = over-the-counter; PAR = perennial allergic rhinitis; SAR = seasonal allergic rhinitis

Source: Datamonitor

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Brand forecast to 2019

Datamonitor makes the following assumptions in its forecasts for Zyrtec, Zyrtec-D, and Xyzal:

Zyrtec forecast assumptions

- In Japan, 10% of Zyrtec patients are forecast to switch to Xyzal starting in Q4 2010, with rapid switching over 5 years;
- historical and forecasted sales are presumed to be prescription only, as IMS MIDAS sales data do not generally capture over-the-counter sales.

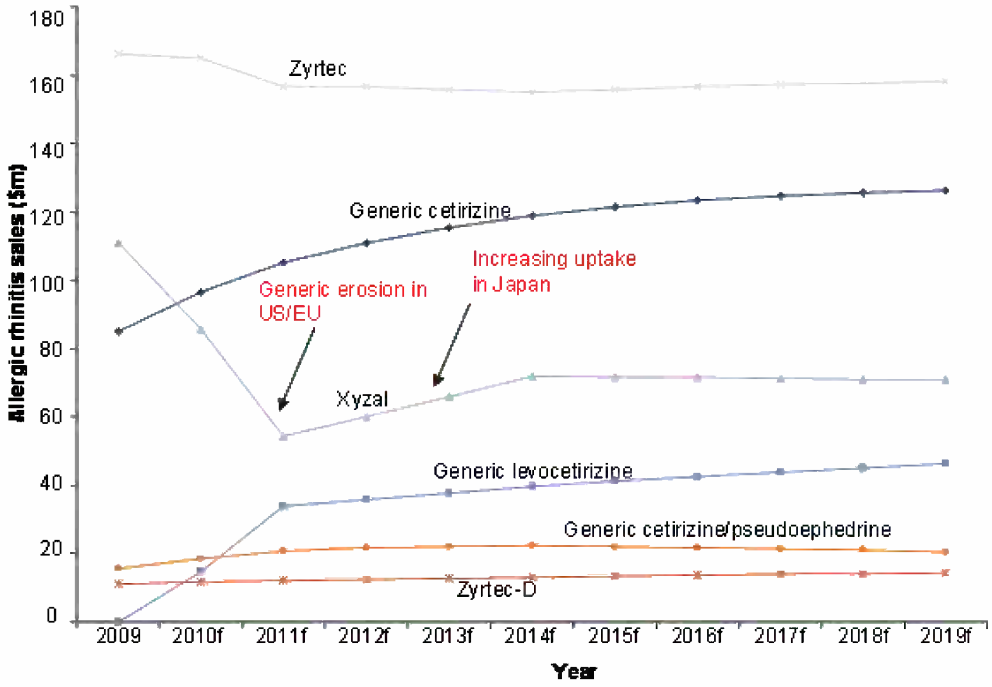
Zyrtec-D forecast assumptions

- As discussed at the start of this chapter, Datamonitor has applied the sales split by indication for antihistamine/decongestant combinations in the US (based on diagnosis value data from MIDAS Prescribing Insights), to the EU for robustness;
- Zyrtec-D is currently not launched in the UK and Japan, and Datamonitor does not expect the product to enter these markets.
- generic Zyrtec-D will continue to grow steadily in the US, keeping brand sales down, it is not expected to enter the EU markets where prescription sales of the brand are low;
- historical and forecasted sales are presumed to be prescription only, as IMS MIDAS sales data do not generally capture over-the-counter sales. .

Xyzal forecast assumptions

- Filed in December 2008, Xyzal is forecast to launch in Q4 2010 in Japan, taking 10% of Zyrtec's market, and 3% of from other branded antihistamines;
- the price of Xyzal in Japan is assumed to be the same as Zyrtec, similar to pricing seen in the EU;
- with Xyzal's 'new use' patent declared invalid and the entrance of generics in France and Spain in 2009, generic erosion is expected across the EU and US from 2010. Based on the experiences with other antihistamines going off-patent, the most rapid generic erosion is expected in the US and Germany, with 95% of the brand shifting to generics. France and Italy are expected to see the least impact, with 15% of the brand shifting to generics in Italy;
- historical and forecasted sales are presumed to be prescription only, as IMS MIDAS sales data do not generally capture over-the-counter sales.

Figure 28: Zyrtec/Zyrtec-D/ Xyzal allergic rhinitis sales by country in the seven major markets ($m), 2009–2019



Seven major markets = US, Japan, France, Germany, Italy, Spain, and the UK

Source: 2010–2019 forecast = Datamonitor; 2009 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010,

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Table 11: Sales forecasts for Zyrtec, Xyzal and Zyrtec-D for allergic rhinitis in the seven major markets ($ 000s), 2009–2019						
	2009	2011f	2013f	2015f	2017f	2019f
Zyrtec						
US	314	189	128	107	99	96
Japan	155,290	147,489	147,890	148,667	150,498	151,918
France	500	180	68	12	0	0
Germany	891	844	836	831	828	825
Italy	6,886	5,485	4,709	4,177	3,814	3,562
Spain	1,228	1,153	1,034	941	868	812
UK	1,275	1,220	1,138	1,090	1,053	1,024
Zyrtec total	**166,384**	**156,560**	**155,803**	**155,825**	**157,160**	**158,237**
Xyzal						
US	85,633	7,690	8,792	9,633	10,212	10,944
Japan	0	33,169	46,515	53,305	53,518	53,682
France	8,832	3,431	2,168	1,416	953	657
Germany	5,289	1,760	1,238	871	563	292
Italy	5,590	4,551	4,229	4,073	3,987	3,932
Spain	4,763	3,459	2,917	2,398	1,901	1,421
UK	894	199	111	64	37	21
Xyzal total	**111,001**	**54,259**	**65,970**	**71,760**	**71,171**	**70,949**
Zyrtec-D						
US	25	20	21	21	21	22
France	570	789	898	985	1,058	1,116
Germany	2,150	1,887	1,679	1,508	1,374	1,270
Italy	5,715	6,941	7,870	8,605	9,192	9,654
Spain	2,656	2,526	2,440	2,371	2,318	2,277
Zyrtec-D total	**11,116**	**12,163**	**12,908**	**13,490**	**13,963**	**14,339**
Franchise total	**288,501**	**222,982**	**234,681**	**241,075**	**242,294**	**243,525**

Source: 2010–2019 forecast = Datamonitor; 2009 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission. DATAMONITOR

The 10-year market forecasts for Zyrtec, Zyrtec-D and Xyzal, for both allergic rhinitis and other indications are outlined separately in the accompanying forecast tool, a downloadable Excel spreadsheet that details the forecasts for these drugs in the seven major markets.

Claritin/Clarinex/Clarinex-D franchise (loratadine/desloratadine; Merck)

Summary takeaways:

- **Franchise products:** Claritin (loratadine); Aerius/Clarinex (desloratadine); Clarinex-D (loratadine/pseudoephedrine);
- **2009 sales:** Claritin: total brand: $269m; allergic rhinitis: $105m; Aerius/Clarinex: total brand: $444m; allergic rhinitis: $158m; Clarinex-D: total brand: $36m; allergic rhinitis: $9m;
- **2019 forecast sales:** Claritin: total brand: $265m; allergic rhinitis: $88m; Aerius/Clarinex: total brand: $207m; allergic rhinitis: $29m; Clarinex-D: total brand: $47m; allergic rhinitis: $2.2m.

Claritin (loratadine) was developed by Schering-Plough and has been on the market in the US and EU since 1988. Through its acquisition of Schering-Plough, Merck now markets the drug. Claritin is available as tablets, RediTabs (rapidly disintegrating tablets) and syrup for children and is approved for the treatment of nasal and non-nasal symptoms of seasonal allergic rhinitis (SAR), and for the treatment of chronic idiopathic urticaria (CIU) in patients 2 years of age and older (Schering Corporation, 2000). In September 2002, Claritin was launched in Japan by Schering-Plough KK and Shionogi for the treatment of allergic rhinitis, CIU and the itching associated with skin diseases such as eczema in adults and children aged 15 years or above. This was followed in October 2007 by Japanese approval for both the tablet and RediTabs formulations of the drug for patients aged 7 years and older (Thomson Pharma, April 2010, Copyright Thomson Scientific).

In May 2001 the US Food and Drug Administration's (FDA) Nonprescription Drugs Advisory Committee and the Pulmonary-Allergy Drugs Advisory Committee examined questions arising from the potential use of Claritin in an OTC setting and recommended that loratadine had an acceptable safety profile for OTC marketing. Although Schering-Plough was initially opposed to the switch, the launch of Aerius/Clarinex, and Claritin's impending patent expiry, ultimately led the company to request that the FDA allow the switch. In November 2002 the FDA approved the switch, and consequently, Schering-Plough launched Claritin as an OTC product (USA Today, 2002; http://www.usatoday.com). However, while this approach severely reduced revenues of generic loratadine, it was only modestly successful in retaining a proportion of the revenues generated by Claritin in 2001. Since IMS MIDAS sales data mainly cover the sales of prescription drugs and because the OTC market is not clearly delineated across all markets, this impact is not broken out in Datamonitor's forecast.

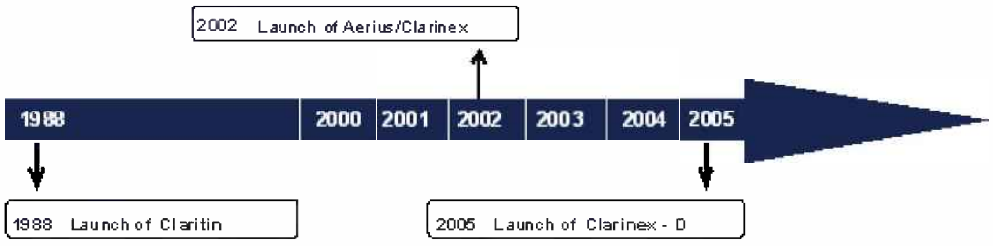
Schering-Plough's planned defense of its Claritin franchise was to switch patients to the follow-on product Aerius/Clarinex (desloratadine), a product containing desloratadine, the active metabolite of loratadine. However, Schering-Plough lost this option when the planned launch of the new molecule was delayed, eventually entering the market after Claritin's patent expiry, launching in the US in January 2002 and the EU in the spring of that year (Thomson Pharma, April 2010, Copyright Thomson Scientific).

Available in syrup and oral formulations, including orally disintegrating tablets (RediTabs), Aerius/Clarinex is indicated for the relief of symptoms associated with SAR in patients 2 years of age and older and PAR in patients 6 months of age and older. It is also indicated for the symptomatic relief of itching and to reduce the number and size of hives in patients with chronic idiopathic urticaria of 6 months of age and older (Schering Corporation, 2005).

Schering-Plough has also developed and launched once-daily and twice-daily Clarinex-D fixed-dose formulations of desloratadine and pseudoephedrine. This oral antihistamine/decongestant combination product was approved by the FDA in March 2005 and launched in the US market in April 2005. Clarinex-D is approved for the relief of the nasal and non-nasal symptoms of SAR including nasal congestion in patients 12 years of age and older (Schering Corporation, 2009). In July 2006 an Marketing Authorization Application (MAA) was submitted to the European Medicines Agency (EMA) for European approval of Clarinex-D and in May 2007 the EMA's Committee for Medicinal Products for Human Use (CHMP) recommended the drug's approval (Thomson Pharma, April 2010, Copyright Thomson Scientific), however as of 2010, the drug has not been launched in the EU.

The timeline of launch dates for this franchise in the US is shown in the following figure.

Figure 29: Claritin, Aerius/Clarinex and Clarinex-D: US launch timeline, 1988–2005



Source: Datamonitor DATAMONITOR

Through its acquisition of Schering-Plough in 2009, Merck now markets these drugs, which fit well into its growing respiratory franchise, contributing to the company's dominance in this area.

Franchise profile

Table 12: Claritin/Clarinex/Clarinex-D (des/loratadine/pseudoephedrine; Merck – franchise profile, 2010

Claritin/Clarinex/Clarinex-D	
Molecule	Claritin (loratadine)
	Clarinase (loratadine/pseudoephedrine)
	Aerius/Clarinex (desloratadine)
	Clarinex-D (desloratadine/pseudoephedrine)
Mechanism of action	Antihistamine (+/- decongestant)
Originator	Sepracor
Marketing company	Merck (formerly Schering-Plough); Shionogi
Primary indication	Claritin: reliever of nasal and non-nasal symptoms of seasonal allergic rhinitis (SAR) and for the treatment of chronic idiopathic urticaria
	Clarinase: relief of nasal and non-nasal symptoms associated with seasonal allergic rhinitis, including nasal congestion, in adults and adolescents over 12 years
	Aerius/Clarinex: relief of the nasal and non-nasal symptoms of seasonal allergic rhinitis in patients 2 years of age and older and of perennial allergic rhinitis in patients 6 months of age and older; symptomatic relief of pruritus, reduction in the number of hives, and size for chronic idiopathic urticaria
	Clarinex-D: relief of nasal and non-nasal symptoms associated with seasonal allergic rhinitis, including nasal congestion, in adults and adolescents over 12 years
Formulation	Oral tablet; orally disintegrating tablet; syrup, Liquid filled capsules
Dosing frequency	Aged 12+ years: 5mg/day; Aged 12 months–11 years: 2.5mg/day: Aged 6–11 months: 2mg/day
Reimbursement status	Claritin: OTC
	Clarinase: OTC
	Aerius/Clarinex: High copay
	Clarinex-D: High copay
First launch date	Claritin: 1988 (US and EU), September 2002 (Japan)
	Clarinex: Seasonal allergic rhinitis: March 2001 (EU), January 2002 (US) Perennial allergic rhinitis: February 2002 (US), September 2006 (EU)
	Clarinex-D: April 2005 (US), approved in EU in July 2006
Primary patent expiry	Claritin: Expired (7MM)
	Aerius/Clarinex: February 2005 (Japan), June 2007 (US), February 2010 (France, Germany, Italy, Spain, UK)
	Clarinex-D: October 2019 (US), October 2020 (France, Germany, Italy, Spain, UK)
Alternative brand names	Clarinex: Aerius
	Clarinase: Claritin-D
2009 sales, 7MM	Claritin: total brand: $269m; allergic rhinitis: $105m
	Aerius/Clarinex: total brand: $444m; allergic rhinitis: $158m
	Clarinex-D: total brand: $36m; allergic rhinitis: $9m
2019 sales, 7MM	Claritin: total brand: $265m; allergic rhinitis: $88m
	Aerius/Clarinex: total brand: $207m; allergic rhinitis: $29m
	Clarinex-D: total brand: $47m; allergic rhinitis: $2.2m

7MM = seven major markets (US, Japan, France, Germany, Italy, Spain, UK)

OTC = over the counter

Source: Datamonitor, Thomson Pharma; Claritin, Clarinex, Clarinex-D, Clarinase prescribing information; MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission. DATAMONITOR

Product positioning

Claritin (loratadine; Merck)

Claritin's patent expiry has had a large impact on its sales, although it appears to inspire enough brand loyalty to remain a competitive product with total brand sales of $271m, and allergic rhinitis sales of $105m, in 2009 across the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK) (Total brand source IMS MIDAS; Allergic rhinitis sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010). Sales in these markets have grown from 2005 to 2009, driven by the Japanese market where pediatric approval in October 2007 gave sales a significant boost (Shinogi, 2007; http://www.shionogi.co.jp).

Claritin lacks approval for perennial allergic rhinitis (PAR), which several other antihistamines have obtained. However, it continues to have relatively strong sales owing to its availability in multiple formulations, such as orally disintegrating tablets and syrups, which makes it an attractive product to various patient populations. Datamonitor does not believe this official label omission prevents its use by PAR patients.

Aerius/Clarinex (desloratadine; Merck)

Interviews with key opinion leaders revealed there is a sense that Aerius/Clarinex offers some improvement in safety and efficacy over Claritin, however, this has not been confirmed with head-to-head studies.

> *"There are probably less side effects with desloratadine, and possibly the efficacy was improved, but I have to say that we do not have any head to head studies. So, this is just something that is a feeling."*
>
> EU key opinion leader

In the US, the product patent for desloratadine expired in October 2004 and the US Court of Appeals ruled that desloratadine was neither a new nor unique ingredient warranting patent protection as it is the active metabolite of loratadine. Schering-Plough was granted a 1,074 day extension on the patent, as well as an additional 6 months for having conducted pediatric trials, extending their marketing exclusivity to June 2007. The FDA Orange Book lists several other patents related to desloratadine that expire in December 2014, and, in addition, Merck, after acquiring Schering-Plough, holds various patents for the product that extent to 2022 (Thomson Pharma, April 2010, Copyright Thomson Scientific).

A number of companies have filed ANDAs for generic versions of desloratadine. Schering-Plough has settled patent litigation with a number of companies, reaching agreements for generic desloratadine to enter the market starting in 2012. In December 2008 Schering and Sepracor settled a patent litigation suit against Dr. Reddy's, granting the company rights to manufacture and market generic versions of the 5mg tablet, 6 months after the launch of the first 12 and 24 hour versions of generic desloratadine plus pseudoephedrine combination tablets with 6 months of market exclusivity, as well as 6 months co-exclusivity for an orally disintegrating tablet. In January 2009 it was also agreed that GeoPharma could launch generic desloratadine on July 1, 2012 with 6 months exclusivity, and with the possibility of an earlier launch under certain circumstances. In April 2009, the patent litigation against Mylan was settled, giving that company the same agreement. The generic version of the drug may be introduced as a prescription medicine or as an over-the-counter version, depending on the status of Clarinex at the time of launch (Thomson Pharma, April 2010, Copyright Thomson Scientific; Mylan, 2009; http://investor.mylan.com).

Although Clarinex did not reach the sales peak attained by its predecessor Claritin, which had sales of $1.9 billion in 2002 prior to patent expiry, Aerius/Clarinex has experienced strong total brand sales in the seven major markets of nearly $457m in 2009, which are expected to diminish due to generic entry in 2012. Of this, $162m was attributed to allergic rhinitis (Total brand source IMS MIDAS; Allergic rhinitis sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010). From 2006 to 2009, the compound annual growth rate (CAGR) was -7%, driven by the US, where the 2007 entrance of Xyzal (levocetirizine; UCB/Sepracor) negatively impacted sales.

Clarinex-D (desloratadine/pseudoephedrine; Merck)

Clarinex-D has a similar label to Allegra-D and a less competitive profile than Zyrtec-D, which has an additional indication for PAR and is approved for the treatment of children 2 years and older. Sales of Clarinex-D have been very low due both to its late introduction to the market after its key competitors and also to its suboptimal profile, with sales in the US of just $36m in 2009. The product is not expected to launch in additional markets, and Datamonitor forecasts annual sales in 2019 to reach just $47m.

SWOT analysis

The following figure highlights the strengths, weaknesses, opportunities and threats (SWOT) of Merck's franchise for allergic rhinitis.

Figure 30: Merck Claritin/Clarinex/Clarinex-D franchise – SWOT analysis for allergic rhinitis, 2010

Strengths	Weaknesses
Claritin: ▪ Available in numerous once-daily oral formulations for adults and children **Clarinex:** ▪ Available in numerous once-daily formulations for adults and children ▪ Indicated for adults and pediatrics for both SAR and PAR **Clarinex-D:** ▪ Available in both once and twice daily oral formulations	**Claritin:** ▪ Lack of PAR indication **Clarinex:** ▪ Launch after generic loratadine reduced switching from Claritin **Clarinex-D:** ▪ Third-to-market
Opportunities	**Threats**
Claritin: ▪ Continue to retain a portion of post-patent sales through OTC availability **Clarinex:** ▪ Differentiate product with new formulations **Clarinex-D:** ▪ Launch in the EU where approval was gained in 2007	**Claritin:** ▪ Patent expiry in all major markets has led to generic erosion of sales **Clarinex:** ▪ Sales have been decreasing in the US since 2007 due to launch of Xyzal (levocetirizine; UCB/Sepracor) ▪ First generics to enter the market in 2012 **Clarinex-D:** ▪ Zyrtec-D reached the market first and has an additional indication for PAR

OTC = over-the-counter; PAR = perennial allergic rhinitis; SAR = seasonal allergic rhinitis

Source: Datamonitor

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Brand forecast to 2019

Claritin forecast assumptions

- Although Claritin's product patent expired in Japan in 2001 (Dolphin, June 2010, Copyright Thomson Scientific), generic loratadine has not entered the Japanese market, and Datamonitor does not expect that it will;
- historical and forecasted sales are presumed to be prescription only, as IMS MIDAS sales data do not generally capture over-the-counter sales.

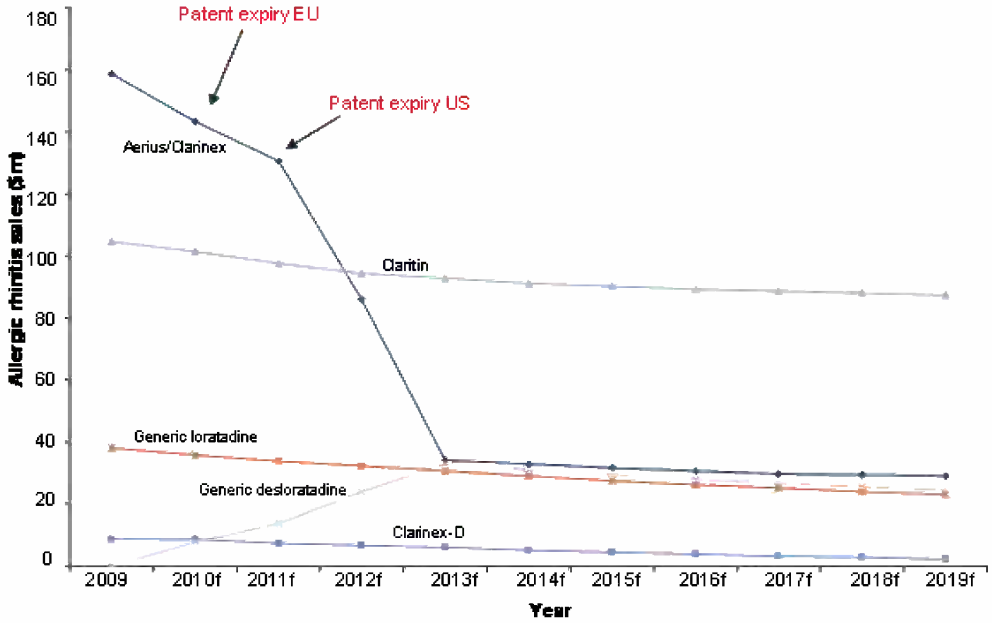
Clarinex forecast assumptions

- As discussed at the start of this chapter, Datamonitor has applied the sales split by indication for antihistamine/decongestant combinations in the US (based on diagnosis value data from MIDAS Prescribing Insights), to the EU for robustness;
- patent expiry in the EU in 2010 and the US in 2012 will erode sales. The fastest erosion will occur in the US and Germany, with 95% of volume share switching to generics. In Spain and the UK, 70% and 80% of share is also forecast to switch. France and Italy will see the slowest and least dramatic switch, with just 15% of share forecast to be lost to generics in Italy;
- historical and forecasted sales are presumed to be prescription only, as IMS MIDAS sales data do not generally capture over-the-counter sales.

Clarinex-D forecast assumptions

- Clarinex-D is currently not launched in Europe or Japan is not expected to enter these markets;
- generic entry is not expected in the US market during the forecast period;
- historical and forecasted sales are presumed to be prescription only, as IMS MIDAS sales data do not generally capture over-the-counter sales.

Figure 31: Aerius/Clarinex/Claritin/Clarinex-D allergic rhinitis sales in the seven major markets ($m), 2009–2019



Seven major markets = US, Japan, France, Germany, Italy, Spain, and the UK

Source: 2010–2019 forecast = Datamonitor; 2009 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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Table 13: Sales forecasts for Aerius/Clarinex, Clarinex-D, and Claritin in allergic rhinitis in the seven major markets ($ 000s), 2009–2019						
	2009	2011f	2013f	2015f	2017f	2019f
Aerius/Clarinex						
US	104,284	99,301	6,121	6,009	5,997	5,985
France	25,156	13,441	12,438	11,693	11,098	10,607
Germany	7,532	2,409	1,573	1,026	624	307
Italy	8,093	7,611	7,924	8,137	8,270	8,343
Spain	10,161	6,649	5,273	4,138	3,144	3,145
UK	3,352	1,098	903	780	685	607
Aerius/Clarinex Total	**158,578**	**130,510**	**34,232**	**31,784**	**29,818**	**28,994**
Clarinex-D						
US	8,568	7,479	5,981	4,525	3,275	2,221
Germany	0	0	0	0	0	0
Clarinex-D Total	**8,568**	**7,479**	**5,981**	**4,525**	**3,275**	**2,221**
Claritin						
US	15,076	12,259	10,483	8,868	7,542	6,478
Japan	86,014	82,046	79,415	78,826	78,779	78,769
France	940	831	764	732	718	711
Germany	18	15	14	14	14	14
Italy	1,750	1,742	1,511	1,409	1,307	1,236
Spain	120	0	0	0	0	0
UK	744	552	424	332	266	218
Claritin Total	**104,663**	**97,444**	**92,610**	**90,181**	**88,626**	**87,427**
Franchise total	**271,809**	**235,433**	**132,823**	**126,491**	**121,719**	**118,641**

Note: Totals may not sum due to rounding.

Seven major markets = US, Japan, France, Germany, Italy, Spain, and the UK

Source: 2010–2019 forecast = Datamonitor; 2009 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission. DATAMONITOR

The 10-year market forecasts for Claritin, Aerius/Clarinex, and Clarinex-D, for both allergic rhinitis and other indications are outlined separately in the accompanying forecast tool, a downloadable Excel spreadsheet that details the forecasts for these drugs in the seven major markets.

Late-stage development compounds recently discontinued

Epinastine (Inspire)

Inspire Pharmaceuticals, under license from Boehringer Ingelheim (BI), was developing an intranasal formulation of epinastine, a non-sedative antihistamine. Inspire licensed the North American rights to the drug in February 2006, under an agreement which saw the company pay an upfront license fee, but with no requirement to pay future milestones. In November 2007 Inspire began a Phase III trial for seasonal allergic rhinitis (SAR). The trial was conducted over 14 days, and was a five-arm placebo-controlled study of 750 patients with a history of SAR to mountain pollen cedar. The primary endpoint was the average change in the reflective total nasal symptom score. However, in April 2008 the company discontinued development after failing to meet the primary endpoint in that trial (Thomson Pharma, June 2010, Copyright Thomson Scientific).

In an earlier Phase II study Epinastine was shown to significantly improve total nasal symptom scores in a 0.1% dose group compared to placebo, although changes in a 0.05% dose group were not significant. Epinastine has been on the market from Boehringer Ingelheim and Daiichi Sanko in Japan since 1994 in an oral formulation for the treatment of asthma, allergic rhinitis, eczema, urticaria and psoriasis vulgaris. Furthermore, a topical ophthalmic formulation was launched in 2004 by Allergan for the treatment of itching associated with conjunctivitis, in the US and EU (Thomson Pharma, June 2010, Copyright Thomson Scientific).

3. NASAL CORTICOSTEROIDS

Key findings

- Nasal corticosteroids are the second highest selling class for allergic rhinitis, making up 27% of sales in the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK) in 2009. That year, allergic rhinitis sales of the class reached $1.4 billion, but key patent expiries over the next ten years are forecast to decrease in value to $1.0 billion by 2019.
- In 2007 GlaxoSmithKline launched a Veramyst (fluticasone furoate), a follow-on product to Flixonase/Flonase (fluticasone propionate) in the US. This was followed by launches in the EU in 2008 and Japan in 2009. While the company aimed to use the new product to defend against generic erosion, generic fluticasone entered the market first, and significant sales were lost. While sales of Veramyst are therefore not expected to reach those seen by Flixonase/Flonase prior to patent expiry, it is forecast to be the highest selling nasal corticosteroid by 2019, with allergic rhinitis sales in the seven major markets reaching $355m.
- While the greatest impact on the class over the next ten years will come from patent expiries, nasal corticosteroids are less vulnerable to generic erosion than other drug classes, as a result of their device. Devices carry a separate patent, which can expire after the molecule, and are difficult for generics companies to replicate. As a result, brand loyalty can be high in this class, and generic entry is forecast to have less of an impact than, for instance, in the oral antihistamine class. Device's are also used to differentiate brands from one another, and with little distinction seen in brands' efficacy and safety, devices are an important factor in physician and consumer choice.

Overview for nasal corticosteroids

Nasal corticosteroids are an important class in the treatment of allergic rhinitis, particularly for more severe disease. In 2009, nasal corticosteroids made up 27% of the allergic rhinitis sales in the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK). That year, sales of nasal corticosteroids for allergic rhinitis in the seven major markets reached $1.4 billion, and with several key products going off-patent, sales are expected to drop to $1.2 billion by 2019.

Nasal corticosteroids are considered to be highly effective, although symptoms may not be eliminated completely, and are the first-line treatment of allergic rhinitis with severe symptoms.

> *"They are a first-line treatment mainly when the symptoms are more severe, and in addition when obstruction is the most important symptom. In other words, if a patient has a nasal obstruction there is a very weak effect from antihistamines, so it is much better to use the steroids, and the nasal steroids are effective."*
>
> EU key opinion leader

> *"Efficacy again is not complete, and people still have grade 2 symptoms, but for a single agent it is probably the best thing for your buck."*
>
> US key opinion leader

Unlike oral treatments, the delivery device used for nasal steroids is an important factor. This is something that can differentiate a product and which can, to some degree, protect a brand after patent expiry. In general, sales erosion of nasal corticosteroids has been milder post-patent than that of antihistamines. Still, as cost is a factor of growing importance, generics still play a role.

> *"The device is crucial, because in the generics, you can put the exact amount of drug but if the device is not working, I mean you have that."*
>
> EU key opinion leader

> *"Patients are not desperately keen on* [generic devices], *but it does not stop a lot of GPs* [general practitioners] *from writing them generically."*
>
> UK key opinion leader

> *"I like the newer products that have more of a spray formulation versus the aqueous, I think they are more patient preferred."*
>
> US key opinion leader

The relatively high cost of nasal corticosteroids can also inhibit patients from using the class entirely, particularly when treatments are not reimbursed.

> *"In Italy, nasal steroids are not reimbursed …*[therefore] *they are used but not as much as they potentially could be."*
>
> EU key opinion leader

While compliance is an issue for all treatments of allergic rhinitis, this is a particular issue for nasal corticosteroids where technique plays a role. Key opinion leaders interviewed by Datamonitor emphasized the importance of correct device usage, with newer devices considered to offer an improvement.

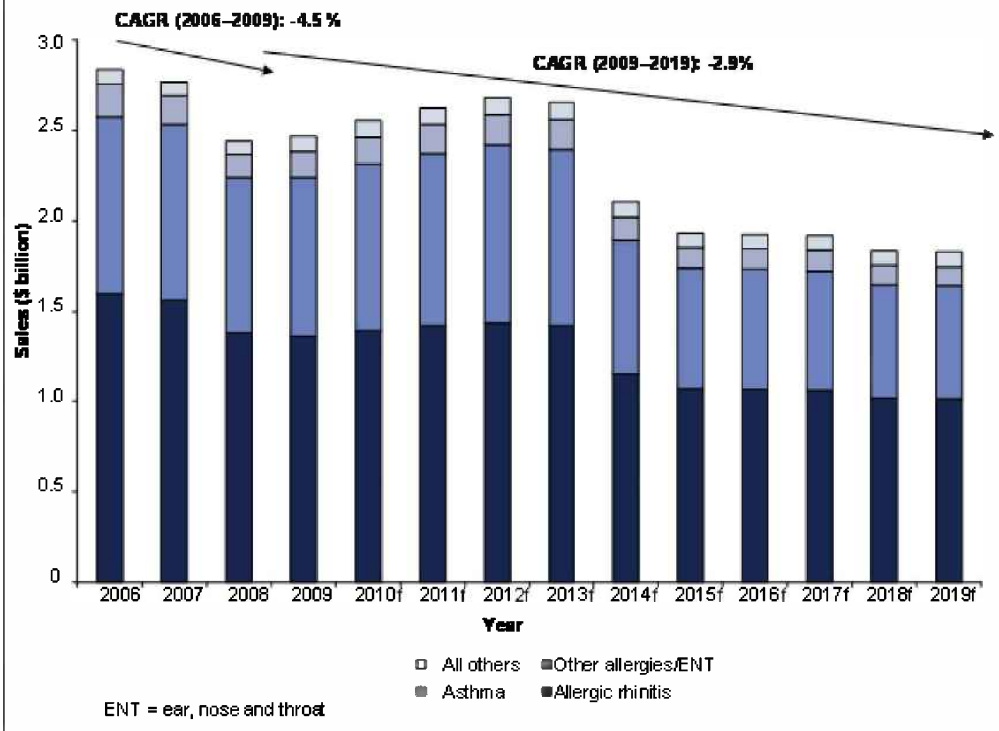
> *"The major challenge is getting people to use them correctly really."*
>
> UK key opinion leader

> *"No question, both Nasonex and Avamys are easy to use devices."*
>
> UK key opinion leader

Nasal corticosteroid market size

Nasal corticosteroid sales reached $2.5 billion in the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK) in 2009, of which, $1.4 billion was for the treatment of allergic rhinitis. Total class sales declined between 2006 and 2009, a decrease caused by Flixonase/Flonase (fluticasone propionate; GlaxoSmithKline) going off-patent and the subsequent entrance of generics. A significant further decline in sales is forecast for the period 2009–2019, with an expected compound annual growth rate (CAGR) of -2.9% reducing sales to $1.8 billion by 2019. This will result from additional patent expiries, including Nasonex (mometasone; Schering-Plough), in 2014 in the US, which will have the greatest impact on the market.

Figure 32: Nasal corticosteroid sales in the seven major markets by indication, 2006–2019



ENT = ear, nose and throat

Source: 2010–2019 forecast = Datamonitor; 2006–09 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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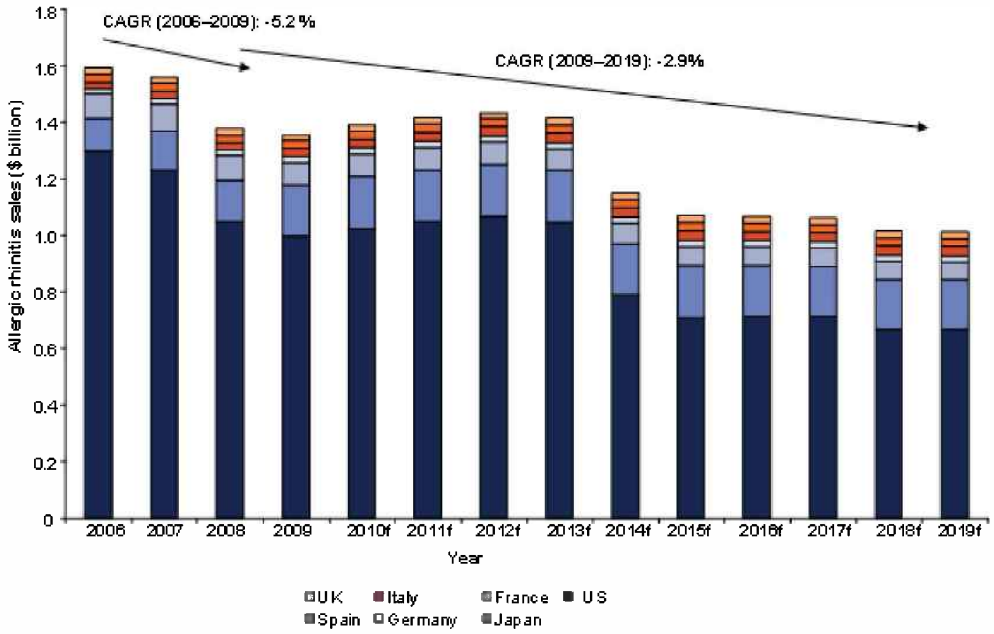
Figure 33 shows sales of nasal corticosteroids for allergic rhinitis by country for the seven major markets from 2006 to 2019. The US significantly dominates sales of this relatively expensive class, accounting for $1 billion, over 75%, of allergic rhinitis sales in the class.

Figure 33: Allergic rhinitis sales of nasal corticosteroids in the seven major markets by country ($ billion), 2009–2019



Source: 2010–2019 forecast = Datamonitor; 2006–09 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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Nasonex (mometasone; Merck)

Summary takeaways:

- **Product:** Nasonex (mometasone);
- **2009 sales:** total brand: $1.2 billion; allergic rhinitis: $613m;
- **2019 forecast sales:** total brand: $218 billion; allergic rhinitis: $106m.

Nasonex (mometasone) was developed and launched by Schering-Plough (now Merck) and entered the European and US markets in 1997. Japanese approval was granted in July 2008, followed by the product's launch in October of that year (Thomson Pharma, April 2010, Copyright Thomson Scientific). Nasonex is indicated for the treatment of the nasal symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adult and pediatric patients 2 years of age and older. It is also indicated for the prophylaxis of the nasal symptoms of SAR in patients 12 years of age and older, and for the treatment of nasal polyps in patients 18 years of age and older (Schering Corporation, 2005). Merck also markets an inhaled formulation of mometasone, Asmanex, for the treatment of asthma, and a topical formulation, Elocon, for the treatment of inflammatory skin conditions.

Drug profile

Table 14: Nasonex – drug profile, 2010

Nasonex	
Molecule	Mometasone
Mechanism of action	Nasal corticosteroid
Originator	Schering-Plough
Marketing company	Merck (formerly Schering-Plough)
Primary indication	Treatment of nasal symptoms of seasonal and perennial allergic rhinitis in patients over 2 years of age; prophylaxis of nasal symptoms of seasonal allergic rhinitis in patients over 12 years of age; treatment of nasal polyps in patients over 18 years of age
Formulation	Nasal spray
Dosing frequency	Aged 12+ years: two sprays in each nostril/day; Aged 2–11 years one spray in each nostril/day
Reimbursement status	Quantity limit/intermediate copay
First launch date	1997 (US and EU)
Primary patent expiry	2012 (EU); 2014 (US)
2009 sales, 7MM	Total brand: $1.2 billion; allergic rhinitis: $613m
2009 sales, 7MM	Total brand: $218 billion; allergic rhinitis: $106m

7MM = seven major markets (US, Japan, France, Germany, Italy, Spain, UK)

Source: Datamonitor, Thomson Pharma; Nasonex prescribing information; MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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Product positioning

Nasonex has one of the widest approved indications within the allergic rhinitis nasal steroid market, conferring an advantage over other products in its class. It is the only treatment approved for prophylaxis of SAR, and was the best-selling nasal steroid in the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK) in 2009, with total brand sales of $1.2 billion, roughly equal to all other nasal steroids combined. Sales for allergic rhinitis made up $618m of the total (Total brand source IMS MIDAS sales data; Allergic rhinitis sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010). Nasonex was approved in 2008 in Japan, where it was the first once-daily nasal steroid to gain approval (Merck, 2008; http://www.merck.com).

Although its competitor, Flixonase (fluticasone; GlaxoSmithKline) went off-patent throughout the seven major markets with generics erosion starting in 2006, sales of Nasonex have experienced strong growth over the period 2006–09with a compound annual growth rate (CAGR) of 8% for the seven major markets. The approval of scent-free formulations of Nasonex in the US and EU in 2004 and 2007 respectively, as well as the product's Japanese approval in 2008 all contributed to this growth (Thomson Pharma, April 2010, Copyright Thomson Scientific).

Nasonex's device is also a strong advantage, and offers improvements over the older nasal steroids. While device selection can vary depending on patient and physician preferences, it may also offer an advantage over Veramyst (fluticasone furoate, GlaxoSmithKline).

> *"I prefer the Nasonex* [device] *because it is lighter and it is more convenient to use. Veramyst is heavier, but again, it is a question of personal opinion."*
>
> EU key opinion leader

Datamonitor expects allergic rhinitis sales of Nasonex in the US and five major EU markets to peak at $646m n 2011. However, generic erosion is anticipated to begin when Nasonex's product patent expires in Europe in 2012. US patent expiry is expected in 2014, However, in November 2009 Apotex filed an Abbreviated New Drug Application (ANDA) for a mometasone furoate nasal spray, challenging Nasonex's patents. In December 2009, Schering filed a patent infringement suit against the company, which automatically stalls the US Food and Drug Administration's (FDA) approval of Apotex's ANDA until May 2012 or until an adverse court decision (Merck, 2010; http://phx.corporate-ir.net). Datamonitor assumes generic erosion will not begin in the US until patent expiry in 2014.

SWOT analysis

The following figure highlights the strengths, weaknesses, opportunities and threats (SWOT) of Nasonex for allergic rhinitis.

Figure 34: Nasonex – SWOT analysis for allergic rhinitis, 2010

Strengths	Weaknesses
• Once-daily • Available in numerous formulations, including scent free • First once-daily nasal corticosteroid to gain approval in Japan • Indicated for both SAR and PAR for patients aged 2+ years	• Epistaxis was relatively common in clinical trials compared to placebo
Opportunities	**Threats**
• Promote alternative formulations to differentiate product	• Patent expiry in 2012 will lead to generic erosion • Launches of Veramyst (fluticasone furoate; GlaxoSmithKline) and Omnair (ciclesonide; Nycomed) crowd the nasal corticosteroid class • Cheap generic versions of key competitor Flixonase (fluticasone propionate) are available

PAR = perennial allergic rhinitis; SAR = seasonal allergic rhinitis

Source: Datamonitor DATAMONITOR

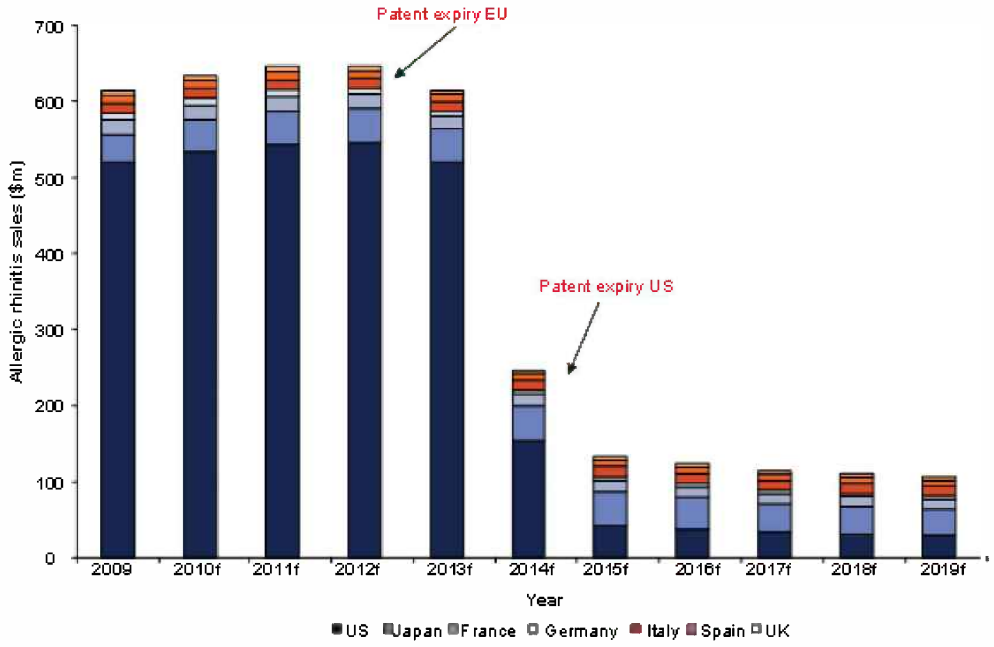
Brand forecast to 2019

- The launch of azelastine/fluticasone in 2012 in the US and 2013 in the EU will take 10% of Nasonex's market share over the following 5 years;
- in the US the launch of Omnair in an hydro-fluoroalkane (HFA) formulation will take 10% of Nasonex's market share over 4 years;
- the launch on Omnair in the EU in 2012 will take 10% of Nasonex's market share in all markets. Uptake will be slow over 3 years;

- patent expiry in the seven major markets, starting in 2012 in the EU, will lead to generic erosion. The speed and extent of patient switching will vary by country, with the greatest shift seen in the UK, and the smallest in Italy, based on the experience of Flixonase/Flonase's patent expiry.

- despite the threat of earlier generic entry, Datamonitor assumes that generic erosion in the US will not occur until the 2014 patent expiry, after which patient switching will be rapid with 90% of patients lost to generics over 4 years.

Figure 35: Nasonex sales in the seven major markets ($m), 2009–2019



Source: 2010–2019 forecast = Datamonitor; 2009 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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Table 15: Sales forecasts for Nasonex in allergic rhinitis in the seven major markets ($ 000s), 2009–2019

	2009	2011f	2013f	2015f	2017f	2019f
US	519,242	543,111	519,500	42,103	34,134	29,620
Japan	36,808	43,797	45,235	45,466	36,466	34,557
France	19,837	19,238	15,739	14,481	13,849	13,302
Germany	8,990	9,418	6,033	5,137	4,581	4,146
Italy	11,814	12,919	13,183	12,849	12,824	13,123
Spain	11,122	11,133	9,424	8,427	8,031	7,629
UK	6,060	6,354	4,694	4,431	4,323	4,349
Total	**613,873**	**645,969**	**613,807**	**132,895**	**114,209**	**106,727**

Note: totals may not sum due to rounding.

Source: 2010–2019 forecast = Datamonitor; 2009 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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The 10-year market forecast for Nasonex, for both allergic rhinitis and for other indications is outlined separately in the accompanying forecast tool, a downloadable Excel spreadsheet that details the forecast for this drug in the seven major markets.

Flixonase/Flonase/Veramyst franchise (fluticasone) GlaxoSmithKline

Summary takeaways:

- **Franchise products:** Flixonase/Flonase (fluticasone propionate); Veramyst (fluticasone furoate);
- **2009 sales:** Flixonase/Flonase: total brand: $160m; allergic rhinitis: $107m; Veramyst: total brand: $220m; allergic rhinitis: $128m;
- **2019 forecast sales:** Flixonase/Flonase: total brand: $158m; allergic rhinitis: $87m; Veramyst: total brand: $585m; allergic rhinitis: $355m.

GlaxoSmithKline launched fluticasone propionate—known as Flonase in the US and Flixonase in the EU, but labeled Flixonase/Flonase for the purposes of this report—in 1993 in Europe and 1995 in the US, after which it was launched in the Japanese market. Spanish marketing rights are held by Almirall where the product is marketed as Fluinol (Thomson Pharma, April 2010, Copyright Thomson Scientific). The drug is indicated for the management of the nasal symptoms of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR) and non-allergic rhinitis in adults and children aged 4 years and older (GlaxoSmithKline, 2007).

Veramyst (fluticasone furoate, also known as Avamys and Allermist) has been developed by GlaxoSmithKline as a once-daily follow-on product to Flixonase/Flonase (fluticasone propionate) whose product patent expired in May 2004 in the US. Veramyst was filed in the US in June 2006 and was subsequently approved in April 2007 after which the product was launched in June 2007. In Europe, the drug is marketed as Avamys, and was filed in July 2006 and approved in January 2008. The first sales were seen in all of the five major European markets (France, Germany, Italy, Spain, and the UK) in 2008, with the exception of the UK, which first saw sales in 2009.

In Japan the drug was approved in February 2009 and launched in June 2009 (Thomson Pharma, April 2010, Copyright Thomson Scientific).

The total branded fluticasone propionate/furoate franchise is forecast to have sales of almost $670m in the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK) in 2019, with $420m for allergic rhinitis (Total brand source IMS MIDAS sales data; Allergic rhinitis sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010).

Drug profile

Table 16: Flixonase/Flonase/Veramyst – franchise profile, 2010

Flixonase/Flonase/Veramyst	
Molecule	Fluticasone
Mechanism of action	Nasal corticosteroid
Originator	GlaxoSmithKline
Marketing company	GlaxoSmithKline
Primary indication	Flixonase/Flonase: management of nasal symptoms of seasonal and perennial allergic rhinitis and non-allergic rhinitis in patients 4 years of age and older
	Veramyst: treatment of symptoms of seasonal and perennial allergic rhinitis in patients 2 years of age and older
Formulation	Nasal spray
Dosing frequency	Aged 12+ years: two sprays in each nostril/day; Aged 2–11 years one spray in each nostril/day
Reimbursement status	High copay
First launch date	Flixonase/Flonase: 1993 (EU); 1995 (US); unknown (Japan)
	Veramyst: 2007 (US); 2008 (EU); 2009 (Japan)
Primary patent expiry	Flixonase/Flonase: Expired (7MM)
	Veramyst: 2021 (US); 2023 (EU)
2009 sales, 7MM	Flixonase/Flonase: total brand: $160m; allergic rhinitis: $107m
	Veramyst: total brand: $220m; allergic rhinitis: $128m
2019 sales, 7MM	Flixonase/Flonase: total brand: $158m; allergic rhinitis: $87m
	Veramyst: total brand: $585m; allergic rhinitis: $355m

7MM = seven major markets (US, Japan, France, Germany, Italy, Spain, UK)

Source: Datamonitor, Thomson Pharma; Claritin, Clarinex, Clarinex-D, Clarinase prescribing information; MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission. DATAMONITOR

Product positioning

Flixonase/Flonase (fluticasone propionate; GlaxoSmithKline)

Flixonase/Flonase's patent has expired in all the seven major markets, with the final patent expiry for the US and Japan in 2005 leading to a drop from its peak total brand sales in the seven major markets of just over $1.3 billion in 2005 to $440m in 2006. Sales have continued to drop year-on-year, as the result of increased generic competition and the launch of once-daily fluticasone, Veramyst, which has helped GlaxoSmithKline to retain part of its allergic rhinitis sales.

Prior to its patent expiry, Flixonase/Flonase was the highest-selling product of its class beating its main competitor Nasonex, although Nasonex subsequently took over Flixonase/Flonase's position and has been at the top of the nasal steroid class since 2006. Still, with its indication for non-allergic rhinitis, the drug remains competitive with a wider indication than most other nasal corticosteroids.

IMS Health has not recorded generic fluticasone sales in the French markets. However, since sales of Flixonase/Flonase have been extremely low in France (just under $5m in 2009), and since Veramyst entered the market in 2008, Datamonitor does not believe that generic fluticasone propionate will be launched in this market.

Total brand sales of Flixonase/Flonase are expected to continue falling owing to generic entry and patient switching, to just under $121m 2019.

Veramyst (fluticasone furoate; GlaxoSmithKline)

GlaxoSmithKline launched Veramyst (fluticasone furoate), also known as Avamys in the UK, as a defense strategy and has attempted to switch patients from Flixonase/Flonase to this newer product. However, the launch of Veramyst came too late to make a significant impact, as generic fluticasone propionate had already entered the market, and the drug is not expected to achieve sales on a par with Flixonase/Flonase.

Veramyst is indicated for the treatment of the symptoms of SAR and PAR in patients 2 years of age and older. This is a wider indication than Flixonase/Flonase which is only approved for the treatment of patients 4 years of age and older. However, the highest-selling nasal steroid, Schering-Plough's Nasonex (mometasone), has the same indication and is a strong competitor with an additional prophylaxis indication.

Although Veramyst is in many ways a line extension of Flixonase/Flonase, GlaxoSmithKline states that it has novel properties that expand its market potential beyond that of its predecessor. Veramyst has been shown to have a significant effect on ocular symptoms, which are traditionally difficult to treat with oral or nasal products. The company further states that the unique and ergonomically designed Veramyst device was created specifically to address patients' concerns. A mist-release button is used to deliver the same amount of medication with each press. Another advantage is a viewing window that allows patients to see the level of remaining medicine (GSK, 2007; http://www.gsk.com).

While there is skepticism regarding Veramyst's differentiation from Flixonase/Flonase in terms of its efficacy and safety, the improvements seen from its device have been noted. Still, this may not be enough to convince physicians to switch patients to the new brand.

"Avamys [Veramyst] *has a better device.* [But], *there is absolutely no difference in terms of efficacy and safety."*

UK key opinion leader

"I have no idea [about the difference between Flixonase/Flonase and Veramyst] *because there is not a single head-to-head study."*

EU key opinion leader

"You do not switch the patient from propionate if it is working in the patient… You do not switch from one drug to the other drug if the drug is effective."

EU key opinion leader

"I would make switches like that was because of the tolerability, just because it has greater tolerability, [Veramyst] *is a very, very fine mist and you barely know that you are putting anything in your nose."*

US key opinion leader

Additionally, its once-daily dosing could provide improved convenience and compliance among patients. However, interviews with key opinion leaders revealed that Flixonase/Flonase is frequently used as a once-daily product meaning the dosing of Veramyst is not necessarily an advantage.

"Whenever it is possible to use [Flixonase/Flonase] *once a day, I use it in my patients."*

EU key opinion leader

Furthermore, given that on-demand use for symptomatic relief is believed to be common with nasal corticosteroids regardless of the prescribing instructions, this advantage may be somewhat limited. Veramyst's device is said to be better and easier to use than traditional devices. The advantages include the delivery of the medication as a fine mist and the location of the 'mist-release button' on the side of the device, which makes it easier to press when the device is held horizontally. A disadvantage is that the spray comes in a glass bottle, although this bottle is set within the device, which should give it some protection from breaking.

A further hurdle will be reimbursement levels and pricing, as it will be difficult to prove that Veramyst is superior to the nasal steroids that are currently available. Datamonitor therefore estimates that annual peak sales will reach only about $546m in the seven major markets in 2019, which is less than half of Flixonase/Flonase's highest annual sales of $1.3 billion in 2005.

SWOT analysis

The following figure highlights the strengths, weaknesses, opportunities and threats (SWOT) of GlaxoSmithKline's franchise for allergic rhinitis.

Figure 36: GlaxoSmithKline's Flixonase/Flonase/Veramyst franchise – SWOT analysis for allergic rhinitis, 2010

Strengths	Weaknesses
Flixonase/Flonase: ▪ Indicated for both SAR and PAR ▪ Additional indication for the treatment of non-allergic rhinitis **Veramyst:** ▪ Once-daily formulation offers improvement over Flixonase/Flonase ▪ Indicated for both SAR and PAR, for patients aged 2+ ▪ Demonstrated effect on ocular symptoms ▪ Novel device	**Flixonase/Flonase:** ▪ Indicated for patients aged 4+ **Veramyst:** ▪ Lacks non-allergic rhinitis indication of predecessor ▪ Entered market after other once-daily nasal corticosteroids
Opportunities	**Threats**
Flixonase/Flonase: ▪ Promote **Veramyst** ▪ Promote further switching from Flixonase/Flonase to retain respiratory franchise	**Flixonase/Flonase:** ▪ Patent expiry in all major markets has led to generic erosion of sales **Veramyst:** ▪ Launched after generic fluticasone, which reduced patient switching from Flixonase/Flonase ▪ Nasonex (mometasone, Schering-Plough) already established on market as once-daily treatment of SAR and PAR

PAR = perennial allergic rhinitis; SAR = seasonal allergic rhinitis

Source: Datamonitor

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Brand forecast to 2019

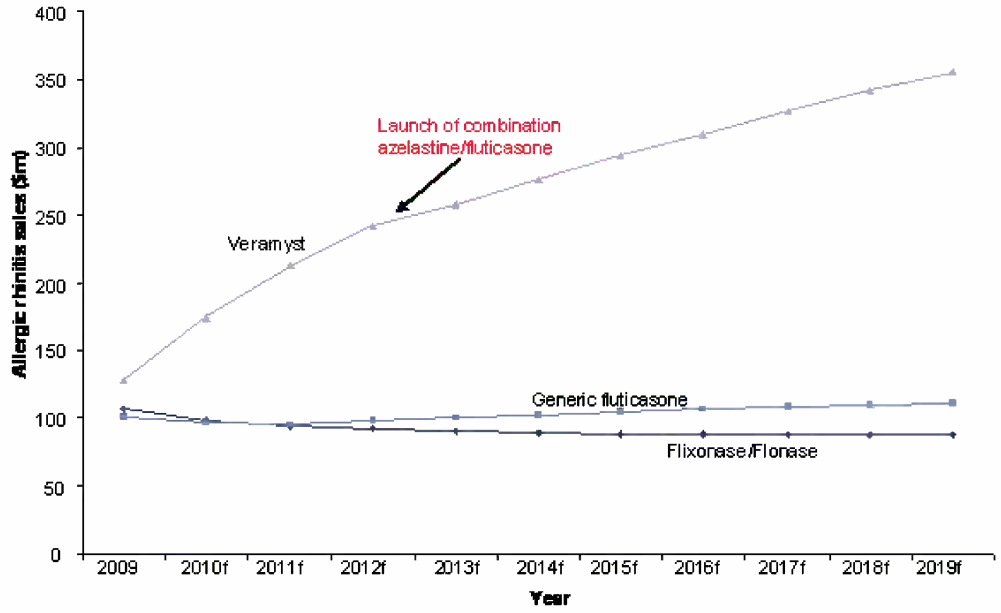
Flixonase/Flonase forecast assumptions

- The launch of azelastine/fluticasone in 2012 in the US and 2013 in the EU will take 10% of Flixonase/Flonase's market share over 5 years;
- the launch of Omnair in the EU in 2012 will take 10% of Flixonase/Flonase's market share in all markets. Uptake will be slow over 3 years;
- although the product's patent has expired in all major markets, generics have not yet entered the French market. Given the low level of sales of the brand, and the fact that Veramyst has already launched, generics are not expected to enter the French market during the forecast period.

Veramyst forecast assumptions

- The launch of Omnair in the EU in 2012 will take 10% of Veramyst's market share in all markets. Uptake will be slow over 3 years;
- the launch of azelastine/fluticasone in 2012 in the US and 2013 in the EU will take 10% of Veramyst's market share over 5 years.

Figure 37: Flixonase/Flonase/Veramyst sales in the seven major markets ($m), 2009–2019



Seven major markets = US, Japan, France, Germany, Italy, Spain, and the UK

Source: 2010–2019 forecast = Datamonitor; 2009 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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Table 17: Sales forecasts for Flixonase/Flonase and Veramyst in allergic rhinitis in the seven major markets ($ 000s), 2009–2019						
	2009	2011f	2013f	2015f	2017f	2019f
Flixonase/Flonase						
US	15,405	5,406	2,621	1,697	1,327	1,176
Japan	77,504	77,031	76,912	76,899	76,897	76,897
France	1,687	1,358	1,115	986	952	927
Germany	504	424	353	303	282	265
Italy	2,831	2,504	2,206	1,980	1,920	1,935
Spain	2,832	2,663	2,425	2,271	2,271	2,265
UK	5,561	5,212	4,634	4,157	3,995	3,977
Flixonase/Flonase Total	**106,325**	**94,598**	**90,267**	**88,293**	**87,643**	**87,442**
Veramyst						
US	100,966	178,299	221,106	258,445	290,551	319,169
Japan	9,198	9,930	10,270	10,376	10,423	10,445
France	7,405	9,508	9,319	8,687	8,508	8,314
Germany	1,231	2,620	3,466	3,944	4,413	4,726
Italy	4,954	7,309	7,700	7,305	7,173	7,211
Spain	3,966	5,097	4,998	4,646	4,555	4,460
UK	296	633	831	882	908	935
Veramyst Total	**128,015**	**213,394**	**257,690**	**294,285**	**326,532**	**355,259**
Franchise total	**234,340**	**307,992**	**347,957**	**382,578**	**414,176**	**442,701**

Note: totals may not sum due to rounding.

Source: 2010–2019 forecast = Datamonitor; 2009 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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The 10-year market forecasts for Flixonase/Flonase and Veramyst, for both allergic rhinitis and other indications are outlined separately in the accompanying forecast tool, a downloadable Excel spreadsheet that details the forecasts for these drugs in the seven major markets.

Rhinocort (budesonide; AstraZeneca)

Summary takeaways:

- **Product:** Rhinocort (budesonide);
- **2009 sales:** total brand: $172m; allergic rhinitis: $116m;
- **2019 forecast sales:** total brand: $33m; allergic rhinitis: $23m.

AstraZeneca has developed and extensively marketed the corticosteroid budesonide in various formulations as Rhinocort for allergic rhinitis, Pulmicort for asthma and Entocort for Crohn's disease. The company has also launched a combination of budesonide and formoterol for the treatment of asthma (Symbicort) (Thomson Pharma, April 2010, Copyright Thomson Scientific).

Rhinocort is available in three nasal formulations: RhinocortAqua (a water-based suspension in a pump spray), RhinocortTurbuhaler (nasal inhalation powder), and Rhinocort pMDI (pressurized metered dose inhaler). and is indicated for the management of symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in patients aged 6 years and older, and perennial non-allergic rhinitis in adults (AstraZeneca, 2010; http://astrazeneca.com).

Drug profile

Table 18: Rhinocort – drug profile, 2010

Rhinocort	
Molecule	Budesonide
Mechanism of action	Nasal corticosteroid
Originator	AstraZeneca
Marketing company	AstraZeneca
Primary indication	Management of symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in patients aged 6 years and older, and perennial non-allergic rhinitis in adults
Formulation	Nasal spray
Dosing frequency	one spray in each nostril/day
Reimbursement status	Step therapy
First launch date	1994 (US); 1995 (EU)
Primary patent expiry	December 2013 (France), October 2017 (US), expired in other EU markets
2009 sales, 7MM	Total brand: $172m; allergic rhinitis: $116m
2019 sales, 7MM	Total brand: $33m; allergic rhinitis: $23m

7MM = seven major markets (US, Japan, France, Germany, Italy, Spain, UK)

Source: Datamonitor, Thomson Pharma; Rhinocort prescribing information; MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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Product positioning

The popular use of budesonide for asthma in children has meant that physicians are less hesitant about prescribing Rhinocort to this patient group, improving the drug's competitive positioning. Furthermore, Rhinocort is one of just two nasal corticosteroids with an indication for non-allergic rhinitis. However, Rhinocort's patent has now expired in most European countries and the drug reached total brand sales of $174m in the US and the five major European markets (France, Germany, Italy, Spain, and the UK) in 2009 (Rhinocort is not launched in Japan), of which $116m was attributed to allergic rhinitis. The vast majority of sales (86%) come from the US, with only minimal use in the EU (Total brand source IMS MIDAS sales data; Allergic rhinitis sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010).

"It has a slightly higher oral bioavailability than the other nasal steroids, and the device is not particularly brilliant, it is virtually unused in the UK."

UK key opinion leader

Sales have declined substantially over the period 2006–09 with a compound annual growth rate (CAGR) of -18%, following the US launches of Veramyst (fluticasone furoate; GlaxoSmithKline) in 2007 and Omnair (ciclesonide; Nycomed) in 2008, which further crowded the nasal corticosteroid market. The additional patent expiries in France in December 2013 and the US in October 2017 are expected to further reduce sales.

SWOT analysis

The following figure highlights the strengths, weaknesses, opportunities and threats (SWOT) of Rhinocort for allergic rhinitis.

Figure 38: Rhinocort – SWOT analysis for allergic rhinitis, 2010

Strengths	Weaknesses
▪ Indicated for both SAR, PAR and perennial non-allergic rhinitis ▪ Available in various nasal formulations including inhaled and spray	▪ Indication for SAR and PAR is only for patients aged 6 and older ▪ Patent expiries in several major markets has led to generic erosion of sales
Opportunities	**Threats**
▪ Use of budesonide for the treatment of children with asthma has encouraged Rhinocort treatment in that age group ▪ Differentiate product by promoting alternative formulations	▪ Competition from Omnair (ciclesonide; Nycomed) and Veramyst (fluticasone furoate; GlaxoSmithKline) launches are eroding sales ▪ Additional patent expiries in France (2013) and the US (2017) will negatively impact sales

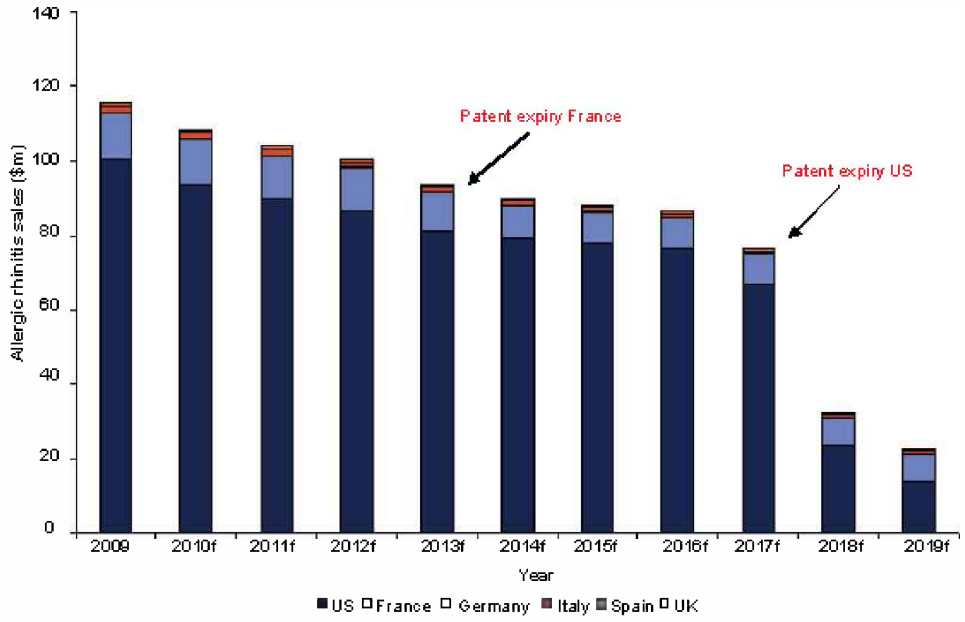
PAR = perennial allergic rhinitis; SAR = seasonal allergic rhinitis

Source: Datamonitor DATAMONITOR

Brand forecast to 2019

- The sales split by indication for Rhinocort in each country is based on diagnosis value estimates from IMS Prescribing Insights data for the US, which are assumed to be the most robust. Wide year-on-year fluctuations were seen in the other major markets which Datamonitor believes do not adequately reflect reality;
- Rhinocort's negative sales trend will continue;
- the launch of azelastine/fluticasone in 2012 in the US and 2013 in the EU will take 10% of Rhinocort's market share over 5 years;
- the launch on Omnair in the EU in 2012 will take 10% of Rhinocort's market share in all markets. Uptake will be slow over 3 years;
- generic erosion will follow the product's patent expiries in December 2013 in France and October 2017 in the US. The extent of generic erosion is based on the experiences of Flixonase/Flonase going off-patent, and will be rapid in the US with 95% of the brand's market share lost to generics over 4 years. In France patient switching will be less dramatic, with just 25% of market share lost to generics, with slow uptake over 10 years;
- in the UK, where generics have been available for a number of years, brand uptake increased in 2008 and 2009 after a generic was withdrawn from the market. However, with the 2009 launch of Sandoz's generic with a pack size that matches Rhinocort, Datamonitor expects further brand erosion, with 30% of the brand's volume shifted to generics.

Figure 39: Rhinocort allergic rhinitis sales in the US and five major EU markets ($m), 2009–2019



Source: 2010–2019 forecast = Datamonitor; 2009 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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Table 19: Sales forecasts for Rhinocort in allergic rhinitis in the US and five major EU markets ($ 000s), 2009–2019						
	2009	2011f	2013f	2015f	2017f	2019f
US	100,441	89,782	81,212	78,072	67,252	13,949
France	12,299	11,677	10,438	8,317	7,726	7,228
Germany	15	18	17	16	15	15
Italy	88	82	72	63	59	57
Spain	1,935	1,519	1,195	963	843	751
UK	920	811	734	641	637	640
Total	**115,699**	**103,889**	**93,668**	**88,072**	**76,532**	**22,640**

Note: totals may not sum due to rounding.
Seven major markets = US, Japan, France, Germany, Italy, Spain, and the UK
Source: 2010–2019 forecast = Datamonitor; 2009 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010,

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The 10-year market forecast for Rhinocort, for both allergic rhinitis and other indications is outlined separately in the accompanying forecast tool, a downloadable Excel spreadsheet that details the forecast for this drug in the seven major markets.

Omnair/Omnaris (ciclesonide; Nycomed/Sepracor)

Summary takeaways:

- **Product:** Omnair/Omnaris (ciclesonide);
- **2009 sales:** total brand: $37m; allergic rhinitis: $21m;
- **2019 forecast sales:** total brand: $44m; allergic rhinitis: $25m.

Nycomed (previously Altana) has developed Omnair/Omnaris (ciclesonide) for the treatment of allergic rhinitis, gaining approval from the US Food and Drug Administration (FDA) in October 2006. Nycomed outlicensed US rights to Omnair/Omnaris to Sepracor in January 2008, who then launched the product in April 2008 (Thomson Pharma, April 2010, Thomson Scientific; Sepracor, 2008a; http://sepracor.com). Omnair/Omnaris is indicated for the treatment of nasal symptoms associated with seasonal allergic rhinitis (SAR) in patients aged 6 years and older, and with perennial allergic rhinitis (PAR) in patients aged 12 years of age and older. Although the FDA indicated that the drug was approvable for children aged 2–11 years, this indication has not been pursued (Thomson Pharma, April 2010, Copyright Thomson Scientific).

According to Nycomed's company website, Omnair/Omnaris is in Phase III development outside of the US (Nycomed, 2010; http://www.nycomed.com). According to Thomson Pharma, Teijin holds the rights to the drug in Japan, and was conducting Phase II trials in Asia by 2005 (Thomson Pharma, April 2010, Copyright Thomson Scientific). However, Datamonitor can find no evidence of further development on the company's website, and therefore does not expect the drug to launch in Japan.

Sepracor also holds the rights to ciclesonide's US pipeline, and is developing Omnair/Omnaris in an hydrofluoroalkane (HFA) nasal metered dose inhaler (MDI) formulation, for which positive Phase III data have been reported.

Ciclesonide is also available from Nycomed as Alvesco for the treatment of asthma.

Drug profile

Table 20: Omnair/Omnaris – drug profile, 2010

Omnair/Omnaris	
Molecule	Ciclesonide
Mechanism of action	Nasal corticosteroid
Originator	Nycomed
Marketing company	Nycomed/Sepracor
Primary indication	Treatment of nasal symptoms associated with seasonal allergic rhinitis (SAR) in patients aged 6 years and older, and with perennial allergic rhinitis (PAR) in patients aged 12 years of age and older.
Formulation	Nasal spray
Dosing frequency	two sprays in each nostril/day
Reimbursement status	High copay
First launch date	2008 (US)
Primary patent expiry	October 2017 (US)
2009 sales, 7MM	Total brand: $37m; allergic rhinitis: $21m
2019 sales, 7MM	Total brand: $44m; allergic rhinitis: $25m

7MM = seven major markets (US, Japan, France, Germany, Italy, Spain, UK)

Source: Datamonitor, Thomson Pharma; Omnaris prescribing information; MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission. DATAMONITOR

Product positioning

In theory, ciclesonide has a great advantage over other corticosteroids in being a safer steroid. In children with moderate-to-severe asthma, ciclesonide's novel properties have been shown to result in a similar clinical effect to fluticasone propionate, but without the suppression in cortisol excretion seen with the comparator (Pederson, S *et al* ., 2009). Furthermore, physicians who have positive experiences with Alvesco, which was approved in the US in January 2008 for the treatment of asthma, may be more willing to try Omnair in patients with allergic rhinitis.

However, with a label for the treatment of SAR in patients over 6 years of age and PAR in patients over 12 years of age, Omnair/Omnaris is less competitive than other nasal corticosteroids, such as Nasonex (mometasone; Merck) and Veramyst (fluticasone furoate; GlaxoSmithKline), which both have indications for younger patients. The effect of this labeling is evidenced by its second year sales, where Omnair/Omnaris reached total brand sales of just $37m in the US, compared to Nasonex with $1 billion, and Veramyst with $171m.

An important driver of Omnair/Omnaris's future sales would be the approval of an HFA nasal MDI formulation, which has the potential to become a first-in-class delivery system for the treatment of allergic rhinitis. Patients may prefer this formulation as it causes less pharyngeal and anterior nose run-off than aqueous nasal sprays (LaForce, C., *et al* ., 2009). Sepracor reported positive Phase III results from its nasal formulation for the treatment of seasonal allergic rhinitis in April, 2009. The double-blind trial involved 707 patients aged 13 and older with a history of SAR. Patients were randomized to receive ciclesonide HFA nasal aerosol 80mcg or 160mcg, or placebo. Both active treatment groups met the primary endpoint by demonstrating statistically significant reductions in the 24-hour reflective Total Nasal Symptoms Score (TNSS) compared to placebo. TNSS assesses common allergy symptoms including nasal congestion, itching, and runny nose. The treatment groups also showed statistically significant differences in both instantaneous TNSS and reflective Total Ocular Symptoms Score (TOSS). The company further reported that the drug was well tolerated with a similar safety profile seen across all groups (Sepracor, 2009; http://sepracor.com).

In March 2008 Sepracor announced that positive Phase II results of the formulation were presented at the American Academy of Asthma and Immunology (AAAAI) Annual Meeting. The study, which included 513 patients aged 12 and older, randomized to receive ciclesonide HFA nasal aerosol 75mcg, 150mcg, 300mcg, or placebo once-daily for up to 2 weeks met both its primary and secondary endpoints. All doses showed a statistically significant improvement over placebo in patient-reported average morning and evening reflective and instantaneous TNSS, and there were no clinically meaningful differences in adverse event rates between the treatment and placebo groups (Sepracor, 2008b; http://sepracor.com).

A number of studies of Omnair in an HFA nasal aerosol formulation for the treatment of PAR have been initiated, the first of which was completed in May 2010. These are summarized in Table 21.

Table 21: Omnair HFA nasal aerosol formulation, ongoing clinical trials for perennial allergic rhinitis, 2010

Study	Status	Indication	Completion date
A 6-month study of once-daily ciclesonide HFA nasal aerosol in the treatment of PAR in subjects 12 years and older	Active, not recruiting	Perennial allergic rhinitis	November 2010
A 6-month safety and efficacy study of once-daily ciclesonide in the treatment of PAR in subjects 12 years and older.	Active, not recruiting	Perennial allergic rhinitis	August 2010
A study on the effects of ciclesonide on the hypothalamic-pituitary-adrenal (HPA) axis.	Completed	Perennial allergic rhinitis	May 2010

HFA = hydrofluoroalkane; PAR = perennial allergic rhinitis

Source: Clinicaltrials.gov, 2010i (http://clinicaltrials.gov/)

As Nycomed's company website states that Omnair/Omnaris is in Phase III development outside of the US (Nycomed, 2010; http://www.nycomed.com), Datamonitor assumes the drug will launch in the EU from 2012. This is, however, based on the assumption that clinical trials will be completed by the end of 2010, with a filing in 2011, which cannot be confirmed. Discussions with key opinion leaders reveal uncertainty regarding the drug's development, and suggest that there is a limited need for Omnair/Omnaris, to the extent that sales are expected to be minimal if it does launch.

"I do not think that there is any movement, I have not heard of anything, it does not mean that there has not been, but I have not heard of anything."

EU key opinion leader

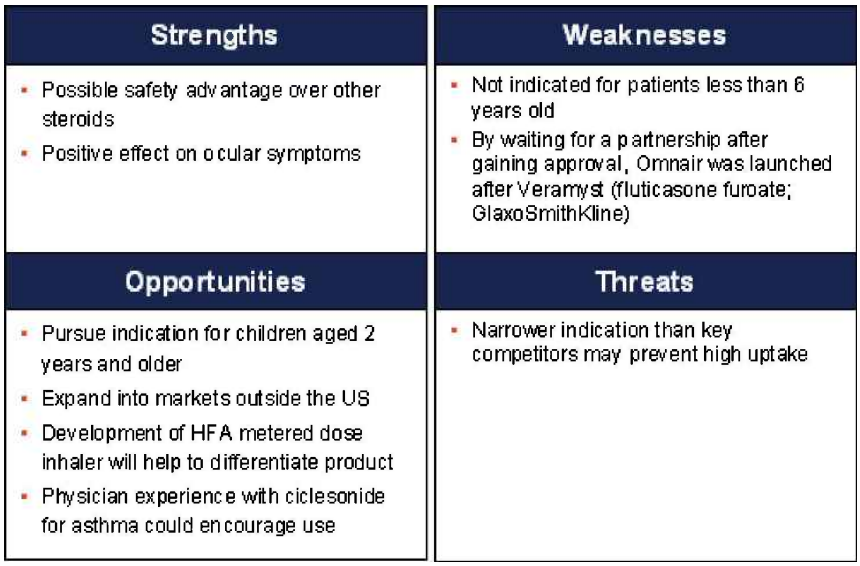
"I do not quite see the advantage to be honest. I mean we have very good nasal steroids which we have no doubts about their efficacy, I cannot see much, it will be a difficult market for them I think."

UK key opinion leader

SWOT analysis

The following figure highlights the strengths, weaknesses, opportunities and threats (SWOT) of Omnair/Omnaris for allergic rhinitis.

Figure 40: Omnair/Omnaris – SWOT analysis for allergic rhinitis, 2010



Source: Datamonitor

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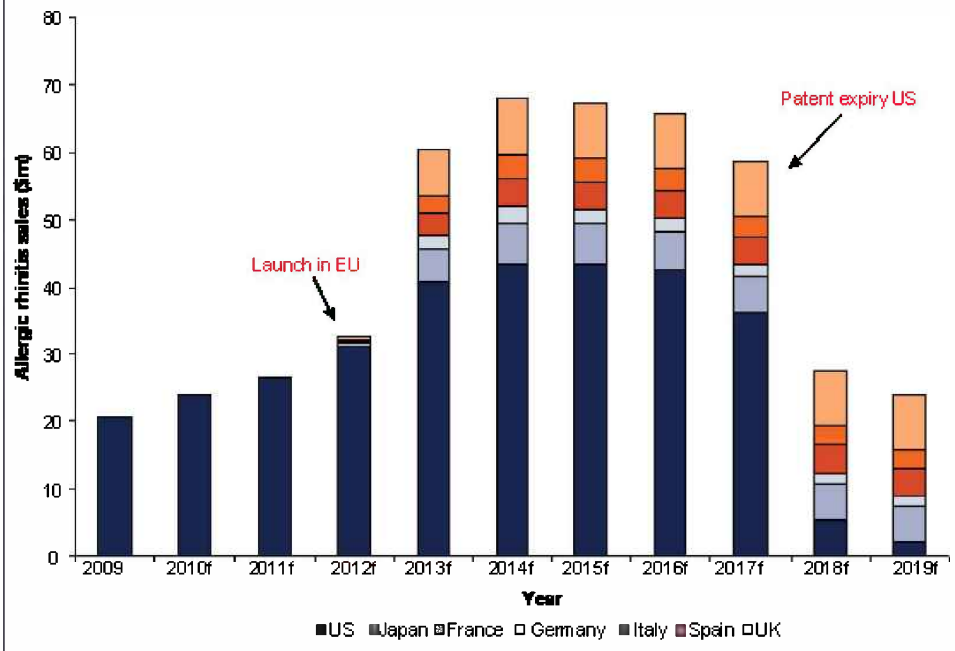
Brand forecast to 2019

- Nycomed's company website states the drug is in Phase III development outside the US, and Datamonitor therefore forecasts the drug will launch in the EU in 2012, taking 10% from other branded nasal corticosteroids with slow uptake over 3 years;
- Datamonitor does not forecast the drug will enter the market in Japan, where there is no indication from Teijin that development is ongoing;
- Omnair/Omnaris is to be priced at a 5% discount to Veramyst (fluticasone furoate) in the EU, which is similar to that seen in the US market;
- Omnair/Omnaris's patent will expire in 2017 in the US, after which rapid generic erosion will occur, with 90% of the brand's sales lost to generics over 2 years;
- Omnair/Omnaris HFA MDI formulation is expected to launch in 2012 in the US, taking 2% from all branded nasal corticosteroids over 4 years.

Figure 41: Omnair/Omnaris allergic rhinitis sales in the seven major markets ($m), 2008–2019



Source: 2010–2019 forecast = Datamonitor; 2009 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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Table 22: Sales forecasts for Omnair/Omnaris in allergic rhinitis in the seven major markets ($ 000s), 2009–2019						
	2009	2011f	2013f	2015f	2017f	2019f
US	20,535	26,475	40,863	43,539	36,246	2,127
Japan	0	0	0	0	0	0
France	0	0	4,875	5,872	5,441	5,238
Germany	0	0	2,038	2,187	1,852	1,597
Italy	0	0	3,172	4,140	4,039	4,049
Spain	0	0	2,823	3,334	3,035	2,888
UK	0	0	6,732	8,212	8,057	8,172
Total	**20,535**	**26,476**	**60,503**	**67,283**	**58,669**	**24,071**

Note: totals may not sum due to rounding.

Source: 2010–2019 forecast = Datamonitor; 2009 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission. DATAMONITOR

The 10-year market forecast for Omnair/Omnaris, both for allergic rhinitis and other indications is outlined separately in the accompanying forecast tool, a downloadable Excel spreadsheet that details the forecast for this drug in the seven major markets.

4. NASAL ANTIHISTAMINES

Key findings

- In 2009 nasal antihistamines made up only a small fraction, 5%, of allergic rhinitis sales in the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK). The low allergic rhinitis sales can be attributed to the nasal formulation of the class, with patients preferring the widely available oral antihistamines. The total sales for all indications equaled $439m in 2009 for the nasal antihistamine class, with allergic rhinitis estimated to be approximately $260m.
- Meda Pharma's Astelin (azelastine) is the highest selling nasal antihistamine, and in 2009 the company successfully launched a once-daily follow-on product Astepro (azelastine) in the US. Astepro is expected to minimize loss of sales to generic azelastine, which are forecast to enter the US market starting in 2010. Significant patient switching has already been seen between the two companies, and by 2011 sales of Astepro are forecast to exceed Astelin in the US. The successful launch of the Astepro is attributed to the development program of the drug, which included head-to-head studies of the two products, clearly demonstrating its advantages.

Overview for nasal antihistamines

Nasal antihistamines made up just 5%, $260m, of allergic rhinitis sales in the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK) in 2009. Their main disadvantage is their nasal formulation, which is difficult to position in a market dominated by tablets.

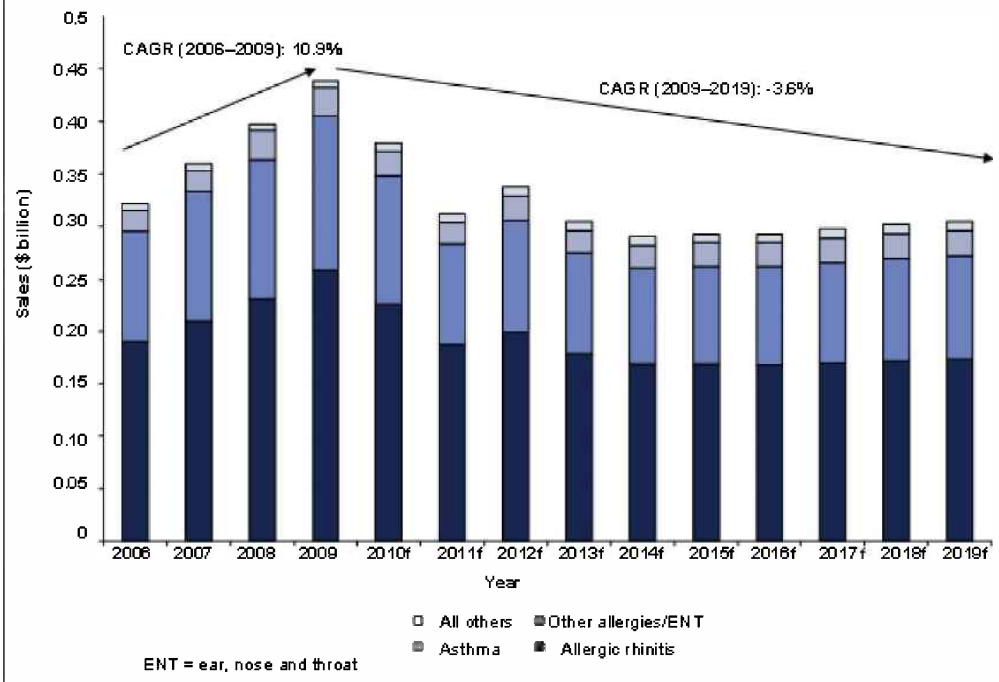
> "[Patients] *prefer tablets, of course they prefer tablets."*
>
> EU key opinion leader

While this is a disadvantage for nasal antihistamines as a monotherapy, there is the potential to combine nasal antihistamines with nasal corticosteroids, which would be an attractive treatment option for patients who require both. Several companies have such combinations in development, and Datamonitor believes the greatest potential for nasal antihistamines lies in these formulations..

Nasal antihistamine market size

The nasal antihistamine market reached $439m in the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK) in 2009, with growth over the period 2006–09 attributable to increased uptake of Astelin (azelastine; Meda Pharma), and the launch of Patanase (olopatadine; Alcon) in the US. Allergic rhinitis sales make up the majority of total class sales, accounting for just under $260m (59%) in 2009. From 2009 to 2019, Datamonitor expects the value of the nasal antihistamine class to shrink, with a compound annual growth rate (CAGR) of -3.6%, following generic versions of azelastine entering the market, and market share shifting to a combination of azelastine and fluticasone. However, increased uptake of Astelin's follow-on product, Astepro (azelastine, Meda Pharma), will dampen the decline in sales.

Figure 42: Nasal antihistamine sales in the seven major markets, by indication ($ billion), 2006–2019



ENT = ear, nose and throat

Source: 2010–2019 forecast = Datamonitor; 2006–09 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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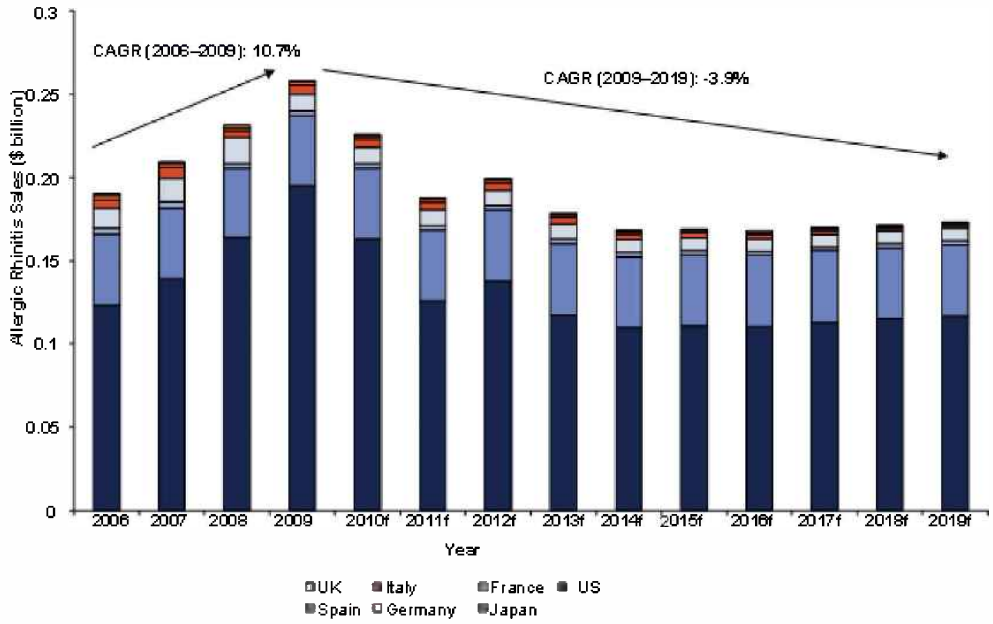
Figure 43 shows allergic rhinitis sales of nasal antihistamines by country in the seven major markets from 2006 to 2019. The US contributes the majority of sales—75% in 2019—and this is expected continue through 2019.

Figure 43: Allergic rhinitis sales of nasal antihistamines in the seven major markets by country ($ billion), 2009–2019



Source: 2010–2019 forecast = Datamonitor; 2006–09 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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Astelin/Astepro (azelastine); Meda Pharma

Summary takeaways:

- **Franchise products:** Astelin (azelastine); Astepro (azelastine);
- **2009 sales:** Astelin: total brand: $235m; allergic rhinitis: $127m; Astepro: total brand: $83m; allergic rhinitis: $44m;
- **2019 forecast sales:** Astelin: total brand: $15m; allergic rhinitis: $8m; Astepro: total brand: $178m; allergic rhinitis: $95m.

Meda Pharma (formerly ASTA Medica) has launched Astelin, an azelastine nasal spray, in the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK) for the treatment of symptoms of seasonal allergic rhinitis (SAR) in patients aged 5 years and older, and for the treatment of symptoms of vasomotor (non-allergic) rhinitis in patients aged 12 years and older. The drug had been launched in the US by 1997. In Europe, the drug is marketed under the trade names Allergodil and Rhinolast, and gained approval by 1999. In Japan, an oral formulation of azelastine is marketed as Azeptin by Eisai, and has been available since 1986 (Thomson Pharma, April 2010, Copyright Thomson Scientific).

Meda Pharma has also developed a once-daily follow-on product of azelastine, which launched as Astepro in the US. Astepro is indicated for the treatment of symptoms of seasonal and perennial allergic rhinitis (PAR) in patients aged 12 years and older (Meda, 2009a; http://www.astepro.com). The new formulation of azelastine was introduced to the US in Q1 2009, and the company gained approval for a higher strength, once-daily version of Astepro in September 2009, which it launched in the US in October 2009 (Meda, 2010b; http://www.meda.se; Meda, 2009b; http://feed.ne.cision.com). According to Meda's company website, registration is in progress for Astepro once-daily in other key markets, although it is not clear which countries are being pursued (Meda, 2010b; http://www.meda.se).

Franchise profile

Table 23: Astelin/Astepro – franchise profile, 2010

Astelin/Astepro	
Molecule	Azelastine
Mechanism of action	Histamine H1 receptor antagonist
Originator	ASTA Medica (now Meda Pharma)
Marketing company	Meda Pharma, Eisai (Japan)
Primary indication	Astelin: treatment of symptoms of seasonal allergic rhinitis (SAR) in patients aged 5 years and older, and for the treatment of symptoms of vasomotor (non-allergic) rhinitis in patients aged 12 years and older
	Astepro: treatment of symptoms of seasonal and perennial allergic rhinitis in patients aged 12 years and older
Formulation	Nasal spray
Dosing frequency	Astelin: two sprays per nostril twice-daily for patients aged 12 years and older, one spray per nostril twice-daily for patients aged 5–11 years
	Astepro: two sprays per nostril once-daily
Reimbursement status	Astelin: intermediate copay
	Astepro: intermediate copay
First launch date	Astelin: 1986 (Japan, oral), 1992 (Germany), 1998 (UK, US)
	Astepro: 2009 (US)
Primary patent expiry	May 2011 (US); expired (EU, Japan)
Alternative brand names	Astelin: Rhinolast, Allergodil, Corifina, Vividrin Akut, Azeptin (Oral)
2009 sales, 7MM	Astelin: total brand: $235m; allergic rhinitis: $127m
	Astepro: total brand: $83m; allergic rhinitis: $44m
2019 sales, 7MM	Astelin: total brand: $15m; allergic rhinitis: $8m
	Astepro: total brand: $178m; allergic rhinitis: $95m

7MM = seven major markets (US, Japan, France, Germany, Italy, Spain, UK)

Source: Datamonitor, Thomson Pharma; Astelin prescribing information; Astepro prescribing information; MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission. DATAMONITOR

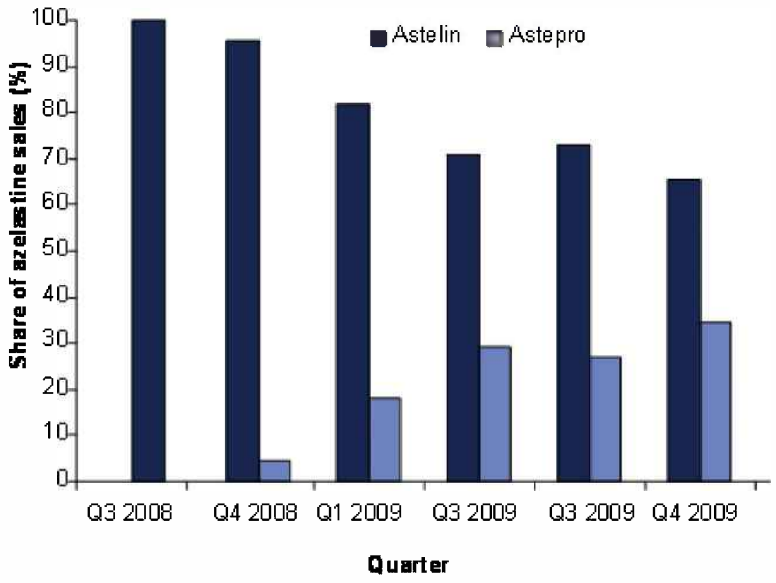
Product positioning

Astelin (azelastine, Meda Pharma)

Astelin's success in the allergic rhinitis market has been limited by its nasal route of administration and twice-daily formulation. Several oral antihistamines have a wider age-indication; Zyrtec, Telfast/Allegra and Aerius/Clarinex are all approved for treatment of children 2 years of age and older. Additionally, the oral route of administration may be preferred in both the pediatric and adult allergic rhinitis markets. Finally, the bitter taste that is associated with Astelin makes it less attractive than its competitors.

However, Astelin dominates within the nasal antihistamine market. In 2008 sales of the drug reached $293m in the seven major markets, but a fall to $233m was seen in 2009 due the successful switch of patients to Astepro in the US. Figure 44 shows the share of the franchise sales from Astelin and Astepro in the US, from Q3 2008, just before the launch of Astepro, to Q4 2009. Datamonitor expects that rapid patient switching will continue so that by the end of 2010, sales of Astepro will exceed those of Astelin in the US market.

Figure 44: US: Astelin and Astepro share of azelastine sales , %, Q3 2008–Q4 2009



Source: MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission

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The US patent of Astelin will expire in 2011; however, Meda Pharma has entered into a number of agreements with generics companies, allowing generic entry to start in 2010. An agreement with Apotex allowed it to launch generic Astelin in March 2010 under license from Meda, and a similar agreement has been made with Cobalt, permitting it to launch its generic in August 2010 (Thomson Pharma, April 2010, Copyright Thomson Scientific; (Meda, 2010b; http://www.meda.se). The agreement with Apotex also allows the company to launch a generic version of Optivar, an ophthalmic solution of azelastine. As of the first half of 2010, only azelastine ophthalmic solution appears on Apotex's product listing, therefore Datamonitor expects generic Astelin will reach the US market in Q3 2010 (Apotex, 2010; http://www.apotex.com).

Astepro (azelastine; Meda Pharma)

Launched in 2009, Astepro has become the first once-daily nasal antihistamine available in the US. While its once-daily dosing offers an advantage over its competitors, Meda reports that Astepro offers additional advantages over its predecessor Astelin, including better tolerance. The Phase III program included over 1,000 patients in placebo-controlled head-to-head trials of Astepro and Astelin. In total, fewer reports of bitter taste and nasal discomfort occurred with Astepro compared to Astelin. Patient-reported symptom relief was also better with the follow-on product (Meda, 2009c; http://feed.ne.cision.com; Meda, 2008; http://feed.ne.cision.com).

"It was not a huge deterrent to Astelin, but the taste issue is an improvement with the newer product."

US key opinion leader

The use of head-to-head trials was a considerable strength for the company. Other companies that failed to conduct head-to-head trials have struggled to see patient switching towards follow-on products as the advantages have not been clearly demonstrated. For example, key opinion leaders interviewed by Datamonitor indicated that patient switching from Zyrtec (cetirizine, UCB) to Xyzal (levocetirizine, UCB/Sepracor) has been limited by the lack trial data comparing the two, so that patients wanting an alternative to Zyrtec are moved to a different molecule entirely. The advantage of the clinical trial design for Astepro has already been seen as there was significant and immediate patient switching in the US from Astelin to Astepro.

According to Meda's company website, registration is in progress for Astepro once-daily in other key markets, although it is not clear which countries are being pursued (Meda, 2010b; http://www.meda.se). Given the low total brand sales seen for Astelin in the five major European markets (France, Germany, Italy, Spain, and the UK) and Japan, which reached just $12m in 2009, Datamonitor does not foresee the launch of the drug in these markets.

Rebranding this new formulation appears to have been successful strategy for Meda. While generics, which are forecast to enter the market in the second half of 2010, are expected to take a percentage of the market share from Astelin, the majority share is expected to shift to Astepro, largely insulating the franchise from Astelin's patent expiry. By 2011, Datamonitor forecasts that just 14% of azelastine sales in the US will be attributed to generics, with Astepro taking 74%, and Astelin retaining 11%. Without the launch of Astepro, an estimated 90% would have been lost to generics.

SWOT analysis

The following figure highlights the strengths, weaknesses, opportunities and threats (SWOT) of Meda Pharma's allergic rhinitis franchise.

Figure 45: Astelin/Astepro franchise – SWOT analysis for allergic rhinitis, 2010

Strengths	Weaknesses
Astelin ▪ Only nasal antihistamine with indication for non-allergic rhinitis **Astepro** ▪ First-to market with once-daily formulation ▪ Approved for both SAR and PAR ▪ Head-to-head trials versus Astelin	**Astelin** ▪ Bitter taste ▪ Nasal formulation less appealing than oral ▪ Twice-daily ▪ Note regarding somnolence in prescribing information **Astepro** ▪ Only indicated for patients aged 12 years and older ▪ Improved tolerance and symptom relief ▪ Note regarding somnolence in prescribing information
Opportunities	**Threats**
Astelin ▪ Continue patient switching to Astepro to avoid significant loss to generics **Astepro** ▪ Expand into additional markets outside the US	**Astelin** ▪ Several oral antihistamines have a wider indication ▪ Generics set to enter the market in 2010 **Astepro** ▪ Generic twice-daily azelastine will provide cheaper alternative

PAR = perennial allergic rhinitis; SAR = seasonal allergic rhinitis

Source: Datamonitor

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Brand forecast to 2019

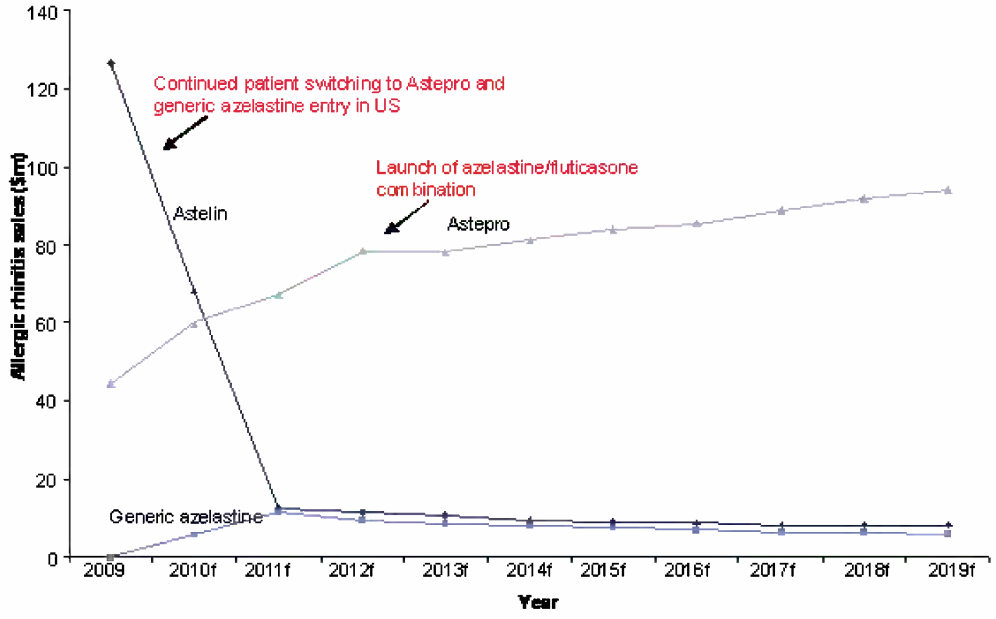
Astelin forecast assumptions

- Launch of the azelastine/fluticasone combination in the US in 2012 and EU in 2013 will lead to a loss of 20% market share over 5 years;
- the product's patent has expired in all seven major markets except the US, where generics will enter in 2010 prior to patent expiry in 2011, leading to the rapid erosion of sales, with 95% of market share lost rapidly over 3 years;
- no generics have launched in the EU, and their future presence is unlikely due to the low sales of the brand in that region.

Astepro forecast assumptions

- 20% market share is rapidly lost to generic entry of Astelin in 2010 in the US;
- launch of the azelastine/fluticasone combination in the US in 2012 will lead to a loss of 20% market share over 5 years;
- Astepro is not forecast to enter the EU market, as there is no indication of development there and sales of Astelin have been marginal;
- approval for Astepro is not expected to be pursued in Japan where there is a strong preference for oral products, and nasal azelastine is not available.

Figure 46: Astelin/Astepro sales in the US and five major EU markets ($m), 2009–2019



Source: 2010–2019 forecast = Datamonitor; 2009 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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Table 24: Sales forecasts for Astelin and Astepro in allergic rhinitis in the US and five major EU markets ($ 000s), 2009–2019						
	2009	2011f	2013f	2015f	2017f	2019f
Astelin						
US	119,413	5,088	3,323	2,503	2,031	1,774
France	2,159	2,152	2,126	1,855	1,728	1,731
Germany	3,051	3,312	3,490	3,142	3,130	3,236
Italy	477	488	503	448	424	430
Spain	1,113	1,008	923	753	665	638
UK	371	365	354	313	296	281
Astelin total	**126,585**	**12,412**	**10,719**	**9,015**	**8,275**	**8,090**
Astepro						
US	44,244	67,487	78,267	84,109	89,004	94,243
Franchise total	**170,829**	**79,899**	**88,986**	**93,124**	**97,279**	**102,333**

Note: totals may not sum due to rounding.

Source: 2010–2019 forecast = Datamonitor; 2009 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010,

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The 10-year market forecasts for Astelin and Astepro, for both allergic rhinitis and other indications are outlined separately in the accompanying forecast tool, a downloadable Excel spreadsheet that details the forecasts for these drugs in the seven major markets.

Patanase (olopatadine; Alcon)

Summary takeaways:

- **Product:** Patanase (olopatadine);
- **2009 sales:** total brand: $38m; allergic rhinitis: $23m;
- **2019 forecast sales:** total brand: $4m; allergic rhinitis: $2m.

Alcon, under license from Kyowa, has developed Patanase, a nasal formulation of the oral dibenzoxepin-selective antihistamine olopatadine. In Q4 2004, Alcon filed a New Drug Application (NDA) with the US Food and Drug Administration (FDA) for seasonal allergic rhinitis (SAR) after which the FDA issued an approvable letter telling Alcon that it needed it to remove one of the nasal spray's inactive ingredients before it could be approved. In October 2007 the amended formulation was filed, and it was approved in April 2008. Although Alcon filed for approval of the formulation in the EU in April 2005, the company withdrew the Marketing Authorization Application (MAA) for commercial reasons in February 2006 (Thomson Pharma, April 2010, Copyright Thomson Scientific).

Patanase nasal spray is indicated for the relief of the symptoms of seasonal allergic rhinitis (SAR) in adults and children 6 years of age and older (Alcon, 2009). Olopatadine is furthermore approved in oral and ophthalmic formulations for the treatment of allergic conjunctivitis (Thomson Pharma, April 2010, Copyright Thomson Scientific). In Japan, Kyowa has developed an oral formulation of olopatadine which launched under the brand name Allelock in 2001 (Kyowa, 2001; http://www.kyowa-kirin.co.jp).

Drug profile

Table 25: Patanase – drug profile, 2010

Patanase	
Molecule	Olopatadine
Mechanism of action	Dibenzoxepin-selective histamine H1-receptor antagonist
Originator	Kyowa
Marketing company	Alcon
Primary indication	Relief of the symptoms of seasonal allergic rhinitis (SAR) in adults and children 6 years of age and older
Formulation	Nasal spray
Dosing frequency	Aged 12+ years: two sprays in each nostril/day; Aged 6–11 years: one spray in each nostril/day
Reimbursement status	High copay
First launch date	2008 (US)
Primary patent expiry	June 2013 (US)
2009 sales, 7MM	Total brand: $38m; allergic rhinitis: $23m
2019 sales, 7MM	Total brand: $4m; allergic rhinitis: $2m

7MM = seven major markets (US, Japan, France, Germany, Italy, Spain, UK)

Source: Datamonitor, Thomson Pharma; Patanase prescribing information; MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission. DATAMONITOR

Product positioning

In 2009, its second year on the market, Patanase reached total brand sales of just $38m in the US, only a fraction of the $233m US sales achieved by its primary competitor Astelin (azelastine, Meda Pharma) for the same year. In order to compete effectively the drug must differentiate itself from Astelin. The efficacy and safety of the two drugs were compared in a 16-day Phase III multicenter, randomized, double-blind placebo-controlled study in patients aged 12 years and older with a history of seasonal allergic rhinitis. While the study showed no statistically significant difference in efficacy between the drugs as measured by a reduction from baseline in reflective Total Nasal Symptom Scores (TNSS), and similar side-effect profiles were shown between the drugs, it did highlight that prevalence and intensity of a bitter taste was significantly lower with olopatadine compared to azelastine (Shah *et al* ., 2009). Alcon also sponsored a Phase IV trial comparing Patanase nasal spray to Flixonase/Flonase (fluticasone propionate; GlaxoSmithKline), a nasal corticosteroid. The trial included 130 patients with seasonal allergic rhinitis who were randomized to receive one of the two treatments twice-daily for 2 weeks. The reflective TNSS decreased by an average of -45.4% for patients treated with Patanase, and by -47.4% for patients treated with fluticasone. There was no statistically significant difference in efficacy between the two treatments over the complete 2-week period, however, Patanase had a faster onset of action for reducing all symptoms, and showed a statistically significant improvement over fluticasone at day 1 (Kaliner *et al* ., 2009).

Despite these results, Patanase's market potential is limited by its route of administration in a market favoring oral antihistamines. Furthermore, with the September 2009 approval of Astelin's once-daily follow-on Astepro (azelastine, Meda Pharma), the twice-daily dosing of Patanase is a strong disadvantage, and sales are expected to reflect this.

SWOT analysis

The following figure highlights the strengths, weaknesses, opportunities and threats (SWOT) of Patanase for allergic rhinitis.

Figure 47: Patanase – SWOT analysis for allergic rhinitis, 2010

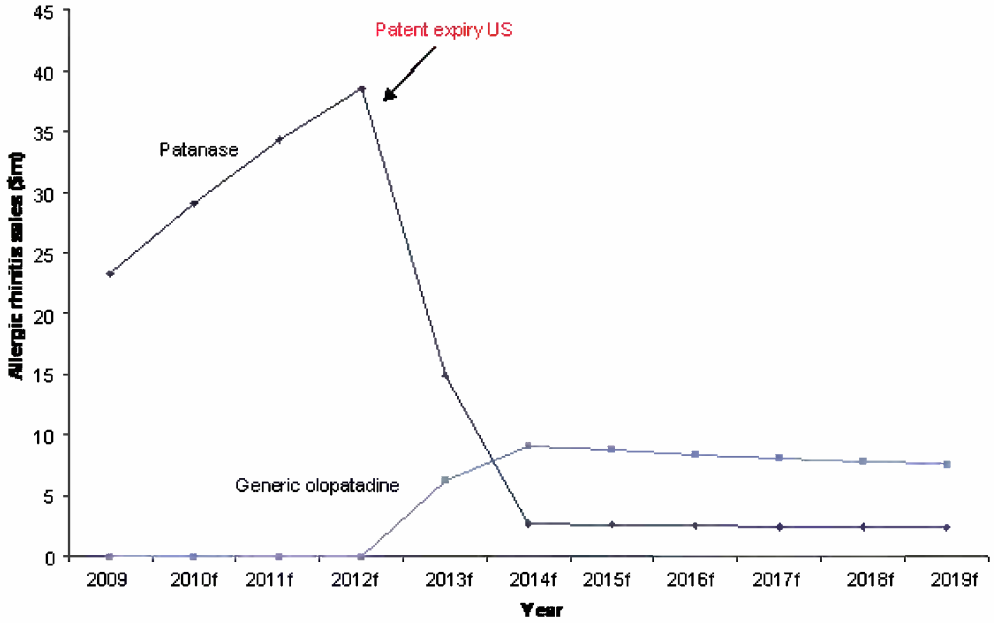
Strengths	Weaknesses
▪ Less prevalence and intensity of bitter taste compared to Astelin (azelastine; Meda Pharma) ▪ Demonstrated faster onset of action compared to Flixonase/Flonase (fluticasone propionate; GlaxoSmithKline)	▪ Nasal formulation ▪ Limited uptake ▪ Only available in US
Opportunities	**Threats**
▪ Promote advantages over competitors ▪ Expand to additional markets	▪ Launch of once-daily Astepro (azelastine; Meda Pharma) reduces attractiveness

Source: Datamonitor DATAMONITOR

Brand forecast to 2019

- After withdrawing an Marketing Authorization Application (MAA) in the EU in April 2005, there has been no indication that the drug will be further developed in that region;
- approval is not expected to be sought in Japan where there is no indication of ongoing development and a strong preference for oral formulations exists;
- 20% of market share will be lost over 5 years due to a combination azelastine/fluticasone launching in the US;
- patent expiry in 2013 in the US will lead to rapid generic erosion with 90% of market share lost to generics over 2 years.

Figure 48: Patanase allergic rhinitis sales in the US ($m), 2009–2019



Source: 2010–2019 forecast = Datamonitor; 2009 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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Table 26: Sales forecasts for Patanase in allergic rhinitis in the US ($ 000s), 2009–2019

	2009	2010f	2011f	2012f	2013f	2014f	2015f	2016f	2017f	2018f	2019f
US	23,372	29,129	34,346	38,540	14,895	2,704	2,627	2,559	2,498	2,440	2,385

Source: 2010–2019 forecast = Datamonitor; 2009 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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The 10-year market forecast for Patanase, both for allergic rhinitis and other indications is outlined separately in the accompanying forecast tool, a downloadable Excel spreadsheet that details the forecast for this drug in the seven major markets

5. ANTILEUKOTRIENES

Key findings

- While only 20% of antileukotriene sales in the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK) in 2009 were for allergic rhinitis, sales for that indication are lucrative, reaching $1 billion in that year. The majority, 56%, of antileukotrienes' $5.1 billion sales in 2009 were for asthma.
- Singulair (montelukast, Merck) is the highest selling antileukotriene, with allergic rhinitis sales of $900m in 2009 in the seven major markets. While the drug will retain its class dominance, sales are forecast to drop substantially with patent expiries in 2012 in the US and EU, and 2016 in Japan. By 2019 Singulair is forecast to have allergic rhinitis sales of just $118m.

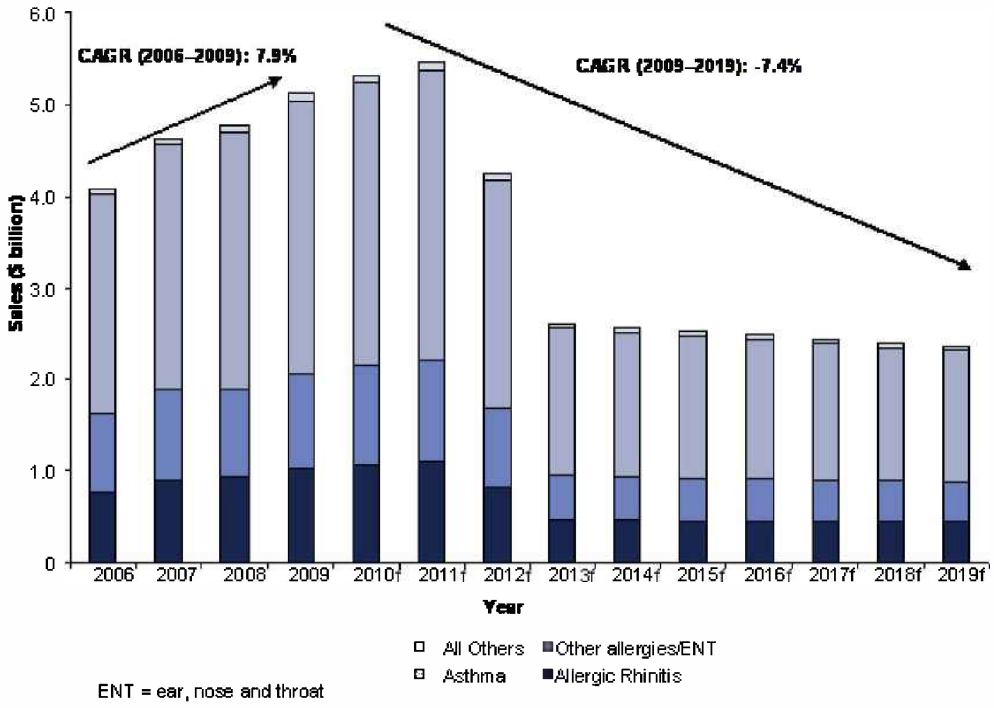
Overview of antileukotrienes

Antileukotrienes accounted for 20% of allergic rhinitis sales in the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK) in 2009. For that year, total sales of antileukotrienes reached $5.1 billion, with $1 billion for allergic rhinitis. However, patent expires over the next 10 years, in particular, that of Singular which will expire in most of the seven major markets in 2012, will have a strong impact on the class, with allergic rhinitis sales forecast to drop to $4.6 billion by 2019.

Antileukotriene market size

Unlike other drug classes indicated for allergic rhinitis, the antileukotriene market is dominated by sales for asthma, which accounted for 57% of antileukotriene sales in the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK) in 2009, with allergic rhinitis accounting for just 20%. The market consists primarily of Singulair (montelukast, Merck), and experienced positive growth over the period 2006–09, with a compound annual growth rate (CAGR) of 7.9%. However, with Singulair going off-patent in the US and EU in 2012, and Japan in 2016, the market should see a dramatic decline, with a CAGR of -7.4% from 2009 to 2019. Antileukotriene sales in the seven major markets are shown by indication in Figure 50.

Figure 49: Antileukotriene sales in the seven major markets by indication ($ billion), 2006–2019



ENT = ear, nose and throat

Source: 2010–2019 forecast = Datamonitor; 2006–09 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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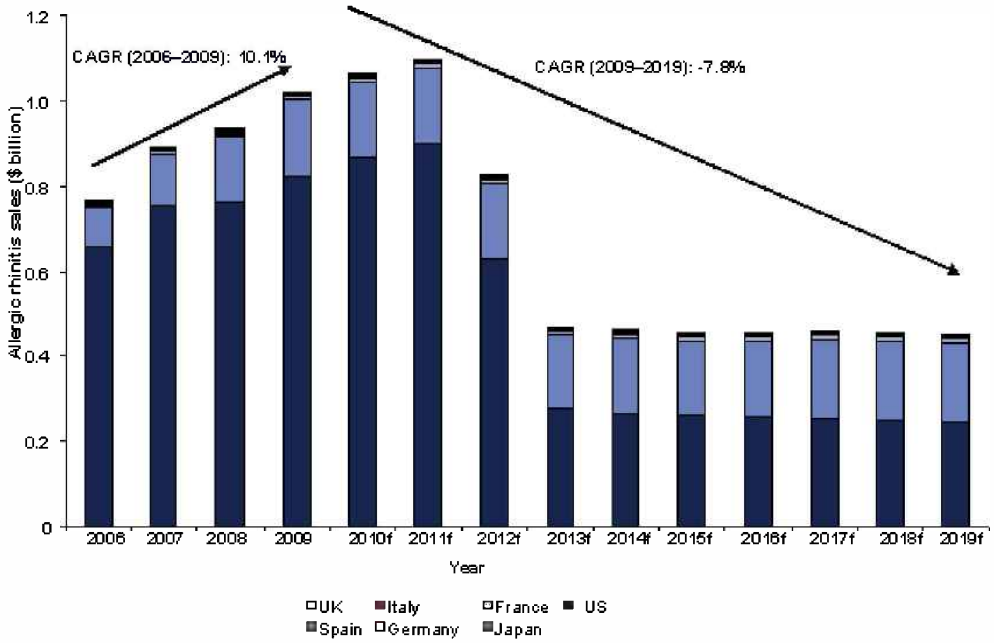
Outside of the US, antileukotrienes are not commonly used for allergic rhinitis. The sales breakdown for antileukotrienes for allergic rhinitis by country is shown in Figure 50. However, in Japan Kipres (montelukast; known as Singulair outside of Japan), was granted approval for the treatment of adult allergic rhinitis in January 2008, followed by its launch in April of that year (Merck, 2010; Thomson Pharma, April 2010, Copyright Thomson Scientific; Pub, 2008; http://www.jpubb.com). As a result Japan's share of the antileukotriene market for allergic rhinitis has increased, and Datamonitor expects further uptake in that country, increasing share from 17% in 2009 to 42% in 2019.

Figure 50: Allergic rhinitis sales of antileukotrienes in the seven major markets by country ($ billion), 2009–2019



Source: 2010–2019 forecast = Datamonitor; 2006–09 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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Singulair (montelukast; Merck and Kyorin Pharmaceuticals)

Summary takeaways:

- **Product:** Singulair (montelukast);
- **2009 sales:** total brand: $4.7 billion; allergic rhinitis: $900m;
- **2019 forecast sales:** total brand: $921m; allergic rhinitis: $118m.

Merck and Kyorin Pharmaceutical's Singulair (montelukast), a leukotriene D4 antagonist, is the gold standard for the antileukotriene class, although there remains a demand for a more effective oral therapy. In the US, Singulair is approved for the relief of symptoms of seasonal allergic rhinitis (SAR) in patients 2 years of age and older and of perennial allergic rhinitis (PAR) in patients 6 months of age and older. Singulair is further indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older, and, in April 2007, the US label was extended to include prevention of exercise-induced bronchoconstriction in patients aged 15 years and older. In Europe, Singulair is indicated for the prophylaxis of asthma, and for the symptomatic relief of seasonal allergic rhinitis in patients with asthma (BNF, 2010; http://bnf.org). In Japan, where the drug is marketed as Kipres, approval was granted for the treatment of adult allergic rhinitis in January 2008, followed by a launch in April of that year (Merck, 2010; Thomson Pharma, April 2010, Copyright Thomson Scientific; JPubb, 2008; http://www.jpubb.com). While the additional indication led to a boost in sales in Japan, the majority of sales in each of the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK) continues to come from the treatment of asthma.

Drug profile

Table 27: Singulair – drug profile, 2010

Singulair	
Molecule	Montelukast
Mechanism of action	Leukotriene D4 antagonist
Originator	Merck
Marketing company	Merck/Kyorin
Primary indication	Relief of symptoms of seasonal allergic rhinitis (SAR) in patients 2 years of age and older and perennial allergic rhinitis (PAR) in patients 6 months of age and older; prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older; and, prevention of exercise-induced bronchoconstriction in patients aged 15 years and older
Formulation	Tablets, chewable tablets and oral granules
Dosing frequency	Once-daily
Reimbursement status	Intermediate copay
First launch date	1998 (US and Europe), 2001 (Japan)
Primary patent expiry	August 2012 (US, France, Germany, Italy, Spain, UK), October 2016 (Japan)
Alternative brand names	Kipres (Japan)
2009 sales, 7MM	Total brand: $4.7 billion; allergic rhinitis: $900m
2019 sales, 7MM	Total brand: $921m; allergic rhinitis: $118m

7MM = seven major markets (US, Japan, France, Germany, Italy, Spain, UK)

Source: Datamonitor, Thomson Pharma; Singulair prescribing information; MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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Product positioning

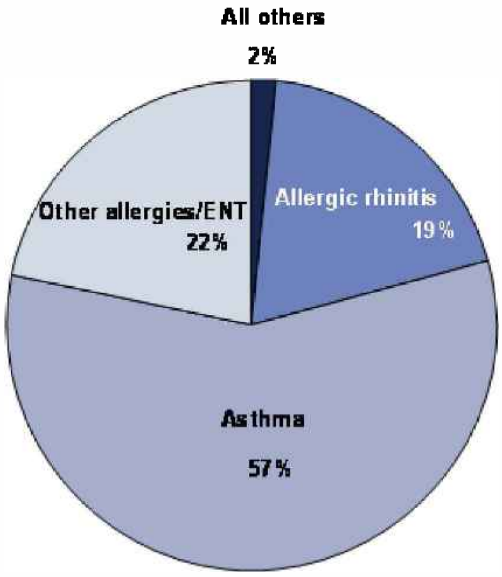
Merck has effectively marketed Singulair's key benefits (including oral administration, once-daily dosing, a range of formulations including a tablet form for adults (10mg), a cherry-chewable tablet (4mg or 5mg) for children aged 2–14 years and oral granules (4mg) for children aged 6 months–5 years) to compensate for its relatively modest clinical efficacy in order to dominate the antileukotriene market.

The majority (57%) of Singulair's 2009 sales in the seven major markets are attributable to asthma. Only 19% of the drug's 2009 total brand sales are attributed to allergic rhinitis, mainly due to its high price in comparison to products such as the oral antihistamines, but it is frequently prescribed for patients with both diseases (Allergic rhinitis sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010).

"[I prescribe Singulair] just in patients who have asthma and allergic rhinitis, and this is something that is quite effective. It is difficult to prescribe it just for rhinitis because of the cost."

EU key opinion leader

Figure 51: Singulair sales by indication, 2009



ENT = ear, nose and throat

Source: 2010–2019 forecast = Datamonitor; 2006–09 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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Total brand sales of Singulair reached $4.7 billion in the seven major markets in 2009. The strongest sales growth over the period 2006–09 came from Japan, owing to the successful addition of the allergic rhinitis indication in Spring 2008, as well as the approval and launch of oral granules for the treatment of children aged 1–5 years in late 2007 (Merck, 2008b; http://www.123jump.com).

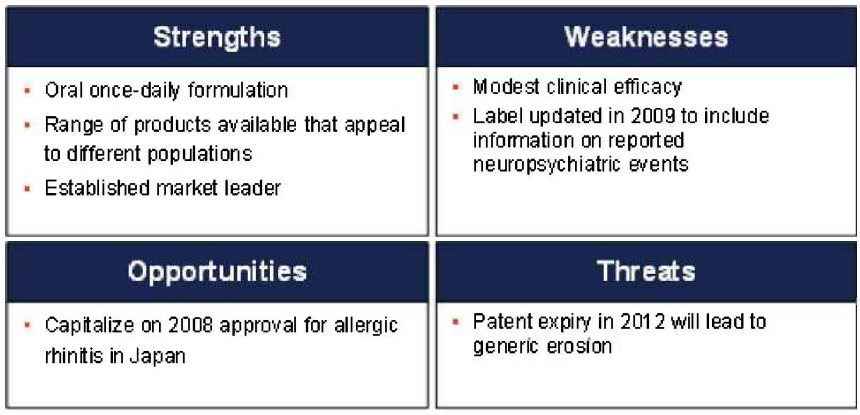
In October 2007, Merck updated both the montelukast worldwide product label and patient product information to include the risk of suicidal thinking and behavior. After investigating the potential link between the use of montelukast and behavioral changes, the US Food and Drug Administration (FDA) issued a notice in June 2009 that the drug's US prescribing information should include a precaution regarding drug-induced neuropsychiatric problems of agitation, aggression, suicidal ideation, suicide, depression, insomnia and irritability. Merck updated the label accordingly in August 2009 (Thomson Pharma, April 2010, Copyright Thomson Scientific).

The changes in product labeling do not seem to have affected prescribing behavior, with sales growth seen in each of the seven major markets. Sales are likely to continue growing until the product's patent expiry in 2012 and sales for allergic rhinitis are expected to be just $117m in the seven major markets in 2019.

SWOT analysis

The following figure highlights the strengths, weaknesses, opportunities and threats (SWOT) of Singulair for allergic rhinitis.

Figure 52: Singulair – SWOT analysis for allergic rhinitis, 2010



Source: Datamonitor

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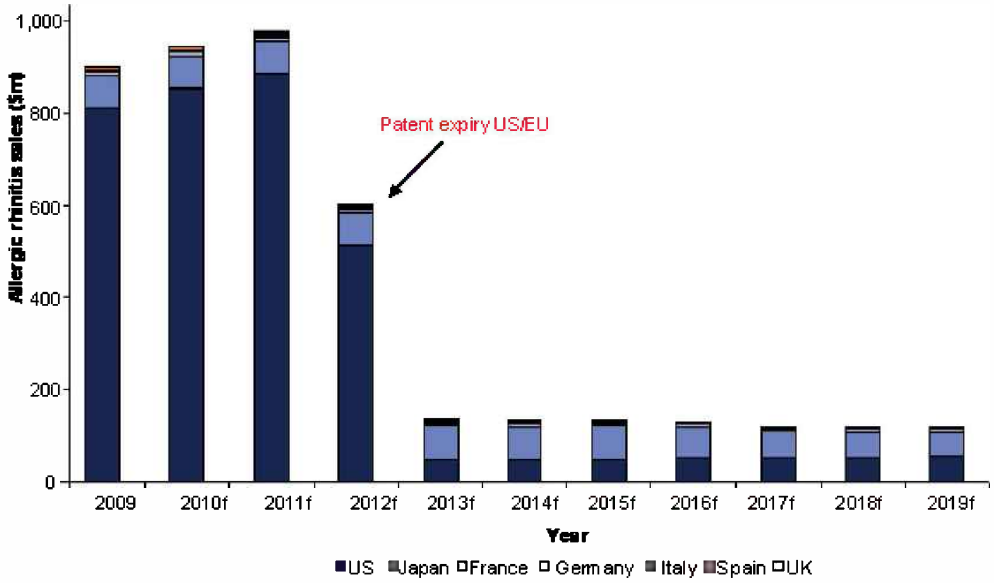
Brand forecast to 2019

- The product's patent will expire in August 2012 in the US, France, Germany, Italy, Spain and the UK and in October 2016 in Japan, leading to sales attrition due to generic competition. Datamonitor benchmarks the extent and speed of erosion in each country against the experiences of antihistamines going off-patent (see 8. CASE STUDY). The greatest volume shift from the branded product to generics is expected in the US, Germany and the UK, ranging from 80 to 95% brand erosion. In France and Spain generic erosion is forecast to reach 55% and 70%, respectively, while the lowest brand erosion is expected in Japan and Italy, with predicted losses of just 30% in Japan and 15% in Italy.

Figure 53: Singulair allergic rhinitis sales in the seven major markets ($m), 2009–2019



Source: 2010–2019 forecast = Datamonitor; 2009 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010,

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Table 28: Sales forecasts for Singulair in allergic rhinitis in the seven major markets ($ 000s), 2009–2019						
	2009	2011f	2013f	2015f	2017f	2019f
US	810,133	883,828	49,767	49,316	50,976	52,247
Japan	70,743	71,128	71,194	71,195	57,057	54,062
France	7,394	8,913	5,505	5,603	5,672	5,699
Germany	2,730	2,638	870	591	401	252
Italy	2,870	3,767	3,797	4,035	4,159	4,218
Spain	3,541	3,415	2,137	1,682	1,317	1,000
UK	1,487	1,519	538	453	394	347
Total	**898,899**	**975,207**	**133,808**	**132,874**	**119,975**	**117,825**

Note: totals may not sum due to rounding.

Source: 2010–2019 forecast = Datamonitor; 2009 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission. DATAMONITOR

The 10-year market forecast for Singulair, for both allergic rhinitis and other indications is outlined separately in the accompanying forecast tool, a downloadable Excel spreadsheet that details the forecast for this drug in the seven major markets.

Onon (pranlukast; Ono Pharmaceuticals)

Summary takeaways:

- **Product:** Onon (pranlukast);
- **2009 sales:** total brand: $340m; allergic rhinitis: $97m;
- **2019 forecast sales:** total brand: $310m; allergic rhinitis: $95m.

Ono Pharmaceutical's Onon (pranlukast) has been highly successful in Japan where Ono is a key player in the antileukotriene market. The drug, an orally active leukotriene antagonist, is available as capsules and as a dry syrup.

Onon was first launched in Japan for the treatment of bronchial asthma in 1995, and gained approval for the further indication of allergic rhinitis in adults in 2000. The company was previously investigating the drug for the treatment of pediatric allergic rhinitis; however development for that indication had been discontinued by June 2007 (Thomson Pharma, April 2010, Copyright Thomson Scientific).

Drug profile

Table 29: Onon – drug profile, 2010

Onon	
Molecule	Pranlukast
Mechanism of action	Leukotriene antagonist
Originator	Ono
Marketing company	Ono
Primary indication	Treatment of bronchial asthma, treatment of allergic rhinitis
Formulation	Oral
Dosing frequency	Once-daily
First launch date	1995 (Japan)
Primary patent expiry	2004 (Japan)
2009 sales, 7MM	Total brand: $340m; allergic rhinitis: $97m
2019 sales, 7MM	Total brand: $310m; allergic rhinitis: $95m

7MM = seven major markets (US, Japan, France, Germany, Italy, Spain, UK)

Source: Datamonitor, Thomson Pharma; MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission. DATAMONITOR

Product positioning

Japanese patients' preference for oral drugs and Ono's local presence have contributed to strong sales of Onon, however, it is no longer the highest selling antileukotriene on the market, having been surpassed by Singulair in 2008. At $608m, Singulair's 2009 sales in Japan were nearly double those of Onon, whose total brand sales were $340m in the same year, of which, 29% were attributed to allergic rhinitis.

Singulair's wider indication makes it the more competitive product, although Onon continued to see growth in sales, with a compound annual growth rate (CAGR) of 3% over the period 2006–09. However, a number of generics entered the Japanese market in 2007, and are expected to reverse Onon's growth and erode its sales over the next 10 years.

SWOT analysis

The following figure highlights the strengths, weaknesses, opportunities and threats (SWOT) of Onon for allergic rhinitis.

Figure 54: Onon – SWOT analysis for allergic rhinitis, 2010

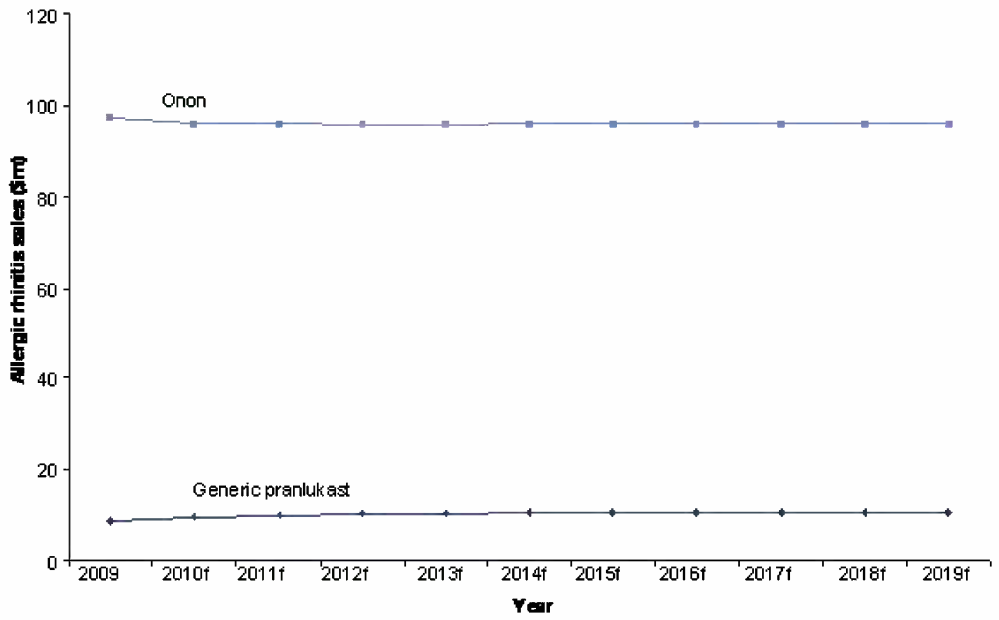
Strengths	Weaknesses
▪ Oral formulation ▪ Strong marketing position within Japan	▪ Narrower indication than Singulair (montelukast, Merck)
Opportunities	**Threats**
▪ Differentiate product with new formulations to appeal to additional patient populations and resist generic erosion	▪ Patent expired in 2009 ▪ Singulair (montelukast, Merck) poses strong threat having gained additional indications

Source: Datamonitor DATAMONITOR

Onon forecast assumptions

- With generics on the market in Japan since 2007, Onon's sales will continue to falter and suffer from generic incursion. Generic erosion will be slow and minimal, consistent with the experience of other drugs in the country.

Figure 55: Onon allergic rhinitis sales in Japan, 2009–2019



Source: 2010–2019 forecast = Datamonitor; 2009 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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Table 30: Sales forecasts for Onon in allergic rhinitis in Japan ($ 000s), 2009–2019											
	2009	2010f	2011f	2012f	2013f	2014f	2015f	2016f	2017f	2018f	2019f
Japan	97,252	95,905	95,837	95,759	95,803	95,816	95,822	95,827	95,829	95,830	95,830

Source: 2010–2019 forecast = Datamonitor; 2009 sales calculated from Prescribing Insights and MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission. DATAMONITOR

The 10-year market forecast for Onon, for both allergic rhinitis and other indications is outlined separately in the accompanying forecast tool, a downloadable Excel spreadsheet that details the forecast for this drug in Japan.

Late-stage development compounds recently discontinued

Loratadine/montelukast (Merck)

In May 2000, Schering-Plough and Merck & Co agreed to jointly pursue the development and marketing of a fixed dose combination tablet of loratadine and montelukast for the treatment of allergic rhinitis symptoms in patients who want relief from nasal congestion. At the time, Schering-Plough held the rights to loratadine, sold as Claritin, while Merck owned montelukast, sold as Singulair, both of which are indicated for the relief of symptoms of allergic rhinitis. Through its acquisition of Schering-Plough, Merck now markets both components. In August 2007 the companies submitted a New Drug Application (NDA) to the US Food and Drug Administration (FDA), however, in April 2008 the FDA issued a non-approvable letter, after which the companies withdrew the application and terminated their agreement (Thomson Pharma, June 2010, Copyright Thomson Scientific).

An antileukotriene/antihistamine combination would theoretically be appealing, as it would offer a simpler treatment regimen to patients requiring both products, while keeping the simplicity of a tablet formulation. Key opinion leaders expressed ongoing interest in its potential, despite the discontinuation of this product's development.

> *"A leukotriene antagonist and an antihistamine, it is a very practical combination, and it is not far off probably the efficacy of a nasal steroid."*
>
> UK key opinion leader

Loratadine and montelukast were studied in combination in several trials and most of them concluded that this combination is not significantly more effective than the separate components or a nasal steroid. Nayak *et al* . (2002) evaluated the effectiveness and tolerability of montelukast, loratadine, and combination therapy with montelukast and loratadine for treating patients with fall seasonal allergic rhinitis (SAR). After a 1-week, single-blind, placebo run-in period, 907 male and female patients aged 15–82 years were randomized to one of four treatments: montelukast 10mg (n = 155), loratadine 10mg (n = 301), combination montelukast 10mg and loratadine 10mg (n = 302), or placebo (n = 149), administered once-daily at bedtime for 2 weeks. The primary endpoint was the daytime nasal symptoms score (mean of congestion, rhinorrhea, pruritus, and sneezing). The study showed that the effect of montelukast/loratadine compared with loratadine alone was not significantly different. Differences for montelukast/loratadine compared with each therapy alone generally showed numerical superiority, and a few endpoints showed differences that were statistically significant.

A second study by Saengpanich *et al*. (2003) compared the effectiveness of nasal fluticasone propionate with that of the combination of loratadine and montelukast in the treatment of SAR. A total of 63 adults with a 2-year history of ragweed sensitivity and a positive skin-prick reaction to ragweed pollen were randomized to receive either 100mcg of fluticasone in each nostril or loratadine/montelukast (10mg/10mg) once-daily in the evening for 2 weeks. The main outcome measures included questionnaire answers, daily nasal symptom scores, eosinophil counts and eosinophil cationic protein (ECP) levels. The researchers found that the median Total Nasal Symptom Score (TNSS) was lower in the fluticasone group but that this difference was not statistically significant. The questionnaire answers showed a dramatic improvement in overall and individual domains for both groups with a significantly greater reduction in nasal symptoms in the fluticasone group. Eosinophil counts and ECP levels were significantly reduced in the fluticasone group.

Finally, Wilson *et al* . (2002) compared loratadine/montelukast with fexofenadine alone for effects on daily measurements (morning/evening) of peak inspiratory flow (PIF) and symptoms. Thirty-seven patients with SAR (skin-prick positive to grass pollen) were randomized into a single-blind, double-dummy placebo-controlled cross-over study during the grass pollen season, comparing 2 weeks of once-daily treatment with fexofenadine 120mg or loratadine/montelukast (10mg/10mg). The study showed that there were significant improvements in all symptoms and PIF compared to pooled placebo with both treatments for all endpoints, but exposed no differences between the two treatment regimens.

6. IMMUNOTHERAPY

Key findings

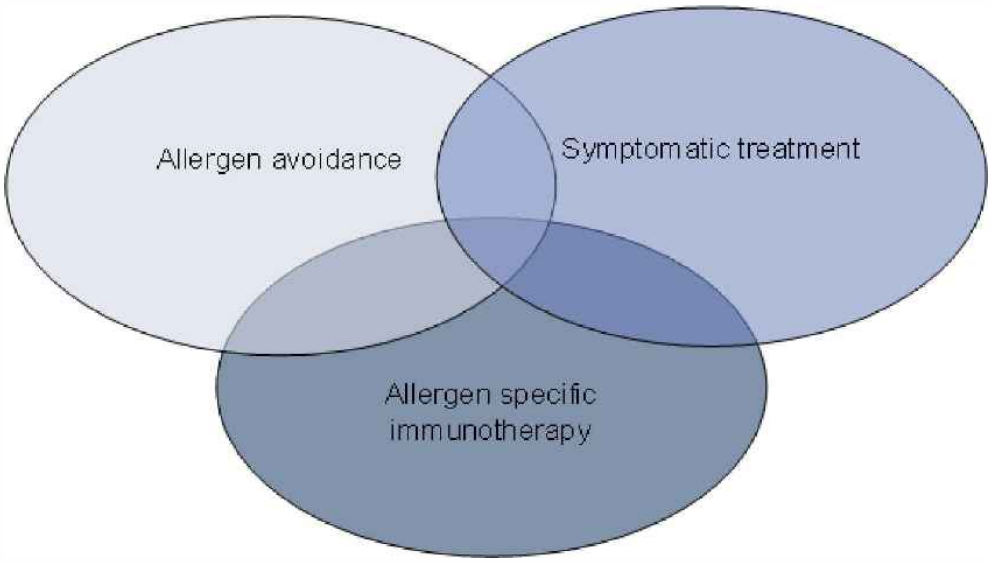
- Updated EU regulations are driving a shift in clinical trial design for allergen immunotherapy, with the first large-scale placebo controlled development programs seen in recent years. As a result, there is a growing body of clinical data, and, while expected to remain a niche market, immunotherapies role in allergic rhinitis is increasing. Cost will remain a key constraint however, and Datamonitor estimates that over a year of treatment, tablet based immunotherapy is roughly 60 times the cost of combined seasonal oral antihistamine and nasal corticosteroid treatment. Companies must therefore promote the long-term advantages of immunotherapy over symptomatic treatment in order to see success.
- In 2006 Grazax (ALK-Abelló) became the first tablet based sublingual immunotherapy to achieve full registration in the EU. Its first-to-market status is a strong advantage, but according to IMS Health sales data uptake has so far been slow. However, with positive long-term follow-up results and a forecasted US launch in 2012, Grazax is expected to become the most profitable allergen immunotherapy by 2019, with sales of $182m in the US and five major EU markets by 2019.
- Datamonitor utilizes a patient based forecast for immunotherapy, benchmarked against historical IMS sales data. Starting with total patient numbers, as calculated in the patient potential section of this report, Datamonitor applies assumptions on factors such as diagnosis rates, severity, access to specialists, and compliance in order to determine the patient pool for individual immunotherapies. These assumptions are derived from literature, discussions with key opinion leaders, and analysis of sales. Using this method, Datamonitor estimates that total sales of three immunotherapies, Grazax (ALK-Abelló), Oralair (Stallergènes), and Pollinex Quattro (Allergy Therapeutics) will reach $295m in the US and five major EU markets by 2019.

Overview of immunotherapy

Allergen immunotherapy involves the administration of gradually increasing quantities of specific allergens, such as pollen extracts, until a dose is reached that effectively reduces disease severity from natural exposure.

It is generally believed that there are three potential approaches to treating allergic rhinitis: allergen avoidance, symptomatic treatment, and allergen-specific immunotherapy. These approaches are possible in isolation, or in combination, as depicted in Figure 56.

Figure 56: Approaches to treating allergic rhinitis



Source: Datamonitor DATAMONITOR

Henrik Jacobi, the head of research and development at ALK-Abelló spoke at the 2010 Annual Congress of the European Academy of Allergy and Clinical Immunology (EAACI) held in London. He acknowledged these three approaches, highlighting that at present there is a strong focus on the immunotherapy option, and that as a result the immunotherapy scene is changing rapidly. Jacobi defined the current value proposition of immunotherapy as two-fold:

- treating patients whose disease is poorly controlled by symptomatic drugs;
- modifying the disease.

ALK-Abelló's Grazax is the only therapy to have approval as a disease-modifying treatment, following positive results from a long-term study. Other companies, including Stallergènes with its product Oralair grasses, are expected to pursue similar indications, strengthening the evidence in favor of immunotherapy's ability to modify disease. Jacobi also offered insight into the potential future role of immunotherapy, including:

- secondary prevention of asthma in patients with allergic rhinoconjunctivitis;
- primary prevention of rhinoconjunctivitis and asthma in sensitized or at risk infants;
- integration of treatment regimens with measurements of biomarkers.

There is evidence to suggest the potential for each of these roles, but significant further investigation is required.

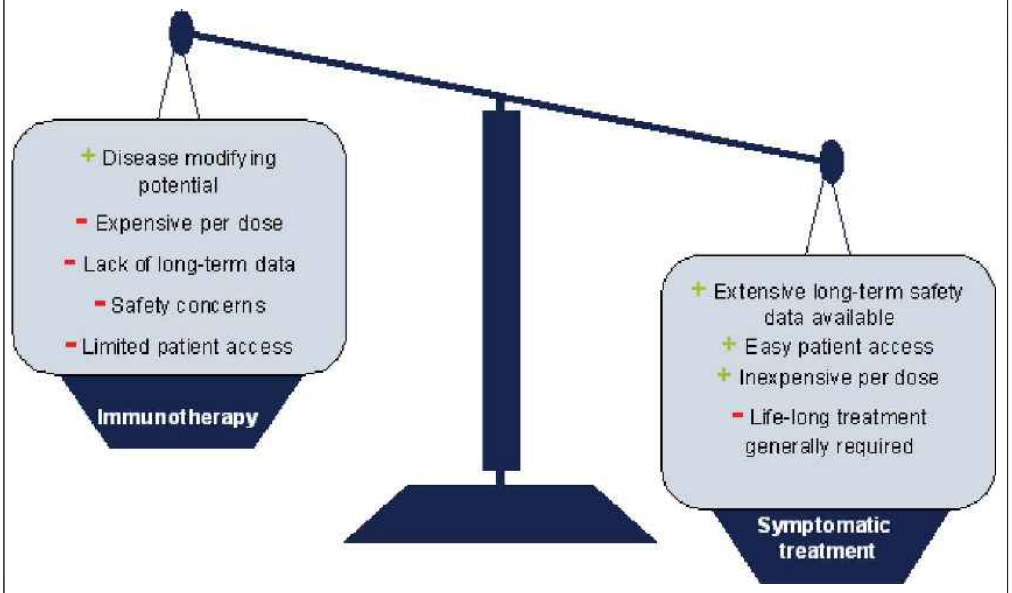
The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, updated in 2008, summarize immunotherapy with the following points (ARIA, 2008):

- allergen-specific immunotherapy was traditionally administered subcutaneously but local routes are now available.
- specific immunotherapy needs a precise diagnosis of immunoglobulin E (IgE)-mediated allergy;
- subcutaneous immunotherapy is effective in adults and children for pollen and mite allergies, but it is burdened by the risks of side effects. These reactions may be life-threatening;
- sublingual immunotherapy is recommended for the treatment of pollen allergy in adults;
- sublingual immunotherapy may be used for the treatment of patients with mite allergy;
- intranasal immunotherapy may be used for the treatment of patients with pollen allergy;
- allergen-specific immunotherapy may alter the natural course of allergic diseases;
- subcutaneous immunotherapy appears to be effective several years after its cessation;
- immunotherapy appears to reduce the development of new sensitizations;
- administered to patients with rhinitis, immunotherapy appears to reduce the development of asthma (secondary prevention of asthma).

Developments in immunotherapy for allergic rhinitis

In the field of allergies, immunotherapy is a significant area with dramatic changes seen over the last few years. For allergic rhinitis in particular, immunotherapy offers a vastly different treatment option to traditional symptomatic treatments. Both options are believed to have distinct advantages and disadvantages, and these are summarized in the following figure.

Figure 57: Symptomatic treatments versus immunotherapy, 2010



Source: Datamonitor DATAMONITOR

While immunotherapy is the only treatment option with disease-modifying potential, its limitations, including safety concerns and cost, diminish this benefit, and mean that symptomatic treatments continue to be the more popular option. Although, while symptomatic treatment is expected to remain the norm, the availability of a growing body of data is expected to help shift perceptions in favor of immunotherapy.

While subcutaneous formulation remains the gold standard, alternative formulations have come into development, most notably sublingual delivery. At the 2010 Annual Congress of the European Academy of Allergy and Clinical Immunology (EAACI), significant attention was paid to the evolution of immunology and recent clinical advances. This was driven by some new entrants to the market, as well as the fact that 2011 will mark the 100th anniversary of immunotherapy.

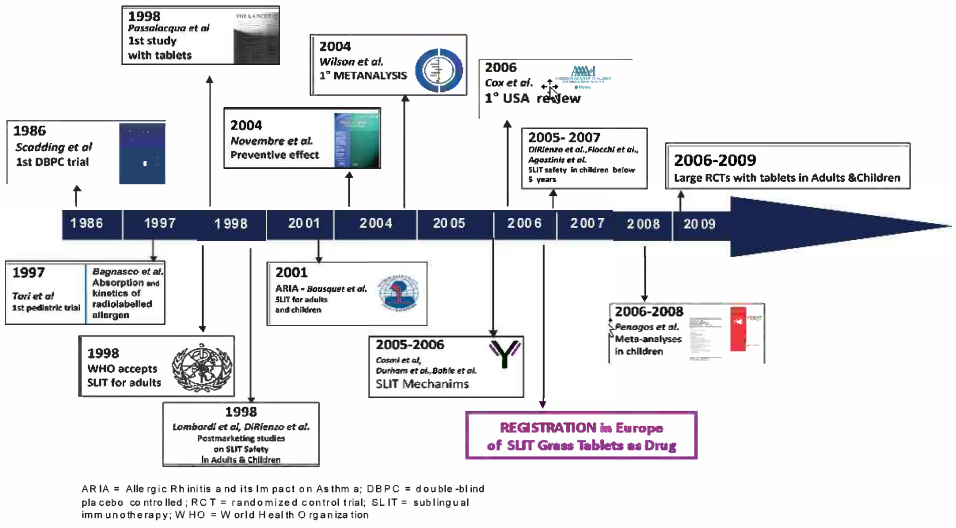
Recent developments, in particular the improvement in clinical trial design for immunotherapy, and following completion of large-scale double-blind studies, have led to a sense of achievement based on the increase in available trial data. During a company sponsored symposium from ALK-Abelló, Adnan Custovic proclaimed that we are "moving from 'I believe' to 'I know'." Key opinion leaders interviewed by Datamonitor also emphasized the shift that has been seen in immunotherapy, with the class now considered to be well documented.

"Immunotherapy is evidence-based, both in rhinitis and asthma, both injectable and sublingual."

EU key opinion leader

In 2009 the World Allergy Organization published a position paper on sublingual immunotherapy (SLIT). While acknowledging that subcutaneous formulation is the current standard in immunotherapy, the paper highlights the development of sublingual therapy, which began in 1986 with the first double-blind placebo-controlled trial, and which has led to the approval of the first sublingual immunotherapy grass tablet as a drug in Europe in 2006. This history of sublingual immunotherapy is shown in Figure 58.

Figure 58: History of sublingual immunotherapy, 1986–2009



ARIA = Allergic Rhinitis and its Impact on Asthma; DBPC = double-blind placebo controlled; RCT = randomized control trial; SLIT = sublingual immunotherapy; WHO = World Health Organization

Source: Datamonitor adapted from Canonica *et al* ., 2009

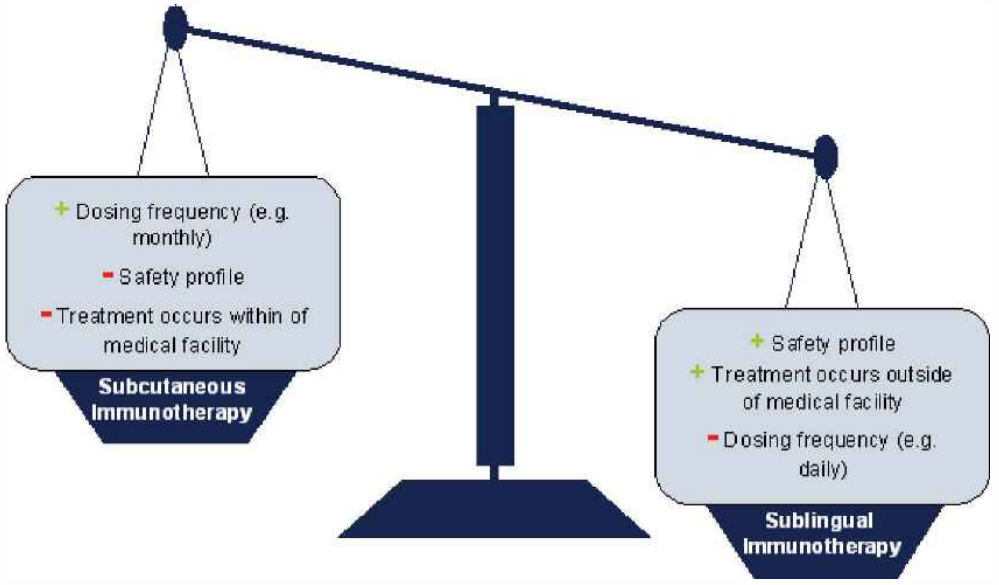
DATAMONITOR

The paper extensively examines the evidence available for sublingual therapy and subcutaneous therapy, in terms of their efficacy and safety. The authors find no difference in efficacy between the two formulations, but that there is a distinct safety advantage seen for sublingual therapy. The paper summarizes the safety of SLIT with the following statements:

- SLIT appears to be better tolerated than subcutaneous immunotherapy (SCIT);
- SLIT should only be prescribed by allergy-trained physicians;
- specific instructions should be given to patients regarding the management of adverse reactions, unplanned interruptions to treatment and situations when SLIT should be withheld;
- the majority of SLIT adverse events appear to occur during the early stage of treatment;
- a few cases of SLIT-related anaphylaxis have been reported but no fatalities;
- risk factors for the occurrence of SLIT severe adverse events have not yet been established;
- there is a need for a generally accepted system of reporting adverse reactions/anaphylaxis (Canonica *et al* ., 2009).

With both subcutaneous and sublingual immunotherapy now available, at least in the EU, for the treatment of allergic rhinitis, it is important to consider the advantages and disadvantages of each. The main advantages of sublingual immunotherapy relate to its safety profile and the possibility for treatment to take place at home. These correspond to the disadvantages of subcutaneous immunotherapy, which are concerns about safety and the need for treatment to take place within a medical facility. While subcutaneous immunotherapy has an advantage over sublingual therapy in terms of less frequent dosing, the strengths of sublingual therapy make it the preferred option. These characteristics are depicted in Figure 59.

Figure 59: Advantages and disadvantages of sublingual and subcutaneous immunotherapy, 2010



Source: Datamonitor

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"I have to say that the safety profile of immunotherapy is nowadays very, very good, really for sublingual immunotherapy."

EU key opinion leader

"Injectable immunotherapy is in many cases costly, because of the treatment and the time that is spent by the patient in going to the office … In addition, the safety might be riskier … the safety profile of the sublingual immunotherapy is demonstrated to be very good."

EU key opinion leader

"In the United States, subcutaneous immunotherapy is the only form that has been approved by the FDA [Food and Drug Administration] *as a formulation. It is given in a medical facility, with 30 minutes wait after injection, and that makes it very inconvenient for patients, and thus you are really only seeing 2–5% of allergic patients that would be appropriate for it that are taking the treatment."*

US key opinion leader

The use of immunotherapy in the treatment of allergic rhinitis has not been widespread, but is expected to rise with the improvements seen in both safety and dosing and the increasing number of products coming through the pipeline.

"There are new immunotherapies now that are coming…more than any other kind of treatments for rhinitis."

EU key opinion leader

In light of the new developments, the patient potential for immunotherapy is yet to be fully realized and depends not only on clinical aspects, but also on patient preferences. Hans Jergen Maling spoke at the EAACI 2010 Annual Congress, discussing the indications for immunotherapy. He suggested that the most important factor for making immunotherapy successful is to identify the patients most likely to benefit from treatment. One option is to profile patients based on age and their duration of disease. Adults that have had the disease for a long period of time have a greater risk of irreversible structural change, making them suboptimal candidates for therapy. Therefore, as it is preferable to start immunotherapy early in the disease process, the optimal patient would be a child. When looking at severity Maling suggested that patients with mild disease or disease of short duration would not constitute the optimal patient, compared to patients with severe disease of long duration, who are therefore more burdened by medication use. Maling profiled two types of allergic rhinitis patient who would make optimal candidates:

- a rhinitis patient with impaired quality of life due to symptoms and reluctance to use pharmacotherapy;
- a rhinitis patient with asthma during high pollen exposure.

The first category highlights the need to focus on quality of life and patient preference, and the second comes from the ability of immunotherapy to treat multiorgan symptoms, where traditional treatment would require the use of multiple medications (nasal spray, eye drops, etc.).

Immunotherapy has been more widely used in Germany than any other major market, although it is not clear why. Discussions with key opinion leaders suggest that a country's healthcare system plays a large role in the potential use of immunotherapy, with both cost and physician access having great significance.

"Basically if you are in a system where you get paid for each time you see a patient, you generate activity that is about seeing patients, if you are in a system that is capitation based, like the UK, then you tend to do the opposite."

UK key opinion leader

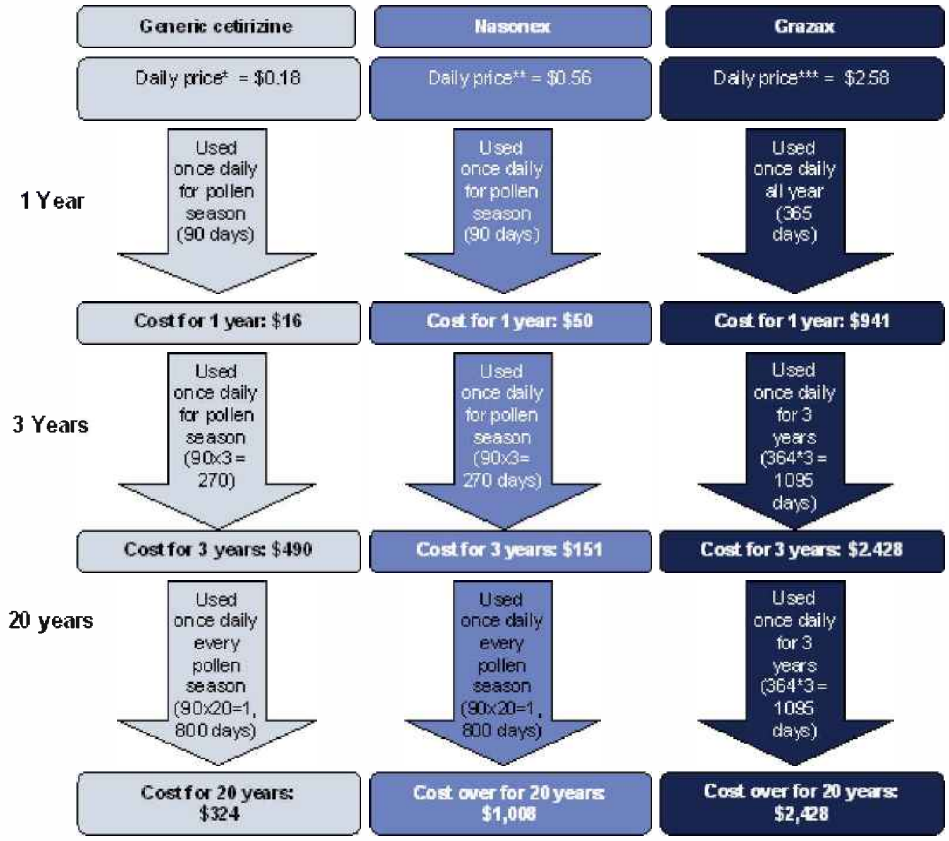
"[Immunotherapy] *is potentially very, very useful. Positioning and practical implementation in day to day practice is something that has to be thought about. I mean it fits very nicely potentially in areas where healthcare systems like to have frequent patients on site, it fits very badly in a capitation based system such as the UK."*

UK key opinion leader

The need for physician access is significant when talking about subcutaneous immunotherapy, as patients must go their doctor for every treatment dose. However, for sublingual immunotherapy this is generally unnecessary. This formulation could therefore reach a larger population, although cost will remain a constraining factor.

Using pricing information for Germany in 2009, Datamonitor calculated the cost of symptomatic versus immunotherapy treatment, assuming both antihistamines and nasal corticosteroids were used for symptomatic treatment. Generic cetirizine has the highest sales in Germany among antihistamines, and Nasonex (mometasone, Merck) among nasal corticosteroids, thus these two products are used to represent their classes. For immunotherapy, the price of Grazax was selected, as it is the first sublingual tablet to gain approval and is expected to increase immunotherapy usage for allergic rhinitis. It was assumed that the grass pollen season lasts 3 months, and that symptomatic treatment is taken for the duration of the season each year. Grazax's cost is calculated on the assumption that it is used every day for 3 years and then stopped. The resulting cost comparison is shown in the following figure. The relative costs are calculated for 1, 3 and 20 years, to get a sense of a patient's drug burden over their lifetime, with the assumption that symptoms can decline naturally with age.

Figure 60: Antihistamine versus immunotherapy cost analysis in allergic rhinitis, Germany, 2009



*Price/standard unit = $0.18, daily price assumes one tablet/day

**Price/standard unit = $0.14, daily price assumed two sprays in each nostril/day (4 standard units/day)

***Price/standard unit = $0.42, daily price assumes one tablet/day

Source: Datamonitor; MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission

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After 1 year of treatment, the cost of Grazax is about $941, roughly 60 times the cost of generic cetirizine. However, Grazax is most likely to be considered for patients with more severe symptoms, who require treatment with both an antihistamine and a nasal corticosteroid. Still, after 1 year Grazax is about 15 times the combined cost of generic cetirizine and Nasonex. A key benefit of immunotherapy is its disease-modifying potential, with long-term follow-up data showing that treatment may be stopped after 3 years. This helps to reduce the cost differential when considering 20 years of treatment, but, even when stopped after 3 years, Grazax remains nearly twice as expensive as combined nasal corticosteroid and antihistamine use for 20 years. This analysis shows it will be very difficult for immunotherapy to compete in the allergic rhinitis market on the basis of price, compelling companies to heavily promote the advantages of immunotherapy over traditional symptomatic treatment in order to be successful.

Datamonitor cannot find evidence of any ongoing review by the National Institute for Health and Clinical Excellence (NICE) into the cost effectiveness of Grazax, however, a positive review will be necessary for the treatment to be successful in the UK.

Methodology and comparative forecasts

Datamonitor provides a forecast for three immunotherapies: Grazax (ALK-Abelló), Oralair Grasses (Stallergènes), and Pollinex Quattro (Allergy Therapeutics). Both Grazax and Oralair Grasses have gained approval in the EU, as the first and second sublingual tablet immunotherapies to reach the market. Datamonitor expects that both will gain approval in the US market in 2012, with Grazax expected to reach the market just before Oralair.

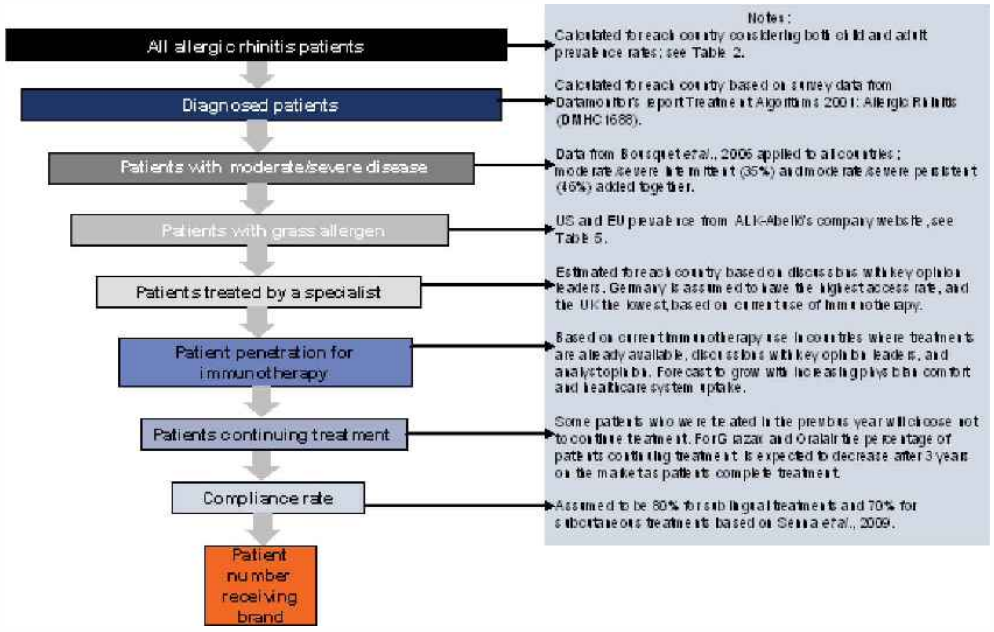
While Grazax has the advantage of first-to-market status, its approval is also a positive factor for Oralair, since by introducing a new class to the market, it will help open the door for additional treatments.

Pollinex Quattro, an injectable vaccine, is currently available on a named patient basis in the EU, where it has been filed, with regulatory approval expected in 2011. Datamonitor therefore forecasts a full European launch in that year. The treatment is not forecast to launch in the US market, where trials are under and US Food and Drug Administration (FDA) mandated clinical hold following a rare adverse event.

Grazax and Oralair both have a formulation advantage over Pollinex Quattro, as oral tablets are easier for patients to administer and the treatments require less physician contact. On the other hand, Pollinex Quattro requires just four injections a year, whereas Grazax is taken daily year round, and Oralair is taken daily for approximately 6 months of the year.

Datamonitor has forecast these immunotherapies using a patient-based approach. Grazax, Oralair, and Pollinex Quattro are expected to share the same potential patient pool as they are both used to treat grass allergy. The following figure highlights the method that Datamonitor used in order to determine the patient potential for these therapies. The total allergic rhinitis population was first considered, based on the epidemiology presented in this report. This was then reduced to include only diagnosed moderate-to-severe patients with a grass allergy. By including only those patients uncontrolled by symptomatic treatments and those with access to a specialist further reduced the patient pool. Datamonitor also assumed that each year a fraction of patients who previously used immunotherapy would not continue treatment; this would initially result from patients opting out of treatment, while for Grazax and Oralair this percentage is assumed to increase once the therapy has been available for 3 years, as this will mark the point when the first cohort will have completed 3 years of treatment. Compliance rates were also taken into account, and are assumed to be higher for sublingual versus subcutaneous therapy, based on available studies. Finally, Datamonitor estimated patient penetration for each therapy from the patient pool. This was determined using IMS sales data from countries where the treatments are already available as a benchmark, as well as discussions with key opinion leaders and analysis of available data.

Figure 61: Patient-based forecast methodology for immunotherapy in allergic rhinitis, 2010



Source: Datamonitor; various see 'Notes'

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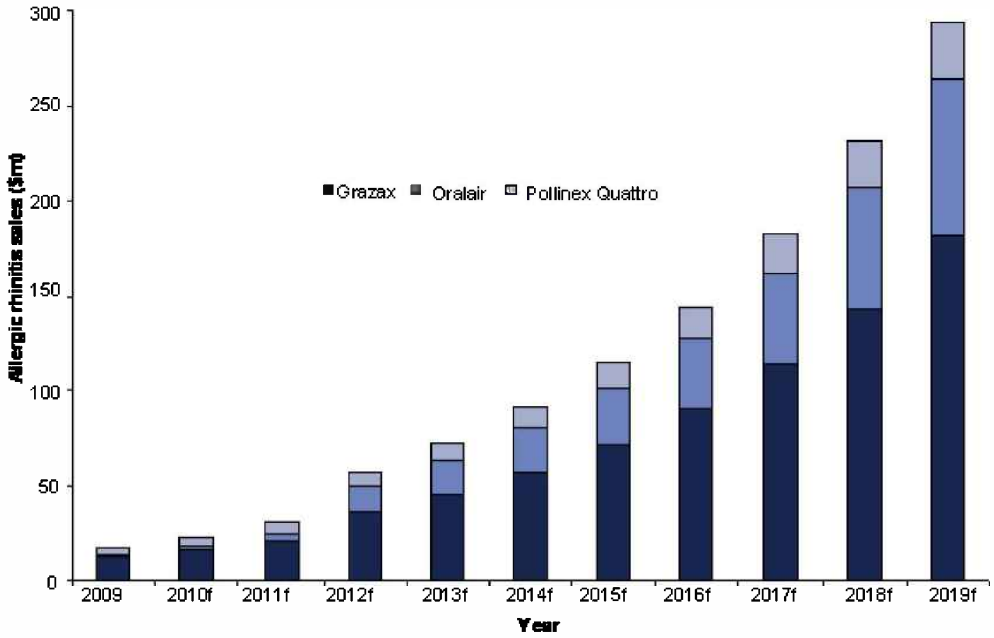
The resulting patient population was multiplied by a 'standard units' volume to enable comparison with the IMS based forecast for symptomatic therapies. This conversion was calculated on an annual basis by factoring the dosing regimen for each drug, and finally this value was multiplied by price to determine a sales forecast. Where the drug was not yet launched and therefore the price was not available, the German price, calculated from IMS sales data, was used as a benchmark.

The relative success of each immunotherapy will depend on its launch date as well as patient preferences. Datamonitor's forecast of these three products is shown in Figure 62. Their combined sales are forecast to reach $295m in the US and five major EU markets by 2019. Grazax is expected to have the highest sales being first-to-market with the highest yearly cost. Pollinex will have the lowest sales, as it is not forecast to enter the US market, and its subcutaneous formulation is a disadvantage.

Figure 62: Grazax, Oralair, and Pollinex Quattro sales in the US and five major EU markets ($m), 2009–2019



Source: 2010–2019 forecast = Datamonitor patient based forecast;
2009 sales = MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission

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IMS data versus company reports sales

Datamonitor uses IMS MIDAS sales data to estimate the allergen immunotherapy market in 2009, and also as a benchmark for the patient based sales forecast to 2019. Given the nature of the immunotherapy market, with products frequently distributed on a named patient basis, IMS MIDAS sales data can underestimate the market, failing to capture all sales. For example, in its 2009 Annual Report, Allergy Therapeutics estimates that the German market for immunotherapy was worth $357m (€284m) in 2009 (Allergy Therapeutics, 2009, http://www.allergytherapeutics.com), however, using IMS MIDAS sales data, Datamonitor estimates that the V1A0 allergen class in Germany totaled $283m in that year. Datamonitor shows company reported sales where available for the brands profiles below in this chapter.

Despite this limitation of the data, Datamonitor finds IMS MIDAS sales data to be the most comparable data available, as sales are available by brand and by country, while company reported data is frequently reported by region or product line. Therefore, in order to be consistent with reporting seven major market sales, and for comparability across products, Datamonitor utilizes this data in estimating the immunotherapy market. This should be taken into account when considering the total immunotherapy market size presented in this report.

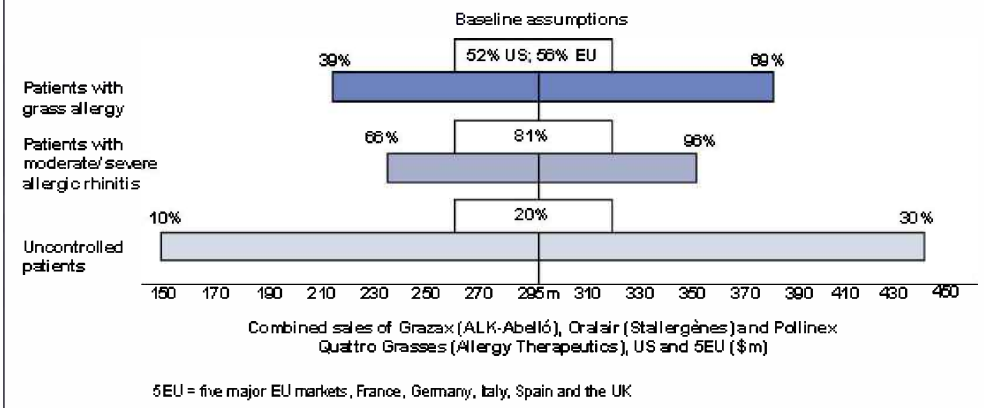
Sensitivity analysis

Sensitivity analysis, shown below in Figure 63, reveals that adjusting the assumptions in Datamonitor's patient based forecast for immunotherapy can have a large impact on sales. Using baseline assumptions, Datamonitor estimates that sales of Grazax (ALK-Abelló), Oralair (Stallergènes), and Pollinex Quattro Grasses (Allergy Therapeutics), will reach $295m by 2019. Datamonitor calculates the impact on sales that would be seen by a change in the percentage of patients with grass allergy, the percentage of patients with moderate to severe disease, or the percentage of patients who are uncontrolled.

Altering the uncontrolled patient assumption is seen to have the greatest impact. Based on discussions at the European Academy of Allergy and Clinical Immunology (EAACI) 2010 Annual Congress, Datamonitor uses an uncontrolled patient rate of 20%, but this is an estimate and falls within a range of possibilities. By decreasing the percentage of uncontrolled patients to 10%, sales of the three immunotherapies is forecast to reach just $147m, while increasing the rate by 10% boosts sales to $442m. Increasing the average percentage of patients in the US and EU with grass allergy by 15% has a smaller impact, increasing sales to $379m by 2019, while changing the estimated number of patients with moderate/severe disease has the least impact, with a 15% increase pushing sales to just $349m.

The 10-year market forecast is presented in the accompanying forecast tool, a downloadable Excel spreadsheet. All assumptions used in the patient based forecast are provided in the spreadsheet, and can be adapted to see the impact of changes on sales.

Figure 63: Datamonitor's sensitivity analysis for immunotherapy sales ($m) in the US and 5EU, 2019



Source: Datamonitor patient based forecast DATAMONITOR

Grazax (ALK-Abelló)

Summary takeaways:

- **Product:** Grazax (grass pollen);
- **2009 sales:** allergic rhinitis: $12m;
- **2019 forecast sales:** allergic rhinitis: $182m.

ALK-Abelló has developed and launched Grazax in several EU countries. The sublingual allergy desensitization therapy, which contains a natural allergen product, is the first-ever tablet based vaccine for grass pollen allergy, and uses Cardinal Health's rapidly dissolving Zydis technology (ALK-Abelló, 2010b; http://www.alk-abello.com; Thomson Pharma, April 2010, Copyright Thomson Scientific). The product was first introduced in Germany in November 2006, with additional launches seen in the EU in 2007, including in the UK. In Italy, the first sales of the drug were seen in 2008 and sales in Spain began in 2009 (Thomson Pharma, April 2010, Copyright Thomson Scientific; IMS MIDAS, IMS Health, March 2010). However, outside Germany, use of the drug has been minimal.

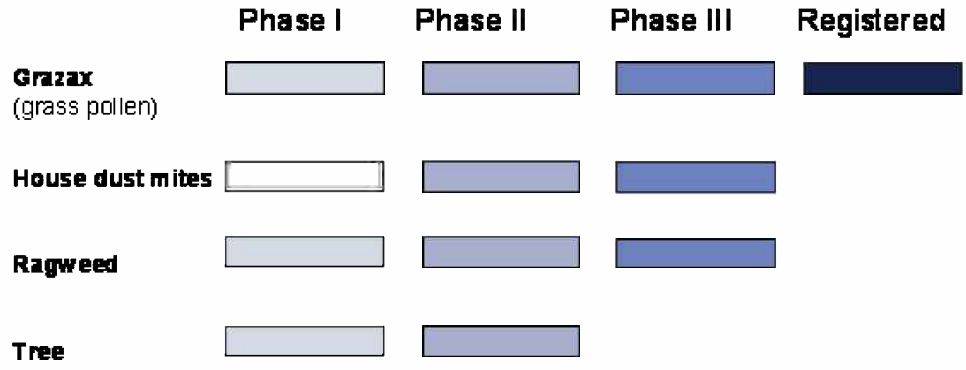
Using IMS MIDAS sales data, Datamonitor estimates that sales of Grazax reached $12m in 2009. ALK-Abelló reports sales of $22.4 million for Grazax in the European market in that year (ALK-Abelló, 2010, http://nozebra.ipapercms.dk). The company notes that the greatest growth for the product was seen in the Northern and Central European regions, which could explain some of the discrepancy in sales as Datamonitor's estimate includes only Germany, Italy, Spain, and the UK. Furthermore, the difference in sales could be impacted by IMS MIDAS sales data's potential to underestimate the immunotherapy class, which is discussed in the section: IMS data versus company reports sales.

The therapy was first approved for use in adults in Europe, and in November 2008 Grazax gained additional approval for use in children in Europe (ALK-Abelló, 2008a; https://newsclient.omxgroup.com). The product is indicated for the treatment of grass pollen induced rhinitis and conjunctivitis in patients with clinically relevant symptoms who have been diagnosed with a positive skin-prick test and/or specific immunoglobulin E (IgE) test to grass pollen (Thomson Pharma, April 2010, Copyright Thomson Scientific). Treatment should only be initiated by physicians with experience in the treatment of allergic disease and it is recommended that the first dose is taken under medical supervision (20–30 minutes) due to the possibility of serious side effects such as anaphylactic shock (NHS, 2007; www.elmmb.nhs.uk).

ALK-Abelló was the first immunotherapy company to co-operate with a major allergic rhinitis player. In January 2007, Schering-Plough signed an agreement on a strategic alliance to develop and commercialize Grazax for the North American market (ALK-Abelló, 2007b; https://newsclient.omxgroup.com). Following, its acquisition of Schering-Plough, Merck is now developing Grazax in the US, where it is in Phase III trials.

ALK-Abelló is developing a number of other tablet-based immunotherapies. Its house dust mite tablet has reached Phase III trials. However, the only trial listed on clinicaltrials.gov for that product is an ongoing Phase II/III trial for patients with asthma, leaving it unclear whether development will be steered towards allergic rhinitis. According to the company, a ragweed tablet has reached Phase III as well, and a tree tablet is in Phase II. Clinicaltrials.gov only lists one completed Phase I trial for each product, completed in 2006 and 2007, respectively. The following figure highlights the development phase reached by each of these products, giving the highest phase reached in any country.

Figure 64: ALK-Abelló tablet program development stages, 2010



Source: Datamonitor adapted from ALK-Abelló, 2009 (http://nozebra.ipapercms.dk)

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Drug profile

Table 31: Grazax – drug profile, 2010

Grazax	
Molecule	Grass pollen
Mechanism of action	Allergen desensitization therapy
Originator	ALK-Abelló
Marketing company	ALK-Abelló/Merck
Primary indication	Treatment of grass pollen induced rhinitis and conjunctivitis in patients with clinically relevant symptoms who have been diagnosed with a positive skin prick test and/or specific IgE test to grass pollen; disease-modifying allergy treatment
Formulation	Sublingual tablet
Dosing frequency	Once-daily for 3 years
Reimbursement status	Wide regional variations in formulary status in EU; not available in US/Japan
First launch date	2006 (EU)
Forecasted launch date	France (2010); US (2012)
2009 sales, 7MM	Allergic rhinitis: $12m
2019 sales, 7MM	Allergic rhinitis: $182m

7MM = seven major markets (US, Japan, France, Germany, Italy, Spain, UK)

IgE = immunoglobulin E

Source: Datamonitor, Thomson Pharma; MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission. DATAMONITOR

Product positioning

As the first company to gain approval for a tablet-based allergy vaccine, ALK-Abelló occupies a strong position in the immunotherapy market. However, since its launch in the EU, sales of Grazax have been marginal, ranging from $11m in Germany, to just $46,000 in Spain according to IMS Health.

The convenience of a subcutaneous tablet is likely to appeal to patients, and is expected to broaden the use of allergy vaccination, however, this has not yet been the case. In the UK, several issues have been highlighted regarding the use of Grazax under the National Health Service (NHS). Firstly, the cost is a factor, with the cost of Grazax over a 60-day grass pollen season estimated at £135, compared to the cost of cetirizine or loratadine of only £3–4. Additionally, as patients are required to take Grazax daily for 3 years, issues of compliance arise. A further issue is that Grazax only treats grass pollen allergy, and it is estimated that just 10% of patients are monosensitized to grass (NHS, 2008; http://www.medicinesmanagementstoke.nhs.uk). These issues apply beyond the UK as well, and are expected to be restrictive factors in all markets where Grazax will launch.

"It is not widely used because of the cost, and because in some places it is reimbursed and in some others it is not. This is the most expensive treatment, immunotherapy treatment, and of course in some cases people are looking for a cheaper treatment. In addition, my experience is not so large, because we do not have that many grass allergy patients."

EU key opinion leader

"Immunotherapy in the UK is virtually unheard of for allergic rhinitis, outside clinical trials. Obviously we have Grazax, sublingual immunotherapy, which has a license and reimbursement but it is practically unused at this point in time because of their lack of health economic data."

UK key opinion leader

While it is the case that patients monosensitized to grass pollen have the most to benefit from the treatment, clinical trials included patients who had allergic rhinitis from additional allergens, provided the symptoms did not overlap with the grass pollen season. At the ALK-Abelló sponsored symposium of the 2010 Annual Congress f the European Academy of Allergy and Clinical Immunology (EAACI), it was announced that 80% of subjects included in the pivotal trials were multisensitized. This suggests that the relevant patient pool extends beyond patients who are monosensitized to grass.

ALK-Abelló has worked to expand the patient potential of Grazax, with approval for use in children achieved in Europe in late 2008. In September 2009, Grazax was further approved as a disease-modifying allergy treatment in the EU, following positive results from a 1-year follow-up study (GT-08), which demonstrated that a significant improvement in patients' eye and nose symptoms and quality of life persisted a year after completion of the recommended 3-year Grazax treatment regimen (ALK-Abelló, 2009; https://newsclient.omxgroup.com). In February 2010 the company announced that results from the fifth year of the study showed the positive effects still remained 2 years after cessation of therapy (ALK-Abelló, 2010a; https://newsclient.omxgroup.com). Peer-reviewed analysis of the complete 5-year study has not yet been published.

Nonetheless, the perception remains that Grazax's place on the market is limited, with only the most severe patients who are unresponsive to alternative treatment options expected to receive this treatment.

"It is difficult to know quite where it fits. They have not done any community-based studies, and that I think is a big weakness of the dataset to date. … the ARIA guidelines put immunotherapy for those who failed on standard treatment, that is quite a small niche effectively."

UK key opinion leader

Clinical trial data

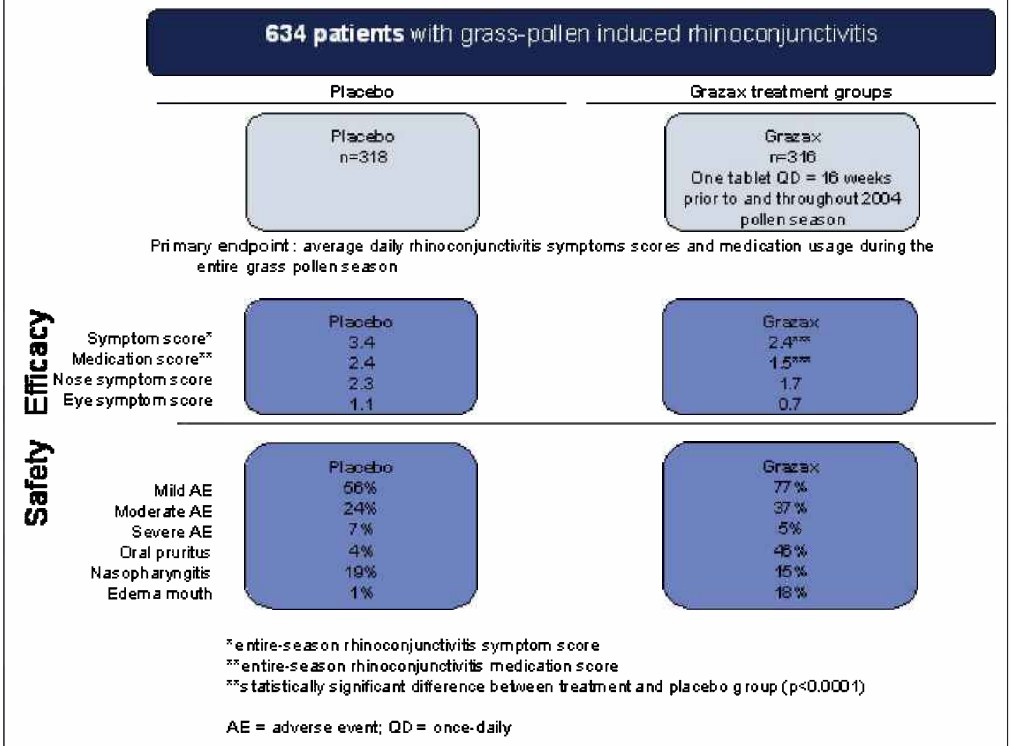
EU clinical trial results

The key evidence for the efficacy of Grazax in Europe came from two large, double-blind, placebo-controlled, randomized clinical studies of people with allergic rhinitis (Dahl *et al* ., 2006; Durham *et al* ., 2006). Both of these studies included adults with a history of grass pollen-induced rhinoconjunctivitis and who had a positive skin prick test and elevated serum allergen-specific IgE to *Phleum pratense* (Timothy grass).

The first trial was a dose-finding study in 855 adults with a history of allergic rhinoconjunctivitis during the grass pollen season which included a comparison of Grazax with placebo. Treatment was initiated about 8 weeks before the start of the 2003 grass pollen season (Durham *et al* ., 2006). Over the entire grass pollen season, there was no significant drop in mean daily rhinoconjunctivitis symptom scores, while the reduction in rescue medication usage scores barely met the normally accepted criteria for statistical significance (P=0.0470). Subgroup analysis suggested that some efficacy may be obtained if treatment were initiated more than 8 weeks before the start of the grass pollen season, while the differences were smaller and less certain when given approximately 8 weeks prior to the expected grass pollen season (Durham *et al* ., 2006).

In a subsequent study, GT-08, 634 adults with at least a 2-year clinical history of significant grass pollen induced rhinoconjunctivitis, compared Grazax, initiated at least 16 weeks before the start of the 2004 grass pollen season, with a placebo (Dahl *et al* ., 2006). The study was double-blinded and was conducted in 51 centers in eight EU countries. Treatment continued for 3 years, followed by 2 years of follow-up. Over the entire 2004 pollen season, both mean daily rhinoconjunctivitis symptom scores and medication scores were significantly lower in the Grazax group compared with the placebo group. The additional reduction in symptom score for the Grazax treatment group compared to placebo was 30%, and 38% in the medication score. These first year results are presented in the following figure.

Figure 65: Grazax: EU adult Phase III results



Source: Datamonitor adapted from Dahl *et al* ., 2006 DATAMONITOR

In addition to meeting the primary endpoints, other significant differences favoring Grazax over placebo were identified as secondary outcomes, including the number of 'well-days' when rescue medication was not required and the mean daily patient-rated symptom scores, with Grazax treated patients experiencing 'well days' 53% of the season, compared to the placebo group with 44%. Despite use of Grazax, the majority of patients in this study used additional rescue medication at some point during the study. The most frequently reported adverse events included oral pruritus (46% in treatment group, 4% in placebo group) as well as mouth edema (19% in treatment group, 1% in placebo groups), and nasopharyngitis, which was equal between groups. The reported severe adverse events included two cases of oral pruritus, four cases of mouth edema, and one case each of fatigue, pharyngeal edema, oral discomfort, and nausea.

Author conclusions: sublingual immunotherapy with grass allergen tablets was an effective treatment for grass pollen–induced rhinoconjunctivitis. Minor local side effects made up the majority of adverse events, and the treatment had a favorable risk-benefit profile, as no anaphylaxis, no use of adrenaline, and no severe systemic adverse events were reported in the study. Therefore, there is the potential for home-based immunotherapy treatment in a broader group of patients.

At the ALK-Abelló sponsored symposium of the 2010 annual congress of the European Academy of Allergy and Clinical Immunology (EAACI), Stephen Durham discussed the long-term results of the study. The statistically significant efficacy seen after the first year of treatment was maintained throughout second and third treatment years, as well as during the 2 years of follow-up. Drop-out rates throughout the period were minimal and similar across both the treatment and placebo groups, with 74% of patients remaining at the end of year 5. With regard to safety, although 70% of patients reported an adverse event in the first year, these were mostly local and minor, and the rate of adverse events converged with the placebo group in years 2 and 3.

The significant reduction in medication score that was seen in years 1–4 was not carried into year 5, and this was attributed to a lower pollen count in that year. However, the combined adjusted symptom score, which combines both symptoms and rescue medication use, was significant across all years. This is particularly impressive as the pollen count dropped in each successive year. The positive results over the follow-up period enabled Grazax's label to claim its place as the only treatment to have an established disease-modifying effect.

An additional important trial regarding Grazax was published in 2007 on the product's cost-effectiveness. This study assessed the quality adjusted life years (QALYs), which takes into account both direct costs (such as medication and physician visits) and indirect costs (productivity losses such as time away from work) caused by allergic rhinitis. One QALY is equal to 1 year of perfect health for a patient and the lower the cost per QALY gained, the more cost-effective the medical intervention. ALK-Abelló reported that Grazax significantly reduced both the use of symptomatic medication compared to placebo and the time lost from work when compared with symptomatic treatment alone. These benefits were reflected in an increased number of QALYs compared to therapy with symptomatic medication alone (Bachert *et al* ., 2007).

Establishing the cost-effectiveness of Grazax is important for a product that costs more than $4 per tablet as it will be directly linked to the levels of reimbursement granted by payers. In Germany and several other European countries, Grazax has received full reimbursement, although cost continues to be central to the restriction of uptake.

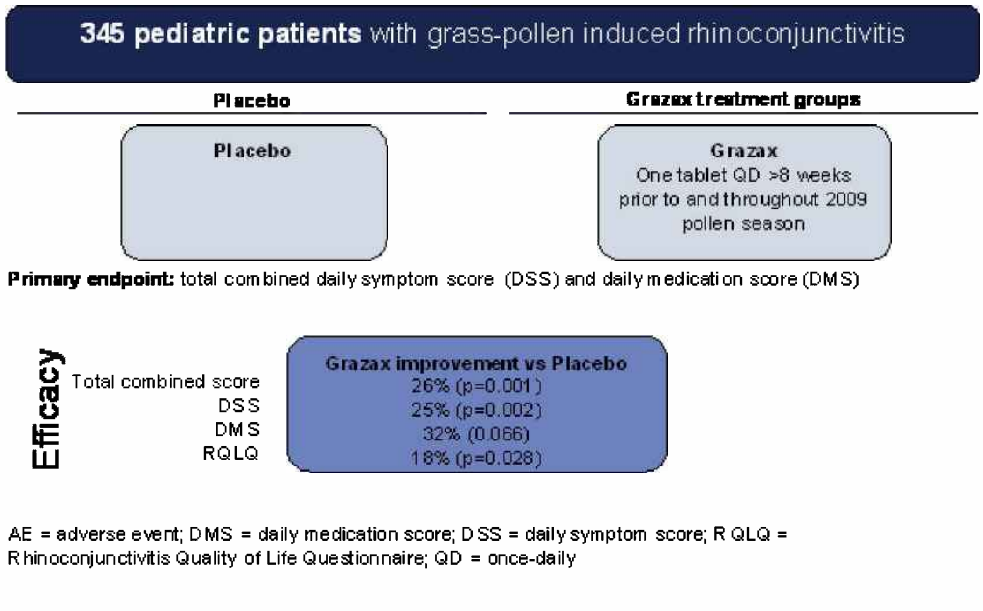
The company is also investigating the therapy in the prevention of asthma in children with grass pollen allergy, with a Phase III trial listed on clinicaltrials.gov as recruiting with expected completion in 2015 (Clinicaltrials.gov, 2010a; http://www.clinicaltrials.gov). This is the first large-scale trial of its kind, and is highly anticipated because it will provide considerable information regarding immunotherapy's potential role in asthma prevention.

US clinical trial results

In the US, ALK-Abelló's partnership with Merck is a strong advantage. A Phase III trial in the US, conducted during the 2007 grass pollen season, failed to meet its primary endpoint of the reduction in patients' allergy symptoms, but the companies reported that the primary endpoint was met for a subset of patients, consistent with results seen in the EU. The majority of subjects in the trial did not have increased rhinoconjunctivitis symptoms during the study's season and researchers linked this fact to the failure of the trial to meet its endpoint. (ALK-Abelló, 2007a; https://newsclient.omxgroup.com). Datamonitor believes that the subset of individuals who responded well consisted of patients who had received treatment more than 8 weeks prior to the start of the pollen season, as this would be consistent with the EU results, and the subsequent Phase III trials commenced earlier treatment. Positive Phase III results of the tablet in adult patients with grass pollen allergic rhinoconjunctivitis in the US were reported in November 2009, and positive results for patients aged 5–17 with the same condition followed in March 2010 (Merck, 2010b; http://www.merck.com; https://newsclient.omxgroup.com). The primary endpoint of these two trials was the average rhinoconjunctivitis daily symptom score (DSS) and the rhinoconjunctivitis daily medication score (DMS) over the entire grass pollen season, and the trials included 439 adults and 345 children, respectively (Clinicaltrials.gov, 2010b; http://clinicaltrials.gov).

The results of the pediatric trial were presented as a late-breaking abstract at the 2010 Annual Meeting of the American Academy of Allergy Asthma and Immunology (AAAAI) (Blaiss *et al* ., 2010). In addition to meeting the primary endpoint, the trial, in which therapy was initiated more than 8 weeks before the start of the 2009 grass pollen season, saw statistically significant results in favor of the treatment for secondary endpoints, including daily symptom score, daily medication score, and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).

Figure 66: Grazax: US pediatric Phase III results



Source: Datamonitor adapted from Blaiss *et al* ., 2010

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The authors reported that the majority of treatment-related adverse events were local application site reactions, and there were no reports of anaphylactic shock.

Author conclusions: pre- and co-seasonal once-daily administration of a grass allergy immunotherapy tablet is clinically effective, well-tolerated, and may be a new therapeutic modality for children with grass pollen allergy.

SWOT analysis

The following figure highlights the strengths, weaknesses, opportunities and threats (SWOT) of Grazax for allergic rhinitis.

Figure 67: Grazax – SWOT analysis for allergic rhinitis, 2010

Strengths	Weaknesses
▪ First oral sublingual immunotherapy to gain approval in the EU ▪ Demonstrated sustained disease modifying effect ▪ Partnership with Merck in the US ▪ Met primary endpoint in Phase III trials in adults and children in the US ▪ Convenient once-daily treatment	▪ Safety concerns ▪ Failed to meet primary endpoint in early Phase III trial in the US ▪ Minimal uptake
Opportunities	**Threats**
▪ Seek regulatory approval in the US ▪ Further investigation into the prevention of asthma in children with grass pollen	▪ High cost is prohibitive with cheaper therapies already available and established in the allergic rhinitis market

Source: Datamonitor

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Brand forecast to 2019

- Datamonitor uses a patient-based forecast for Grazax;
- in new markets Grazax will be priced at a level similar to that in Germany ($/standard unit = $2.58, such that 3 years of daily treatment = $2,825)
- as clinical trials included patients with grass pollen-induced rhinoconjunctivitis, it is assumed that all use of the drug will be for allergic rhinitis;
- already available elsewhere in the EU, Grazax will launch in France in 2010;
- following the positive pivotal Phase III trials in the US, filing is expected by 2011, with approval and launch in 2012;
- market potential will be shared with Oralair Grasses and Pollinex Quattro;

- a small percentage of patients will drop out of the market each year after Grazax has been available for 3 years, as patients successfully complete the therapy. This is assumed to have started in Germany in 2009, and is forecast to start in the UK in 2010, Italy and Spain in 2012, France in 2013, and the US in 2015.
- the patient population for Grazax is derived from the assumptions shown in the Table 32. For a discussion of these assumptions, please see the section: Methodology and comparative forecasts.

Table 32: Grazax patient-based forecast assumptions, 2010

	Germany		France		Italy		Spain		UK		US	
	2010	2019	2010	2019	2010	2019	2010	2019	2010	2019	2010	2019
Total patient potential (000s)*	687	675	536	555	424	427	258	274	580	605	2,857	3,067
Access to treatment from a specialist (%)	33	33	17	17	17	17	17	17	13	13	17	17
Access to treatment from a specialist (000s)	227	223	91	94	72	73	44	47	75	79	486	521
Moderate-severe grass allergen patient penetration (%)	7.50	38	2	21	2	21	3	27	2	10	0	19
Moderate-severe grass allergen patient penetration (000s)	12	63	2	20	1	15	1	12	2	8	–	98
Patients continuing treatment (%)	95	95	98	95	98	95	98	95	95	95	98	95
Patients continuing treatment (000s)	12	60	2	19	1	15	1	12	1	8	–	93
Compliance rate (%)	80	80	80	80	80	80	80	80	80	80	80	80
Compliant patients (000s)	9	48	1	15	1	12	1	9	1	6	–	75
Total SUs (365 per patient/per year)	3,457	17,526	521	5,549	412	4,270	313	3,420	418	2,253	–	27,229
$ cost/SU	2.60	2.73	2.60	2.73	2.60	2.73	2.60	2.73	2.60	2.73	2.60	2.73
Grazax total sales ($ 000s)	**8,988**	**47,890**	**1,356**	**15,163**	**1,071**	**11,668**	**814**	**9,344**	**1,087**	**6,156**	**–**	**74,401**

*This is the total moderate-to-severe allergic rhinitis population that is diagnosed, has grass allergy, and is uncontrolled.

SU = IMS standard unit

Source: Datamonitor DATAMONITOR

Table 33: Sales forecasts for Grazax in allergic rhinitis in the US and five major EU markets ($ 000s), 2009–2019						
	2009	2011f	2013f	2015f	2017f	2019f
US	0	0	14,778	24,903	43,072	74,401
France	0	1,783	2,989	5,160	8,848	15,163
Germany	11,120	14,787	21,535	31,331	45,220	65,305
Italy	187	1,363	2,347	4,031	6,860	11,668
Spain	46	1,075	1,815	3,156	5,431	9,344
UK	837	1,321	1,950	2,870	4,206	6,156
Total	**12,190**	**20,329**	**45,414**	**71,453**	**113,636**	**182,037**

Note: totals may not sum due to rounding.

Source: 2010–2019 forecast = Datamonitor patient based forecast; 2009 sales = MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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The 10-year market forecast for Grazax is outlined separately in the accompanying forecast tool, a downloadable Excel spreadsheet that details the forecast for this drug in the seven major markets. 2009 sales are from IMS MIDAS sales data, IMS Health, March 2010, and Datamonitor used a patient-based forecast for 2010-19 sales.

Stalair Program (Stallergènes)

Summary takeaways:

- **Franchise products:** Oralair Grasses (grass pollen); Stalair Betv1 (birch pollen); Actair (house dust mite); Stalair Ragweed (ragweed pollen);
- **2009 sales:** Oralair Grasses: allergic rhinitis: $1m;
- **2019 forecast sales:** Oralair Grasses: allergic rhinitis: $82m

Stallergènes is developing a number of products for immunotherapy as part of the Stalair program. Oralair Grasses, a sublingual tablet formulation containing a freeze-dried extract of grass pollen allergen, was the first of these products to gain approval and launch in the EU.

Datamonitor estimates that sales of Oralair reached $1m in 2009, based on IMS MIDAS sales data for the seven major markets, which only recorded sales in Germany. However, Stallergènes reports sales of the product of $3.7m (€3m) in that year, which may reflect the underestimation of IMS MIDAS sales data in the immunotherapy class, as discussed in the section:

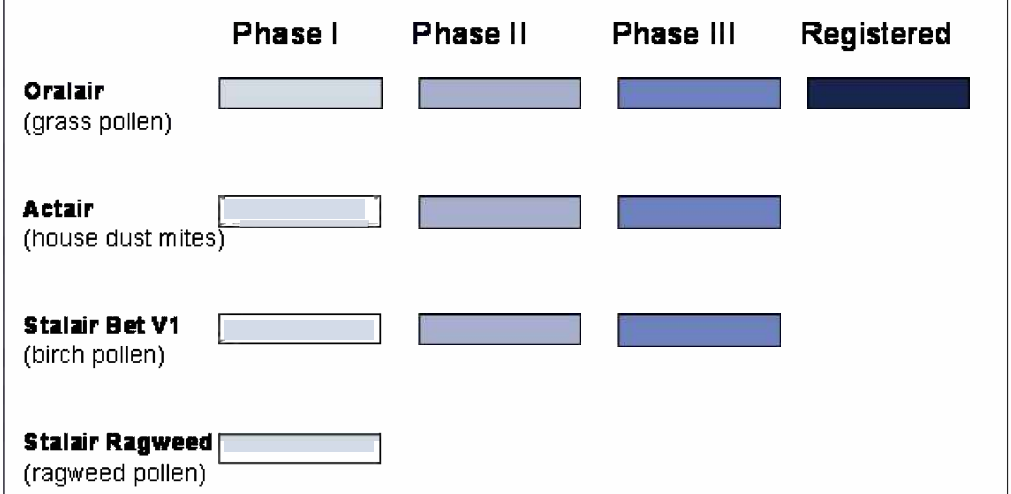
IMS data versus company reports sales.

The product is the second of its kind to gain European approval, starting with marketing authorization for the treatment of adults in Germany, which was awarded in June 2008, followed by a pediatric expansion in that country which was granted in January 2009 (Stallergènes, 2008; http://www.stallergenes.com; Stallergènes, 2009a; http://www.stallergenes.com). Through a Mutual Recognition Procedure, using Germany as the reference member state, Oralair Grasses obtained approval in the EU for both adults and children in November 2009 (Stallergènes, 2009a; http://www.stallergenes.com). Oralair is indicated for patients suffering from severe rhinoconjunctivitis caused by grass pollens, who are inadequately controlled using symptomatic treatments. Stallergènes is also developing the treatment in the US, where it is in Phase III development.

Additional products being developed in the Stalair program include Stalair Betv1, a recombinant allergen of birch pollen, and Actair, a dust mite immunotherapy tablet, which have both been in Phase IIb/III studies. Furthermore, the company is developing Stalair Ragweed, which is in Phase I (Stallergènes, 2009b; http://www.stallergenes.com).

The following table provides an overview of the development stages reached by the Stalair program. The phase shown for each product is the highest phase reached in any country.

Figure 68: Stalair program development stages, 2010



Source: Datamonitor adapted from Stallergènes, 2009b (http://www.stallergenes.com)

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Product profile

Table 34: Stalair – franchise profile, 2010

Oralair Grasses/rBetv1/Actair

Molecule	Pollen
Mechanism of action	Allergen desensitization therapy
Originator	Stallergènes
Marketing company	Stallergènes
Primary indication	Treatment of grass pollen/birch pollen/dust mite induced rhinoconjunctivitis
Formulation	Sublingual tablet
Dosing frequency	Daily for 4 months prior to, and throughout, pollen season for 3 years
Reimbursement status	Wide regional variations in formulary status in EU; not available in US/Japan
First launch date	Oralair Grasses: 2008 (Germany)
	Stalair Betv1: not launched
	Actair: not launched
Forecasted launch date	Oralair Grasses: 2011 (EU); 2012 (US)
	rBetv1: not forecast
	Actair: not forecast
2009 sales, 7MM	Oralair Grasses: allergic rhinitis: $1m
2019 sales, 7MM	Oralair Grasses: allergic rhinitis: $82m

7MM = seven major markets (US, Japan, France, Germany, Italy, Spain, UK)

Source: Datamonitor, Thomson Pharma; MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission. DATAMONITOR

Product positioning

Oralair Grasses (pollen; Stallergènes)

Oralair Grasses launched in Germany 2 years after ALK-Abelló's Grazax, making it the second tablet-based allergy vaccine to reach the market. In 2009 sales in Germany were $991,000 compared to Grazax which achieved sales of $11m in the same market. Although Oralair Grasses achieved approval throughout the EU in November 2009, Stallergènes has announced that price and reimbursement assessment procedures will be implemented on a country by country basis prior to additional launches (Stallergènes, 2009; http://www.stallergenes.com). Datamonitor therefore forecasts Oralair Grasses will roll out in the EU in 2011.

In the US, development of Oralair Grasses marginally trails that of Grazax, with the first positive results from a Phase III study, called VO61.08, reported in April 2010, just 5 months after positive results were reported for Grazax in the country (Stallergènes, 2010; http://www.stallergenes.com). In announcing the results, the company stated that the trial is pivotal for a Marketing Authorization Application (MAA) for Oralair in the US, which is being planned for early 2011. However, Datamonitor believes a pediatric study will need to be conducted in the US, as was done for Grazax, in order to expand the patient potential there.

While Oralair Grasses is at a disadvantage to Grazax, as it lags behind in development, it has the potential to learn from the experiences of ALK-Abelló's introduction of Grazax to various markets. Furthermore, a key advantage is that while Grazax is taken daily throughout the year, Oralair Grasses is started 2 months before the season and then during the season, at which point it is stopped until the following year. This provides an advantage in terms of both cost and convenience. However, it does require that patients be diligent in resuming treatment prior to subsequent pollen seasons, and therefore at a time when symptoms are not present.

> *"There is a big difference in terms of periods of administration. So, Grazax is all year round whereas Oralair has a shorter period of intake."*
>
> EU key opinion leader

> *"I think Stallergènes need to look very carefully at what happens with Grazax first to be honest. It is a tough marketplace, the UK."*
>
> UK key opinion leader

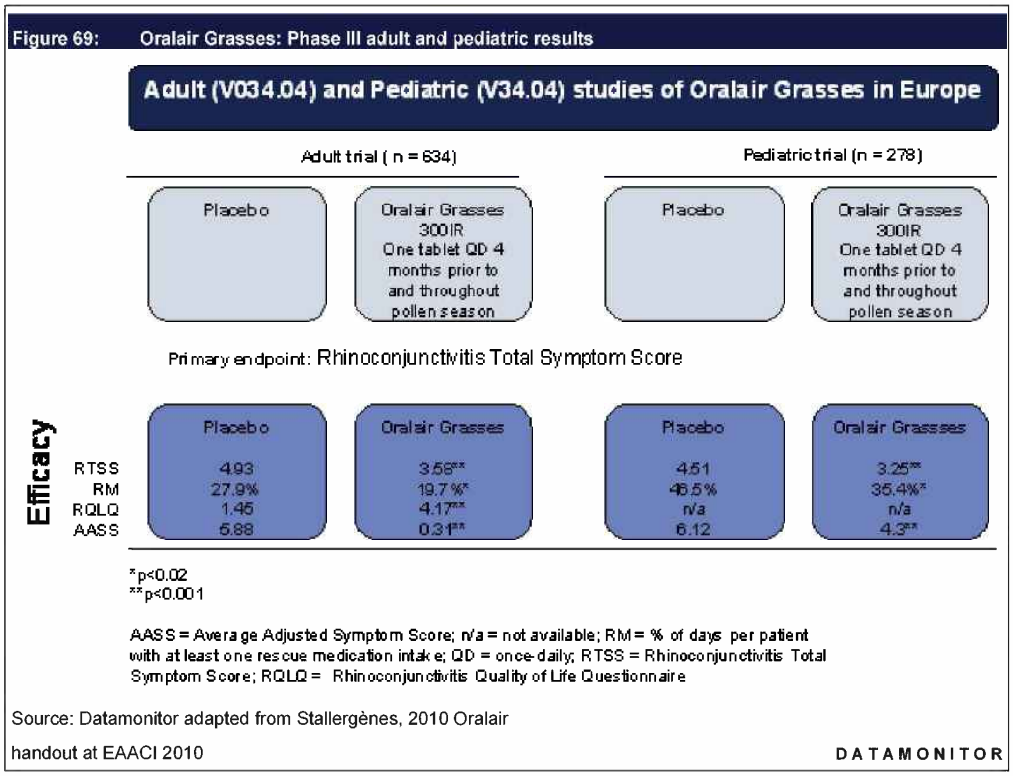
While Stallergènes has entered into several agreements with local companies, including Canadian company Paladin, in order to promote its products, an agreement with a larger respiratory player will be necessary to optimize its commercial opportunities. In a March 2010 analyst meeting presentation Stallergènes announced that a partner is needed in the US by Q2 2011 (Stallergènes, 2010; http://finance.stallergenes.com).

Clinical trial data

EU clinical trial results

Oralair Grasses has had successful Phase III trials in both pediatrics and adults in the EU. Both trials included four arms including placebo, treatment with Oralair 100 IR, treatment with Oralair 300 IR, and treatment with Oralair 500 IR. In both cases efficacy was similar for the 300 IR and 500 IR doses, and based on a favorable safety profile, the lower dose was selected as optimal. The results of the placebo and 300 IR groups in each of these trials are presented in the following figure.

Figure 69: Oralair Grasses: Phase III adult and pediatric results



Source: Datamonitor adapted from Stallergènes, 2010 Oralair handout at EAACI 2010

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At the Stallergènes sponsored symposium of the 2010 European Academy of Allergy and Clinical Immunology (EAACI) Annual Congress, Randof Brehler discussed the results of the clinical trial program for Oralair in the EU, noting that adults and pediatrics were seen to have similar efficacy and safety profiles, with the absence of serious systemic effects, and most observed adverse events being mild or moderate and of short duration. On the basis of the substantial Phase III development program conducted in the EU, Brehler concluded that Oralair Grasses is a safe and effective first-line therapy for patients suffering from moderate-to-severe grass pollen allergy.

In the same symposium Hans Jorgen Maling commented on post-hoc analysis that was carried out on the pediatric trial. Patients were divided into three groups on the basis of the severity of their symptoms on entry, and it was observed that the greatest efficacy was within the most severe group.

At the end of 2009, Stallergènes announced positive 3-year results from a long-term EU study of the therapy. The VO53.06 study is a randomized, double-blind, placebo-controlled study conducted over 5 years, which includes 633 adult patients with grass-pollen related allergic rhinoconjunctivitis. Two treatment arms are included, where patients have been given a daily dose of a 300 IR sublingual tablet, with one group starting treatment 4 months prior to the pollen season, and the other starting 2 months before. During the first 3 years of the study, the treatment arms received Oralair for 5–6 months until the end of the pollen season. After the 3-year treatment regimen, patients will be followed up for an additional 2 years. The results presented in December 2009 covered the third year analysis, and showed that the two treatment groups demonstrated a statistically significant reduction in their Average Adjusted Symptom Score (AASS) compared to placebo therapy (P<0.0001) (Stallergènes, 2009c; http://www.stallergenes.com). This primary endpoint was accepted by the European Medicines Agency (EMA) in 2008 for allergic rhinitis trials. The following table provides an overview of the results seen in each of the first 3 years, which suggest not only sustained efficacy, but also an increase in efficacy over time, which could offer an advantage over Grazax.

Table 35: Oralair – Three year results

	Season 1	Season 2	Season 3
Median difference of reduction in Average Adjusted Symptom Score (AASS) compared to placebo*	30%	40%	49%

*Average of two treatment arms

Source: Stallergènes, 2009c; http://www.stallergenes.com

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At the Stallergènes sponsored symposium of the 2010 European Academy of Allergy and Clinical Immunology (EAACI) Annual Congress was suggested that 3 years of treatment is the optimal situation, but until the follow-up years have been completed, it cannot be established how well the effect will be sustained. Historically it has been seen that 1 year of treatment is insufficient, and there is limited evidence to suggest no added benefit will be seen after 3 years of therapy. However, as Oralair Grasses has shown an unexpected progressive result in each subsequent year, there is the possibility that an added effect would be seen if treatment were continued into additional years.

US clinical trial results

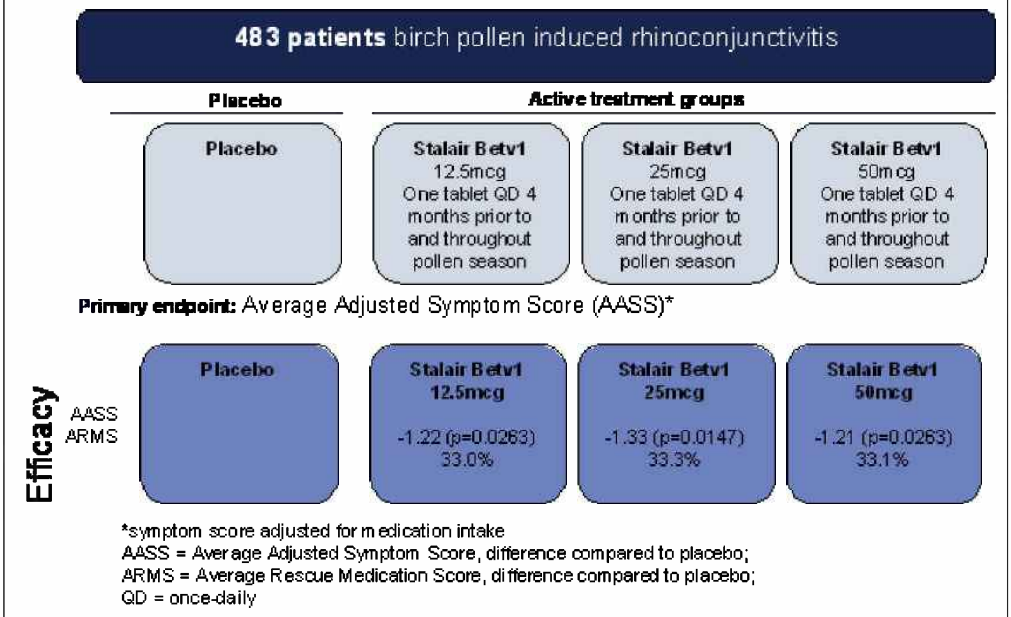
In April 2010 Stallergènes announced positive preliminary results from a US study. The pivotal study, VO61.08, was randomized, double-blind, and placebo-controlled trial, and it included 473 adult patients suffering from grass-pollen induced rhinoconjunctivitis. The primary endpoint was the reduction of a combined score, which took into account both symptoms and rescue drug use. The trial met that primary endpoint, demonstrating a statistically significant reduction in the combined score of the arm treated with Oralair, compared with the placebo arm. The company stated that the magnitude of the results was similar to that seen in the EU studies, and further that Oralair was well tolerated (Stallergènes, 2010; http://www.stallergenes.com). In-depth analysis of these data has not yet been released.

Stalair Betv1 (pollen, Stallergènes)

Stallergènes recombinant birch pollen allergen, Stalair Betv1, another sublingual immunotherapy tablet, met its primary endpoint in a Phase IIb/III trial. The preliminary results of the trial were reported by the company in September 2009. The trial, called VO59.08 was conducted during the 2009 pollen season, and was a randomized, double-blind, placebo-controlled study of 483 adult patients across eight European countries. The trial included patients suffering from rhinoconjunctivitis symptoms who were allergic to birch pollen. Three treatment groups were included, which received 12.5mcg, 25mcg or 50mcg of rBetv1, as well as a placebo group. A statistically significant reduction in the primary endpoint of Average Adjusted Symptom Score (AASS), was seen for all three treatment groups ($0.002<p<0.03$). Over the season the reduction in AASS for the treatment groups was approximately 25%, peaking at about 30%. The company noted that overall tolerance was good, particularly for the 12.5mcg and 25mcg group, but no information was given detailing the additional adverse events for the higher dose group. Stallergènes intends to use the study to select the optimal dose and initiate a pivotal Phase III study to be used for a Marketing Authorization Application (MAA) with the European Medicines Agency (Stallergènes, 2009b, http://www.stallergenes.com).

Peer-reviewed results of this trial were presented in June 2010 at the European Academy of Allergy and Clinical Immunology (EAACI) Annual Congress, and are shown in the following figure.

Figure 70: Stalair Betv1: Phase IIb/III trial results



Source: Datamonitor adapted from Rak *et al* ., 2010 DATAMONITOR

Author conclusions: this is the first clinical trial to demonstrate placebo-controlled clinically relevant efficacy of a recombinant allergen sublingual immunotherapy tablet in birch-related rhinoconjunctivitis in adults. As is usually observed with sublingual immunotherapy, the side effects were generally mild to moderate and the safety profile was good.

Datamonitor comments: the results of this study are encouraging, and rBetv1 is the most advanced birch pollen allergen, suggesting that the drug will enjoy first-to-market status should continuing development be successful. However, according to Stallergènes, the birch pollen season lasts just 1–2 months (Stallergènes, 2009b, http://www.stallergenes.com). This could reduce the clinical need for an allergen, however, the company also notes that the season is intense, which suggests that patients may be eager to seek lasting relief from their symptoms. Additional information on the treatment's safety is required.

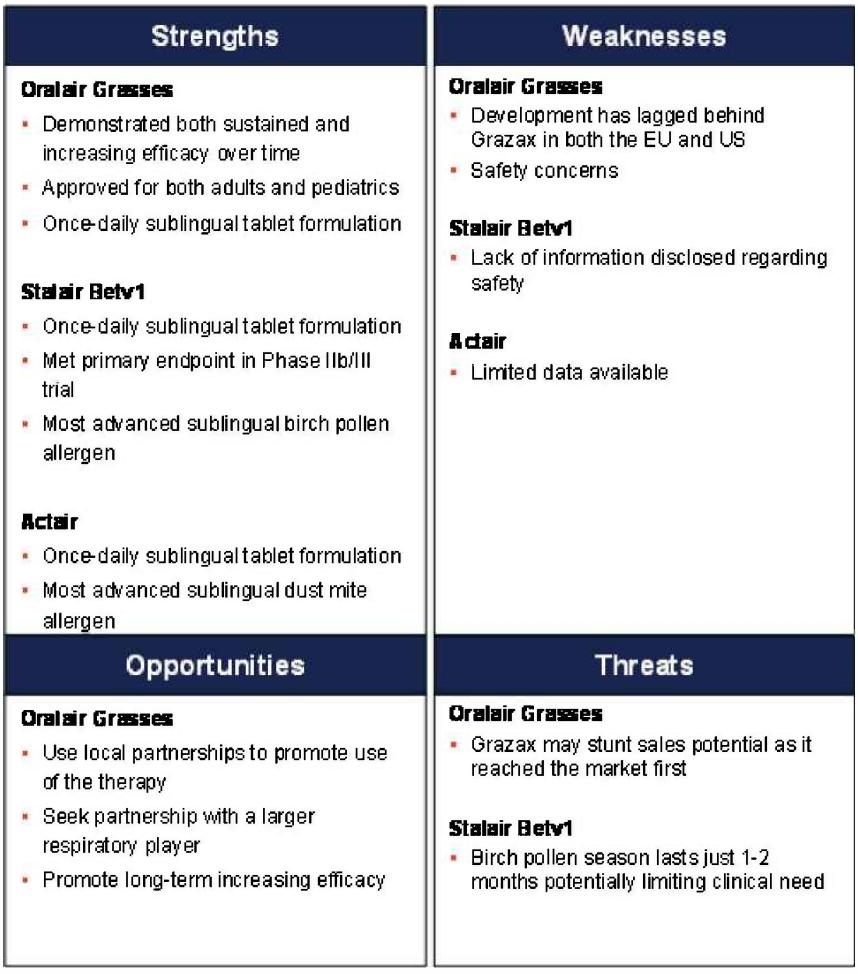
Actair (dust mite; Stallergènes)

Stallergènes's Stalair program also includes Actair, a dust mite allergen that has been in a Phase IIb/III clinical trial, VO57.07. Stallergènes announced positive first-year results from the trial in April 2009. The study included 509 patients over seven countries. Two treatment groups were included, who received either a 300 IR tablet daily or 500 IR tablet daily, and these groups were compared to placebo. Treatment was given for a full year in 2008. The company stated that the two treatment groups demonstrated a statistically significant improvement compared to placebo ($p<0.0136$) in the Average Adjusted Nasal Symptom Score during the last 3 months of the year, the primary endpoint. Rescue medication was permitted throughout the trial, with the Adjusted Average Symptom Score (AASS) improving by 20% in both treatment groups. As no difference was seen between the treatment groups, the 300 IR tablet has been selected. The company highlighted that Actair was effective from the fourth month of treatment, and this unexpectedly quick onset of action, together with a good observed safety profile, means that treatment with Actair can address the needs of patients with moderate-to-severe forms of dust mite induced perennial allergic rhinitis (Stallergènes, 2009; http://www.stallergenes.com). The company has further stated that the trial will be pivotal to the EU registration process, and that data regarding short-term efficacy in pediatric patients are anticipated in Q2 2011 (Stallergènes, 2010; http://finance.stallergenes.com)

SWOT analysis

The following figure highlights the strengths, weaknesses, opportunities and threats (SWOT) of the Stalair Program.

Figure 71: Stalair Program – SWOT analysis for allergic rhinitis, 2010



Source: Datamonitor DATAMONITOR

Brand forecast to 2019

- Datamonitor uses a patient-based forecast for Oralair;
- Oralair Grasses will roll out in additional EU countries in 2011;
- in the US, Oralair Grasses will be filed in 2011 and launched in 2012;
- in new markets Oralair Grasses will be priced on a par with that in Germany ($4 tablet);
- a small percentage of patients will start to drop out of the market each year once Oralair Grasses has been available for 3 years, based on successful completion of the therapy;
- the patient population for Oralair is derived from the assumptions shown in Table 36. For a discussion of these assumptions, please see the section: Methodology and comparative forecasts.

Table 36: Oralair patient-based forecast assumptions, 2010

	Germany		France		Italy		Spain		UK		US	
	2010	2019	2010	2019	2010	2019	2010	2019	2010	2019	2010	2019
Total patient potential (000s)*	687	675	536	555	424	427	258	274	580	605	2,857	3,067
Access to treatment from a specialist (%)	33	33	17	17	17	17	17	17	13	13	17	17
Access to treatment from a specialist (000s)	227	223	91	94	72	73	44	47	75	79	486	521
Moderate-severe grass allergen patient penetration (%)	2	13	0	8	0	8	0	8	0	3	0	19
Moderate-severe grass allergen patient penetration (000s)	3	28	–	8	–	6	–	4	–	2	–	98
Patients continuing treatment (%)	98	95	98	95	98	95	98	95	98	95	98	95
Patients continuing treatment (000s)	3	27	–	7	–	6	–	4	–	2	–	93
Compliance rate (%)	80	80	80	80	80	80	80	80	80	80	80	80
Compliant patients (000s)	3	21	–	6	–	5	–	3	–	2	–	75
Total SUs (365 per patient/per year)	486	3,865	–	1,067	–	821	–	526	–	329	–	13,614
$ cost/SU	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00
Oralair total sales ($ 000s)	**1,969**	**15,720**	–	**4,340**	–	**3,340**	–	**2,140**	–	**1,336**	–	**55,370**

*This is the total moderate/severe allergic rhinitis population that is diagnosed, has grass allergy, and is uncontrolled.

SU = IMS standard unit

Source: Datamonitor

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Table 37: Sales forecasts for Oralair in allergic rhinitis in the US and five major EU markets ($ 000s), 2009–2019						
	2009	2011f	2013f	2015f	2017f	2019f
US	0	0	11,280	18,808	32,262	55,370
France	0	530	905	1,499	2,549	4,340
Germany	991	2,752	4,161	6,501	10,097	15,720
Italy	0	418	711	1,171	1,976	3,340
Spain	0	256	440	733	1,252	2,140
UK	0	307	448	632	919	1,336
Total	**991**	**4,263**	**17,945**	**29,344**	**49,055**	**82,246**

Source: 2010–2019 forecast = Datamonitor patient based forecast; 2009 sales = MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission DATAMONITOR

The 10-year market forecast for Oralair Grasses is outlined separately in the accompanying forecast tool, a downloadable Excel spreadsheet that details the forecast for this drug in the seven major markets.

Pollinex Quattro (Allergy Therapeutics)

Summary takeaways:

- **Product:** Pollinex Quattro (grass pollen);
- **2009 sales:** allergic rhinitis: $4m;
- **2019 forecast sales:** allergic rhinitis: $30m.

Allergy Therapeutics is developing Pollinex Quattro, a range of pollen-allergy vaccines, for both the US and EU markets. Pollinex Quattro is an ultra-short course vaccine requiring four shots at weekly intervals. Three technologies are incorporated into the vaccines; natural allergens are chemically modified to improve safety and allow for delivery at higher doses, depot technology provides prolonged desensitization and further improved tolerability, and the immuno response is enhanced and directed by an adjuvant: monophosphoryl lipid A (MPL) (Allergy Therapeutics, 2008; http://www.allergytherapeutics.com).

Datamonitor provides a sales forecast for the seven major markets for both Pollinex Quattro Grass, and the entire Pollinex range of products, which, combined, are estimated to have reached $21m in 2009, using IMS MIDAS sales data. In their 2009 Annual Report, Allergy Therapeutics reports sales for the Pollinex range of $27m (£18.2m) (Allergy Therapeutics, 2009, http://www.allergytherapeutics.com). While this is believed to be global, rather than seven major market sales, the difference may also represent the underestimation of IMS MIDAS sales data in the immunotherapy class, which is discussed in the section: IMS data versus company reports sales.

The Allergy Therapeutics company website lists four clinical development programs for Pollinex Quattro products: grasses (registered EU, Phase III US), ragweed (Phase III in the US), trees (Phase II US and EU) and Japanese cedar (Preclinical) (Allergy Therapeutics, 2010; http://www.allergytherapeutics.com). However, clinical development of the Pollinex Quattro range has been on hold in the US since 2007. In July 2007, the company announced that activity on its ragweed clinical studies (R301) had been placed on hold by the US Food and Drug Administration (FDA) while the agency fully assessed the report of a rare adverse event classified as 'possibly related' to the study drug. Allergy Therapeutics said it did not agree that the adverse event, a rare neurological condition, was related to treatment, and that it planned to meet the FDA as soon as possible to determine its next steps. The trial, which was fully recruited at the time, had to be moved to the observation phase due to the approaching pollen season. The clinical hold has also affected the development of Pollinex Quattro grasses in the US (Allergy Therapeutics, 2007; http://www.allergytherapeutics.com). As of 2010 the clinical hold remains, although Allergy Therapeutics continues to work with the FDA with the aim of continuing development. The company believes that the FDA's review of GlaxoSmithKline's New Drug Application (NDA) for the vaccine Cervarix, which provided additional information on the action of MPL containing vaccines, and which received a strong positive recommendation from an advisory committee, will help to support the potential for Pollinex Quattro in the US (Allergy Therapeutics, 2010; http://www.allergytherapeutics.com).

In the EU, Pollinex Quattro for grass allergy is available on a named-patient basis and was submitted to the Germany Regulatory authority, the Paul Ehrlich Insitut (PEI) in Germany in March 2009. The company plans to use the PEI as a Reference Member State for Europe-wide registration through the EU Mutual Recognition Procedure (MRP). At the time of filing, Allergy Therapeutics expected approval from 2010 (Allergy Therapeutics, 2009; http://www.allergytherapeutics.com). However, in March 2010 the company announced the review was taking longer than anticipated, and the revised target launch date is now 2011 (Allergy Therapeutics, 2010; http://www.allergytherapeutics.com).

Datamonitor forecasts Pollinex Quattro grasses will gain approval and launch in the EU in 2011. A launch is not forecast for the US where the future of the clinical development program remains uncertain.

Product profile

Table 38: Pollinex Quattro grass – drug profile, 2010

Pollinex Quattro grass	
Molecule	Pollen
Mechanism of action	Allergen desensitization therapy
Originator	Allergy Therapeutics
Marketing company	Allergy Therapeutics
Primary indication	Treatment of seasonal allergic rhinoconjunctivitis
Formulation	Sublingual tablet
Dosing frequency	Four injections over 3 weeks prior to pollen season
Launch date	Launched 2009 (Germany); 2011 (EU)
2009 sales, 7MM	Allergic rhinitis: $4m
2019 sales, 7MM	Allergic rhinitis: $30m

7MM = seven major markets (US, Japan, France, Germany, Italy, Spain, UK)

Source: Datamonitor, Thomson Pharma; MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission. DATAMONITOR

Product positioning

Allergy Therapeutics' strategy differs from that of other key companies involved in immunotherapy as it focuses on subcutaneous immunotherapy products that require short courses as opposed to the long-term use needed for sublingual immunotherapy products. The recent move towards sublingual dosing in the overall immunotherapy market may mean that the company will face an uphill struggle with its subcutaneous products. It is difficult to predict how physicians and patients will choose between shorter injectable courses and longer sublingual courses. While a key advantage of sublingual versus subcutaneous therapy is thought to be the convenience of home therapy, this is generally thought of in comparison to monthly injections, whereas Pollinex Quattro requires only four injections in total. Still, patients are unlikely to choose such a treatment except in cases where symptoms are very severe and debilitating.

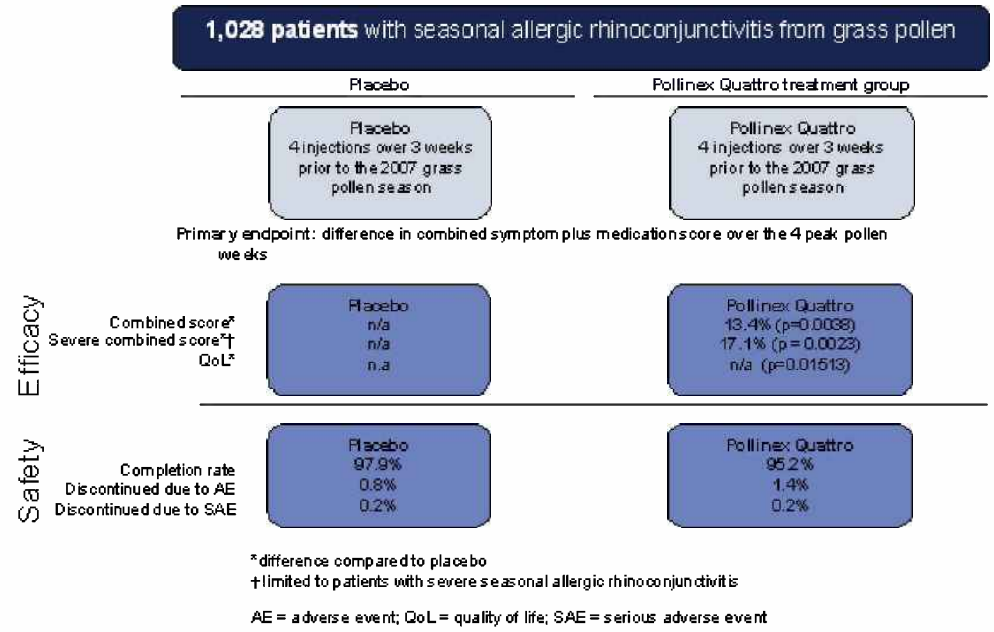
"There is really absolutely no role in the UK [for an injectable vaccine] *other than in very severe patients."*

UK key opinion leader

Clinical trial data

The results of the pivotal Phase III trial of Pollinex Quattro grasses, G301, which were used for filing the treatment in Germany, were presented at the European Academy of Allergology and Clinical Immunology in 2008. The double-blind placebo-controlled study compared the combined symptom and medication score of patients given four injections of Pollinex Quattro with those receiving placebo. Over 1,000 patients were included from 84 locations in the US, Canada, and Europe. The results of the trial are presented in the following figure.

Figure 72: Pollinex Quattro Grass – Phase III trial results



Source: Datamonitor adapted from Allergy Therapeutics, 2008;
http://www.allergytherapeutics.com

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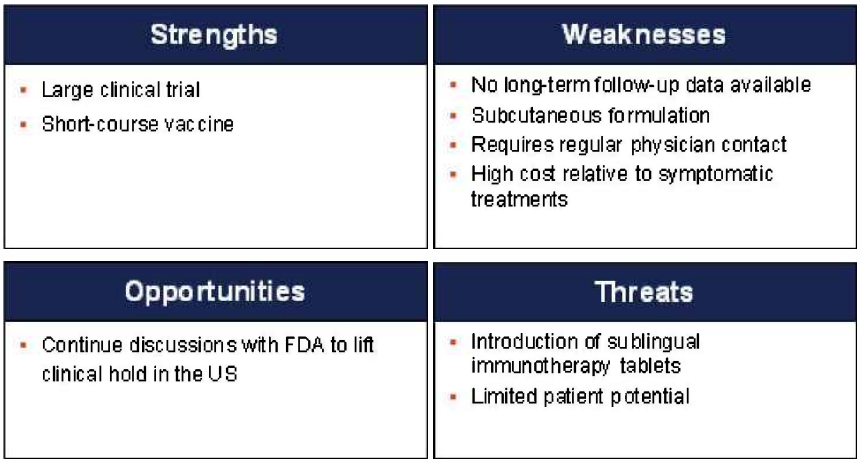
It was further reported that adverse events were generally mild and transitory, and mainly related to local area site reactions.

The trial benefited from a large patient population and the results point towards a clinical benefit of Pollinex Quattro grass vaccine which is well tolerated. The benefit is larger for patients with severe symptoms, and Datamonitor expects the patient potential will be limited to this group.

SWOT analysis

The following figure highlights the strengths, weaknesses, opportunities and threats (SWOT) of Pollinex Quattro Grass.

Figure 73: Pollinex Quattro Grass – SWOT analysis for allergic rhinitis, 2010



Source: Datamonitor

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Brand forecast to 2019

- Pollinex Quattro grass will roll out across the EU in 2011;
- in new markets Pollinex Quattro will be priced similar to that in Germany ($187 per injection);
- patients are not forecast to drop out of the market as long-term follow-up data are not available to demonstrate that treatment can be stopped after a given timescale;
- a launch is not forecast in the US where development remains on hold;
- the patient population for Pollinex Quattro is derived from the assumptions shown in the following table.

Table 39: Pollinex Quattro Grass patient based forecast assumptions, 2010

	Germany		France		Italy		Spain		UK	
	2010	2019	2010	2019	2010	2019	2010	2019	2010	2019
Total patient potential (000s)*	687	675	536	555	424	427	258	274	580	605
Access to treatment from a specialist (%)	33	33	17	17	17	17	17	17	13	13
Access to treatment from a specialist (000s)	227	223	91	94	72	73	44	47	75	79
Moderate-severe grass allergen patient penetration (%)	4	18	0	8	0	8	0	8	1	2
Moderate-severe grass allergen patient penetration (000s)	8	40	–	8	–	6	–	4	–	1
Patients continuing treatment (%)	98	98	98	98	98	98	98	98	98	98
Patients continuing treatment (000s)	8	39	–	8	–	6	–	4	–	1
Compliance rate (%)	70	70	70	70	70	70	70	70	70	70
Compliant patients (000s)	5	28	–	5	–	4	–	3	–	1
Total SUs (365 per patient/per year)	22	110	–	21	–	16	–	10	1	4
$ cost/SU	187	189	187	189	187	189	187	189	104	100
Pollinex Quattro Grass total sales ($ 000s)	**4,064**	**20,845**	–	**3,989**	–	**3,069**	–	**1,967**	**108**	**381**

*This is the total moderate/severe allergic rhinitis population that is diagnosed, has grass allergy, and is uncontrolled.

SU = IMS standard unit

Source: Datamonitor DATAMONITOR

Table 40: Sales forecasts for Pollinex Quattro for allergic rhinitis in the five major EU markets ($ 000s), 2009–2019						
	2009	2011f	2013f	2015f	2017f	2019f
France	0	470	805	1,376	2,342	3,989
Germany	3,907	4,882	7,033	10,139	14,522	20,844
Italy	0	371	632	1,075	1,816	3,069
Spain	0	227	391	673	1,150	1,967
UK	80	122	161	214	286	381
Total	**3,987**	**6,072**	**9,021**	**13,478**	**20,116**	**30,251**

Note: totals may not sum due to rounding.

Source: 2010–2019 forecast = Datamonitor patient based forecast; 2009 sales = MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission.

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The 10-year market forecast for Pollinex Quattro is outlined separately in the accompanying forecast tool, a downloadable Excel spreadsheet that details the forecast for this drug in the five major EU markets.

Fornix's sells allergy division to ALK-Abelló

Fornix Biosciences, a Dutch company, is developing Oralgen Grass Pollen. This sublingual immunotherapy utilizes a grass pollen extract and is being developed for the potential treatment of grass pollen allergic rhinitis. The company filed a marketing application in the Netherlands, and in 2008 Fornix announced that the Dutch Medicines Evaluation Board had rejected the treatment, on the basis of results from a pan-European Phase II/III study. The company further announced that it had begun an appeal in 2007.

The Phase II/III dose-ranging trial included 605 patients and considered three different doses of Oralgen. A substantial decrease in allergic complaints was observed for the highest dose, with a significant reduction in the use of allergy medications, while the two lower doses did not reach statistically significant efficacy.

Following the treatment's rejection, Fornix initiated a follow-up study, and in November 2009 the Dutch Medicines Evaluation Board did not overturn the rejection and concluded there was still insufficient evidence of Oralgen's efficacy. The company continued to appeal, and in February 2010 a court hearing ruled to dismiss the appeal. At that time, the company was taking advice regarding a further appeal. However, in June 2010 Fornix announced the sale of its allergy division to ALK-Abelló. Datamonitor does not expect further development of Oralgen grass pollen, as ALK-Abelló has its own sublingual immunotherapy for grass pollen allergy; Grazax (Fornix, 2010a; http://www.fornix.nl; Fornix 2010b; http://www.fornix.nl; Fornix 2008; http://www.fornix.nl).

Allergopharma moving into sublingual immunotherapy

German company Allergopharma markets a number of subcutaneous immunotherapy products, and is also developing a sublingual immunotherapy for the treatment of allergies caused by several pollens. Clinicaltrials.gov lists four Allergopharma sponsored trials of sublingual immunotherapies, these include three double-blind Phase III trials of grass pollen extract, and one open-label Phase II trial of a birch pollen extract (Clinicaltrials.gov, 2010d; http://clinicaltrials.gov). Each of these trials is being conducted in Germany, and the treatment appears to be in the form of sublingual drops. With development of sublingual tablets in the EU, the company could be at a disadvantage.

Roxall and Dr. Beckman collaboration

In Germany, Roxall and Dr. Beckmann are collaborating on the development of two subcutaneous immunotherapies. The first is based on a glutaraldehyde-polymerized allergen grass extract, CLUSTOID. One trial is listed on clinicaltrials.gov, pertaining to CLUSTOID grass pollen (Thomson Pharma, May 2010, Copyright Thomson Scientific). The trial, sponsored by Roxall, is a Phase III efficacy and safety study of 121 patients in Germany with allergic rhinitis/rhinoconjunctivitis due to grass pollen and/or rye pollen. The primary endpoint is a symptom and medication score. The study is listed as ongoing, but has not been updated since its primary completion date of November 2009, so it is not clear if the trial has been finished (Clinicaltrials.gov, 2010e; http://clinicaltrials.gov).

The two companies are also developing a subcutaneous immunotherapy of a modified dust mite allergen extract. Two efficacy and safety Phase III trials are listed on clinicaltrials.gov, with completion dates in January and February 2011. Both trials are located in Spain and have a symptom and medication score as their primary endpoint. One of the trials is already recruiting, while the other is not yet open for recruitment (Clinicaltrials.gov, 2010f; http://clinicaltrials.gov).

The companies also appear to be collaborating on sublingual immunotherapies, which are in preclinical development (Thomson Pharma, April 2010, Copyright Thomson Scientific).

Greer developing sublingual immunotherapy

Greer has conducted clinical trials on at least three sublingual immunotherapies for the potential treatment of allergic rhinitis. The most advanced is for ragweed pollen allergy. A Phase III trial began in March 2008 in the US. The randomized double-blind placebo-controlled trial includes 458 patients with moderate-to-severe rhinoconjunctivitis (Thomson Pharma, May 2010, Copyright Thomson Scientific). The primary endpoint is the average Rhinoconjunctivitis Daily Symptom Score over the pollen season. While clinicaltrial.gov lists the primary completion date as October 2008, the trial has not been updated since June 2008, and is still listed as ongoing (Clinicaltrials.gov, 2010g; http://clinicaltrials.gov/). It is therefore not clear whether or not further development has been initiated.

The company has also conducted clinical trials on a sublingual Timothy grass allergen extract, and a sublingual dust mite allergen extract. In March 2008 data from Phase IIb trial of the grass extract were presented. The mean allergy symptom scores and medication use did not significantly increase during the grass pollen season, which was attributed to low levels of pollen over the season. For the dust mite allergen, safety data presumed to be from a Phase II trial were presented at the American Academy of Allergy Asthma and Immunology (AAAAI) Annual Meeting in March 2009. Thirty-one patients were included, of whom four withdrew due to possible treatment-related effects. However, no systemic reactions were observed, and the authors concluded that the treatment was generally safe and tolerable (Thomson Pharma, May 2010, Copyright Thomson Scientific). There are no trials listed on clincialtrials.gov for either the Timothy grass allergen extract or the dust mite allergen, such that it is not clear if further development is ongoing.

7. PIPELINE DYNAMICS

Key findings

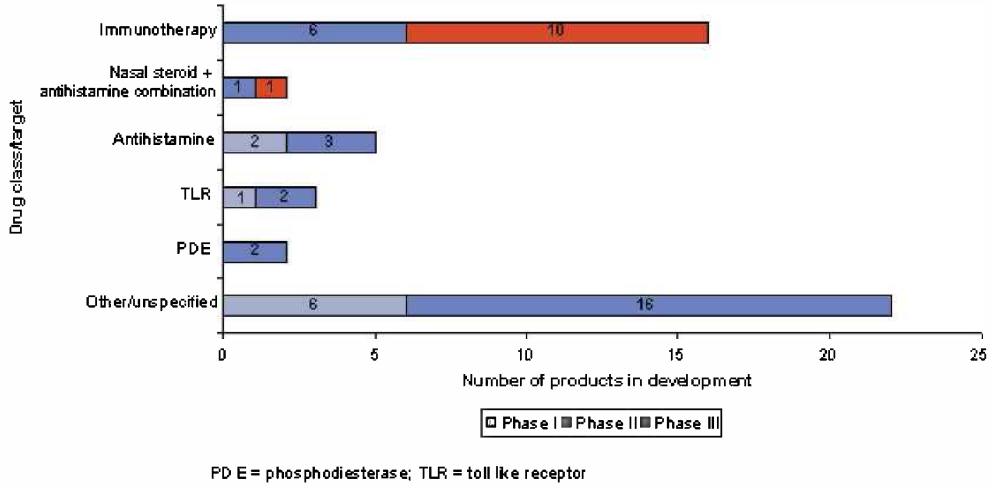
- Datamonitor has identified 50 products in clinical (Phase I to Phase III) development for allergic rhinitis. Immunotherapy is the most commonly seen class in the pipeline, with 16 products in development. The majority of these products are oral, which highlights the increasing move away from subcutaneous immunotherapy. However, many of these products are being developed, as is traditionally seen for immunotherapy, by small highly specialized companies, and with the increasingly strict requirements within the EU for immunotherapy registration, Datamonitor believes that only a handful are involved in clinical development programs that will be sufficient to reach the market.
- Two nasal steroid/antihistamine combinations are in late-stage development. Meda Pharma's azelastine/fluticasone combination is the most advanced, having reached Phase III. Datamonitor forecasts this combination to gain approval and launch in the US in 2012, and in the EU in 2013. If successful, it will introduce a new class to the allergic rhinitis market, offering patients with severe disease a simplified treatment option. Discussions with key opinion leaders reveal that a nasal antihistamine/corticosteroid combination is highly anticipated, and Datamonitor forecasts that azelastine/fluticasone will reach allergic rhinitis sales of $139m in the US and five major EU markets by 2019.

Pipeline overview

Datamonitor identified 50 products in clinical (Phase I to Phase III) development for allergic rhinitis, with an additional 17 products found to be in preclinical development for the disease. While currently occupying a niche market, immunotherapy dominates the pipeline, with 16 products in development. Many of these are oral products, highlighting the move away from subcutaneous formulations in that class. Two nasal steroid/antihistamine combinations are in late-stage development, one in Phase II and one in Phase III, which are expected to offer a simplified treatment option to patients requiring both products.

Figure 74 shows products in Phase I to Phase III development by class and development and it is interesting to see that only immunotherapies and one nasal steroid/antihistamine combination are currently in Phase III. With numerous treatment options currently available for allergic rhinitis, novel therapies will need to differentiate themselves from the current treatment options, and offer an alternative in order to succeed, and these classes are believed to do just that. For immunotherapy, many products are being developed by small niche companies, and limited information is available regarding their development progress. However, with key changes in immunology development, including the movement towards developing large placebo-controlled trials, this class is expected to change significantly, as more data become available.

Figure 74: Products in development for allergic rhinitis by class/target, 2010



PDE = phosphodiesterase; TLR = toll like receptor

Source: Thomson Pharma, April 2010, Copyright Thomson Scientific; www.clinicaltrials.gov.

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Table 41 provides an overview of all products in preclinical to Phase III development for the treatment of allergic rhinitis.

Table 41: Products in development for allergic rhinitis, 2010

Molecule/code/brand	Class/target	Originator company (Partner)	Formulation	Highest Phase
Stalair Betv1	Immunotherapy	Stallergènes	Oral	III
Pollinex Quattro Grass	Immunotherapy	Allergy Therapeutics	Subcutaneous	III
grass pollen	Immunotherapy	Fornix BioSciences	Oral	III
recombinant grass pollen allergens	Immunotherapy	Allergopharma	Subcutaneous	III
recombinant birch pollen allergen	Immunotherapy	Allergopharma	Subcutaneous	III
azelastine + fluticasone	Nasal steroid + nasal antihistamine	Meda (Cipla)	Nasal	III
dust mite allergen	Immunotherapy	Roxall Medizin (Dr Beckmann Pharma)	Subcutaneous	III
polymerized vaccine	Immunotherapy	Dr Beckmann Pharma (Roxall Medizin)	Subcutaneous	III
Olea europaea-containing vaccine	Immunotherapy	Laboratorios Leti	Oral	III
ragweed extract	Immunotherapy	Greer Laboratories	Oral	III
House dust mites/Actair	Immunotherapy	Stallergènes	Oral	III
BI-671800	Unspecified	Boehringer Ingelheim	Oral	II
RPL-554	PDE 3;PDE 4	King's College London (Verona Pharma)	Nasal	II
SUN-1334H	Histamine H1 receptor	Sun Pharmaceutical Industries	Oral	II
AZD-8848	TLR-7	Dainippon Sumitomo Pharma Co (AstraZeneca)	Nasal	II
PF-3654746	Histamine H3 receptor	Pfizer	Oral	II
Trichuris suis ova	Unspecified	University of Iowa (Ovamed)	Oral	II
CYT-003-QbG10	TLR-9 gene; Immunoglobulin G	Cytos Biotechnology AG	Subcutaneous	II
mometasone + oxymetazoline	Alpha 1 adrenoceptor	Schering-Plough (now Merck)	Nasal	II
QAX-576	IL-13 modulator	Novartis	Intravenous	II
anatibant	Bradykinin B2 receptor	Fournier Pharma (Xytis)	Injectable	II
JNJ-39220675	Unspecified	Johnson & Johnson	Oral	II
VAK-694	Unspecified	Novartis	Intravenous	II
BLX-LSAID	Leukocyte inhibitor	Inflazyme Pharmaceuticals	Oral	II
TA-270	5-lipoxygenase	DIC Corporation	Oral	II
budesonide + azelastine	Nasal steroid + nasal antihistamine	CyDex Pharmaceuticals	Nasal	II
KP-496NS	Leukotriene D4 antagonist; Thromboxane A2 antagonist	Kaken Pharmaceutical	Nasal	II
recombinant human CC10	Uteroglobin	Claragen	Nasal	II
grass pollen-derived peptides	Immunotherapy	Biotech Tools	Oral	II
dust mite allergen extract	Immunotherapy	Greer Laboratories	Oral	II
QAV-680	Unspecified	Novartis	Oral	II
OX-914	PDE4 inhibitor	Inflazyme Pharmaceuticals	Oral	II
MRX-4	Phospholipase A2	Morria Biopharmaceuticals	Nasal	II
AM-3301	Unspecified	Meiji Seika Kaisha (Amalyte Pharmaceuticals)	Nasal	II
Phleum pratense-containing vaccine	Immunotherapy	Laboratorios Leti	Oral	II
CYT-005-allQbG10	Immunotherapy	Cytos Biotechnology	Subcutaneous	II

Table 41: Products in development for allergic rhinitis, 2010

Molecule/code/brand	Class/target	Originator company (Partner)	Formulation	Highest Phase
Timothy grass extract	Immunotherapy	Greer Laboratories	Oral	II
Lolium perenne/Cynodon dactylon-containing vaccine	Immunotherapy	Laboratorios Leti	Oral	II
EPI-12323	Adenosine receptor	EpiGenesis Pharmaceuticals	Inhaled	II
chitin microparticle nasal spray	T-lymphocyte modulator; Cytokine modulator	CMP Therapeutics	Nasal	II
CP-118	Histamine receptor	Collegium Pharmaceutical	Unspecified	II
CAL-101	Phosphoinositide-3 kinase delta	ICOS Corp (Calistoga Pharmaceuticals)	Oral	I
PCI-32765	Btk tyrosine kinase	Celera Group (Pharmacyclics)	Oral	I
DP-1	Histamine H4 receptor	Palau Pharma	Oral	I
Z-207	Unspecified	Zeria Pharmaceutical	n/a	I
PF-3654764	Unspecified	Pfizer	Oral	I
VTX-1463	TLR-8	VentiRx Pharmaceuticals	Nasal	I
ASP-1001	Histamine release modulator	Asphelia Pharmaceuticals	Nasal	I
BMEC-1217B	Unspecified	Industrial Technology Research Institute (Medigreen Biotechnology)	Oral	I
andolast	Potassium channel stimulator	Rottapharm Madaus	Inhaled	I
bepotastine	Histamine H1 receptor	Tanabe Seiyaku	Nasal	Preclinical
CRTH2 receptor antagonists	G-protein coupled receptor-44	Amira Pharmaceuticals	Oral	Preclinical
ADC-3680	G-protein coupled receptor-45	Argenta Discovery (Pulmagen Therapeutics)	Oral	Preclinical
ADC-9971	G-protein coupled receptor-46	Argenta Discovery (Pulmagen Therapeutics)	Oral	Preclinical
JNJ-38224342	Unspecified	Johnson & Johnson	Oral	Preclinical
dust mite allergen immunotherapy	Immunotherapy	Roxall Medizin (Dr Beckmann Pharma)	Oral	Preclinical
pollen allergen immunotherapy	Immunotherapy	Roxall Medizin (Dr Beckmann Pharma)	Oral	Preclinical
methscopolamine + antihistamine (allergic rhinitis), Cornerstone Therapeutics	Acetylcholine receptor antagonist; Histamine receptor antagonist	Cornerstone BioPharma	Oral	Preclinical
pegylated diphenhydramine	Histamine receptor	Nektar Therapeutics	Oral	Preclinical
histamine H1 antagonists	Histamine H1 receptor	Dainippon Sumitomo Pharma	n/a	Preclinical
HF-1020	CD89 agonist; Immunoglobulin G1 agonist	University of Bristol (Trident Pharmaceuticals)	n/a	Preclinical
T2CA	Unspecified	Dharma Biomedical	n/a	Preclinical
prostaglandin D2 antagonists	DP prostanoid receptor	Merck & Co	n/a	Preclinical
IVN-birch	Unspecified	ImVisioN Therapeutics	Injectable	Preclinical
prostaglandin D2 antagonists	G-protein coupled receptor-44	Array BioPharma	n/a	Preclinical
dual H1/H3 antagonists	Antihistamine	GlaxoSmithKline	n/a	Preclinical
pollen allergen vaccine	Allergen	Wolwo Biotech Co	Oral	Preclinical

IL = interleukin; PDE = phosphodiesterase; TLR = toll-like receptor

Source: Thomson Pharma, April 2010, Copyright Thomson Scientific; www.clinicaltrials.gov.

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Azelastine/Fluticasone (MP2902; Meda/Cipla)

Summary takeaways:

- **Product:** Azelastine/fluticasone combination;
- **2019 forecast sales:** total brand: $277m; allergic rhinitis: $139m.

Meda and Cipla have collaborated to develop a combination of azelastine and fluticasone for the potential treatment of allergic rhinitis. In 2009 the companies expanded their partnership to incorporate additional markets beyond the US, including Australia, Brazil, Europe, Japan and South Korea. Under the agreement, Cipla will manufacture the product (Meda, 2009; http://www.meda.se/). According to Meda, the two components, which dominate the nasal antihistamine and corticosteroid markets as monotherapies, could provide patients with a more effective treatment for allergic rhinitis when used in combination, compared to the currently available therapies (Meda Annual Report, 2009; http://www.meda.se). Meda's company website states the combination product is in Phase III development, with the remaining clinical trials expected to reach completion in the second half of 2010 (Meda, 2010a; http://www.meda.se). However, according to clinicaltrials.gov, four safety and efficacy studies of the product, sponsored by Meda, were completed in 2008–2009, but the site does not list any ongoing trials of the drug (clinicaltrials.gov, 2010c; http://clinicaltrials.gov).

Drug profile

Table 42: Azelastine/fluticasone – drug profile, 2010

Azelastine/fluticasone	
Molecule	Azelastine/fluticasone
Mechanism of action	Nasal corticosteroid/antihistamine combination
Originator	Meda
Marketing company	Cipla
Targeted indication	Seasonal allergic rhinitis
Formulation	Nasal spray
Dosing frequency	Azelastine hydrochloride 548mcg/fluticasone propionate 200mcg twice-daily
Estimated launch date	2012 (US); 2013 (EU)
2019 sales, 7MM	Total brand: $277m
	Allergic rhinitis: $139m

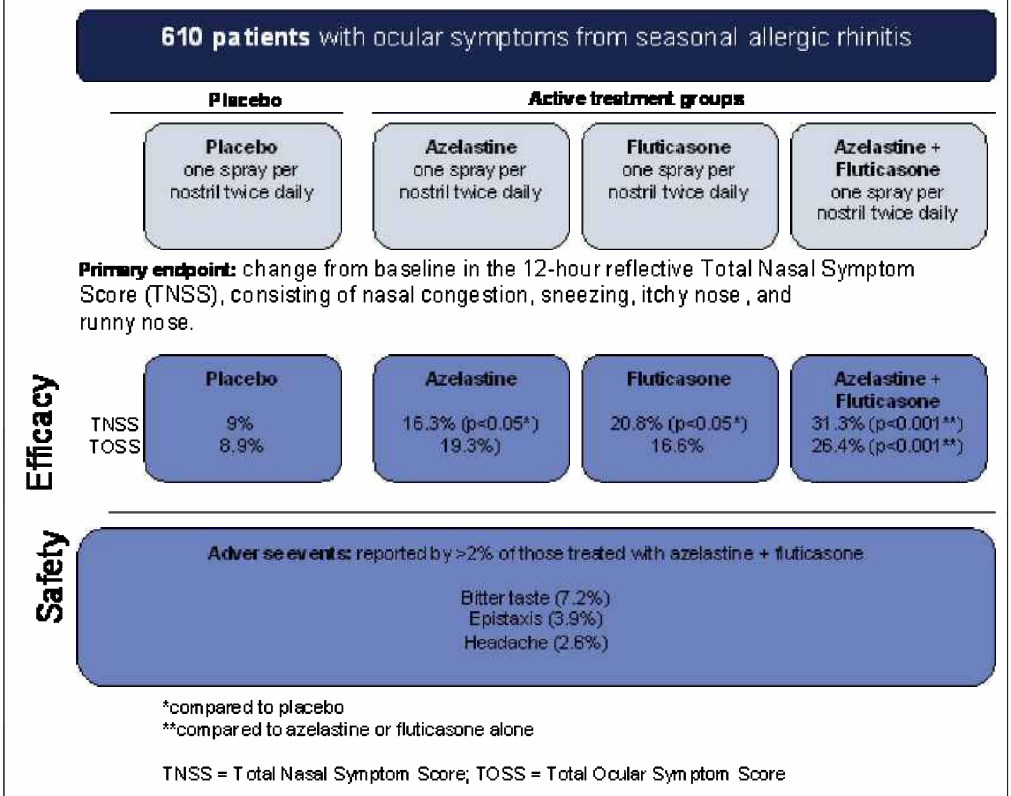
7MM = seven major markets (US, Japan, France, Germany, Italy, Spain, UK)

Source: Datamonitor, Thomson Pharma; MIDAS sales data, IMS Health, March 2010, Copyright ©, reprinted with permission. DATAMONITOR

Clinical trial data

While four company-sponsored Phase III trials of the combination were completed between 2008 and 2009, the results from only one of the trials have been made available. The efficacy and safety study was a randomized, double-blind, placebo-controlled trial in patients with moderate-to-severe seasonal allergic rhinitis (SAR), which took place during the 2007/08 Texas Mountain Cedar season. The results of the trial, which met the primary endpoint of change from baseline in the 12-hour reflective Total Nasal Symptom Score (TNSS) are presented in the figure below.

Figure 75: Azelastine/fluticasone – Phase III trial results



Source: Datamonitor adapted from Hampel *et al*., (2008) DATAMONITOR

Author conclusions: a significant clinical benefit from azelastine combined with fluticasone nasal spray was seen compared to either drug alone. Patients who require combination therapy to effectively manage allergic rhinitis should benefit from the availability of the two drugs in a single delivery device.

Datamonitor conclusions: the results of the trial are promising as not only did the combination perform well compared to placebo, but also compared to treatment with the individual components alone. These positive results suggest that a combination of azelastine and fluticasone has the potential to be the first nasal antihistamine plus corticosteroid combination to reach the market in the US.

This and the additional Phase III trials of azelastine/fluticasone that have completed are summarized in the following table.

Table 43: Azelastine/fluticasone – completed Phase III trials

Study	Number of participants	Primary endpoint	Completion date
A study to evaluate the safety and effectiveness of a nasal spray to treat seasonal allergies	832	12-hour reflective Total Nasal Symptom Score	June 2008
A study evaluating the safety and effectiveness of a nasal spray to treat seasonal allergies	779	12-hour reflective Total Nasal Symptom Score	November 2008
A study to evaluate the safety and effectiveness of a nasal spray to treat seasonal allergies	1,800	12-hour reflective Total Nasal Symptom Score	July 2009
A study to evaluate the safety and effectiveness of a nasal spray to treat seasonal allergies.	610	12-hour reflective Total Nasal Symptom Score	February 2008

Source: Clinicaltrials.gov, 2010h (http://clinicaltrials.gov)

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Product positioning

Meda/Cipla's azelastine/fluticasone combination product is very attractive as it has the possibility to become the first nasal steroid plus antihistamine combination delivered in a single device to gain approval in the US. While nasal antihistamines have seen marginal sales compared to other classes for allergic rhinitis, the potential to combine them with a nasal corticosteroid is highly anticipated. This can offer a significant improvement to patients who require both types of treatment, by improving dosing and therefore compliance.

> *"Two sprays is a bit of a challenge for patients. When we have combinations, then I think that is more likely to be used."*
>
> UK key opinion leader

> *"I think there is quite a large* [patient] *potential, because I think once people get a real efficacy benefit of their nasal therapy, then they are likely to want to use it."*
>
> UK key opinion leader

> *"Combining the two, providing it provides the efficacy of each taken individually, together, if not greater efficacy, then I think it would be a real plus."*
>
> US key opinion leader

Cost will be a factor as the high relative price of nasal corticosteroids is seen to inhibit use. Datamonitor therefore assumes that the combination product will be priced at a 20% discount to the price of Astelin (azelastine, Meda) and Nasonex (mometasone, Merck), as these are both patent protected.

> *"It depends also on the cost but I think that it could be a good proposal."*
>
> EU key opinion leader

While CyDex poses potential competition as it is developing a combination of azelastine with the corticosteroid budesonide, the company has not yet begun Phase III trials so it will likely enter the market second.

SWOT analysis

The following figure highlights the strengths, weaknesses, opportunities and threats (SWOT) of azelastine/fluticasone.

Figure 76: Azelastine/fluticasone – SWOT analysis for allergic rhinitis, 2010

Strengths	Weaknesses
▪ Most advanced nasal corticosteroid/nasal antihistamine combination therapy ▪ Convenient dosing (single device) ▪ Large clinical trial program	▪ Nasal formulation ▪ Limited data available
Opportunities	**Threats**
▪ Continue development in additional markets	▪ Market potential limited to patients requiring both types of treatment ▪ Other combination products are moving through the pipeline

Source: Datamonitor

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Brand forecast to 2019

- The product is forecast to launch as the first nasal steroid/antihistamine combination in the US in Q4 2012 and in the EU in Q4 2013;
- azelastine/fluticasone is forecast to take 10% of the branded nasal steroid market and 20% of the smaller nasal antihistamine market;
- the price for azelastine/fluticasone is likely to be at a 20% discount on the combined brand price of Astelin (azelastine, Meda) and Flixonase/Flonase (fluticasone), as the components of these products make up the combination therapy. The discount is expected as only one device is required, and to promote the use of the combination. The resulting price in each country where the product will launch is shown in the following table.

Table 44: Azelastine/fluticasone price/standard unit in the US and the five major EU markets, 2010				
Country	Year*	Astelin (azelastine) Price/SU**	Flixonase/Flonase (fluticasone) Price/SU**	Azelastine/fluticasone Price/SU***
US	2012	$0.41	$0.09	$0.40
France	2013	$0.08	$0.04	$0.10
Germany	2013	$0.45	$0.12	$0.45
Italy	2013	$0.18	$0.23	$0.32
Spain	2013	$0.10	$0.20	$0.24
UK	2013	$0.08	$0.14	$0.18

*This is the year that the combination product is forecast to launch

**Price per standard unit (SU) is calculated based on IMS data trended forward to the launch year. It is calculated as $ sales divided by standard units.

***Price per standard unit (SU) of the azelastine/fluticasone combination is calculated to be a 20% discount to the combined launch year price of Astelin and Flixonase/Flonase.

Source: Calculated from MIDAS sales data, IMS Health,

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- a launch is not expected in Japan where there is a strong preference for oral products, and where nasal azelastine is not currently available.

Table 45: Sales forecasts for azelastine/fluticasone in allergic rhinitis in the US and five major EU markets ($ 000s), 2009–2019								
	2012f	2013f	2014f	2015f	2016f	2017f	2018f	2019f
US	5,184	46,585	60,453	75,000	89,757	91,101	92,275	93,283
France	0	559	4,563	5,679	6,769	7,796	8,236	8,669
Germany	0	633	5,742	6,716	7,610	8,450	9,172	9,574
Italy	0	384	3,452	4,467	5,522	6,582	6,658	6,727
Spain	0	541	3,792	4,578	5,202	5,754	6,225	6,592
UK	0	781	7,590	9,798	12,021	14,165	14,418	14,631
Total	**5,184**	**49,483**	**85,592**	**106,236**	**126,881**	**133,847**	**136,984**	**139,475**

Note: totals may not sum due to rounding.

Source: 2010–2019 forecast = Datamonitor DATAMONITOR

The 10-year market forecast for azelastine/fluticasone, for both allergic rhinitis and other indications, is outlined separately in the accompanying forecast tool, a downloadable Excel spreadsheet that details the forecast for this drug in the US and five major EU markets. The breakdown of azelastine/fluticasone sales by indication is based on the products that it takes market share from.

CDX-313 (azelastine/budesonide; CyDex)

CyDex is developing a fixed dose nasal spray formulation of budesonide plus azelastine, called CDX-313, to be delivered with its Captisol technology, for the potential treatment of seasonal allergic rhinitis (SAR). In March 2009 the company reported positive results for the combination from a Phase II trial in Canada. At the same time, it announced that it was planning a Phase III trial with an undisclosed development and commercialization partner (CyDex, 2009; http://www.CyDexpharma.com).

Drug profile

Table 46: CDX-313– drug profile, 2010

CDX-313	
Molecule	Azelastine/budesonide
Mechanism of action	Nasal corticosteroid/antihistamine combination
Originator	CyDex
Marketing company	CyDex
Targeted indication	Seasonal allergic rhinitis
Formulation	Nasal spray
Dosing frequency	Twice daily
Estimated launch date	Not forecast
2019 sales, 7MM	Not forecast

7MM = seven major markets (US, Japan, France, Germany, Italy, Spain, UK)

Source: Datamonitor, Thomson Pharma DATAMONITOR

Clinical trial data

Results from a Phase II Canadian trial were presented at the American Academy of Allergy Asthma and Immunology (AAAAI) Annual Conference in March, 2009 in Washington DC, US. The trial was a randomized, double-blind placebo-controlled cross-over study including 108 ragweed allergic patients, who were studied in an environmental exposure chamber. The study compared Captisol-enabled 32mcg budesonide and 137mcg azelastine delivered in one device to the two molecules delivered in two devices, and to placebo. The mean change from baseline in Total Ocular Symptom Scores (TOSS), which included itchy/gritty, red/burning and tearing/watering eyes, was found to be significantly greater than placebo (P<000.1) in both the treatment groups from 40 minutes post-dose until 10 hours. Treatment with the two molecules in a single spray compared to two separate sprays was found to provide the same or greater TOSS relief, with no statistically significant difference recorded, although longer-lasting relief of red/burning eyes was seen for the single-spray combination. The authors concluded that Captisol-enabled budesonide plus azelastine and consecutive administration of the two molecules provide similar and significant long-lasting relief of all allergic ocular symptoms, with the single spray combination offering a more convenient dose format (Patel, *et al.* , 2009).

Product positioning

Although CyDex's combination poses a novel treatment option as there are currently no nasal antihistamine and steroid combinations available in a single device, the product's development lags behind Meda's combination and is not expected to reach the market first. Unlike Meda's combination, which also uses azelastine, CyDex's combination has not yet been tested against its individual components, and will need to do so in order to justify its use.

Despite announcing in March 2009 that it is planning a Phase III trial with a partner, CyDex's company website states, as of Q2 2010, that Phase II trials of the combination have been completed and that it is now seeking a partner (CyDex, 2010; http://www.CyDexpharma.com). Datamonitor therefore believes that initiation of Phase III is on hold, and does not provide a forecast for the product.

8. CASE STUDY

Introduction

The greatest impact on the allergic rhinitis market over the next 10 years is expected to come from key products going off-patent and subsequent generic entry. The impact of this will vary across the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK) based on market dynamics, and Datamonitor has investigated the speed and extent of generic erosion that has been seen for nasal corticosteroids and oral antihistamines which have already gone off-patent, in order to gain a better understanding of the future impact expected on the market.

For nasal corticosteroids, the impact of Flixonase/Flonase (fluticasone furoate, GlaxoSmithKline) going off-patent was considered, and for oral antihistamines, Claritin (loratadine, Merck) and Telfast/Allegra (fexofenadine, Sanofi-Aventis) were investigated. Datamonitor has calculated the extent of generic erosion of these products by quarter in each market, starting with the quarter of generic entry. However, this does not necessarily correspond to the quarter that each product went off-patent. Datamonitor has also calculated yearly generic erosion, based on the average of four quarters, for up to 4 years after generic entry, depending on data availability. The share of generic erosion was based on volume, rather than sales, therefore representing patients shifting from the brand to the generic. These calculations were used in Datamonitor's forecast model, as predictions of how generic entry will impact the market over the next 10 years.

Table 47 provides an overview of the findings of this case study, showing average annual generic erosion for each of the products considered, in each of the seven major markets. In general, the US and Germany were seen to have the largest and quickest generic erosion, while Italy and Japan are less prone to generic switching. Furthermore, while antihistamines see rapid patient switching post-patent, nasal corticosteroids appear to be better insulated from generic entry, which is believed to be due to the use of a device with these products. Devices can be difficult to replicate, and often have a patent that extends beyond the molecule patent.

Table 47: Generic erosion of selected allergic rhinitis treatments in the seven major markets

	Generic erosion: Yearly average post-generic entry (%)			
	Average of 1–4 quarters after generic entry	Average of 5–8 quarters after generic entry	Average of 9–12 quarters after generic entry	Average of 13–16 quarters after generic entry
Claritin (loratadine)				
US	55	68	84	n/c
Japan	n/a	n/a	n/a	n/a
France	36	57*	n/a	n/a
Germany	85	98	99	99
Italy	9	11	14**	n/a
Spain	10	20	48	72
UK	50	75	85	93***
Telfast/Allegra (fexofenadine)				
US	70	91	92	93
Japan	n/a	n/a	n/a	n/a
France	13	38	47*	n/a
Germany	19	n/a	n/a	n/a
Italy	11**	n/a	n/a	n/a
Spain	4	n/a	n/a	n/a
UK	8	37	64	n/a
Flixonase/Flonase (fluticasone)				
US	70	90	91	93
Japan	15	21	26	26**
France	n/a	n/a	n/a	n/a
Germany	20	42	54	n/a
Italy	2	3	4	n/a
Spain	1	9	20*	n/a
UK	22	28	26	28

*based on 3 quarters during period

**based on 2 quarters during period

***based on 1 quarter during period

n/a = not available; n/c = not calculated

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Nasal corticosteroids

Flixonase/Flonase (fluticasone, GlaxoSmithKline) has gone off-patent in each of the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK), and generics have entered in all regions except France. In general, generic erosion has been lower with Flixonase/Flonase than with oral antihistamines, which is likely attributable to the use of a device with nasal corticosteroids, which can create consumer loyalty to a product and make it more difficult for generic companies to compete.

The impact of generic entry in each of the seven major markets except France is shown in the following figures, starting with the US. In each figure, quarterly generic erosion is shown, with the quarter prior to generic entry specified. Yearly generic erosion is given as the average quarterly erosion in each year.

Figure 77: Generic erosion of Flixonase/Flonase, in the US, Q4 2005–Q4 2009

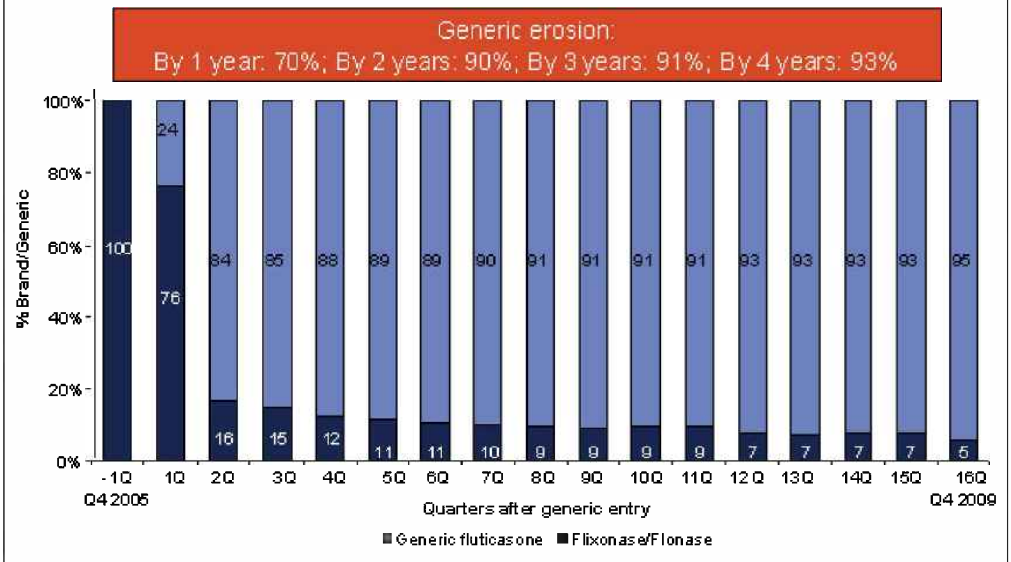

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Figure 78: Generic erosion of Flixonase/Flonase in Japan, Q2 2006–Q4 2009

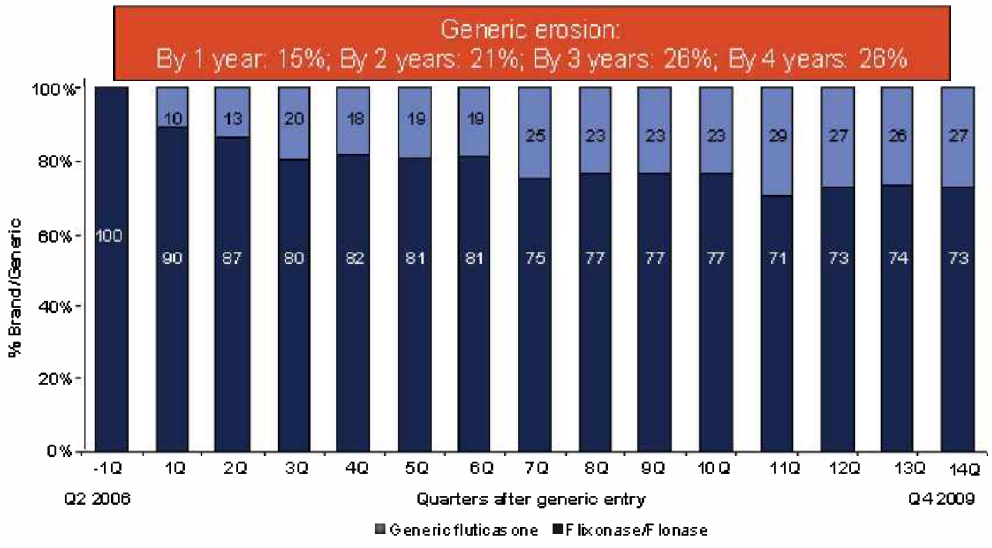

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Figure 79: Generic erosion of Flixonase/Flonase in Germany, Q4 2006–Q4 2009

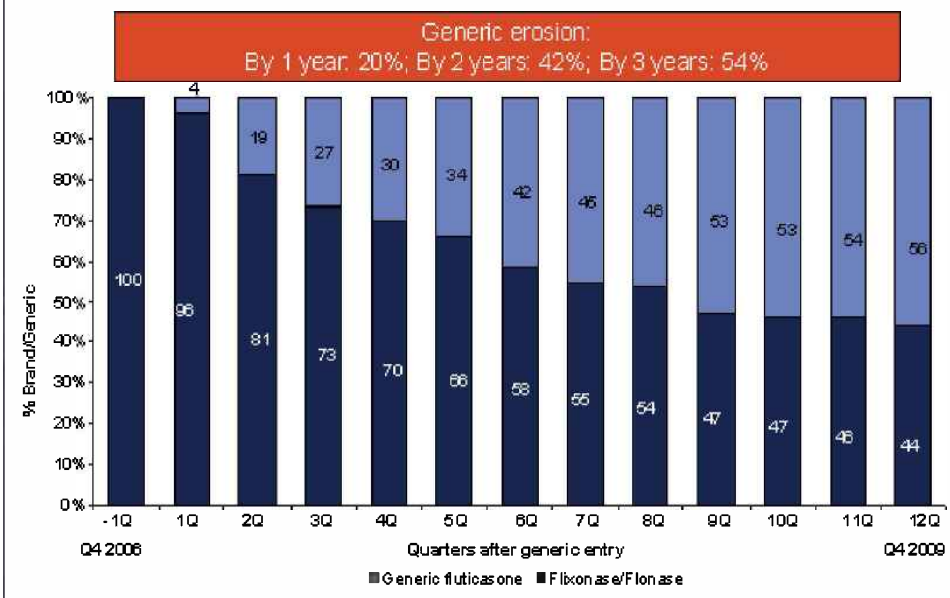

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Figure 80: Generic erosion of Flixonase/Flonase in Italy, Q3 2006–Q4 2009

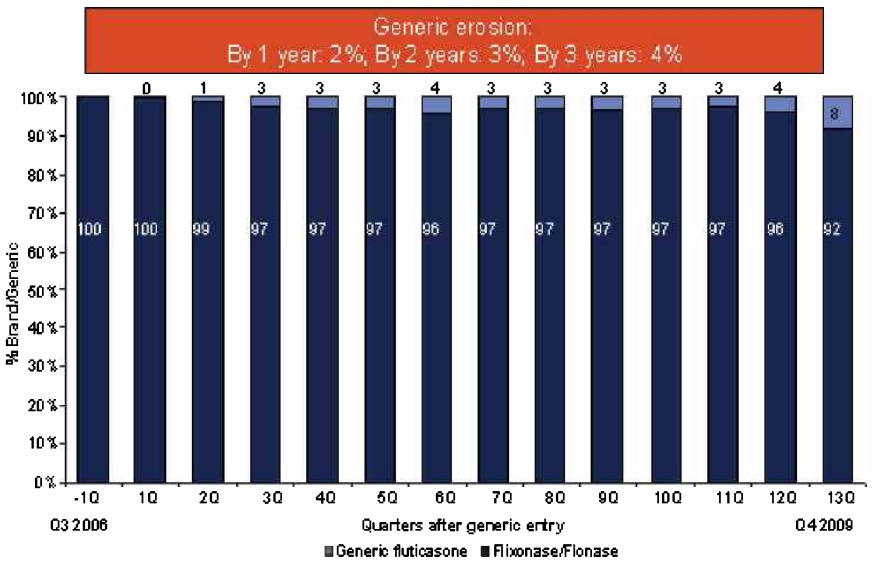

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Figure 81: Generic erosion of Flixonase/Flonase in Spain, Q1 2007–Q4 2009

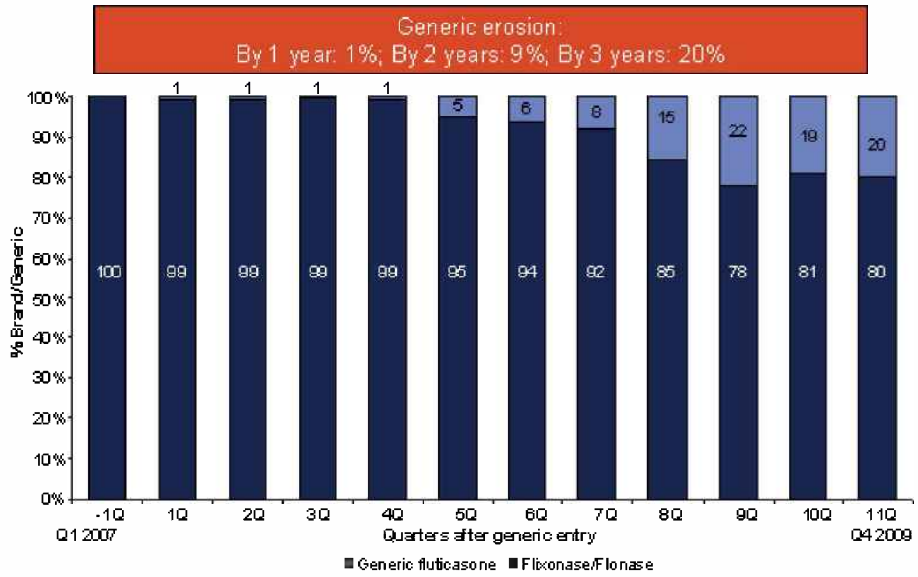

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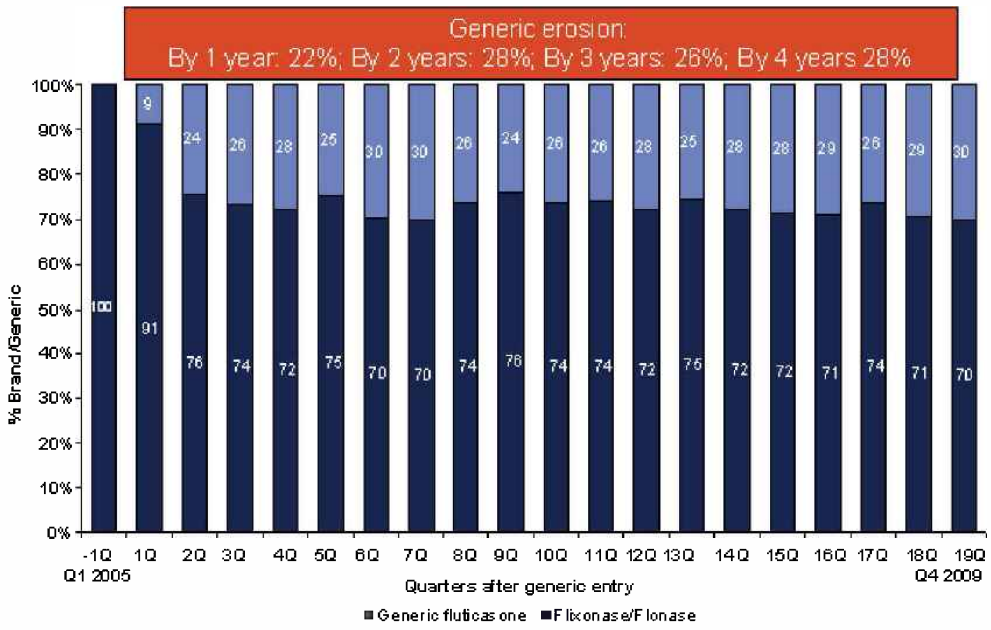
Figure 82: Generic erosion of Flixonase/Flonase in the UK, Q1 2005–Q4 2009



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Antihistamines

With their oral tablet formulation, antihistamines are easily replicable and highly prone to generic erosion. The patents of Telfast/Allegra (fexofenadine; Sanofi-Aventis) and Claritin (loratadine; Merck) have expired in each of the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK), and generics have entered all markets except Japan. Generic erosion has generally been swift, with significant share shifting to generics starting during the first quarter of generic entry. The exception is in Italy, where after 1 and 3 years of generic availability, Telfast and Claritin have only lost 11% and 13% of their share, respectively. This demonstrates the differences in both patient choice and market dynamics that exist between countries.

The impact of generic entry in each of the seven major markets except Japan is shown in the following figures, starting with the US. In each figure, quarterly generic erosion is shown, with the quarter prior to generic entry specified. Yearly generic erosion is given as the average quarterly erosion in each year.

Figure 83: Generic erosion of antihistamines in the US, Q4 2002–Q4 2005 and Q2 2005–Q4 2009

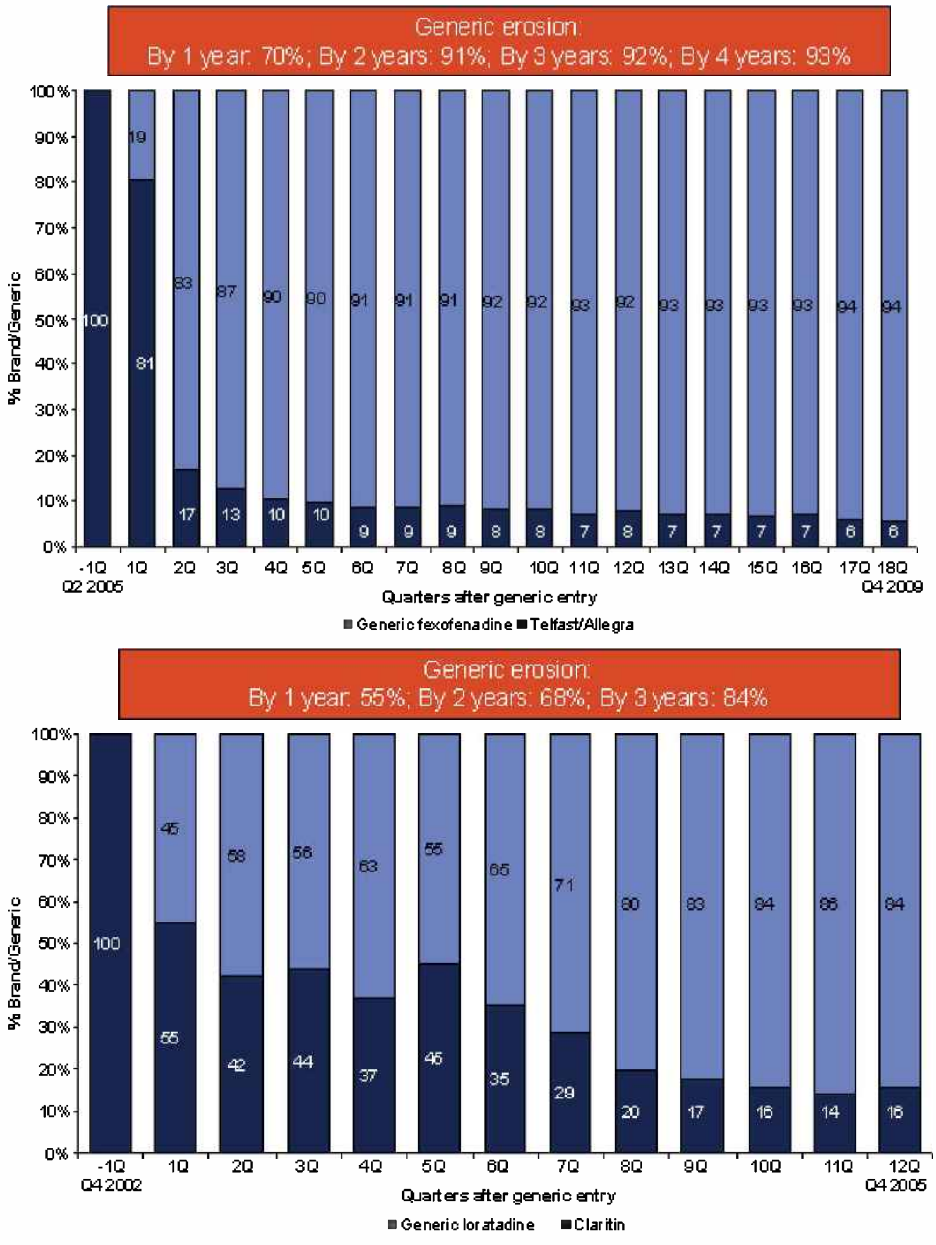

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Figure 84: Generic erosion of antihistamines in France, Q1 2007–Q4 2009 and Q1 2008–Q4 2009

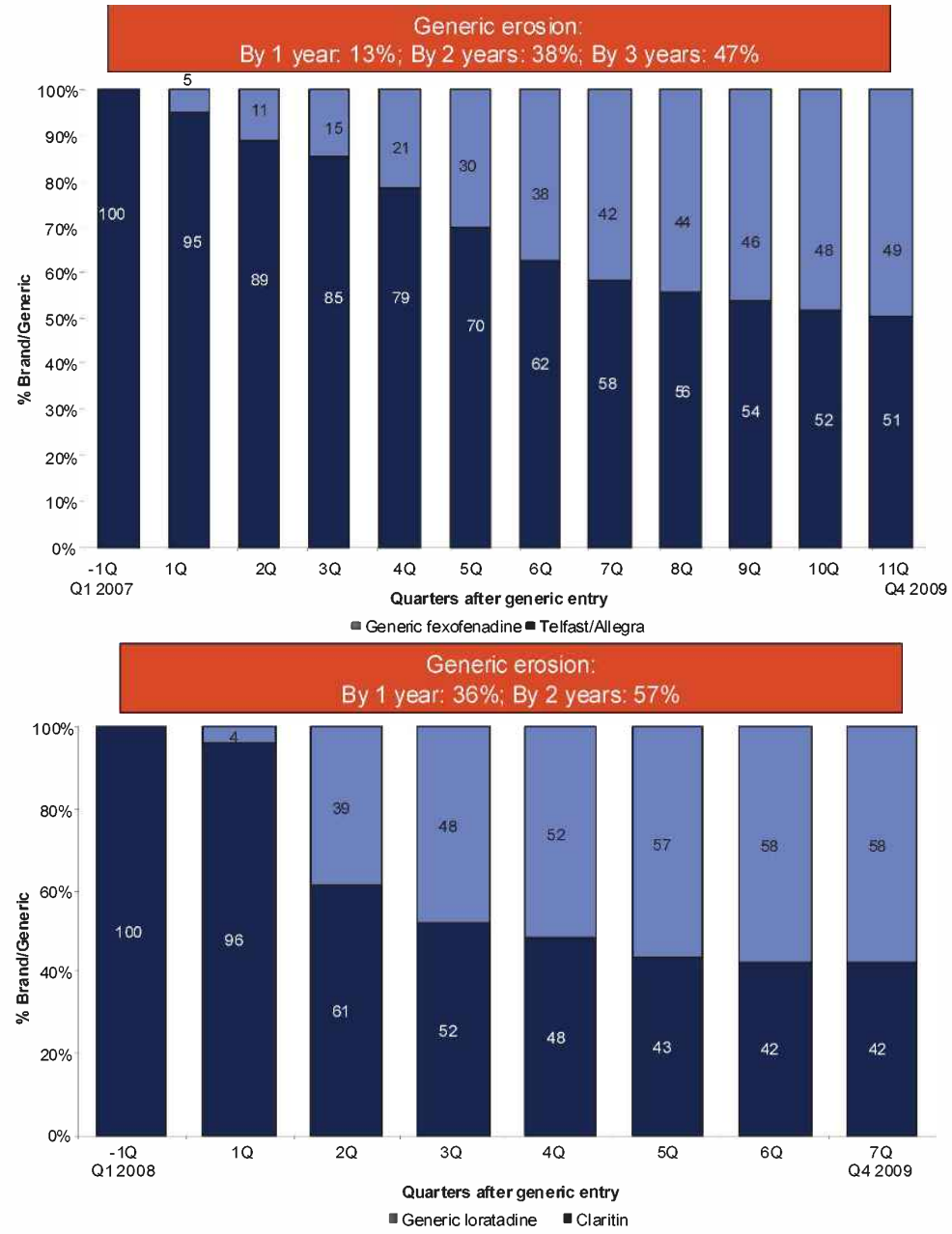

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Figure 85: Generic erosion of antihistamines in Germany, Q4 2008–Q4 2009 and Q1 2001–Q4 2005

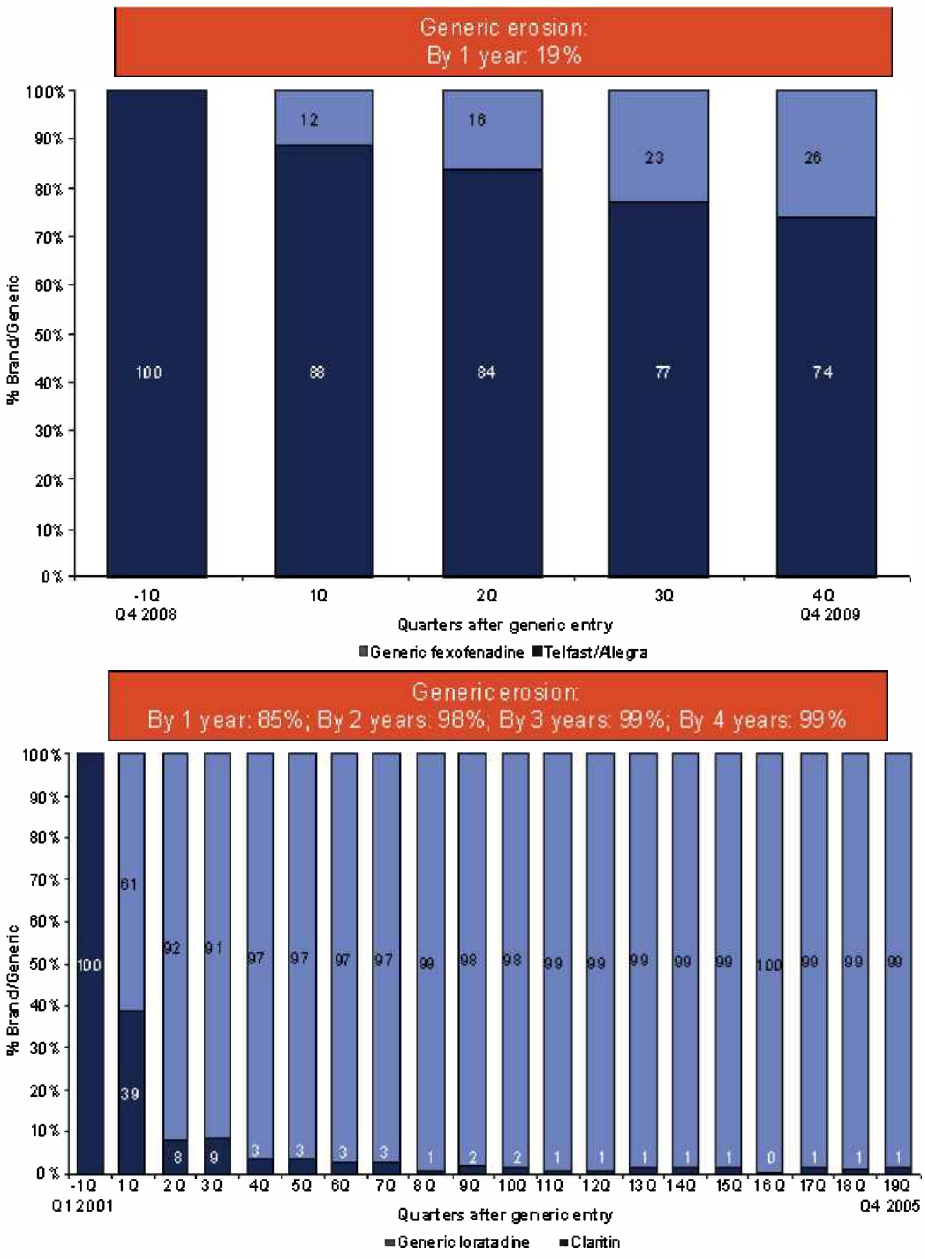

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Figure 86: Generic erosion of antihistamines in Italy, , Q1 2009–Q4 2009 and Q2 2007–Q4 2009

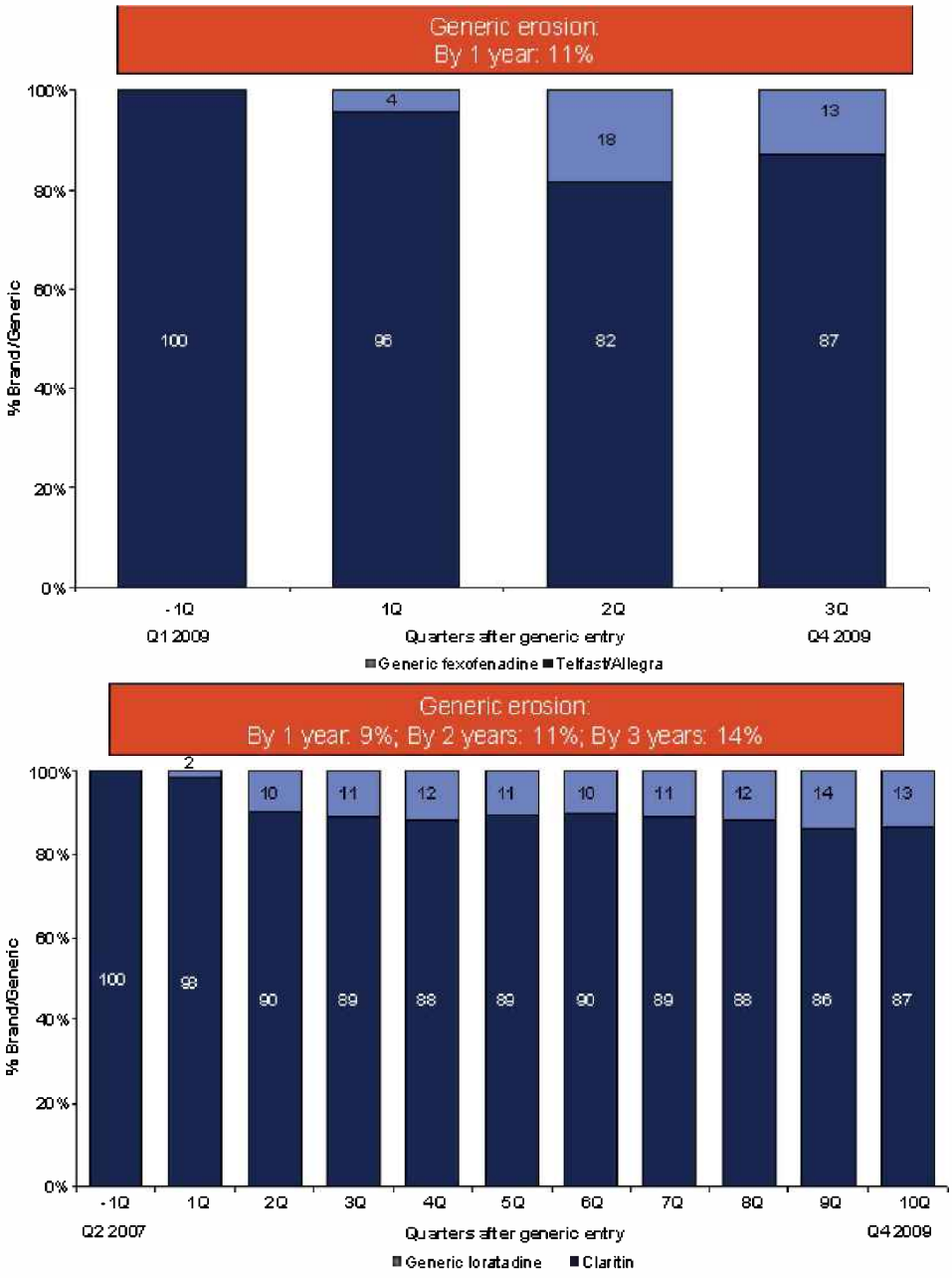

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Figure 87: Generic erosion of antihistamines in Spain, , Q3 2008–Q4 2009 and Q1 2001–Q4 2005

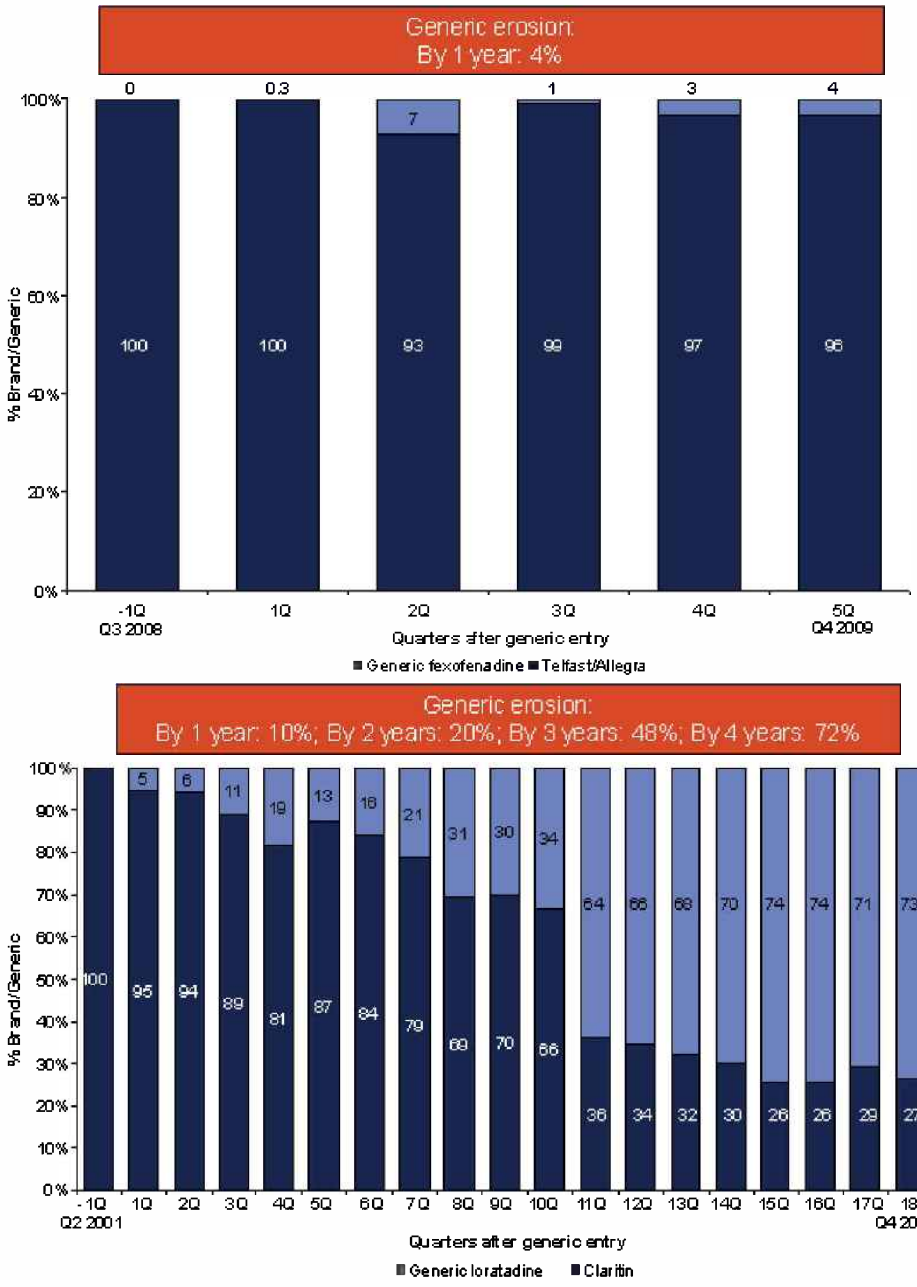

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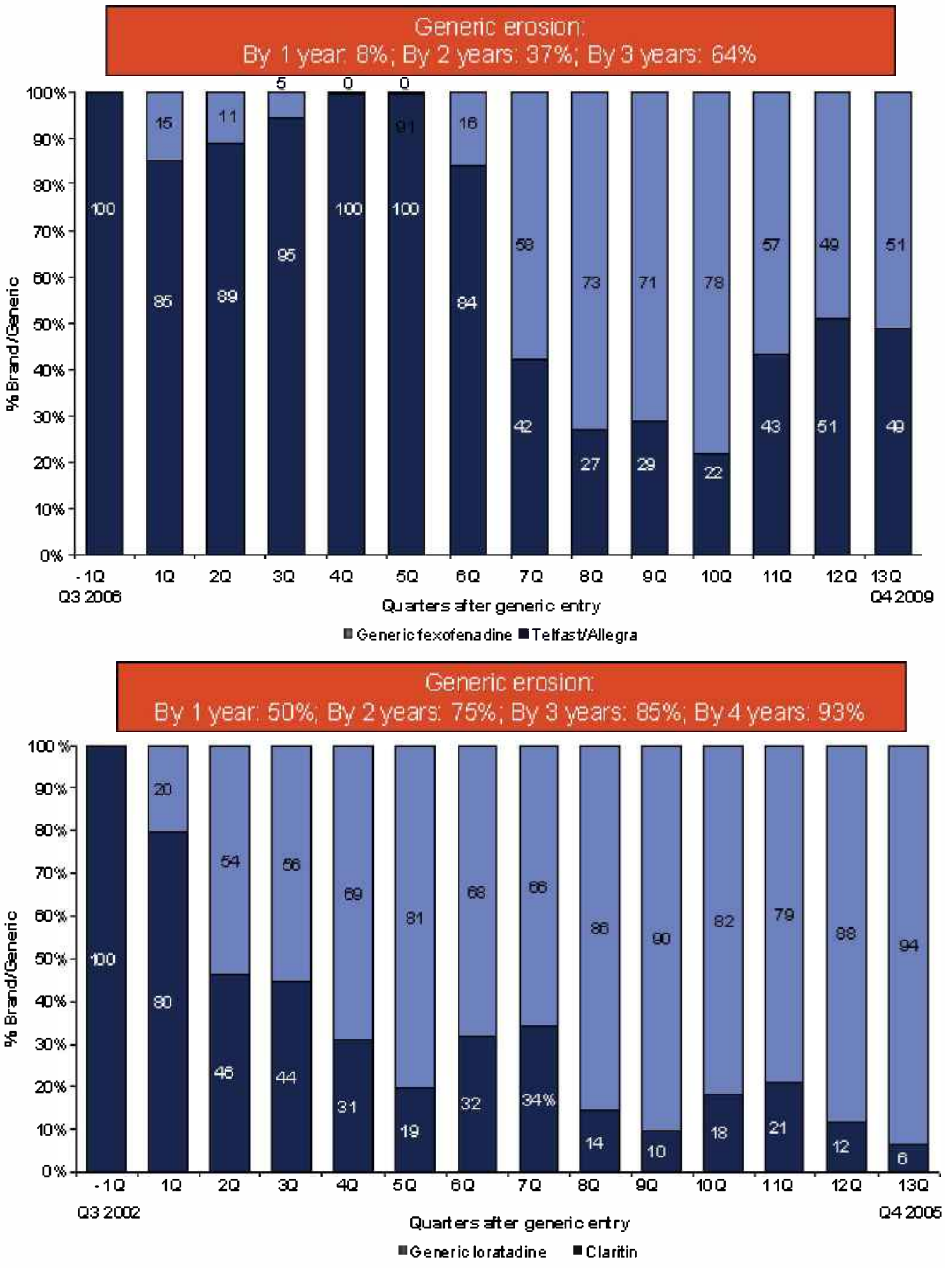
Figure 88: Generic erosion of antihistamines in the UK, , Q3 2006–Q4 2009 and Q3 2002–Q4 2005



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APPENDIX A – MARKET ASSUMPTIONS

Forecasting assumptions

New product launches

The following table summarizes the new product launches that Datamonitor includes in its forecast for this report.

Table 48: Datamonitor's estimated launch dates for key late-stage pipeline allergic rhinitis in the seven major markets, 2010–2019

Drug	US	Japan	France	Germany	Italy	Spain	UK
Azelastine/fluticasone	2012	n/f	2013	2013	2013	2013	2013
Omnair/Omnaris (ciclesonide)	L	n/f	2012	2012	2012	2012	2012
Xyzal (levocetirizine)	L	2010	L	L	L	L	L
Grazax	2012	n/f	2010	L	L	L	L
Oralair	2012	n/f	2011	L	2011	2011	2011
Pollinex-Quattro	n/f	n/f	2011	L	2011	2011	L

L = launched; n/f = not forecast

Source: Datamonitor DATAMONITOR

Patent expiries

The following table summarizes the patent expiries that Datamonitor includes in its forecast for this report. In cases where generics are expected to enter the market prior to patent expiry, the estimated generic launch date is given.

Table 49: Estimated generic launch dates for allergic rhinitis products in the seven major markets, 2010–2019

Brand (molecule)	US	Japan	France	Germany	Italy	Spain	UK
Telfast/Allegra (fexofenadine)	Expired	Feb 2014	Expired	Expired	Expired	Expired	Expired
Allegra-D 24hr (fexofenadine/ pseudoephedrine)	Nov 2012	n/a	n/a	n/a	n/a	n/a	n/a
Xyzal (levocetirizine)	Sep 2012	n/a	Sept 2013	Sept 2013	Jan 2016	Jan 2016	Jan 2016
Clarinex-D (desloratadine/ pseudoephedrine)	Oct 2019	n/a	Oct 2020	Oct 2020	Oct 2020	Oct 2020	Oct 2020
Nasonex (mometasone)	2014	n/a	2012	2012	2012	2012	2012
Rhinocort (budesonide)	Oct 2017	n/a	Dec 2013	Expired	Expired	Expired	Expired
Omnair/Omnaris (ciclesonide)	Oct 2017	n/a	n/a	n/a	n/a	n/a	n/a
Astelin (azelastine)	Mar 2010	Expired	Expired	Expired	Expired	Expired	Expired
Patanase (olopatadine)	Jun 2017	n/a	n/a	n/a	n/a	n/a	n/a
Singulair (montelukast)	Aug 2012	Oct 2016	Aug 2012	Aug 2012	Aug 2012	Aug 2012	Aug 2012

The seven major markets comprise of the US, Japan, France, Germany, Italy, Spain and the UK; n/a = not applicable

Source: Datamonitor; Dolphin, May 2010, Copyright Thomson Scientific DATAMONITOR

Data definitions, limitations and assumptions

Standard units

The term 'standard unit' is used to describe the number of standard dose units sold. It is determined by taking the number of counting units (the number of tablets, milliliters of liquid, grams of ointment) sold divided by the standard unit factor. The standard unit factor is the smallest common dose of a product form as defined by IMS Health. For example, for oral solid forms, the standard unit factor is one tablet or capsule. It is one teaspoon (5ml) for syrup forms and one ampoule or vial for injectable forms.

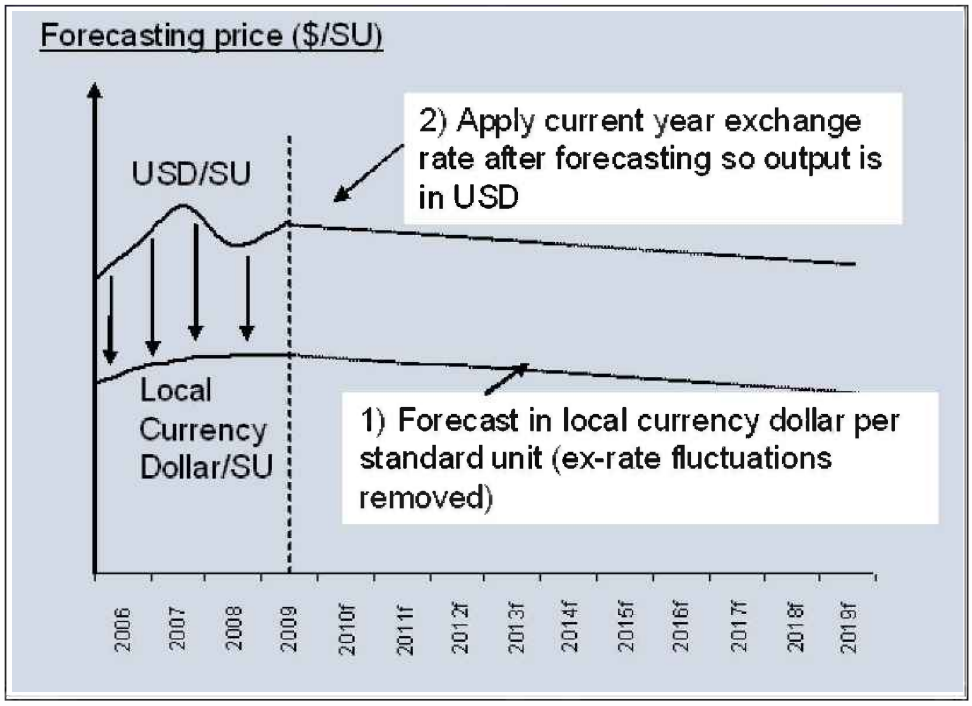
Derivation of sales forecasts and pricing trends

The forecasts for each drug are originally produced in terms of volume (standard units). For symptomatic treatments, standard units are obtained from the IMS MIDAS sales data. For immunotherapy products, Datamonitor calculated volume based using a patient-based method. Sales forecasts are then created by multiplying the volume figures by a predicted 'price per standard unit'. (The historical 'price per standard unit' is calculated for each year by dividing the total product sales by the total number of standard units for that product. The historical prices are then trended forward to the end of the forecast period.) In the case of the novel pipeline products, the price can be the average market price or it can be modified to be comparable to similar branded products, taking into account dosing discrepancies and any expected price premiums due to novelty. Prices are calculated individually for each product in each country. Please refer to the Excel model that accompanies this report for the forecast methodology.

Exchange rates

Fluctuations in dollar (USD) exchange rates can have a significant impact on Datamonitor's time-series forecasting when using historical sales trends from IMS Health. Therefore, Datamonitor forecasts are based on a constant exchange rate by using the local currency dollar (LCD) variable to calculate price trends. All final forecast sales data is converted back to USD also using a constant exchange rate.

Figure 89: Methodology for forecasting price to remove impact of currency fluctuations on trend



Source: Datamonitor

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APPENDIX B – ALLERGIES PREVALENCE SOURCES

Sources

The following table provides the sources used to estimate the prevalence of allergic diseases in the section: Prevalence of key allergic diseases. For each country, the prevalence rate was applied to 2010 population projections were calculated from the UN World Population Prospects: 2008 revision.

Table 50: Prevalence of allergic diseases in selected countries, 2010

Country	Allergic asthma	Atopic dermatitis	Food allergies	Urticaria
US	Gergen et al., 2009	Hanifin et al., 2007	Zuberbier et al., 2004	Gaig et al., 2004
Japan	Hirayama et al., 2001	Kawaguchi et al., 1999, Kusunoki et al., 2009, Sugiura et al. 1998, Muto et al. 2003	Zuberbier et al., 2004	Gaig et al., 2004
France	Burney et al., 1996	Aragonés et al., 2009	Kanny et al., 2001	Gaig et al., 2004
Germany	Burney et al., 1996	Aragonés et al., 2009	Zuberbier et al., 2004	Gaig et al., 2004
Italy	de Marco et al., 2003	Aragonés et al., 2009	Zuberbier et al., 2004	Gaig et al., 2004
Spain	Burney et al., 1996	Aragonés et al., 2009	Zuberbier et al., 2004	Gaig et al., 2004
UK	Burney et al., 1996	Aragonés et al., 2009	Young et al., 1994	Gaig et al., 2004
Brazil	Burney et al., 1996	Williams et al. 1999	Young et al., 1994	Gaig et al., 2004
Russia	Burney et al., 1996	Williams et al. 1999	Young et al., 1994	Gaig et al., 2004
India	Burney et al., 1996	Williams et al. 1999	Young et al., 1994	Gaig et al., 2004
China	Ma et al., 2009	Williams et al. 1999	Young et al., 1994	Gaig et al., 2004

*Applied prevalence from Spain

*Applied prevalence from Germany

Source: see above

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APPENDIX C

Contributing experts

The following key opinion leaders were interviewed as part of this report:

Dr. Walter Canonica, Professor of Allergy and Respiratory Diseases, chairman of the Allergy and Respiratory Diseases Clinic and director of the Specialty School of Pulmonary Diseases at Genoa University in Genoa, Italy.

Dr. Linda Cox, Assistant Clinical Professor of Medicine at University of Miami School of Medicine and Nova Southeastern University School of Osteopathic Medicine, Allergy and Asthma Center, Ft. Lauderdale, Florida, USA.

Dr. David Price, Professor of Primary Care Respiratory Medicine, University of Aberdeen, Aberdeen, UK.

Conferences attended

Datamonitor attended the following related conferences in 2010:

American Thoracic Society (ATS) 2010 Annual Conference, held in New Orleans, USA May 14–19, 2010.

European Academy of Allergy and Clinical Immunology (EAACI) 2010 Annual Congress, London, UK, June 5–9, 2010.

Report methodology

About Datamonitor

Datamonitor is a leading business information company specializing in industry analysis.

Through its proprietary databases and wealth of expertise, Datamonitor provides clients with unbiased expert analysis and in-depth forecasts for six industry sectors: Healthcare, Technology, Automotive, Energy, Consumer Markets, and Financial Services. The company also advises clients on the impact that new technology and eCommerce will have on their businesses.

Datamonitor maintains its headquarters in London, and regional offices in New York, Frankfurt and Hong Kong. The company serves the world's largest 5,000 companies.

About Datamonitor Healthcare

Datamonitor Healthcare provides a total business information solution to the pharmaceutical and healthcare industries. Its key strength is its in-house analysts and researchers, who have strategy, market, disease and company expertise. Datamonitor Healthcare's services are based on specialist market analysis teams covering the following areas:

- Cardiovascular Disease;
- Central Nervous System;
- Immune Disorders and Inflammation;
- Infectious Disease;
- Respiratory;
- Oncology;
- Women's Health;
- Urology;
- Pharmaceutical strategy (publishing under the 21st Century Insight brand);
- eHealth (publishing under the eHealthInsight brand);
- Competitive intelligence (publishing under the PharmaVitae brand);
- Medical technologies;
- Healthcare consulting;
- Forecasting and modeling.

Team members are regularly interviewed by, for example, the Wall Street Journal, the BBC, Washington Post, Financial Times, In Vivo, Pharmafocus and MedAdNews, and frequently present at industry conferences in the US and Europe. Below is a brief overview of Datamonitor's analysis capabilities in the Disease area.

About the Disease analysis team

Datamonitor's Disease teams study patient potential, treatment patterns, current and future market dynamics, development pipeline and strategic issues in the market, highlighting latest trends and new opportunities in the Disease therapy area. The team supports the following products:

- Pipeline Analysis: insight into the 'Drugs of Tomorrow' – developmental drugs set to enter the market, and their impact on clinical practice and the use of existing therapeutics;
- Commercial Analysis: in-depth analyses of changing market dynamics, developing commercial strategies, and the impact of market events on commercial opportunities;
- Stakeholder Analysis: analysis of what the key stakeholders in the healthcare sector expect from the Pharma industry – how practicing physicians really prescribe drugs and their expectations of the next generation of therapeutics, and analysis of issues driving prescribing behavior.

Datamonitor consulting

We hope that the data and analysis in this report will help you make informed and imaginative business decisions. If you have further requirements, Datamonitor's consulting team may be able to help you. For more information about Datamonitor's consulting capabilities, please contact us directly at consulting@datamonitor.com.

Disclaimer

The facts of this report are believed to be correct at the time of publication but cannot be guaranteed. Please note that the findings, conclusions and recommendations that Datamonitor delivers will be based on information gathered in good faith from both primary and secondary sources, whose accuracy we are not always in a position to guarantee. As such, Datamonitor can accept no liability whatever for actions taken based on any information that may subsequently prove to be incorrect.