DATAMONITOR

Commercial and Stakeholder Perspectives: Allergic Rhinitis

Is there life after Claritin?

AC Classes: R6A0, R1A1, R1A4, R1A6, R1A7, R1B0.

Countries: US, Japan, France, Germany, Italy, Spain and UK

Reference Code: DMHC1936

Publication Date: 09/2004

PLAINTIFFS' TRIAL EXHIBIT
PTX0098
exhibitsticker.com

www.datamonitor.com

Datamonitor USA
245 Fifth Ave
4th Floor
New York, NY 10016
USA

t: +1 212 686 7400
f: +1 212 686 2626
e: usinfo@datamonitor.com

Datamonitor Europe
Charles House
108-110 Finchley Road
London NW3 5JJ
United Kingdom

t: +44 20 7675 7000
f: +44 20 7675 7500
e: eurinfo@datamonitor.com

Datamonitor Germany
Messe Turm
Box 23
60308 Frankfurt
Deutschland

t: +49 69 9754 4517
f: +49 69 9754 4900
e: deinfo@datamonitor.com

Datamonitor Asia Pacific
Room 2413-18, 24/F
Shui On Centre
6-8 Harbour Road
Hong Kong

t: +852 2520 1177
f: +852 2520 1165
e: hkinfo@datamonitor.com

MEDA_APTX03505576

PTX0098-00001
CIPLA LTD. EXHIBIT 2021 PAGE 1

ABOUT DATAMONITOR HEALTHCARE

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:

Anne Delaney, Director of Research and Analysis, +44 (0)20 7675 7221, adelaney@datamonitor.com

About the immune disorders and 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;
- analysis of current physician attitudes and perception;
- scenario-based revenue and epidemiology forecasting;
- supporting presentations and spreadsheets of data and key conclusions.

The IDI team is headed by Simon Wright, he holds an MBA from London Business School, and a BSc (Hons) Biological Chemistry and can be contacted on +44 (0)20 7675 7844 or swright@datamonitor.com.

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505577

PTX0098-00002
CIPLA LTD. EXHIBIT 2021 PAGE 2

CHAPTER 1 EXECUTIVE SUMMARY

Objective of the analysis

The objective of this analysis of the allergic rhinitis market is to enable the reader to:

- quantify future size and scope of market and potential for new products;
- benchmark pipeline against currently marketed products;
- formulate launch strategies;
- quantify the impact of key patent expiries;
- develop commercial strategies across the seven major markets.

Scope and focus

Commercial and Stakeholder Perspectives Allergic Rhinitis explores trends and developments within patent expiry and over-the-counter status vs. prescription-only availability. Qualitative opinion leader research and qualitative IMS data are used to analyze current therapeutic dynamics and forecast future sales. Issues analyzed include:

- the impact of patent expiry and changes in government regulation and attitude to generics are explained;
- the effect of prescription (Rx) to over-the-counter (OTC) drug switches as a strategic move or by governmental pressure and the reaction of the US insurance market;
- sales forecasts for leading brand drugs, based on historical data and event analysis.

Analysis in this report is based on sales and promotional data provided by IMS Health. Datamonitor also interviewed physicians, specialists, in the US, Europe and Japan about their experiences and opinions on the allergic rhinitis market.

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505578

PTX0098-00003
CIPLA LTD. EXHIBIT 2021 PAGE 3

The following opinion leaders were interviewed by Datamonitor during the course of this report:

- Professor Bruce Bochner, Professor of Medicine, Johns Hopkins Asthma and Allergy Center, Baltimore, US;
- Dr Michiko Haida, Head of the Division of Allergy and Respiratory Diseases, Department of Internal Medicine, Hanzomon Hospital, Tokyo, Japan;
- Dr Eckard Hamelmann, Head of the Respiratory Infections and Asthma work-group, Charité-Virchow Hospital, Berlin, Germany;
- Professor William Reed Henderson, Jr, Professor of Medicine, Head, Allergy Section, University of Washington, US;
- Professor Anthony Barrington (Barry) Kay, Professor and Director, Department of Allergy and Clinical Immunology, Imperial College School of Medicine, UK.

Datamonitor insight into the allergic rhinitis market

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

- *in 2003, 91% of the total promotional spend in the US and the five EU countries was spent on detailing physicians. Accurately targeting the appropriate physicians is critical to effective detailing. The physician specialists prescribing treatments for allergic rhinitis are numerous and wide ranging in the US, Germany and Japan. However, the other EU countries are heavily skewed towards PCP treatment of allergic rhinitis;*
- *the impact of patent expiry on Claritin (loratadine) has seen wide-ranging country variances, in terms of both revenue and prescription volume sales adjustments for the brand, molecule and class. Germany, the US and the UK experienced the largest reduction in brand revenue sales values, whereas generic erosion was minimal in Japan and the remaining EU countries;*
- *careful consideration of the impact of patent expiry on Claritin, provides several points as to how other antihistamines may be impacted by similar events. The 2007 Zyrtec (cetirizine) patent expiry, and a favorable outcome for the generics companies in the Allegra (fexofenadine) patent legislation, are two such events.*

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505579

PTX0098-00004
CIPLA LTD. EXHIBIT 2021 PAGE 4

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.

This report is produced in three parts:

1. 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;

2. Excel document: contains forecasts on a country-by-country basis for the seven major markets. Country, region and class/brand charts can be generated in this file for both volume and value units;

3. PowerPoint executive presentation: shares Datamonitor's key insight into the market with supporting data and recommendations.

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505580

PTX0098-00005
CIPLA LTD. EXHIBIT 2021 PAGE 5

TABLE OF CONTENTS

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505581

PTX0098-00006
CIPLA LTD. EXHIBIT 2021 PAGE 6

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505582

PTX0098-00007
CIPLA LTD. EXHIBIT 2021 PAGE 7

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505583

PTX0098-00008
CIPLA LTD. EXHIBIT 2021 PAGE 8

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505584

PTX0098-00009
CIPLA LTD. EXHIBIT 2021 PAGE 9

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505585

PTX0098-00010
CIPLA LTD. EXHIBIT 2021 PAGE 10

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505586

PTX0098-00011
CIPLA LTD. EXHIBIT 2021 PAGE 11

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505587

PTX0098-00012
CIPLA LTD. EXHIBIT 2021 PAGE 12

CHAPTER 2 PATIENT POTENTIAL

Patient potential

The number of patients requiring treatment is continually rising, driven by a number of factors:

- air pollution, specifically particulates;
- public awareness resulting in increasing physician diagnosis;
- the hygiene hypothesis, which links the adoption of the modern westernized lifestyle to rises in allergic disease through a lack of early life exposure to microorganisms.

Although allergic rhinitis is not a life-threatening disease it is classified as a major chronic respiratory disease due to its:

- prevalence;
- impact on quality of life;
- impact on work/school performance;
- economic burden;
- links with asthma.

In March 2003, the US department of Health and Human Services produced an evidence report on the management of AR in the working age population, concluding that AR is associated with direct costs of up to $4.5 billion. Indirect costs due to 2.5 million work days and two million school days lost in the US alone add up to an estimated $7.7 billion annually (McCrory *et al.*, 2003).

Allergic Rhinitis and its Impact on Asthma (ARIA) is a project carried out by non-governmental group working with the World Health Organization. The ARIA investigation has clarified long-suspected links with asthma and rhinitis. It also gives highlights the fact that rhinitis is considered a strong risk factor for asthma. The European Community Respiratory Health Survey (ECRHS) found high association between the two conditions; for example, one French cohort revealed that 22.5% of adults with rhinitis had asthma as well (Leynaert *et al.*, 1999).

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505588

PTX0098-00013
CIPLA LTD. EXHIBIT 2021 PAGE 13

"The awareness ... [of allergic rhinitis] … is certainly increasing with more studies on this problem, but also as people are staying indoors more with greater exposure to indoor allergens [dust mites, animals, cockroaches], and are less active, which is contributing to the problem." – US opinion leader

Epidemiology

Studies into the prevalence of AR are hampered by a lack of consistency in how the disease is defined. It is clinically defined as a symptomatic disorder of the nose induced by an IgE-mediated inflammation after exposure of an allergen to the membranes lining the nose. The recent ARIA initiative recommended the classification of allergic rhinitis symptoms as persistent or intermittent, rather than perennial and seasonal.

The four main symptoms of the disease are an itchy nose, sneezes, nasal obstruction and rhinorrhea. The reported prevalence varies depending on the number of symptoms required to define AR. An International Consensus Report on the Diagnosis and Management of Rhinitis in 1994 agreed that the standard should be two or more symptoms.

Table 1: Classification of allergic rhinitis

Classification	Symptoms
	Frequency and duration
Intermittent	Occur over <4 days/week or over <4 weeks
Persistent	Occur over <4 days/week and over >4 weeks
	Severity of symptoms
Mild	Normal sleep No impairment of daily activities, sport, leisure, work, school No troublesome symptoms
Moderate-severe	Impairment of daily activities, sport, leisure, work, school Troublesome symptoms

Source: ARIA DATAMONITOR

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

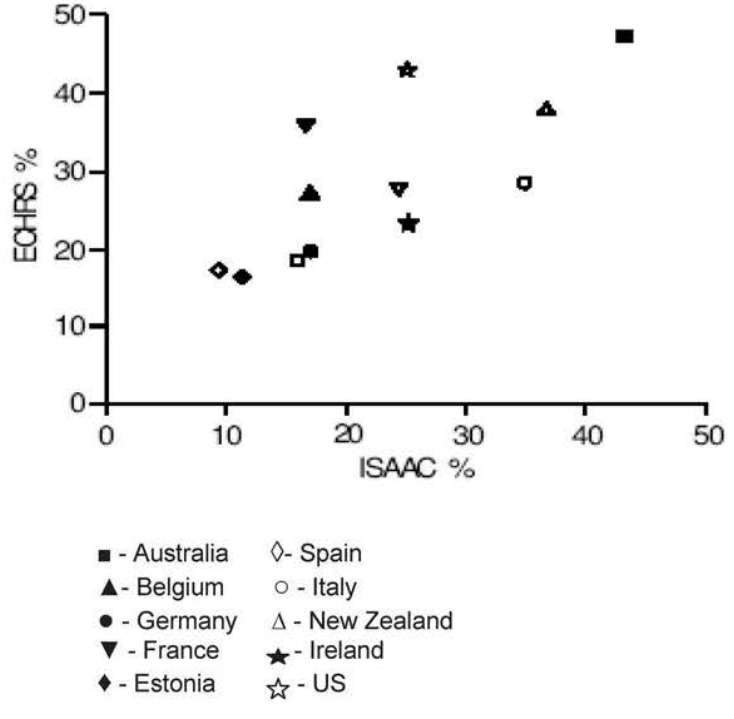
MEDA_APTX03505589

PTX0098-00014
CIPLA LTD. EXHIBIT 2021 PAGE 14

Age variance

Prevalence is usually higher in adults, peaking at around 20 years of age, than in children and pensioners, as shown in Germany in Figure 4. This variance as a result of age also makes epidemiology studies difficult to compare, for example the ISAAC study was carried out in 13–14 year olds, whereas the ECRHS involved adults between the age of 20 and 44. A comparison in Figure 1 between these two large-scale studies shows that, although a good correlation is observed (61%), ISAAC prevalence results are generally lower due to the study being carried out below the age of peak prevalence (Pearce *et al.*, 2000).

Figure 1: Correlation of incidence of hayfever ever in ECRHS (II) and ISAAC (I)



Source: Pearce *et al.*, 2000

DATAMONITOR

This report is a licensed product and is not to be photocopied

MEDA_APTX03505590

PTX0098-00015
CIPLA LTD. EXHIBIT 2021 PAGE 15

Global prevalence

The prevalence of allergic rhinitis is estimated in the seven major markets using epidemiology studies and research data.

Table 2: Global prevalence of allergic rhinitis, 2004

Country	[1]Total 2004 population (000's)	Prevalence (%)	AR population (000's)
US [2]	286,376	19.8	56,702.4
Japan [3]	127,309	19.6	24,952.6
France [4]	59,757	24.6	14,700.2
Germany [5]	82,335	18.2	14,985.0
Italy [6]	56,884	17.1	9,727.1
Spain [7]	39,500	14.1	5,569.5
UK [8]	59,081	26.4	15,597.4

Source: Various (see below)
1 = UN database figures
2 = National Health Survey, 2001; Crown, 2003; Slavin, 1994
3 = Okuda, 2003; Nakamura *et al.*, 2002
4 = ECRHS; Charpin *et al.*, 2000 ; WAO
5 = ECRHS
6 = Olivieri *et al.*, 2002; Verlato *et al.*, 2003
7 = ECRHS; Azpiri *et al.*, 1999
8 = ECRHS; Sibbald, Rink, 1991

DATAMONITOR

Methodology

US

The National Health Interview Survey of 2001, published by the CDC, recorded a total of nearly 21 million hayfever sufferers in the US. This refers to the seasonal aspect of allergic rhinitis, and each respondent was defined as having been told by a doctor, or other healthcare professional in the past 12 months, that they had hayfever. However, allergic rhinitis has been reported in up to 80% of asthma sufferers (Slavin, 1994) and more recently it has also been reported that 79% of allergic rhinitis patients suffer from SAR, leaving 21% with PAR (Crown, 2003). To obtain the prevalence of both seasonal and persistent allergic rhinitis, an average percentage was found, taking into account prevalence rhinitis with comorbid asthma and of PAR giving an estimate of 19.8% of the population.

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

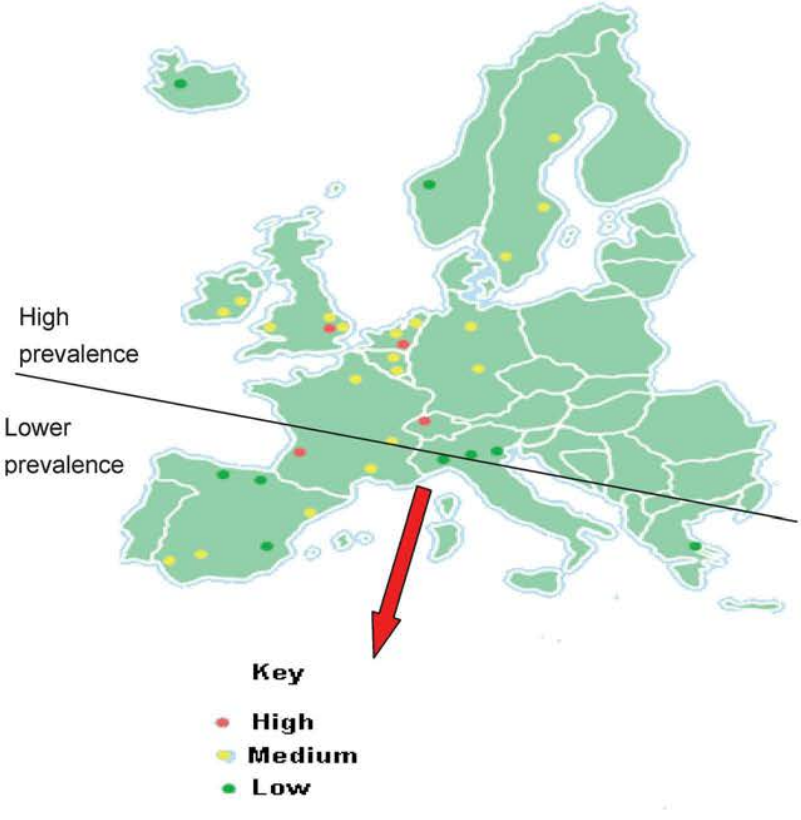
MEDA_APTX03505591

PTX0098-00016
CIPLA LTD. EXHIBIT 2021 PAGE 16

EU

The European Community Respiratory Health Survey (ECRHS), completed in 1996, is the most comprehensive study of AR in Europe. The study had a sample of approximately 140,000 20 to 44-year olds, from 22 countries.

Figure 2: Relative prevalence in the EU



Source: ECRHS I, 1996

DATAMONITOR

A northwest to southeast diagonal divide exists in AR prevalence rates in Europe. The atopy data in Figure 2 exemplifies this, showing Greece, Italy and Spain as having lower rates than their European neighbors. Atopy refers to the link between allergic reactions that create diseases such as allergic rhinitis or urticaria. However, the results of new studies show that this line is proceeding south in line with the overall global increase in AR.

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505592

PTX0098-00017
CIPLA LTD. EXHIBIT 2021 PAGE 17

France

The 1996 ECRH survey published prevalence data for nasal allergy in four major centers in France. These values were significantly higher than the median value for the study, which was 20.9%. However, they are comparable to UK values.

Table 3: ECRHS results, France, 1996

France ECRHS	Bordeaux	Grenoble	Montpellier	Paris	Average
	30.2	28.1	34.4	30.3	**30.75**

Source: Burney *et al.*, 1996

DATAMONITOR

It can be seen in a comparison between all the European figures that the more urban areas, or larger cities have a higher prevalence of AR than that found in rural areas. Therefore, to obtain a more representative figure for France, Datamonitor combined this information with two other sources when estimating an overall figure.

Charpin *et al.* (2000) gave prevalence values for hayfever of approximately 18% for teenagers and 25% for young adults. The World Allergy Organization gives France a prevalence of 5.9%. By taking an average of the comparative age ranges, a figure of 24.6% prevalence was estimated.

Germany

A number of studies have been carried out in Germany in allergy prevalence in recent years. The ECRHS is the largest cohort and provides the basis for this prevalence figure. However, a useful study was published in 1993 into two genetically similar populations who were exposed to different levels of living conditions and environmental pollution. It was carried out in the former East and West Germany and provides insight into the evolution and causative factors of the condition. Typical symptoms of rhinitis were reported of 16.6% in East Germany and 19.7% in West Germany. The average of the ECRHS values was used to estimate 2004 prevalence.

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505593

PTX0098-00018
CIPLA LTD. EXHIBIT 2021 PAGE 18

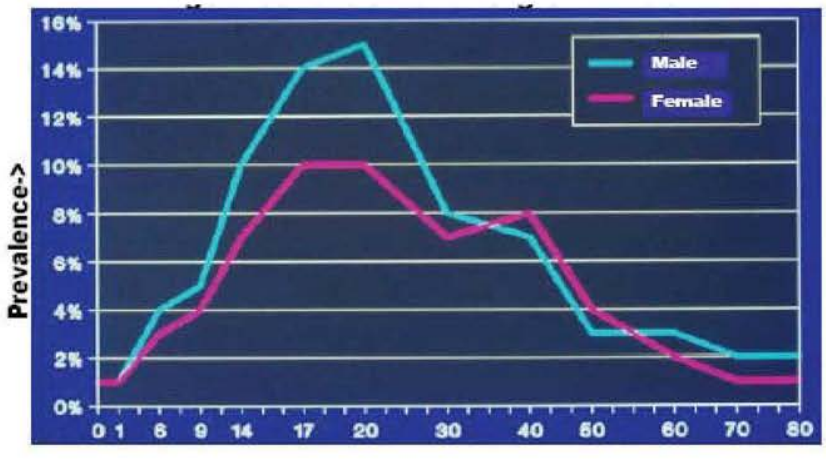
Table 4: ECRHS results, Germany, 1996			
Germany ECRHS	**Erfurt**	**Hamburg**	**Average**
	13.4	23	**18.2**

Source: Burney *et al.*, 1996

DATAMONITOR

The age distribution in Germany is displayed in Figure 3 below, and shows that the value found in the ECRHS, from ages 20 to 44, falls in the peak to medium prevalence range and will not be an accurate representation of other ages.

Figure 3: Age distribution of allergic rhinitis, Germany (%), 1995



Source: Mosges *et al.*, 1995

DATAMONITOR

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505594

PTX0098-00019
CIPLA LTD. EXHIBIT 2021 PAGE 19

Italy

The Italian prevalence was estimated using the ECRHS data and two more recent epidemiological studies in that area.

Table 5: ECRHS results, Italy, 1996

Italy ECRHS	Pavia	Turin	Verona	Average
	12.5	16	16.9	**15.13**

Source: Burney et al, 1996

DATAMONITOR

A study of data collected in northern Italy showed a higher prevalence of 15.9% (Olivieri *et al*, 2002) than the average figure reported from the ECRHS data.

In 2003, a study into the prevalence of AR showed a clear increase from the data collected for the ECRHS. The survey involved 6,876 people between the ages of 20 and 44 years and resulted in a prevalence of 18.3% (Verlato *et al.*, 2003). An average of the two later studies was taken to estimate 2004 prevalence.

Spain

A total of six centers were involved in the 1996 ECRHS.

Table 6: ECRHS results, Spain, 1996

Spain ECRHS	Albacete	Barcelona	Galdakao	Huelva	Oviedo	Seville	Average
	12.1	13.1	12.6	17.6	13.4	15.5	**14.05**

Source: Burney *et al.*, 1996

DATAMONITOR

A 1999 study of 2,216 people, carried out in northern Spain, shows comparable results. It also investigated prevalence across regions and age ranges. It was found that prevalence was increased in the Atlantic climatic area, when compared to the Oceanic area. The peak age was shown to be between 20 and 25 years old (Azpiri *et al.*, 1999).

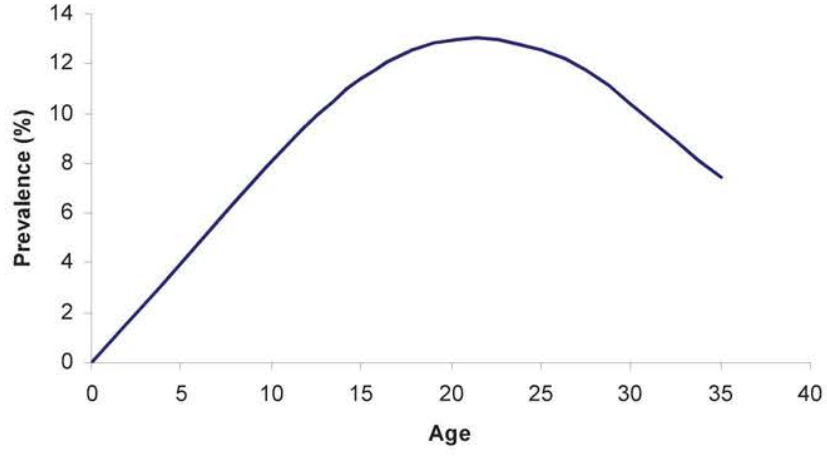
© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505595

PTX0098-00020
CIPLA LTD. EXHIBIT 2021 PAGE 20

Figure 4: Pollinosis in different age ranges, Spain (%), 1999



Source; Azpiri *et al.*, 1999

DATAMONITOR

UK

The UK has a considerably higher number of AR sufferers, in comparison to the rest of Europe, in most studies. This is illustrated by the data on the UK from the ECRHS.

Table 7: ECRHS Results, UK, 1996

UK ECRHS	Caerphilly	Cambridge	Ipswich	Norwich	Average
	23.6	29.2	26.7	28.3	**26.95**

Source: Burney *et al.*, 1996

DATAMONITOR

This average prevalence correlates closely with a 1991 study at a general practice in London in which a minimum rhinitis prevalence of 24% was reported (Sibbald, Rink, 1991). This number was added to the ECRHS results and an average was found.

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505596

PTX0098-00021
CIPLA LTD. EXHIBIT 2021 PAGE 21

Japan

Okuda published the most recent study into AR in Japan, in the Annuls of Allergy, Asthma and Immunology, in September 2003. This study investigated the epidemiology of Japanese cedar pollinosis throughout Japan. This is a form of seasonal allergic rhinitis that coincides with the peak of the pollen season for the Japanese cedar. The results from a nationwide survey of 5,624 subjects gave an age-adjusted prevalence of 19.4%, with an estimated prevalence of 13.1% after correction of possible bias. An earlier study by Nakamura *et al.*, published in 2002, gives a perennial AR prevalence of 19.8% and it states that allergic rhinitis due to causes other than pollen shows similar results.

Japanese cedar pollinosis does not cover the whole range of causes for AR, therefore an average of the two higher rates of prevalence will be taken into account for perennial rhinitis and AR caused by other allergens.

However, according to Japanese opinion leaders the prevalence of SAR may be slightly down this year, mainly due to climatic variations:

> *"The number of patients coming in for Japanese cedar pollen allergy was dramatically reduced this year, because the weather in July 2003, was too cool for the pollen to mature."* – Japanese opinion leader

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505597

PTX0098-00022
CIPLA LTD. EXHIBIT 2021 PAGE 22

Loratadine: the gold standard in allergic rhinitis

Antihistamines are the most commonly prescribed class of medication for AR (Corren, 2000). Loratadine is a second-generation H_1 antihistamine and, as of December 2002, is available OTC and in a generic form in many countries. Its main advantage over the first-generation antihistamines is a non-sedating action, due to a larger molecular structure that does not pass through the brain barrier as easily as the first generation.

Although it is off patent, this drug is still considered the best non-sedating antihistamine for the majority of patients. The large marketing spend used in the promotion of Claritin to some extent explains the brand loyalty shown when this was a prescription drug. However, the late 2002 switch to OTC shows that increasing competition has eroded this lead with US prescription sales of Claritin down 83% for the third quarter of 2003 to $68m (MIDAS Sales Data, IMS Health, April 2004).

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

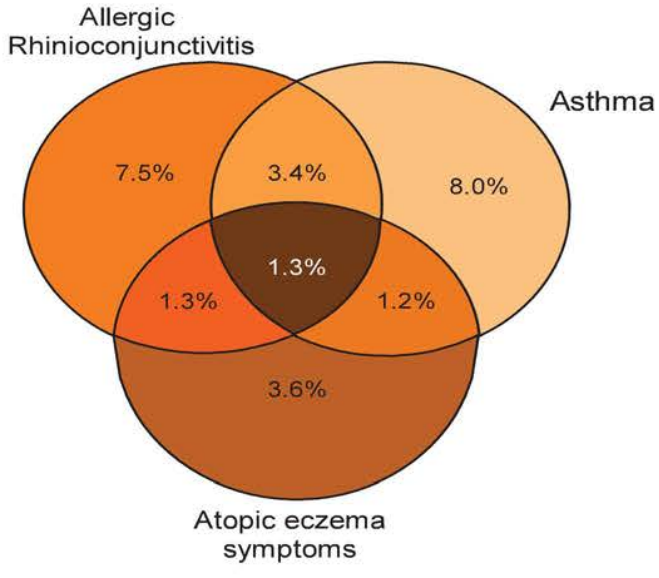
MEDA_APTX03505598

PTX0098-00023
CIPLA LTD. EXHIBIT 2021 PAGE 23

Associated pharmaceutical markets and indications

Allergic rhinitis can be comorbid with other atopic diseases such as asthma and eczema. Some treatments are indicated for two or more of these diseases due to the similar mechanism of disease action.

Figure 5: Relationship between asthma, rhinitis and eczema



All symptoms relate to a 12-month period

Source: ISAAC, 1998

DATAMONITOR

As can be seen in Figure 5, on a global basis, 7.2% suffer from at least two of the three disorders. This leads to close linking of medication for all these indications.

Asthma and associated market

The inflammatory response in asthma is similar to that which occurs in AR. AR itself is a known risk factor for asthma, and the link has been confirmed by the Allergic Rhinitis and its Impact on Asthma (ARIA) study. Laynaert *et al.* published a study in January 2004 into the association between these two conditions and found that 74–81% of subjects with asthma also reported suffering from rhinitis. Conversely, the risk of asthma increased in those with rhinitis. It concluded that a strong association

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505599

PTX0098-00024
CIPLA LTD. EXHIBIT 2021 PAGE 24

existed between asthma and rhinitis that was not fully explained by shared risk factors, including atopy.

The decline in value of the US allergy market, following the OTC switch and patent expiry of Claritin, and five separate, ongoing, generic legal challenges to Aventis's Allegra (fexofenadine), will lead to increasing overlap between drugs used to treat these two disease markets. For example, Aventis is pursuing an asthma indication for its antihistamine drug Allegra and in January 2003, the FDA approved Merck's asthma drug Singulair for allergic rhinitis. To date, the only therapy that has been shown to prevent asthma is immunotherapy (IT), but significant safety concerns and a protracted treatment regimen mean that, at best, immunotherapy accounts for 2–4% of the $9 billion allergy market. A number of biotechnology firms are attempting to overcome the disadvantages of current IT treatment, but discovery of a commercially viable allergy vaccine presents enormous difficulties.

Idiopathic urticaria and associated market

Urticaria, also known as hives, is a dermatological reaction, which presents as pale red swellings on any part of the skin. It can be caused by a number of agents including certain food groups, drugs and insect stings or as a response to viral infection. It can last for anything from a few hours to years, although the majority of cases disappear within 24 hours.

Treatment consists mainly of antihistamines, or an adrenaline injection in the case of severe reactions. Loratadine proved an efficient agent in the treatment of the chronic urticaria in 71% of patients in a 1994 Polish study (Siergiejko *et al.*, 1994). Therefore, products indicated for allergic rhinitis often have an urticaria indication as well. This proves useful in the highly competitive advertising of new drugs; however, some OTC products are used for indications other than those they are approved for.

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505600

PTX0098-00025
CIPLA LTD. EXHIBIT 2021 PAGE 25

CHAPTER 3 GLOBAL MARKET DEFINITION AND OVERVIEW

Market definition

The World Health Organization (WHO) uses the Anatomical Therapeutic Chemical (ATC) classification system. The WHO ATC system is a modification of the European Pharmaceutical Marketing Research Association (EphMRA) drug classification system, the Anatomical Classification of Pharmaceutical Products. IMS and Datamonitor use EphMRA's Anatomical Classification of Pharmaceutical Products.

For the purposes of the forecasting in this report, Datamonitor has defined the allergic rhinitis market as comprising the following EphMRA Anatomical Classification (AC) drug classes:

- R1A1: nasal corticosteroids;
- R1A4: nasal anti-infectives;
- R1A6: nasal anti-allergic agents;
- R1A7: nasal decongestants;
- R1B0: systemic nasal preparations;
- R6A0: systemic antihistamines.

However, products such as Singlair (montelukast) that fall into the Leukotrienes AC class are not included in this report. The sales data is not split by diagnosis and, as Singulair is primarily indicated for asthma, this product is not included in the forecast. Further detail and forecasting for Singulair can be found in *Commercial Insight: Asthma and COPD* (Datamonitor, September 2004, DMHC2004).

The R1B0 class refers to combination treatments, for example the antihistamine plus decongestant combinations such as Zyrtec-D and Allegra-D. Within this class are a number of treatments containing many ingredients. In the forecasts these are grouped under the active molecule name with a ++ following it to distinguish this group from that of the single molecule.

Figure 6 shows how the prescriptions written for an allergic rhinitis diagnosis are split by AC drug classes. The market defined in this report accounts for an average of 64% of the allergic rhinitis diagnosis over the last three years. The remaining 36% is

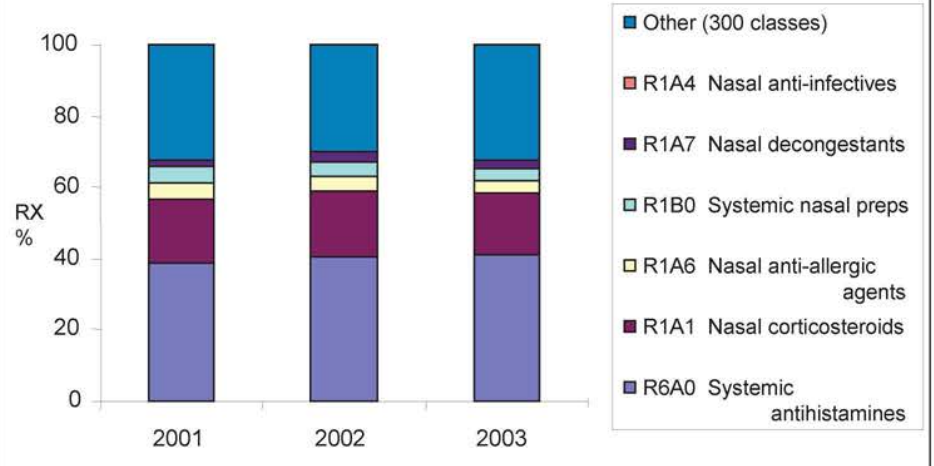
This report is a licensed product and is not to be photocopied

MEDA_APTX03505601

PTX0098-00026
CIPLA LTD. EXHIBIT 2021 PAGE 26

comprised of many other products split into 300 AC classes. This huge variation in treatments indicates the lack of a cure for this condition, and the individual nature of patients' responses to treatments drives the use of a wide range of treatments.

Figure 6: Prescriptions for allergic rhinitis by AC class (%), 2001–03



Source: Prescribing Insight Data, IMS Health, April 2004,

Copyright ©, reprinted with permission

ims™ DATAMONITOR

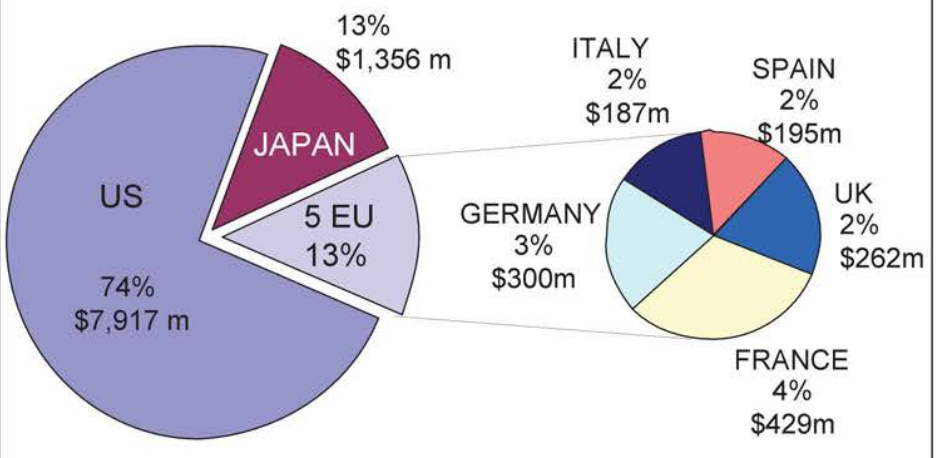
MEDA_APTX03505602

PTX0098-00027
CIPLA LTD. EXHIBIT 2021 PAGE 27

Global allergic rhinitis market analysis

The global sales for allergic rhinitis treatments are predicted to be dominated by the US in 2004, which will produce 74% of the sales from the seven major markets.

Figure 7: Seven major market allergic rhinitis sales (US$), 2004



Source: Datamonitor, Commercial Insight Forecasting Methodology; MIDAS Sales Data, IMS Health, April 2004, Copyright ©, reprinted with permission.

ims™ DATAMONITOR

The global allergic rhinitis sales are also dominated by one class of treatment: systemic antihistamines.

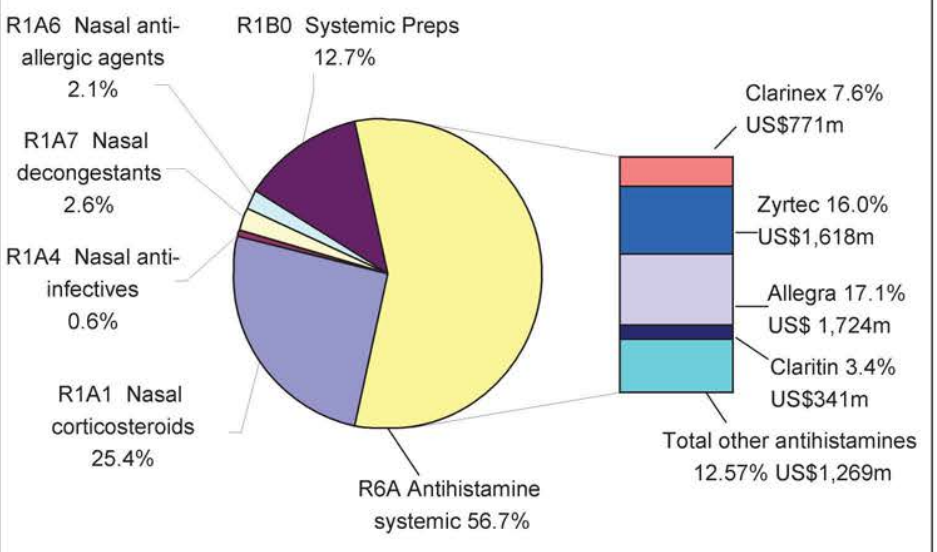
Figure 8 shows the major blockbuster brands in this class to currently to be Zyrtec (cetirizine) and Allegra (fexofenedine), with global sales accounting for approximately 16% and 17% of the market, respectively.

This report is a licensed product and is not to be photocopied

MEDA_APTX03505603

PTX0098-00028
CIPLA LTD. EXHIBIT 2021 PAGE 28

Figure 8: Global allergic rhinitis sales, AC class, 2003



Source: MIDAS Sales Data, IMS Health, April 2004, Copyright ©, reprinted with permission.

ims™ DATAMONITOR

Antihistamine market performance

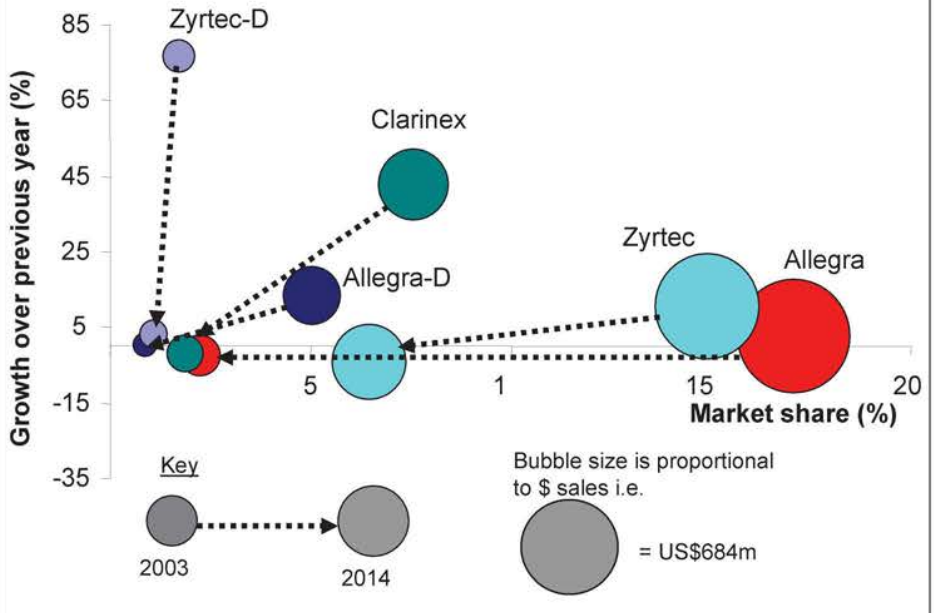
The global antihistamine market is also driven by US sales, which accounts for 57% of the market. However, the upcoming patent expiries will reduce the sales in this class dramatically. By 2014, the majority of the major brand's patents will have expired. Figure 9 shows how most of the major brands are forecast to have decreasing year-on-year sales over the period to 2014, with market share dropping below 5%.

This report is a licensed product and is not to be photocopied

MEDA_APTX03505604

PTX0098-00029
CIPLA LTD. EXHIBIT 2021 PAGE 29

Figure 9: US antihistamine leading brands (%), 2003 and 2014



Source: Datamonitor, Commercial Insight Forecasting Methodology; MIDAS Sales Data, IMS Health, April 2004, Copyright ©, reprinted with permission

ims™ DATAMONITOR

Please refer to the Excel forecast analysis tool for detailed forecast sales by country, class, molecule and brand to 2014.

Corticosteroid market performance

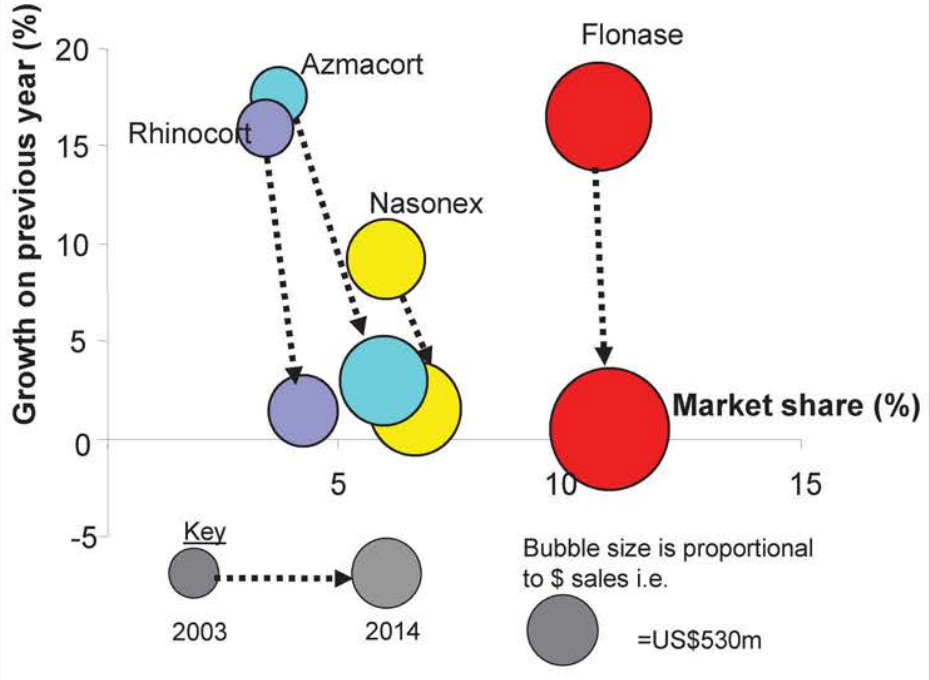
The US corticosteroid market also plays an important part in the global class value. Although product patent expiry is an issue for a number of these brands, the patents covering formulations and delivery mechanisms are forecast to provide additional protection from generic erosion in the forecast period. Therefore, in contrast to the antihistamines, Figure 10 shows increasing market share and sales for these brands, but at a slowing rate.

This report is a licensed product and is not to be photocopied

MEDA_APTX03505605

PTX0098-00030
CIPLA LTD. EXHIBIT 2021 PAGE 30

Figure 10: US nasal corticosteroid leading brands (%), 2003 and 2014



Source: Datamonitor, Commercial Insight Forecasting Methodology; MIDAS Sales Data, IMS Health, April 2004, Copyright ©, reprinted with permission

This report is a licensed product and is not to be photocopied

CHAPTER 4 KEY BRAND ASSESSMENT AND FORECASTING ASSUMPTIONS

Key brand strengths and weaknesses

Each brand is assessed on its internal (strengths and weaknesses) characteristics, which should then be compared to the country-specific external (opportunities and threats) factors identified in chapter five. This allows a complete assessment of not only clinical characteristics, but the positioning of the company against its competitors.

Company and product performance are given equal 50:50 weightings, with individual factors within these categories given a weighting in order of importance. Each brand is then scored according to the definition below, and an overall score obtained.

Table 8: Company-specific factors, weighting and score definitions

	Weight	2	1	0	-1	-2
2004 company revenue forecast ($bn)	15	20 +	10 – 20	5 – 10	1–5	0 – 1
2003 respiratory portfolio revenues ($bn)	15	4 +	3–4	2–3	1–2	0–1
Historical promotional spend ranking	10	Top 3	4th–6th	7th–9th	9th–12th	12+
Specialist and PCP sales force capability	10	Globally strong in many areas	Globally strong in respiratory only	Both US + EU	One of US or EU	1 country only
Total	**50**					

Source: Datamonitor

DATAMONITOR

For products marketed by or licensed to a number of companies, increased likely resources are taken into account when allocating scores.

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505607

PTX0098-00032
CIPLA LTD. EXHIBIT 2021 PAGE 32

Table 9: Product-specific factors, weighting and score definitions

	Weight	2	1	0	-1	-2
Efficacy	15	Steroid	Combination	Enhanced Chemical Entity	Second-generation	First-generation
Patent status*	10	10+ years	5–10 years	3–5 years	2–3 years	0–2 years
Delivery	10	Oral		Inhaled/ nasal spray		Injected
Administration frequency	5	Weekly		Once daily		Twice + daily
Severity of side effects (In comparison to other AR treatments)	10	None	Mild	Moderate (2^{nd}-gen AHs)	Severe (Steroids)	Very severe
Total	**50**					

* Patent expiry could also be classified an external threat from generic erosion, and this factors influence may vary depending on the specific countries generic market, as the US is the largest market this patent expiry is expected to have the most impact on the brand.

Source: Datamonitor DATAMONITOR

The scoring outlined above is based on opinion leader research, for example, the differentiation of class efficacy:

> *"I think for run of the mill allergic rhinitis, all the intra-nasal corticosteroids work and work reasonably."* – US opinion leader

> *They [antihistamines] all have the same sort of efficacy, the desloratadine may have a little bit of advantage due to even less sedating side effects."* – German opinion leader

> *"Overall there is not much difference in the comparative studies of efficacy in allergic rhinitis, comparing between loratadine, fexofenadine, cetirizine."* – US opinion leader

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505608

PTX0098-00033
CIPLA LTD. EXHIBIT 2021 PAGE 33

Event type one – antihistamine patent expiry

Assessment of the impact of an antihistamine patent expiry in the forecasting model is based on the following factors:

- generic competition (i.e. paragraph IV ANDA filings with the FDA);
- comparison to impact of Claritin expiry in respective countries (see case study two);
- country-specific historical generic erosion;
- expiry order within class (i.e. first to go off patent will have the highest impact (in the US Claritin sales fell by 92% from their highest point, as a result of patent expiry and OTC status), second will have less of an impact, all those following will be considerably less affected).
- a marketing impact is also predicted on patent expiry due to the reduction in strong advertising and physician detailing forces in the market. This impact also includes the impact of predicted OTC status (highlighted in the US) for newly generic molecules, based on the effect of the Claritin patent expiry on the market.

Event type two – nasal corticosteroid patent expiry

The effect of a patent expiry on nasal corticosteroids differs from the effect on antihistamines. For example, budesonide, the active ingredient in Rhinocort, went off patent in 1992, but no generic competition exists for allergic rhinitis treatment in the US. Other countries only show a small impact on Rhinocort sales from generic competition. This is explored in more detail in case study two, but in the majority of countries the impact of expiry is forecast to be negligible.

The following factors influence the impact of patent expiry of the steroidal active ingredient:

- complexity and patent status of delivery mechanism and formulation of active ingredient;
- comparison to impact of budesonide patent expiry in respective country.

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505609

PTX0098-00034
CIPLA LTD. EXHIBIT 2021 PAGE 34

Event type three – new product launch

The impact of new product launches is assessed in the largest global markets (i.e. US and Japan) to create a more realistic market forecast. In Japan, these product have already been launched elsewhere, but in the US the following pipeline products are included:

Alvesco (ciclesonide)

Drug overview

Alvesco (ciclesonide) is an inhaled corticosteroid that has been developed by Altana and Aventis. The drug received its first market approval in February 2004, when the Australian Health Agency approved the drug for the treatment of asthma in adults and children aged 12 and over. Aventis has applied for approval in the US, Altana expects approval in the UK, the reference member state for the EU, by mid 2004 for asthma with the allergic rhinitis indication currently in Phase III and therefore estimated to follow a year later. Altana negotiated a partnership with Aventis, in March 2001, for the clinical development of ciclesonide in the US. Aventis filed an NDA in the US in December 2003 and has also commenced studies investigating a combination for asthma of ciclesonide and formoterol, to compete with the blockbuster similar combination of Seritide (salmeterol/fluticasone), marketed by GSK. Patents protect ciclesonide until 2013 in the US and 2011 in all other countries.

Teijin is responsible for the development of ciclesonide in Japan. The company has announced that Phase III trials have been completed, and that application for approval will be filed in 2004. The drug will likely be launched for asthma in Japan in 2005.

An intranasal formulation of the drug is being developed for the treatment of allergic rhinitis. According to Altana, the intranasal formulation is in Phase II/III trials for AR; Teijin also has marketing rights for this formulation in Japan, Korea and Taiwan. Altana has suggested that the primary focus will remain on the US market for this formulation, due to the size of the intranasal steroid market. Alvesco is forecast to enter the allergic rhinitis market in the US only.

Clinical trial results

Data presented at the 60th annual AAAAI meeting showed the intranasal formulation of ciclesonide, in development for the treatment of allergic rhinitis, to be well tolerated and effective in the two highest doses. Measured by total nasal symptom score, investigators found an average change in baseline of -4.19 for placebo, -4.81 with 25 micron g/day, -4.79 with 50 micron g/day, -5.33 with 100 micron g/day, and -5.83 with

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505610

PTX0098-00035
CIPLA LTD. EXHIBIT 2021 PAGE 35

200 micron g/day. A low incidence of adverse events included headache and pharyngitis.

INS37217

Drug overview

INS 37217 is an anti-allergic compound in development by Inspire. It finished a Phase III trial in May 2003, the results of which are under further investigation. In April 2004, Inspire began a US, multicenter, double-blind, randomized, parallel-dose Phase II study to assess INS-37217 ophthalmic as a first-line therapy of rhegmatogenous retinal detachment.

Trial results

The results of a large, multicenter trial of INS37217 Intranasal in patients with perennial allergic rhinitis (PAR) were announced by Inspire in May 2003. The trial was a randomized, parallel-group, double-blind, placebo-controlled study designed to assess the safety and efficacy of INS37217 Intranasal in a 10mg/mL non-preserved nasal spray formulation. The 28-day study was conducted in 630 patients at 24 centers across the US.

In this study, INS37217 Intranasal was well tolerated but did not meet the primary endpoint of significantly reducing the total nasal symptom score over the 28-day treatment period versus placebo. The total nasal symptom score was a composite of four symptoms: rhinorrhea (runny nose), nasal congestion, nasal itching and post-nasal drip. The reduction in symptoms for INS37217 Intranasal was less than that seen in the previously reported Phase I and II studies in PAR and common cold.

Although the primary endpoint was not met, patients receiving INS37217 Intranasal had a decreased incidence of respiratory-related infection as compared to patients on placebo. This finding will require further evaluation. Inspire is conducting various secondary analyses and is planning an experts' meeting to review the study data in detail and determine potential next steps for the program.

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505611

PTX0098-00036
CIPLA LTD. EXHIBIT 2021 PAGE 36

Antihistamine analysis

Allegra franchise key facts

Table 10: Allegra: key facts	
Generic	Fexofenedine
Originator	Sepracor, Albony Molecular, Labopharm
Marketing companies	Aventis
2003 global sales [1]	Allegra = $1,581.8m (Allegra D = $454m)
2002–03 sales growth [1]	Allegra = 4.6% (Allegra D = 13.2%)
Indications	Seasonal allergic rhinitis, chronic idiopathic urticaria (adults and children age 6+)
Launch date [2]	1996 (US), 1997 (UK), 2000 (Japan, Germany)
Patent expiry date [3, 4]	Aug 2012 (US), June 2013 (EU), Aug 2013 (Japan). These patents are currently under dispute
Alternative brand names	Telfast (US)
Key clinical trials	Bernstein *et al.*, 1997

NB. Facts refer to fexofenadine unless otherwise stated

Source:

1 = MIDAS Sales Data, IMS Health, April 2004, Copyright ©, reprinted with permission

2 = IDdb, August 2004, Copyright Thomson Scientific

3 = Dolphin, August 2004, Copyright Thomson Scientific

4 = FDA Orange Book

ims™ DATAMONITOR

This report is a licensed product and is not to be photocopied

Table 11: Allegra events, 2003–04

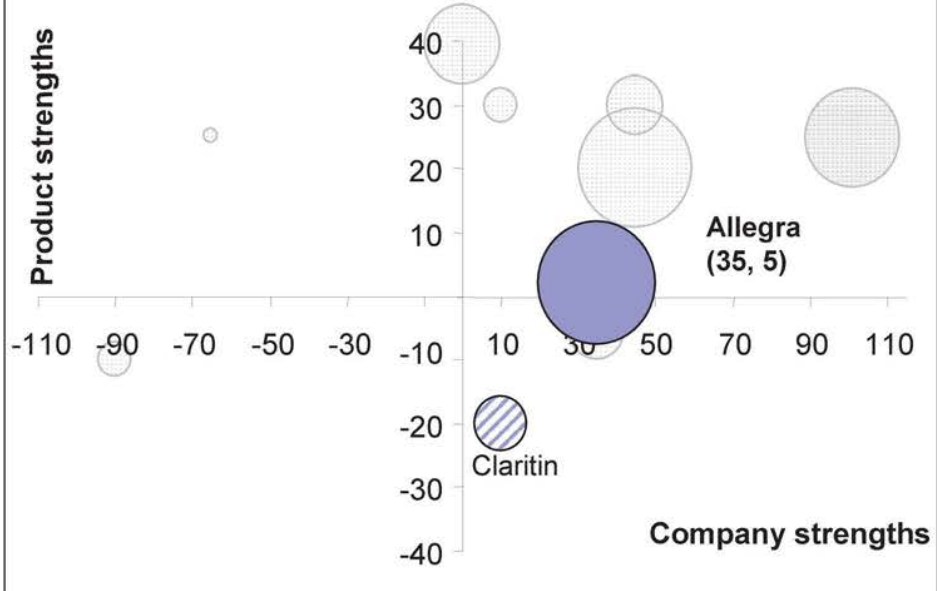
Date	Event
July 2004	FDA gives Barr tentative approval for generic fexofenadine, pending the result of 2005 litigation
June 2004	Aventis merges with Synofi-Synthelabo
March 2004	Aventis joins a lawsuit against Barr
June 2003	Real-world trial results announced at European Academy of Allergology and Clinical Immunology
March 2003	Dr Reddy's lab adds to patent challenges on Allegra

Source: Datamonitor

DATAMONITOR

Allegra strategic analysis and forecast assumptions

Figure 11: Allegra company and product strength comparison



- Aventis competes successfully against the larger pharmaceutical companies with this product
- The main product threat comes from possible generic erosion

Source: Datamonitor

DATAMONITOR

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505613

PTX0098-00038
CIPLA LTD. EXHIBIT 2021 PAGE 38

Table 12: Allegra company and product scores

Strengths/weaknesses	Weighting	Score	Total	Notes
Company				
2004 company ethical sales (forecast) [1]	15	1	15	$19,565m
2003 respiratory portfolio revenues [1]	15	0	0	$2,831m
2003 promotional spend ranking [2]	10	0	0	$330.70m
Sales force capability	10	2	20	Global
			35	
Product				
Efficacy	10	0	0	
Patent status	15	-2	-30	Currently in dispute with 7 generics companies
Delivery	10	2	20	Oral
Administration frequency	5	1	5	Once daily
Severity of side effects	10	1	10	Mild-none
			5	

Source:

1= Datamonitor, PharmaVitae company reports

2= Promotional Data, IMS Health, April 2004, Copyright ©, reprinted with permission

ims™ DATAMONITOR

A total of 58 patents cover fexofenadine and fexofenedine in combination with pseudoephedrine, however, only one of these is key to maintaining exclusivity. Datamonitor has assumed the following dates based on market opinion and court proceedings.

US

Sales activity of the Allegra (fexofenadine) were reported by Aventis in April 2004 to have declined 11.9% worldwide to $392m, while US sales fell 12% on Q4 sales. In the previous two years, Q1 sales had always been slightly up on the Q4 sales of the previous year due to the seasonal nature of this market. This drop in Q1 sales for

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505614

PTX0098-00039
CIPLA LTD. EXHIBIT 2021 PAGE 39

Allegra shows how badly the US market leader has been affected by the OTC and generic competition of loratadine.

Allegra is expected to be severely impacted by generic competition beginning in 2005. Aventis has filed patent infringement lawsuits against seven companies currently seeking approval to produce and market generic versions. Those companies include Barr, Impax, Teva, Mylan and Dr. Reddy's Labs. Datamonitor believes that the generic companies are likely to prevail in this case (see case study one), although the date when they will be able to enter the market is less certain. Share, in terms of prescription volume, is forecast to decrease by 75%, less than the Claritin patent expiry of 82% decrease, but greater than forecast expiries for many other brands discussed in this report.

The performance of Allegra in the US continues to be adversely affected by over-the-counter (OTC) products as well as changes in reimbursement for prescription antihistamines by managed care organizations.

Allegra-D is covered by a combination patent from Aventis, expiring in July 2018. As the patent on a similar combination, Clarinase (loratadine and pseudoephedrine) has no generic competitors in the US, the Allegra-D patent is forecast to maintain exclusivity throughout the period of forecast.

EU

In the EU, fexofenadine is covered by patent EP-00759904 filed by Merrell Dow. It covers the product derivative of terfenadine and expires in April 2015. However, Datamonitor predicts success in the US for the generic challengers of this patent, therefore generic competition is forecast from the beginning of 2005 in the majority of EU countries. Prescription sales will immediately be reduced by 75% in Germany, based on the high historical amounts of generic competition for Claritin. Interestingly, in Germany the comparative price of Allegra seems to have been raised as the volume of sales has fallen in the last year. In the UK, an SPC extends the fexofenadine patent to April 2005, competition is forecast to begin in Q2 2005 with a 75% reduction in volume. France, Italy and Spain are forecast to show the least impact, at a 40% volume decrease, as in all countries no generic versions of loratadine were picked up by IMS sales in 2003.

Allegra-D does not appear to be covered by formulation patents in the EU, and falls under the fexofenadine patent filed by Sepracor expiring in 2013. However, as it is not launched in the EU at present, and not predicted to be in the future, patent expiry is not evented in this forecast.

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505615

PTX0098-00040
CIPLA LTD. EXHIBIT 2021 PAGE 40

Japan

Two Japanese patents cover Allegra, one of which expired in 2000 and the other, JP-03041954, expires in August 2013. This second patent covers the optically pure form of terfenadine, fexofenadine. The current patent dispute occurring in the US may impact on Japanese sales, but based on the lack of generic competition for expired loratadine, and the low level of generic prescribing in general here, the impact is forecast to be very low.

The approval in April 2002 for the atopic dermatitis indication in Japan has boosted sales, and helps to drive the predicted future leading position of Allegra in this market.

Allegra-D is not available in Japan, but numerous antihistamine systemic combinations exist in this market. This combination class has suffered as a result of the introduction of the second-generation antihistamines, but in 2000, before the new products reached maturity, the combinations class had revenues of $77m. Datamonitor predicts that the Allegra-D formulation would be successful in this market, and the market tendency towards branded products would also reduce generic competition problems currently suffered by fexofenadine in other markets. Launch is forecast for 2006.

> *"Probably yes [there is a market for combinations in Japan], to give quick relief for a short period of time, though I personally feel that corticosteroids if taken properly would give more permanent effect than either anti-histamine or the decongestant."* – Japanese opinion leader

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505616

PTX0098-00041
CIPLA LTD. EXHIBIT 2021 PAGE 41

Zyrtec franchise key facts

Table 13: Zyrtec: key facts	
Generic	cetirizine
Originator	UCB
Marketing companies	See below Table 15
2003 global sales [1]	Zyrtec = $1,649.4 Zyrtec D (inc 24hr) = $156.6m
2002–03 sales growth [1]	Zyrtec = 9.2% Zyrtec D = 79.6%
Indications	Seasonal allergic rhinitis, chronic idiopathic urticaria (adults and children age 6+)
Launch date [2]	1989 (France, UK, Italy), 1990 (Spain, Germany), 1996 (US), 1998 (Japan)
Patent expiry date [3,4]	June 2007 (US), Feb 2007 (UK), Feb 2002 (France, Germany, Spain, Italy, Japan)
Alternative brand names	Zyrtec (US/Japan), Zirtec/Virlix/Formistin (EU) Cirrus (Zyrtec D, EU)
Key clinical trials	Molkhou *et al.*, 1996; Meltzer *et al.*, 1996 ; Horak F *et al.*, 2001; Pitsiu *et al.*, 2004

Source:
1 = MIDAS Sales Data, IMS Health, April 2004, Copyright ©, reprinted with permission
2 = IDdb, August 2004, Copyright Thomson Scientific
3 = Dolphin, August 2004, Copyright Thomson Scientific
4 = FDA Orange Book

ims™ DATAMONITOR

UCB has a complex marketing structure for cetirizine, involving a number of small and large companies that are strong in their respective, commonly domestic, countries. A large number of companies (including GSK, Abbott, Aventis, Pfizer and Synthelabo) have entered into sales agreements with UCB, allowing the drug access to all major markets. Cetirizine was approved in the US in 1995, almost eight years after filing the NDA, where it is co-promoted by Pfizer and UCB.

This report is a licensed product and is not to be photocopied

MEDA_APTX03505617

PTX0098-00042
CIPLA LTD. EXHIBIT 2021 PAGE 42

This strategy has contributed considerably to its success. The more disappointing sales for Zyrtec-D may be due to the fact that it is currently only marketed by UCB in most EU markets. Table 14 shows the marketing arrangement.

Table 14: UCB licensing relationships for the marketing of cetirizine

Relationship	License region	Company
Licensor	UK, Germany	UCB
Licensees	US	Pfizer
	Japan	Daiichi
		Sumito Chemical
	Spain	Almirall Prodesfarma
		Lacer
	Italy	Lusofarma
		Mediolanum
	France	Sanofi-Synthelabo

Source: Datamonitor DATAMONITOR

© Datamonitor (Published 09/2004)

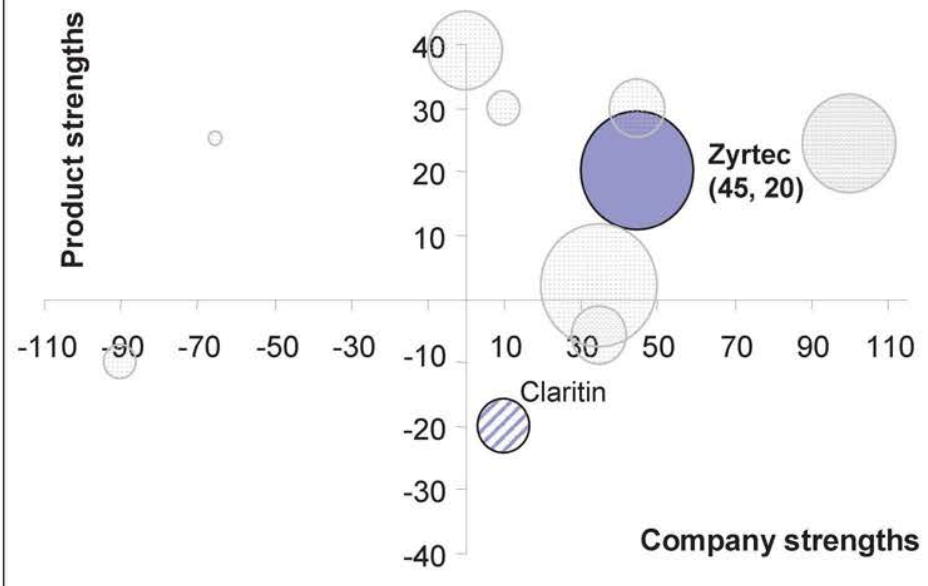
This report is a licensed product and is not to be photocopied

MEDA_APTX03505618

PTX0098-00043
CIPLA LTD. EXHIBIT 2021 PAGE 43

Zyrtec strategic analysis and forecast assumptions

Figure 12: Zyrtec* product and company strength comparison



- Zyrtec has strong sales, and is well positioned in terms of both company and product strengths
- The major weakness is patent expiry in 2007.

* Not including other cetirizine formulations

Source: Datamonitor

DATAMONITOR

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505619

PTX0098-00044
CIPLA LTD. EXHIBIT 2021 PAGE 44

Table 15: Zyrtec company and product scores

Strengths/ weaknesses	Weighting	Score	Total	Notes
Company				
2004 company revenue forecast[1]	15	1	15	UCB + Pfizer resources increases score
2003 respiratory portfolio revenues[1]	15	0	0	$806m
2003 promotional spend ranking[2]	10	1	10	UCB = $54.82m, but numerous marketing partnerships increase promotional spend
Sales force capability	10	2	20	UCB partnered with numerous EU companies inc. Pfizer increases sales force
			45	
Product				
Efficacy	10	-1	-10	Second generation
Patent status	15	0	0	June 2007 (US)
Delivery	10	2	20	Oral
Administration frequency	5	0	0	Once daily
Severity of side effects	10	1	10	Mild
			20	

Source

1= Datamonitor, PharmaVitae company reports

2= Promotional Data, IMS Health, April 2004, Copyright ©, reprinted with permission

ims™ DATAMONITOR

US

Patent expiry is forecast in December 2007, with a high impact on what is predicted to be a blockbuster drug (sales over US$1 billion) in the US by 2005. At present there is paragraph IV filing for Zyrtec –D listed on the FDA website (http://www.fda.gov/cder/ogd/ppiv.htm). Datamonitor expects this unnamed generic company to launch generic Zyrtec at the end of 2007, along with the decongestant combination. In August 2004 the generics company Mylan received tentative approval

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505620

PTX0098-00045
CIPLA LTD. EXHIBIT 2021 PAGE 45

from the FDA to market cetirizine when its patent expires. Patent expiry for both Zyrtec and Zyrtec-D is forecast to produce a 70% shift in volume from the brand to generic competitors.

EU

The cetirizine patent has already expired in France, Italy, Germany, UK and Spain, all of which, except Italy, show generic competition.

In Italy and Spain the Zyrtec sales value includes those for Virlix and Formistin brands, which are brands of cetirizine licensed out to Mediolanum and Lusofarmo, respectively. Zyrtec-D has also been marketed in Italy under the name Reactine since 2003, but this split is maintained in the model, as it highlights the differences in brand marketing power on the same product.

Japan

Cetirizine is the second highest-selling antihistamine in Japan, but has already lost patent protection in that market. Sales from 2000 to 2002 dropped as a result of the launch of Claritin and Allegra into the Japanese market.

The Zyrtec-D formulation is not yet available in this market, but is forecast to launch around 2007 (See Japan section for Allegra-D). Zyrtec has not been as successful as Allegra in the Japanese market, and therefore the launch of the decongestant combination is not predicted to have such a large uptake.

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505621

PTX0098-00046
CIPLA LTD. EXHIBIT 2021 PAGE 46

Xyzal key facts

Table 16: Xyzal: key facts	
Generic	levocetirizine
Originator	Sepracor (US)
Marketing companies	UCB (EU)
2003 global sales [1]	$28.4m
2002–03 sales growth [1]	173.9%
Indications	Seasonal and perennial allergic rhinitis, chronic idiopathic urticaria
Launch date [2]	2001 (Germany, UK), 2003 (Spain, Italy, France)
Patent expiry date [3, 4]	Dec 2007 (US), Feb 2002 (France, Italy, Japan), Feb 2007 (UK, Germany), Aug 2004 (Spain)
Alternative brand names	Xyzall (EU), Xusal (Germany)
Key clinical trials	XPERT (Xyzal in Persistent Rhinitis Trial)[5], 2003, Leynadier F et al, 2001

Source:

1 = MIDAS Sales Data, IMS Health, April 2004, Copyright ©, reprinted with permission

2 = IDdb, August 2004, Copyright Thomson Scientific

3 = Dolphin, August 2004, Copyright Thomson Scientific

4 = FDA Orange Book

5= European Academy of Allergology and Clinical Immunology, Paris, 2003

ims™ DATAMONITOR

© Datamonitor (Published 09/2004)

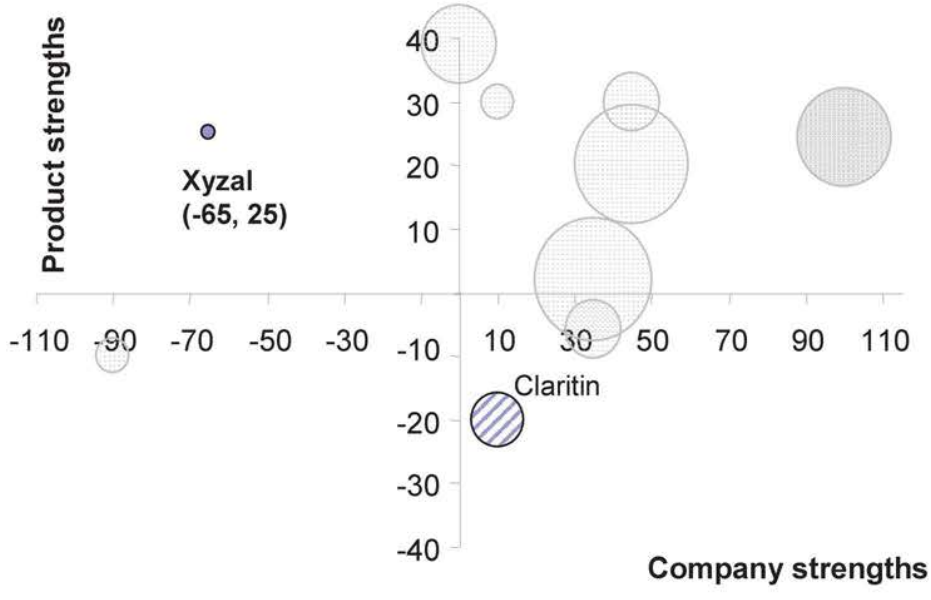
This report is a licensed product and is not to be photocopied

MEDA_APTX03505622

PTX0098-00047
CIPLA LTD. EXHIBIT 2021 PAGE 47

Xyzal strategic analysis and forecast assumptions

Figure 13: Xyzal product and company strength comparison



- The comparatively small scale of UCB positions this product below most antihistamines on the horizontal axis
- However, as an enhanced chemical entity with more than three years patent life remaining, the product is strong

Source: Datamonitor

DATAMONITOR

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505623

PTX0098-00048
CIPLA LTD. EXHIBIT 2021 PAGE 48

Table 17: Xyzal company and product scores

Strengths/weaknesses	Weighting	Score	Total	Notes
Company				
2004 company revenue forecast[1]	15	-1	-15	$1,690m
2003 respiratory portfolio revenues[1]	15	-2	-30	$806m
2003 promotional spend ranking[2]	10	-2	-20	$54.89m
Sales force capability	10	0	0	UCB = US/EU mainly
			-65	
Product				
Efficacy	10	0	0	Enhanced chemical entity
Patent status	15	-1	-15	Feb 2007 (some EU counties already expired)
Delivery	10	2	20	Oral
Administration frequency	5	0	0	Once daily
Severity of side effects	10	2	20	None
			25	

Source:

1= Datamonitor, PharmaVitae company reports

2= Promotional Data, IMS Health, April 2004, Copyright ©, reprinted with permission

ims™ DATAMONITOR

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505624

PTX0098-00049
CIPLA LTD. EXHIBIT 2021 PAGE 49

US

Levocetirizine has not been launched in the US, and UCB/Sepracor has not stated any intention to do so in the near future. Levocetirizine is predicted to go off patent in December 2007 in the US, therefore Datamonitor predicts that it will not be launched in this market, as the time available for exclusive sales is so limited, and other markets sales have not been comparable to its metabolite cetirizine. Therefore, there is no impact on the market from this patent expiry. Generic companies may take this opportunity but they would have to raise awareness of this product themselves. Opinion leaders view the differentiation between levocetirizine and cetirizine to be insignificant in the minds of prescribing physicians, a fact reflected in the poor European sales. For these reasons no or insignificant generics are currently predicted.

> *"We don't have that available in the US, but from what I've seen I don't see any real difference. I think the only difference is that you give a smaller dose because you're giving a fully effective drug."* – US opinion leader

EU

Patent EP58146, which covered levocetirizine, expired in February 2002. However, in the UK and Germany, SPCs were granted in March 2002, with an expiry date of February 2007. The impact of the 2007 patent expiry is predicted to be highest in Germany at an 80% loss in volume sales, with a similar effect in the UK market of a 70% drop.

Despite apparent patent expiry in France and Italy, launch occurred in 2003, with no generic competition. This may be due to the later patent from Sepracor (EP-00663828) covering the use of levocetirizine in allergic disease, which expires in 2013. This patent is quoted by UCB, but as a 'new use' patent this is not the primary patent and may not cover the product, leaving it vulnerable to generic competition. France and Italy also showed no generic competition for Claritin (loratadine) indicating that this could also be a country-specific anomaly in antihistamine generic competition.

Spain's levocetiritine patent expired in August 2004, and has been evented in the forecast model as having a small impact of only a 40% decrease in volume occurring after six years. This follows the trend set by Claritin in this market.

Japan

Levocetirizine is not currently available in Japan, and no market-specific patent appears to exist beyond the expired 2002 product patent. This product is not predicted to launch here.

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505625

PTX0098-00050
CIPLA LTD. EXHIBIT 2021 PAGE 50

Clarinex key facts

Table 18: Clarinex: key facts	
Generic	desloratadine
Originator	Sepracor
Marketing companies	Schering-Plough
2003 global sales [1]	$790.4m
2002–03 sales growth [1]	49.2%
Indications	Seasonal and perennial allergic rhinitis (indoor and outdoor allergies), chronic idiopathic urticaria, (SAR = Adults and children age 2+, PAR and CIU = Adults and children age 6 months+)
Launch date [2]	2001
Patent expiry date [3, 4]	April 2004 (US), Feb 2005 (Japan, EU)
Alternative brand names	Aerius, Neoclarityn (EU)
Key clinical trials	Salmun *et al.*, 2002; Meltzer *et al.*, 2000

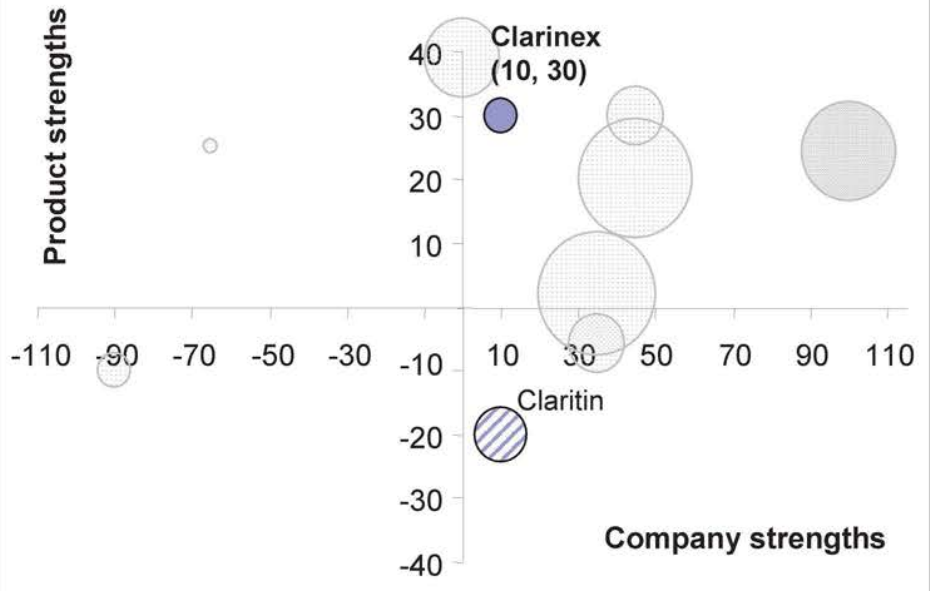
Source:
1 = MIDAS Sales Data, IMS Health, April 2004, Copyright ©, reprinted with permission
2 = IDdb, August 2004, Copyright Thomson Scientific
3 = Dolphin, August 2004, Copyright Thomson Scientific
4 = FDA Orange Book

ims™ DATAMONITOR

This report is a licensed product and is not to be photocopied

Clarinex strategic analysis and forecasting assumptions

Figure 14: Clarinex product and company strength comparison



- Clarinex (desloratadine) scores highly in this analysis, but sales do not reflect this, as the patent expiry of Claritin (loratadine) has resulted in a similar product which more readily available and at a cheaper price

Source: Datamonitor

DATAMONITOR

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505627

PTX0098-00052
CIPLA LTD. EXHIBIT 2021 PAGE 52

Table 19: Clarinex company and product scores				
Strengths/weaknesses	**Weighting**	**Score**	**Total**	**Notes**
Company				
2004 company revenue forecast [1]	15	0	0	$6,338m
2003 respiratory portfolio revenues[1]	15	0	0	$2,003m
2003 promotional spend ranking[2]	10	-1	-10	$181.24m
Sales force capability	10	2	20	Global
			10	
Product				
Efficacy	15	0	0	
Patent status	10	-2	-20	Patent Exp – Oct 2004
Delivery	10	2	20	Oral
Administration frequency	5	0	0	Once daily
Severity of side effects	10	1	10	Mild
			30	

Source:

1= Datamonitor, PharmaVitae company reports

2= Promotional Data, IMS Health, April 2004, Copyright ©, reprinted with permission

ims™ DATAMONITOR

US

Clarinex's patent expired in April 2004, but has a pediatric extension until October 2004. The impact of patent expiry is predicted to be less than that for Allegra and Claritin in the US, with only a 65% shift in brand volume. This is based on little estimated generic competition, as no ANDAs are apparent for desloratadine at the FDA, and also the fact that availability of generic loratadine is already eroding sales.

In September 2004, the FDA approved the use of Clarinex Syrup for the relief of symptoms associated with seasonal allergic rhinitis in children two years and older and perennial allergic rhinitis (PAR) and chronic idiopathic urticaria, or hives, in children as young as six months.

EU

The European patent, EP-0015387, covering desloratadine is due to expire in February 2005. However, in the UK, a number of SPC and alternative patents exist,

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505628

PTX0098-00053
CIPLA LTD. EXHIBIT 2021 PAGE 53

which are forecast to extent patent life in that market. The latest of these is an SPC extension on the above product patent that expires in February 2010.

The impact of this patent expiry is predicted to vary across the five European countries forecast and is further detailed in the forecast analysis tool and in Table 20.

Table 20: EU variations in Clarinex patent expiry impact

	Estimated decrease in brand volume on patent expiry (%)	Years to maximum impact	Notes
France	50	10	This rate of decline is comparable to both Claritin and Zyrtec in the French market
Germany	80	2	Strong predicted generic competition boosts the impact predicted in Germany
Italy	65	10	A smaller impact is reached over a longer period of time
Spain	45	5	Spain shows smallest impact
UK	75	3	Strong generic competition is predicted

Source: Datamonitor DATAMONITOR

Japan

The Clarinex patent in Japan is scheduled to expire in February 2005. However, due to the fact that Claritin appears to have been launched after its patent expiry in this market, this fact is not forecast to prevent the launch of Clarinex in Japan. Schering-Plough has not yet indicated a launch date for Clarinex in this market. However, due to Schering-Plough's existing marketing partnership with Shionogi and the success of Claritin in the Japanese market, Datamonitor believes that Clarinex will be launched within the 10-year forecasting window, and estimates the date at 2009.

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505629

PTX0098-00054
CIPLA LTD. EXHIBIT 2021 PAGE 54

Ebastel analysis

Table 21: Ebastel: key facts

Generic	Ebastine
Originator	Almirall Prodesfarma
Marketing companies	Chiesi (Italy), Dainippon, Meiji Seika (Japan)
2003 global sales [1]	$148m
2002–03 sales growth [1]	9.9%
Indications	Seasonal and perennial allergic rhinitis, chronic urticaria, adults and children aged two years and over
Launch date [2]	1990 (Spain, France, Italy, Germany, Japan)
Patent expiry date [3, 4]	July 2004 (US), Aug 2004 (France, Italy, Germany, Japan), June 2005 (Spain)
Alternative brand names	Kestine, Evastel
Key clinical trials	Gehanno P *et al.*, 1996; Campbell *et al.*, 1996

Source:

1 = MIDAS Sales Data, IMS Health, April 2004, Copyright ©, reprinted with permission

2 = IDdb, August 2004, Copyright Thomson Scientific

3 = Dolphin, August 2004, Copyright Thomson Scientific

4 = FDA Orange Book

ims™

DATAMONITOR

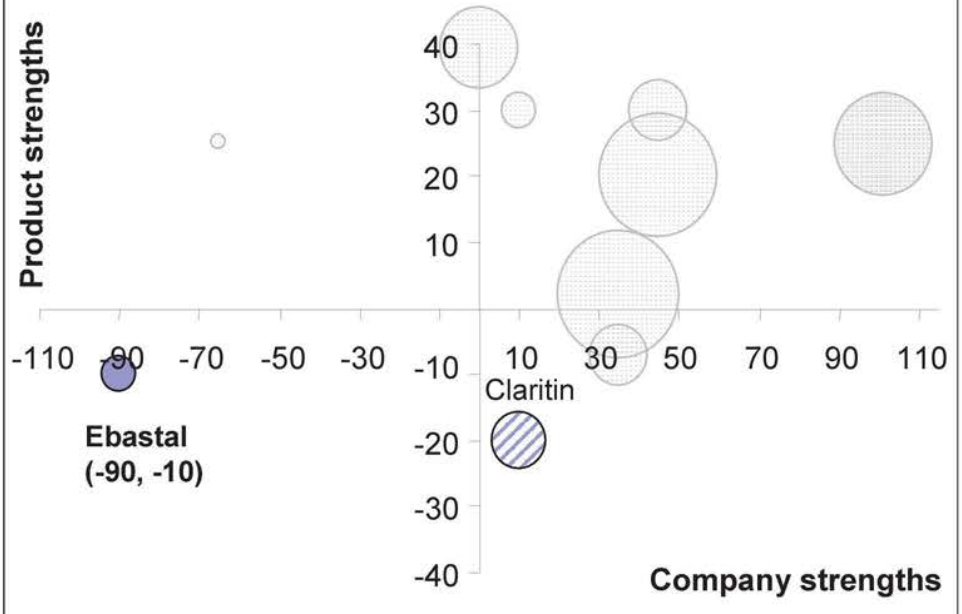
© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505630

PTX0098-00055
CIPLA LTD. EXHIBIT 2021 PAGE 55

Ebastel strategic analysis and forecasting assumptions

Figure 15: Ebastel product and company strength comparison



- Almirall's comparatively small resources place this product low on the strengths scoring
- However, despite being currently unavailable in the US, sales are promising and indicated a good basis for additional formulations to combat upcoming patent expiry

Source: Datamonitor

DATAMONITOR

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505631

PTX0098-00056
CIPLA LTD. EXHIBIT 2021 PAGE 56

Table 22: Ebastel company and product scores				
	Weighting	**Score**	**Total**	**Notes**
Company				
2004 company revenue forecast[1]	15	-2	-30	$810m
2003 respiratory portfolio revenues[1]	15	-2	-30	$141m
2003 promotional spend ranking[2]	10	-2	-20	$52.92m
Sales force capability	10	-1	-10	Regional
			-90	
Product				
Efficacy	10	-1	-10	Second generation
Patent status	15	-2	-30	August 2004
Delivery	10	2	20	Oral
Administration frequency	5	0	0	once daily
Severity of side effects	10	1	10	Mild - dry mouth, headache (Gehanno P *et al.*, 1996)
			-10	

Source:

1= Datamonitor, PharmaVitae company reports

2= Promotional Data, IMS Health, April 2004, Copyright ©, reprinted with permission

ims™ DATAMONITOR

US

Ebastel is not currently marketed in the US and, as its patent expired there in July 2004, Almirall is not expected to market it there.

EU

The EU patent expired in most countries in August 2004, and in June 2005 in Spain. The impact of patent expiry varies according to country historical trends for previously expired antihistamines, and is estimated to be highest in Germany at an 80% shift in brand volume to generic molecules. France and Spain have a similar impact of 40% shift occurring quickly, whereas Italy shows a 40% impact reached in six years.

This report is a licensed product and is not to be photocopied

In the UK, an SPC maintains exclusivity until December 2004, but Ebastel is not launched in this market as no sales are recorded for the product by IMS.

In Italy, the Ebastel figure includes sales under the brand name Clever from Chesi, who brought the rights to market ebastine in 2001.

Japan

Sales from 2000 to 2002 dropped as a result of the launch of Claritin and Allegra into the Japanese market. The Japanese patent for Ebastel expired in August 2004, which is evented in the forecast as a drop of 30% in volume over a period of four years. This is similar to the impact of Alesion patent expiry but is estimated to be slightly less due as it is not the first antihistamine to be available as a generic.

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505633

PTX0098-00058
CIPLA LTD. EXHIBIT 2021 PAGE 58

Corticosteroid analysis

Nasonex key facts

Table 23: Nasonex: key facts

Generic	mometasone
Originator	Schering-Plough
Marketing companies	Shionogi (Japan)
2003 global sales [1]	$1,275.6m
2002–03 sales growth [1]	10.9%
Indications	Seasonal and perennial allergic rhinitis, (adults 12 years and over)
Launch date [2]	1997 (US, UK), 1999 (EU)
Patent expiry date [3, 4]	July 2014 (US – aerosol formulation patent); June 2012 (EU – aerosol formulation patent), June 2005 (EU – product patent), Jan 2002 (Japan- product patent)
Alternative brand names	Elocon (topical formulation)
Key clinical trials	Herbert *et al.*, 1996; Graf *et al.*, 1996

Source:

1 = MIDAS Sales Data, IMS Health, April 2004, Copyright ©, reprinted with permission

2 = IDdb, August 2004, Copyright Thomson Scientific

3 = Dolphin, August 2004, Copyright Thomson Scientific

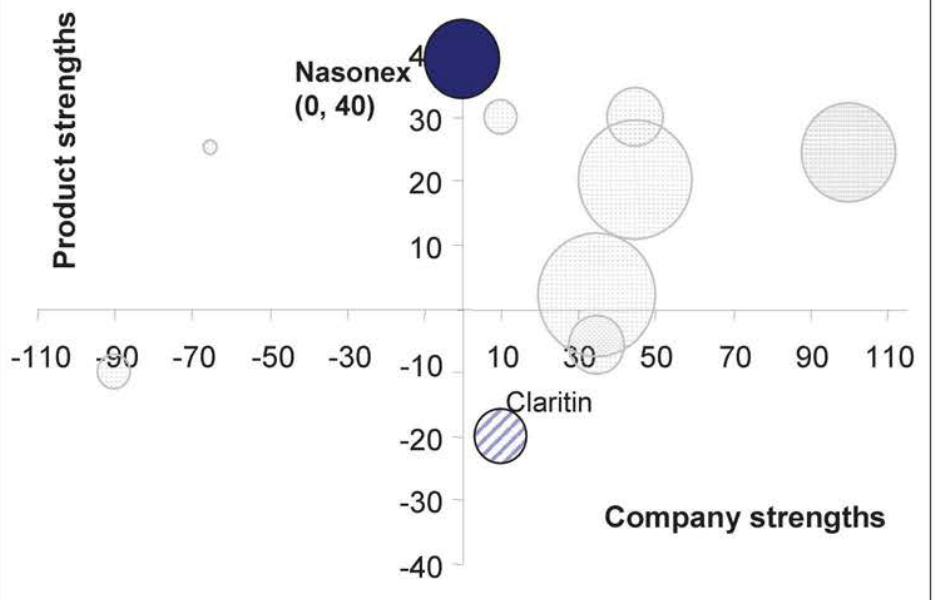
4 = FDA Orange Book

ims™ DATAMONITOR

This report is a licensed product and is not to be photocopied

Nasonex strategic analysis and forecasting assumptions

Figure 16: Nasonex product and company strength comparison



- Nasonex is a popular treatment among opinion leaders, with the product strengths reflecting this
- In terms of sales in the class, it is second only to Flonase, but cannot compete with antihistamine sales

Source: Datamonitor

DATAMONITOR

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505635

PTX0098-00060
CIPLA LTD. EXHIBIT 2021 PAGE 60

Table 24: Nasonex company and product scores

Strengths/weaknesses	Weighting	Score	Total	Notes
Company				
2004 company revenue forecast [1]	15	0	0	$6,338m
2003 respiratory portfolio revenues[1]	15	0	0	$2,003m
2003 total promotional spend ranking [2]	10	-1	-10	$181.24m
Sales force capability	10	1	10	UCB and Shiongi
			0	
Product				
Efficacy	10	2	20	
Patent status [1]	15	2	30	2014 (US), product patent expiry passed [1]
Delivery	10	0	0	Nasal spray
Administration frequency	5	0	0	Once daily
Severity of side effects	10	-1	-10	
			40	

1 = If the main product patent has expired the formulation patent is assumed to be sound, adding to the product strength.

Source:

1= Datamonitor, PharmaVitae company reports

2= Promotional Data, IMS Health, April 2004, Copyright ©, reprinted with permission

ims™ DATAMONITOR

US

The orange book contains a patent for the aerosol formulation of mometasone for use in allergic rhinitis, which expires in January 2014. The active ingredient mometasone has already expired; therefore the aerosol formulation patent is predicted to continue to cover this product. A scent-free Nasonex product was approved by the FDA in August 2004.

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505636

PTX0098-00061
CIPLA LTD. EXHIBIT 2021 PAGE 61

EU

The Nasonex product patent (EP-00057401) is due to expire in France, Germany and the UK in June 2005, when the SPC covering it expires. In Italy, where Nasonex is also distributed under the brand name Rinelon, the product patent expired in 2002. No generics are currently available and it is assumed that the formulation patents that do not expire until 2012 cover this product throughout the EU. A reduction in sales volume is forecast in Germany and Italy in 2012 due to predicted generic erosion.

Japan

The product patent in Japan expired in 2002, with no generic competition. The formulation patent is due to expire here in 2012, but no impact is forecast due to the nature of the Japanese market, and evidence from previous corticosteroid patent expiries in Japan.

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505637

PTX0098-00062
CIPLA LTD. EXHIBIT 2021 PAGE 62

Rhinocort analysis

Table 25:	Rhinocort: key facts
Generic	budesonide
Formulations	Rhinocort Aqua (a water-based suspension in a pump spray), Rhinocort Turbuhaler (nasal inhalation powder), and Rhinocort pMDI (pressurized metered dose inhaler).
Originator	AstraZeneca
Marketing companies	Fujisawa, Teva, Orion
2003 global sales [1]	$418.1m
2002–03 sales growth [1]	17.6%
Indications	Seasonal and perennial allergic rhinitis, perennial non-allergic rhinitis, treatment and prevention of nasal polyposis
Launch date [2]	1994 (US)
Patent expiry date [3, 4]	Budesonide expired in 1993 but formulation/ use/process patents exist in the US EU and Japan
Alternative brand names	Pulmicort
Key clinical trials	Jankowski R *et al.*, 1999; Linden M *et al.*, 1999

Source:

1 = MIDAS Sales Data, IMS Health, April 2004, Copyright ©, reprinted with permission

2 = IDdb, August 2004, Copyright Thomson Scientific

3 = Dolphin, August 2004, Copyright Thomson Scientific

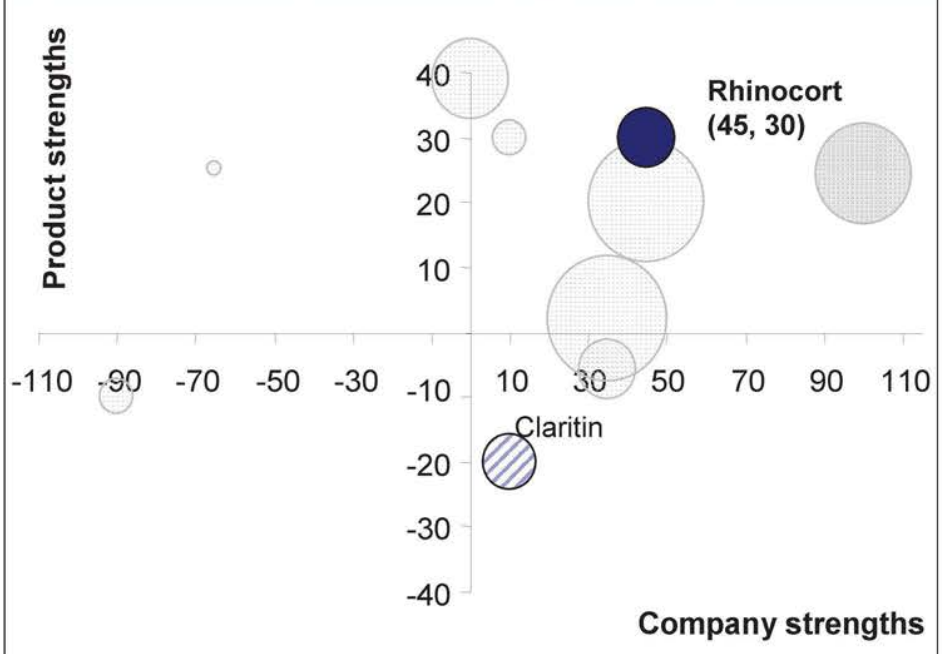
4 = FDA Orange Book

ims™ DATAMONITOR

This report is a licensed product and is not to be photocopied

Rhinocort strategic analysis and forecasting assumptions

Figure 17: Rhinocort product and company strength comparison



- Rhinocort is backed by AstraZeneca, which has a strong respiratory portfolio
- Despite a low score for general steroid side effects, it has strong patent coverage for the aqueous formulation, which has resisted generic erosion as budesonide is already off patent

Source: Datamonitor DATAMONITOR

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505639

PTX0098-00064
CIPLA LTD. EXHIBIT 2021 PAGE 64

Table 26: Rhinocort company and product strength scores

Strengths/weaknesses	Weighting	Score	Total	Notes
Company				
2004 company revenue forecast[1]	15	1	15	$19,745m
2003 respiratory portfolio revenues[1]	15	0	0	$2,261m
2003 total promotional spend ranking [2]	10	1	10	$453.59m
Sales force capability	10	2	20	Global
			45	
Product				
Efficacy	10	2	20	
Patent status	15	2	30	Formulation patent expires in 2017 (US), product patent expiry passed
Delivery	10	0	0	
Administration frequency	5	-2	-10	Usually used twice daily
Severity of side effects	10	-1	-10	
			30	

Source:

1= Datamonitor, PharmaVitae company reports

2= Promotional Data, IMS Health, April 2004, Copyright ©, reprinted with permission

ims™ DATAMONITOR

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505640

PTX0098-00065
CIPLA LTD. EXHIBIT 2021 PAGE 65

US

The formulation patent for Rhinocort is due to expire in 2017, outside the forecasting window. The FDA approved a change for Rhinocort's pregnancy rating to Category B for the treatment of allergic rhinitis, which may encourage more physicians to prescribe it. All other intranasal corticosteroids approved by the FDA for the treatment of allergic rhinitis are rated Pregnancy Category C.

EU

The product patent for budesonide expired in 1993 across the EU. AstraZeneca has many patents covering the formulation and delivery device associated with Rhinocort, the latest of which expires in 2014. The validity of these patents may come into dispute before 2014, but Datamonitor does not predict a significant impact within the forecast window.

Japan

In Japan, a similar situation exists to that in the EU. The product patent expired in May 1993, but the latest patent coving Rhinocort is a process patent expiring in 2010. No impact is forecast due to the nature of the Japanese market, and evidence from previous corticosteroid patent expiries in Japan.

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505641

PTX0098-00066
CIPLA LTD. EXHIBIT 2021 PAGE 66

Flonase analysis

Table 27: Flonase: key facts	
Generic	fluticasone
AR formulation	Flonase aqueous nasal spray
Originator	GlaxoSmithKline
Marketing companies	Almirall Prodesfarma
2003 global sales [1]	$1,073.9m
2002–03 sales growth [1]	16.7%
Indications	Seasonal and perennial allergic rhinitis
Launch date [2]	1994 (Japan) 1995 (US, EU)
Patent expiry date [3,4]	May 2004 (US pediatric extension), March 2005 (Germany, UK, France)
Alternative brand names	Flixonase, Flunase, Flixotide
Key clinical trials	Scadding GK *et al.*, 1995

Source:

1 = MIDAS Sales Data, IMS Health, April 2004, Copyright ©, reprinted with permission

2 = IDdb, August 2004, Copyright Thomson Scientific

3 = Dolphin, August 2004, Copyright Thomson Scientific

4 = FDA Orange Book

ims™ DATAMONITOR

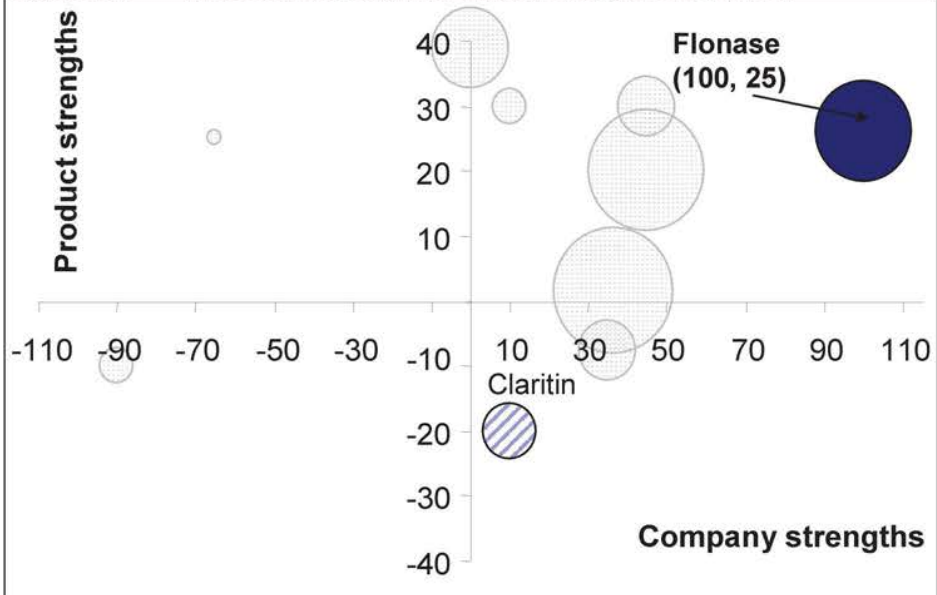
© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505642

PTX0098-00067
CIPLA LTD. EXHIBIT 2021 PAGE 67

Flonase strategic analysis and forecasting assumptions

Figure 18: Flonase product and company strength comparison



- Flonase is marketed by GSK, and has the strongest company profile in the market
- The impact of the 2004 product patent expiry is predicted to be insignificant.

Source: Datamonitor

DATAMONITOR

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505643

PTX0098-00068
CIPLA LTD. EXHIBIT 2021 PAGE 68

Table 28: Flonase company and product strength scores				
Strengths/weaknesses	**Weighting**	**Score**	**Total**	**Notes**
Company				
2004 company revenue forecast [1]	15	2	30	US$29,219m
2003 respiratory portfolio revenues[1]	15	2	30	US$7,214m
2003 total promotional spend ranking[2]	10	2	20	US$636.83m
Sales force capability	10	2	20	Global
			100	
Product				
Efficacy	10	2	20	
Patent status	15	1	15	May 2004, (but US-marketing exclusivity Nov 2006)
Delivery	10	0	0	Nasal spray
Administration frequency	5	0	0	Daily
Severity of side effects	10	-1	-10	
			25	

Source:

1= Datamonitor, PharmaVitae company reports

2= Promotional Data, IMS Health, April 2004, Copyright ©, reprinted with permission

ims™ DATAMONITOR

> *"Flonase in my practice is not the most popular because a lot of patients feel it's too much liquid and they don't like the scent. So I actually end up using a lot more Nasacort and Rhinocort, which are scent free."* – US opinion leader

US

The fluticasone product patent expired in May 2004 in the US, but has exclusivity until November 2006 due to the results of a long-term longitudinal growth study and pediatric safety information. Ivax submitted an ANDA with the FDA in March 2003 for a generic aqueous nasal spray for use in allergic rhinitis. The difficulty of producing a bioequivalent nasal spray while not infringing on other formulation or delivery patents can be enough to deter generic competition altogether. GSK's citizen petition, posted

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505644

PTX0098-00069
CIPLA LTD. EXHIBIT 2021 PAGE 69

June 2, 2004, urged the FDA not to approve generic versions of Flonase until the agency releases a final guidance on establishing bioavailability and bioequivalence for products that act locally and are not systemically absorbed into the bloodstream. Datamonitor predicts that Ivax will have to complete Phase III clinical trials to prove the efficacy of any novel delivery methods or formulations for their product. The regulatory framework for these generic approvals is constantly evolving around these issues. Ivax also has its own product, loteprednol etabonate, for allergic rhinitis, and is planning Phase III US trials in 2004, as a result Datamonitor predicts that generic competition will not reach the market in the near future.

EU

Patent expiry occurs in March 2005 across the EU, but no impact is forecast in this market. A European patent covers an aerosol formulation of fluticasone and expires in November 2011, although numerous other formulation patent cover the product in the EU until 2015. Generic competition is not forecast here due to uncertainty surrounding the date.

Japan

According to the Datamonitor calculation of Flonase sales in Japan, it is the largest-selling nasal corticosteroid, with sales of six times its nearest rival Vanceril (beclometasome). It was launched in Japan in 1994, and dominates the nasal corticosteroid market here. The product patent for fluticasone expired in 2001 in the Japanese market.

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505645

PTX0098-00070
CIPLA LTD. EXHIBIT 2021 PAGE 70

Nasacort analysis

Table 29: Nasacort key facts	
Generic	triamcinolone acetonide
AR formulation	Nasocort AQ
Originator	Aventis (formerly Rhone-Poulenc Rorer),
Marketing companies	Kos pharmaceuticals (Global rights acquired in March 2004)
2003 global sales [1]	$503.2m
2002–03 sales growth [1]	6.5%
Indications	Seasonal and perennial allergic rhinitis in adults and children age 6 +, asthma
Launch date [2]	1996 (US) 1997 (EU)
Patent expiry date [3, 4]	Jan 2007 (US-formulation) March 2005 (EU-formulation)
Alternative brand names	-
Key clinical trials	Condemi J *et al.*, 2000; Koepke JW *et al.*, 1997

Source:

1 = MIDAS Sales Data, IMS Health, April 2004, Copyright ©, reprinted with permission

2 = IDdb, August 2004, Copyright Thomson Scientific

3 = Dolphin, August 2004, Copyright Thomson Scientific

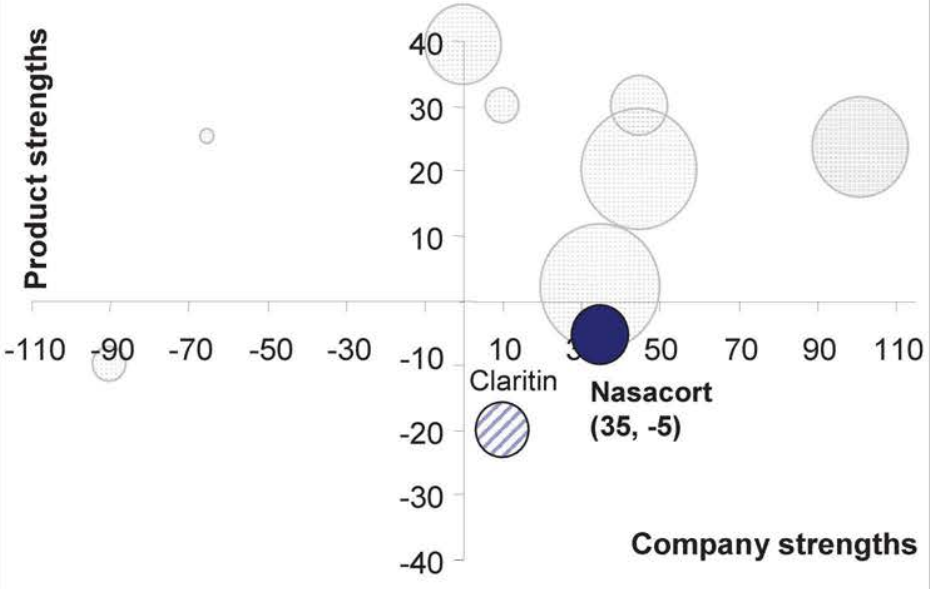
4 = FDA Orange Book

ims™ DATAMONITOR

This report is a licensed product and is not to be photocopied

Nasacort strategic analysis and forecasting assumptions

Figure 19: Nasacort product and company strength comparison



- The product patent for Nasacort AQ active ingredient triamcinolone acetonide is due to expire in 2007, creating a possible threat.
- However, later formulation and delivery patent are predicted to extent exclusivity, meaning it will have little effect.

Source: Datamonitor

DATAMONITOR

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505647

PTX0098-00072
CIPLA LTD. EXHIBIT 2021 PAGE 72

Table 30: Nasacort company and product strength scores

Strengths/ weaknesses	Weighting	Score	Total	Notes
Company				
2004 company revenue forecast [1]	15	1	15	US$19,565m
2003 respiratory portfolio revenues[1]	15	0	0	US$2,831m
2003 promotional spend ranking[2]	10	0	0	US$33.70m
Sales force capability	10	2	20	Global
			35	
Product				
Efficacy	10	2	20	
Patent status	15	-1	-15	Jan 2007 US formulation patent (no data on EU/Japan country specific)
Delivery	10	0	0	Nasal spay aq
Administration frequency	5	0	0	Once daily
Severity of side effects	10	-1	-10	
			-5	

Source:

1= Datamonitor, PharmaVitae company reports

2= Promotional Data, IMS Health, April 2004, Copyright ©, reprinted with permission

ims™ DATAMONITOR

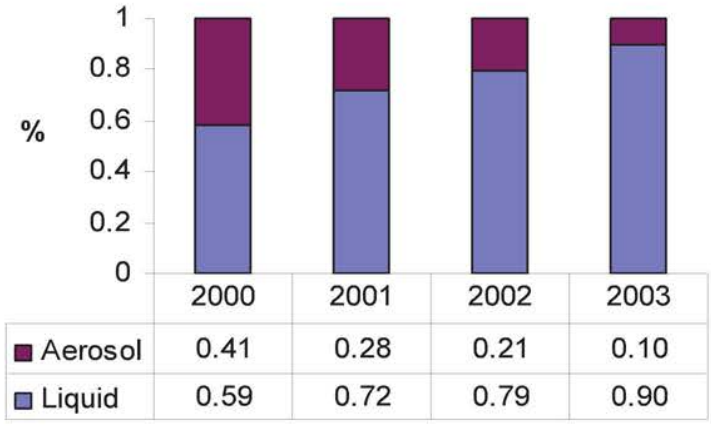
Sales data for triamcinolone acetonide are from the nasal corticosteroid AC class. These sales figures refer to the nasal topical metered-dose liquid formulation (Nasacort AQ) in all countries except the US where the value is made up of both the liquid and aerosol formulations. Figure 20 shows the formulation split, and the aerosol version can be seen to be rapidly decreasing in sales in favor of the liquid formula. Therefore sales across all seven countries are considered to be comparable as the sales of Nasacort AQ.

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505648

PTX0098-00073
CIPLA LTD. EXHIBIT 2021 PAGE 73

Figure 20: Nasacort US sales formulation split (%), 2000–03



Source: MIDAS Sales data, IMS Health, April 2004, Copyright ©, reprinted with permission

ims™ DATAMONITOR

US

The aqueous formulation patented by Aventis is not due to expire until July 2016. Despite parent expiry of the active ingredient, the aqueous nasal formulation of product looks likely to be free from generic competition for some time. However, the older formulation for the aerosol dispenser expires in January 2007. Datamonitor predicts that this competition will be insignificant as the aqueous formulation is much more preferred now, as shown in Figure 20.

In April 2004, the FDA approved Nasacort HFA nasal aerosol for the treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in adults and children aged six and older. When marketed, this will be the only nasal aerosol intranasal corticosteroid available in the US that contains hydrofluoroalkane (HFA) rather than chlorofluorocarbons (CFCs). The launch is currently planned for December 2004.

> *"Nasacort is about to come out with an HFA propellant for intra-nasal use and I think that will be popular because a lot of patients don't like the feel of a liquid spray."* – US opinion leader

This report is a licensed product and is not to be photocopied

MEDA_APTX03505649

PTX0098-00074
CIPLA LTD. EXHIBIT 2021 PAGE 74

EU

Nasacort AQ was launched in the UK and France in February 1997 and in 13 other EC countries in December 1997. The EU formulation patent is not predicted to expire within the forecast time frame.

Decongestant analysis

Decongestants help dry nasal congestion and work by shrinking vessels in the nose. By reducing blockage, they decrease the risk of developing sinusitis caused by viruses or bacteria. Many over-the-counter decongestants are available, either in tablet form or as nasal or inhaled decongestants that are applied directly into the airways as sprays, drops or vapors.

Decongestant market performance

Oral delivery

Oral decongestants come in many brands, which mainly differ in their ingredients. The most common active ingredient is pseudoephedrine (Sudafed, Actifed, Drixoral). The alternative decongestant, phenylpropanolamine (PPA) was taken off the market in 2000. The FDA recommends that consumers read the labels of OTC drug products to determine if the product contains PPA.

Nasal delivery

The major hazard with nasal-delivery decongestants, particularly long-acting forms is a cycle of dependency and rebound effects. The 12-hour brands pose a particular risk for this effect. This effect works in the following way:

- with prolonged use (more than three to five days), nasal decongestants lose effectiveness and even cause swelling in the nasal passages;
- the patient then increases the frequency of their dose. The congestion worsens and the patient responds with even more frequent doses, in some cases to as often as every hour;
- individuals then become dependent on them.

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505650

PTX0098-00075
CIPLA LTD. EXHIBIT 2021 PAGE 75

CHAPTER 5 ENVIRONMENTAL ASSESSMENTS

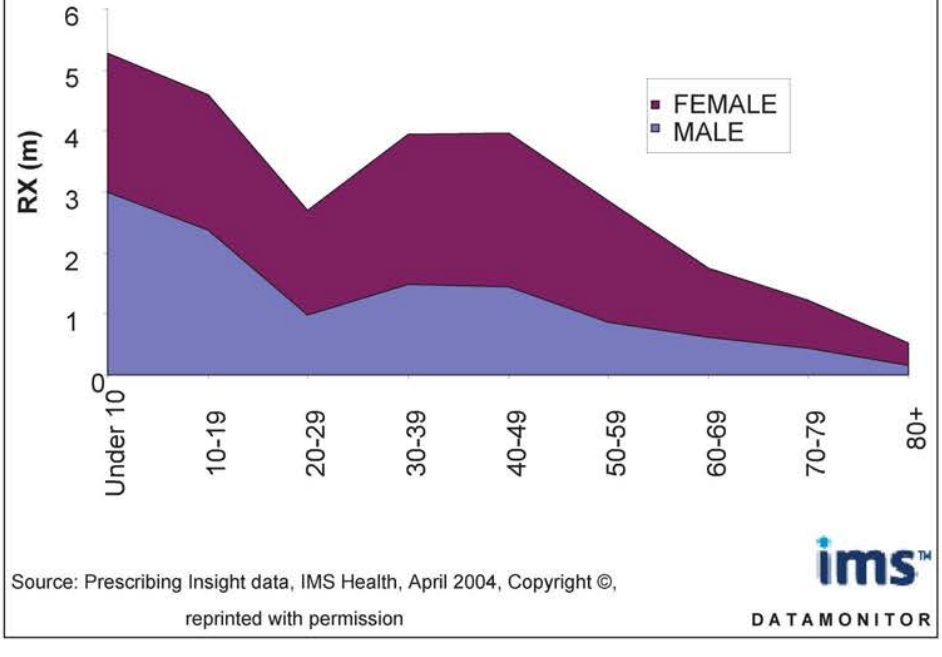
Current and future opportunities and threats in the allergic rhinitis market

This section will outline environmental factors that will provide or threaten growth in the market. The global market is sectioned into US, Japan and EU, with any country specific issues highlighted within the EU. Each can also be judged in terms of patient demographics, by age and sex, creating obvious opportunities or threats within target groups.

US: opportunities and threats

The patient demographics outlined in Figure 21 show a large proportion of prescriptions written for patients under 10 years. There is a dip in prescription for 20- to 29-year olds in both sexes.

Figure 21: Patient demographic for allergic rhinitis prescription volumes, US, 2003



Source: Prescribing Insight data, IMS Health, April 2004, Copyright ©, reprinted with permission

This report is a licensed product and is not to be photocopied

MEDA_APTX03505651

PTX0098-00076
CIPLA LTD. EXHIBIT 2021 PAGE 76

> *"I think the drop at age 20–29 is primarily due to healthcare coverage, most US jobs have fewer health benefits. So, it would be the age group that has been the hardest hit with unemployment, the recent college graduates not finding jobs and when they do find a job it doesn't have the health benefits that most positions would have had previously."* – US opinion leader

Opportunities

Growth in prescription drug spend

Prescription drug spending is projected to remain one of the fastest-growing sectors in the US economy, although the rate of growth is declining, from 13.4% in 2003 to 12.9% in 2004.

Legal use of DTC advertising

Allergy medication has made good use of DTC advertising in the US market, for example AstraZeneca's 'Tough on Nasal Allergies, Gentle on the Nose' Rhinoceros and butterfly advertising campaign for Rhinocort, which was produced in collaboration with NetPlus Marketing, has been praised by industry advertising standards. Total promotional spend in 2003 for the US allergy market was US$377.2 m (MIDAS Promotional Data, IMS Health, April 2004)

Over 65s prescription drugs covered by Medicare reform

In 2006, the Medicare reforms will allow over 65s to only pay 25% of co-payments up to $2,250, at a monthly premium of $35. From May 2004 until 2006, a discount card scheme will be available from pharmacy benefit managers (PBMs). However, only 8.8% (IMS Prescribing Insights, IMS Health, March 2004) of prescription for allergic rhinitis drugs come from patients age 65 and over, producing only a small lift in the overall market.

Threats

Hatch-Waxmann 2003 updates

New patents no longer protect older drugs, as a result of new pro-generic rules that were implemented in June 2003 to try and reduce some of the litigation that accompanies patent challenges.

The patent expiry of Claritin (loratadine) in the US in December 2002 led to an influx of generic loratadine onto the market. This cheaper antihistamine created a fall in both Claritin sales and, less dramatically, other leading antihistamine brands. Allegra

This report is a licensed product and is not to be photocopied

(fexofenedine) faces generic erosion in 2004 increasing the competition from generic versions, impacting on the market as a whole as patients find it easier to switch to cheaper versions.

Variation in HMO co-payments

The brand with the lower co-payment will automatically be selected by the patient. Efficacy is relatively similar across the leading brands; therefore the cost to the patient will be the deciding factor. The level of co-pay varies across HMOs, which may lead to a leveling out of this factor

FDA initiative for antihistamine switch to OTC status

The Durham-Humphrey Amendment of 1951 gives the FDA the power it requires to force a drug over the counter. This law states that only drugs selected by the FDA can be designated prescription, all others default to OTC status.

The Department of Health and Human Services (DHHS) 2004 US Budget indicated the FDA's intention to increasing switches as a means of improving public health (http://www.fda.gov/oc/oms/ofm/budget/2004/BIB.htm). The budget states that the FDA aims to become more proactive in recommending key potential prescription (Rx)-to-OTC switches, and $1m has been allocated to improving OTC approval and assessment processes. The aim is to further consumer empowerment in self-medication as well as provide a way to reduce consumer health care costs for certain ailments such as allergic rhinitis.

One scenario that could benefit pharmaceutical companies is having dual status for a drug. This would allow an Rx and OTC product with the same brand name to appear on the market simultaneously. Both drugs would be under patent protection. However, the OTC version would be available in a lower dose than the Rx. The Rx version would be covered by insurance.

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

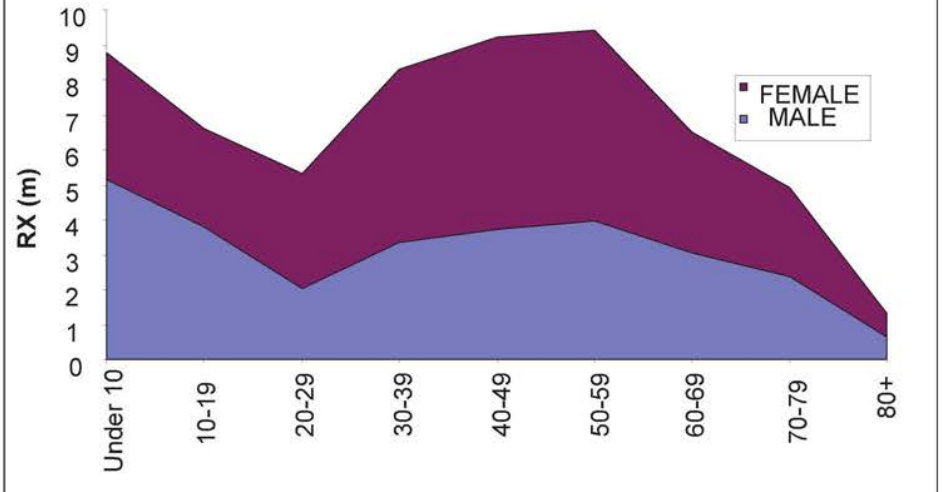
MEDA_APTX03505653

PTX0098-00078
CIPLA LTD. EXHIBIT 2021 PAGE 78

Japan: opportunities and threats

The patient demographics outlined in Figure 22 show a large proportion of prescriptions written for patients under 10 years. There is a dip in prescription for 20- to 29-year olds in both sexes, as with the US.

Figure 22: Patient demographic for allergic rhinitis prescription volumes, Japan, 2003



Source: Prescribing Insight data, IMS Health, April 2004,

Copyright ©, reprinted with permission

ims™ DATAMONITOR

> *"One possibility ... [for the high number in under 10-year olds]…is the need to perform better in schools which requires higher level of concentration. I have seen in the past some young patients aged 10–15 in my allergy clinic coming in to receive treatment 'because their teachers in school wanted them to go to a doctor' because they believed that the symptoms are hindering them from better performance at school."* – Japanese opinion leader

Conversely, opinion leader research found that a possible reason for the drop prescriptions for patients age 20–29 is similar to that in other countries: people at this age tend to be particularly career or possible family orientated, leaving little time for visits to the doctor for a non life-threatening disease.

MEDA_APTX03505654

PTX0098-00079
CIPLA LTD. EXHIBIT 2021 PAGE 79

> *"The drop in prescription between 20–29 probably reflects lack of time allowed to make a visit for a disease which do not risk their life"* – Japanese opinion leader

Opportunities

Pharmaceutical affairs Law 2003

One of the major changes to be made to Japanese law is the introduction of product specific drug approvals as opposed to the manufacture/import-based marketing authorization currently operated. This switch is expected to be implemented by 2005 and will allow the manufacturer and marketer to be different entities so that foreign companies operating outside Japan can directly market their products.

Little switching of products to OTC status

Products remain prescription only in Japan long after they have switched to OTC in other countries. The 2003 changes to the pharmaceutical law have increased post-marketing surveillance requirements and also regulations on the provision of information to both patients and healthcare professionals for OTC drugs. These tougher requirements are also expected to be implemented by 2005.

> *"Many patients who come to our office prefers to come to us because of safety issues. Some come after trying several drugs over the counter but without an adequate effect."* – Japanese opinion leader

> *"However, another influencing factor is the economy since many people now have less time and money, which forces them to take over the counter medicines rather than to visit a doctor"*

Low level of generic prescribing

Generic prescribing is very low in Japan, when compared to international standards. They now account for 10–12% of total sales volume (Ethical Pharmaceutical Manufacturers Association, 2003). A general attitude among prescribers is that any cost savings made do not outweigh the possible safety risks and inconsistent supply. This represents an opportunity for foreign companies coming into Japan whose patent is close to expiry as the impact on sales will be less. However, the level of generic prescribing is rising due to government initiatives such as higher co-payment fees and the separation of prescribing and dispensing. This factor will turn into a threat in the future if generic growth continues at above pharmaceutical market average, as it is currently increasing at 7% per year.

This report is a licensed product and is not to be photocopied

MEDA_APTX03505655

PTX0098-00080
CIPLA LTD. EXHIBIT 2021 PAGE 80

New generic drugs

The price calculation for new generic drugs has been changed from 0.8 to 0.7 times the price of the new drug. The Ethical Manufacturers Association, an organization of generic drug manufacturers, noted price discrepancies in new generic products and the new pricing structure was implemented in the 2004 pricing reviews. (All generic launches in the forecast therefore follow this rule).

The result is less profit for generic manufacturers, which may discourage generic competition in a market where it is already difficult.

Threats

Data confidentiality

Data confidentiality and exclusivity has emerged as a key issue for the research-based pharmaceutical industry in the past two years. The 2001 Public Information Access Law requires broad disclosure of information by both regulators and the pharmaceutical industry, and innovative companies complain that commercially valuable information is being released. A Drug Master File is scheduled for introduction in 2005, and aims to increase the level of data confidentiality. The Japanese industry federation has also petitioned the government to increase the data protection period by eight years, to make it comparable to the EU.

Price cuts

Every two years the Japanese price revision system aims to bring reimbursement prices in line with the actual prices in the marketplaces, usually resulting in a cut. In the April 2004 reimbursement changes, anti-allergics (excluding antihistamines) received an average price cut of 7.1%, the third largest in the pharmaceutical market. The MHLW acknowledge that this price regime has a negative effect on the development of the pharmaceutical industry, but reforms are unlikely to take place until 2007–08.

EU: opportunities and threats

Opportunities

EU expansion

The addition of 10 new countries to the EU offers opportunities for pharmaceutical companies, but it is vital to understand the market conditions within each country before launching products there.

Extention of patent protection

This report is a licensed product and is not to be photocopied

MEDA_APTX03505656

PTX0098-00081
CIPLA LTD. EXHIBIT 2021 PAGE 81

In December 2003, patent protection for new medicines, which formerly extended between six and 10 years from when a medicine went on sale, was standardized at 10 years across the European Union. However, two years before the protection expires, generic drugs makers will be able to start the application process for approval to sell their generic drugs. This concession makes it easier for them to get their versions on the market as soon as patent protection expires.

Patients tend to opt for branded products if price differences are relatively small. A lowering of generic prices will encourage more patients to choose generics. In addition, the lowering of generic prices will also place more pressure on branded products, especially, when reference-pricing systems, particularly in Germany and Italy, are based on generic medicine prices.

Threats

No DTC advertising

The advertising of prescription medicines to the general public is prohibited throughout the EU, and member states are also allowed to ban advertising of reimbursed products. OTC products may be advertised to the public, but all advertisements must include: the name of the product, directions for its use and an instruction to read the package leaflet carefully.

Parellel imports

Parallel imports are now estimated to account for some 4–5% of all EU pharmaceutical sales. The UK and Germany are the most important target countries for parallel imports and Germany has even passed legislation to encourage the dispensing of parallel imports. The products are mostly exported from lower-priced southern EU countries.

However, the widely held belief that the addition of 15 more countries to the EU would result in lower priced drugs being imported has been dispelled by a recent report by IMS. It was found that for a number of recently launched innovative products, prices in central and Eastern Europe were actually higher than in the 15 EU countries (Haigh J 'Separating the myths from the reality: East-West parallel trade', IMS, October 14, 2003).

EU country-specific demographics

The following five figures outline the patient demographics for France, Germany, Italy, Spain and the UK. The Mediterranean countries of Italy and Spain do not show the trend of low prescription volume in the 20–29 age range.

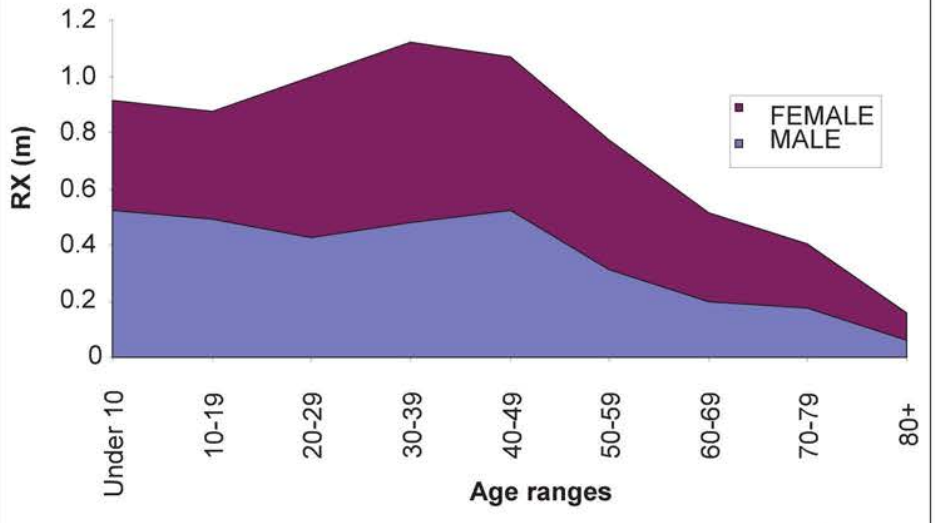
This report is a licensed product and is not to be photocopied

MEDA_APTX03505657

PTX0098-00082
CIPLA LTD. EXHIBIT 2021 PAGE 82

France

Figure 23: Patient demographic for allergic rhinitis prescription, France, 2003



Source: Prescribing Insight data, IMS Health, April 2004,

Copyright ©, reprinted with permission

ims™ DATAMONITOR

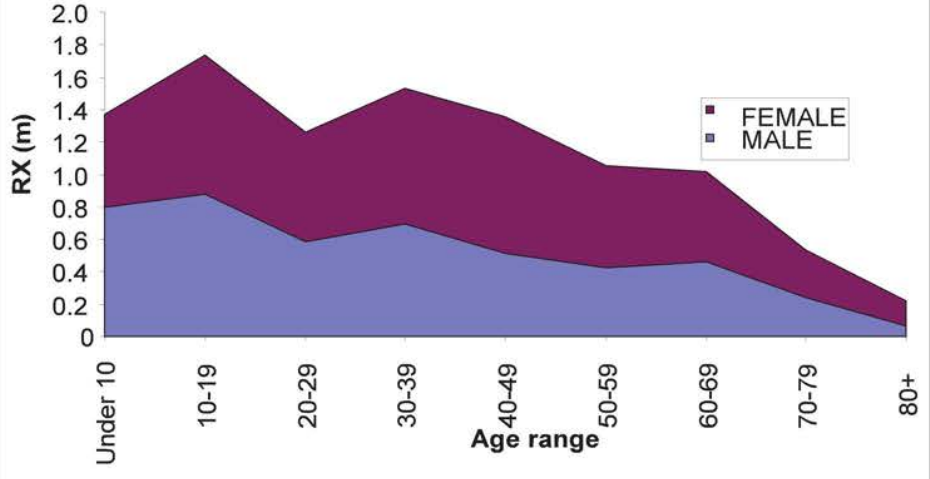
MEDA_APTX03505658

PTX0098-00083
CIPLA LTD. EXHIBIT 2021 PAGE 83

Germany

"This decrease is just due to the adolescents, so that the patients grow out of their disease." – German opinion leader

Figure 24: Patient demographic for allergic rhinitis prescription, Germany, 2003



Source: Prescribing Insight data, IMS Health, April 2004,

Copyright ©, reprinted with permission

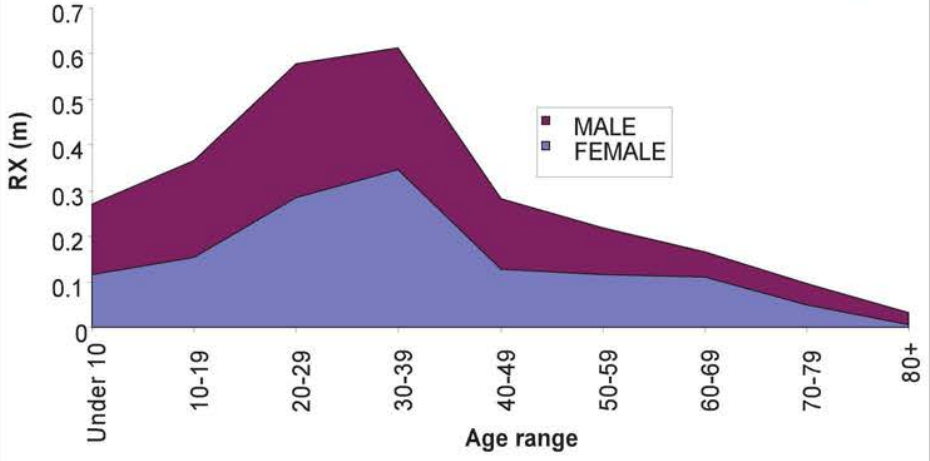
ims™ DATAMONITOR

MEDA_APTX03505659

PTX0098-00084
CIPLA LTD. EXHIBIT 2021 PAGE 84

Italy

Figure 25: Patient demographic for allergic rhinitis prescription, Italy, 2003



Source: Prescribing Insight data, IMS Health, April 2004, Copyright ©, reprinted with permission

ims™ DATAMONITOR

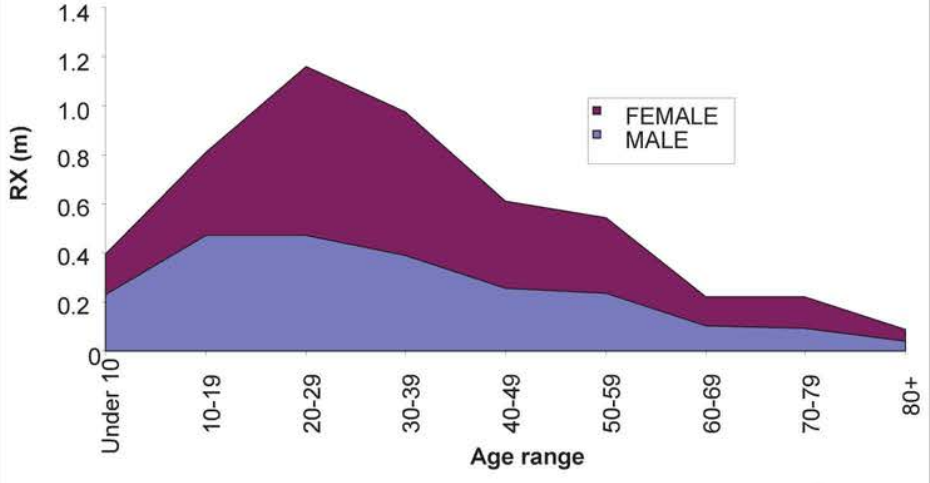
This report is a licensed product and is not to be photocopied

MEDA_APTX03505660

PTX0098-00085
CIPLA LTD. EXHIBIT 2021 PAGE 85

Spain

Figure 26: Patient demographic for allergic rhinitis prescription, Spain, 2003



Source: Prescribing Insight data, IMS Health, April 2004,

Copyright ©, reprinted with permission

ims™

DATAMONITOR

This report is a licensed product and is not to be photocopied

MEDA_APTX03505661

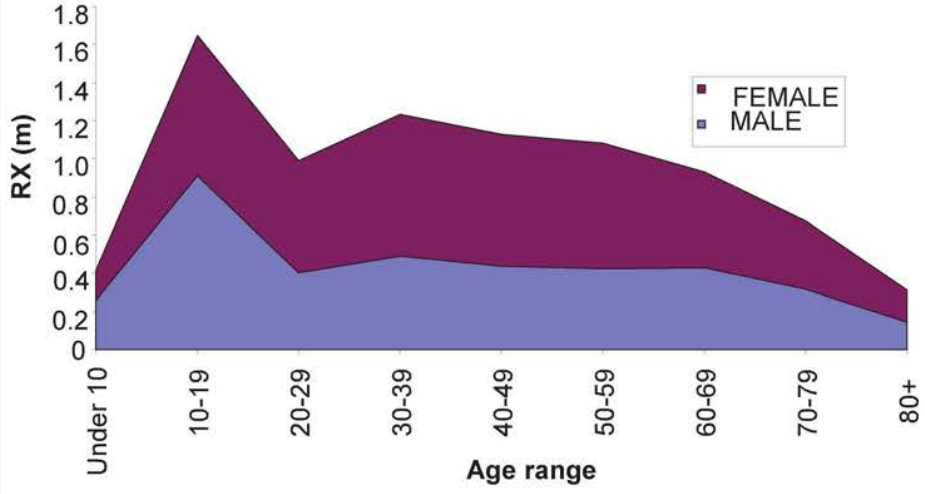
PTX0098-00086

CIPLA LTD. EXHIBIT 2021 PAGE 86

UK

> *"It is very, very easy here to get virtually everything OTC, and that is the line of least resistance. Busy jobs, can't be bothered to go to GPs therefore if they can get a quick fix from a chemist, that would be the least line of resistance and I think that is the way hayfever in this country is dealt with and that is the policy of the government, we don't have any allergy specialists, so we will just make everything available OTC and we will make the pharmacists the allergy specialists."* – UK opinion leader

Figure 27: Patient demographic for allergic rhinitis prescription, UK, 2003



Source: Prescribing Insight data, IMS Health, April 2004,
Copyright ©, reprinted with permission

ims™ DATAMONITOR

MEDA_APTX03505662

PTX0098-00087
CIPLA LTD. EXHIBIT 2021 PAGE 87

CHAPTER 6 CASE STUDIES

Case study one – Impact of regulatory change on patent protection for allergic rhinitis treatment

Small changes in intellectual property and patent law can result in substantial and even unintended consequences. It is important to incorporate these changes into market assessment and forecasts as the patent position is the key factor in the strength of the brand and therefore the greatest threat to profitability.

Frivolous patents or genuine discoveries?

This debate as to the validity of a patent is at the heart of most generic challenges and the ensuing litigation. Many of the patents involved in litigation have been issued years after the drug was first approved. Changes to the existing law aim to change this practice, which will influence sales of drugs targeted by generic companies.

It is worth noting that at present the majority of drugs do not simply go off patent (Green, 2002). The branded companies continue to obtain patents throughout the life of a drug and list them all in the Orange book. Generic competition usually starts not because there is no patent, but when all the listed patents have been proven invalid or have been avoided.

It is the burden of the generic company to prove invalidity within the lifetime of the patent.

New patents no longer protect old drugs

It is this excessive protection that has been reduced by amendments to the Hatch-Waxman Act in June 2003. The effect on generic approvals in the US will create a global knock on effect in the industry with Europe likely to not only follow, but to learn from the US market reactions.

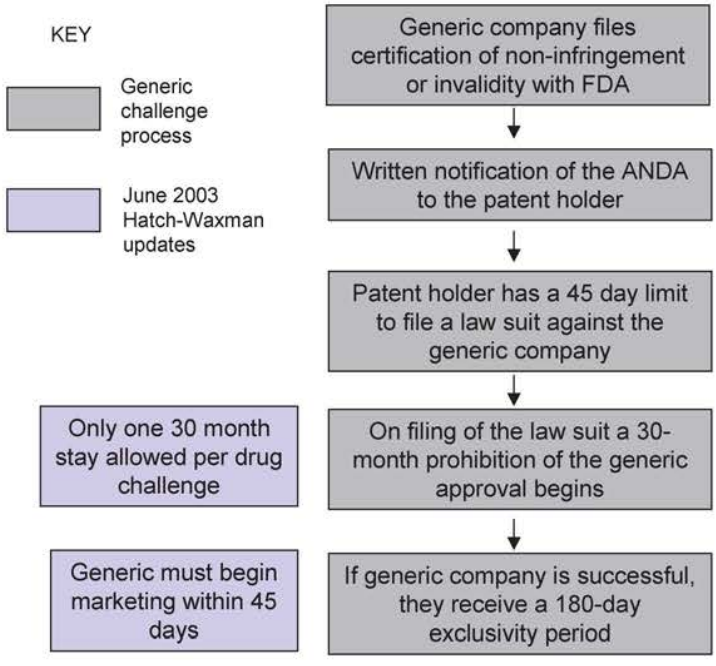
© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505663

PTX0098-00088
CIPLA LTD. EXHIBIT 2021 PAGE 88

Figure 28: Generic approval process



Source: Datamonitor DATAMONITOR

Pharmaceutical patent law states that the patent holder does not have to prove the merit of the patent that has been challenged, as in other patent litigation. Therefore the 30-month statutory stay is granted even if the patent does not have a strong case.

The June 2003 amendment has prevented the practice of 'chaining' patent lawsuits, which involves the brand name company registering an additional patent after the generic applicant has filed its ANDA. More than one 30-month stay may be generated as a result. The amendment only allows one 30-month stay per generic drug challenge, therefore closing the loophole left in the 1984 act.

The 45-day rule aims to prevent the brand companies creating incentives to keep the generics off the market.

The filing of patents for aspects of the 'old' drug, such as formulation, packaging and delivery, increases the amount of litigation required for a generic challenge. For

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505664

PTX0098-00089
CIPLA LTD. EXHIBIT 2021 PAGE 89

example, the formulation patent on Rhinocort is currently keeping generic competition at bay, with the active ingredient budesonide having lost protection in 1998.

Other strategies currently used are outlined below, and have particular relevance to the antihistamine class as metabolite patents cover leading brands such as Allegra and Clarinex.

Submarine patents

The skill required here is to keep a patent pending for the optimum period of time at the US PTO. Issuing of that patent shortly before a basic patent expires will clearly prolong the exclusivity period.

Metabolites

This strategy has been used by Aventis, and is particularly relevant to the upcoming trials involving the patent challenge of Allegra. It involves the staggered patenting of metabolites of the original drug in an attempt to extent the exclusivity. For example, before Seldane (terfenadine) was withdrawn from the market, the generic competition was prevented by the patent that covers its metabolite, fexofenadine. This same patent is now being challenged.

Polymorphs

Patents are also filed in the Orange Book for different forms of a drug. Some molecules can exist in various structures (polymorphs), which have little meaningful therapeutic difference, but allow a new patent to be listed even if the structure is not actually used in the commercial drug product. The result of this is to again increase litigation for the generic company, as they must prove that all listed polymorphs are either not infringed or invalid.

Formulation/delivery device patents

This method has been applied to asthma and allergic rhinitis drugs available through the use of an inhaler of metered delivery device. When the main product patent expires the generic company must find a way to circumnavigate the patents for the formulation and/or the method of delivery used in the branded product, while maintaining bioequivalence. This is a costly and difficult task, and may result in a request for clinical trials to prove the efficacy of the new formulation or delivery method found by the generics company.

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505665

PTX0098-00090
CIPLA LTD. EXHIBIT 2021 PAGE 90

Implications of changes on the antihistamine market

Xyzal (levocetirizine) is the active enantiomer of Zyrtec (cetirizine), and may therefore come under attack from generic manufacturers, as it is a metabolite of the old drug and so covered in that patent.

At the end of October 2003, a petition for a hearing in the case of *Schering Corp v. Geneva Pharm et al.* was denied. This case represents important potential changes in patent law that will influence the outcome of the Allegra challenge and any future litigation. The case arose from the patent infringement suit initiated by Schering against Geneva and a number of other generic drug companies. The patents covering loratadine ('233) and the one covering desloratadine ('716) were under scrutiny, with the generics claiming that patent '716 was invalid as the prior patent implied the existence of the metabolite, even though it was not specifically mentioned. Schering argued that there was no publicly available information on the fact that loratadine converts to desloratadine on oral administration, therefore the '233 patent could not anticipate the '716 patent. However, the court disagreed with this and held that the desloratadine patent was invalid.

The knock-on effect of this decision will be negative for ethical pharmaceutical companies looking to bring NMEs to market, especially those that are producing drugs that have an active metabolite mechanism, as a precedent has been set. Metabolite patents may no longer have any significant value, and as Allegra is essentially a metabolite of Seladane, whose patent has already expired, the outcome of the September 2004 trial does not look good for Aventis.

> *"Schering-Plough had hoped to extend its exclusive hold over Claritin to 2004 and beyond because of a related patent on Clarinex. Clarinex is created in the human body when people swallow Claritin, and Clarinex's patent expires in 2004. Schering-Plough argued that anyone swallowing a generic version of Claritin would create Clarinex in their body without the company's permission. By selling their Claritin knockoffs, generic manufacturers would induce patients into undertaking this infringement, Schering-Plough argued, and such inducement is illegal. This argument has been used by other drug makers – and dismissed by other judges." – Wall Street Journal*, August 2002

This report is a licensed product and is not to be photocopied

MEDA_APTX03505666

PTX0098-00091
CIPLA LTD. EXHIBIT 2021 PAGE 91

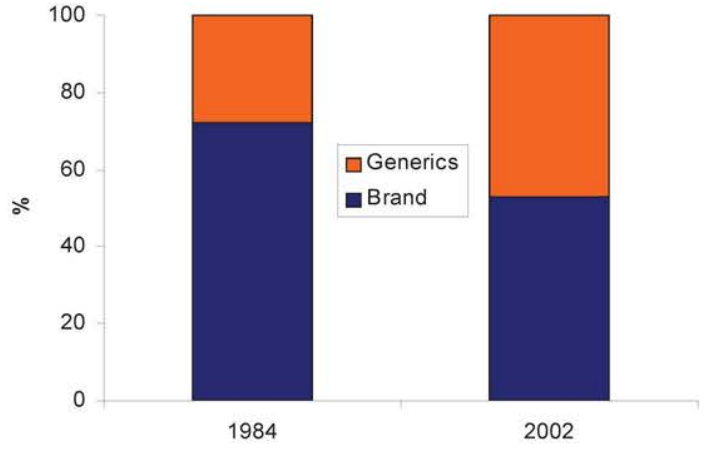
Regulatory positions on generic approvals

US

In June 2003, the FDA announced its intention to increase both funding and staffing at the Office of Generic Drugs (OGD) in 2004, in an effort to speed the generic review and approval process. The government appears committed to using generic substitution to reduce pharmaceutical inflation. This followed the introduction of new pro-generic rules that were implemented in 2003 to try and reduce some of the litigation that accompanies patent challenges.

Generics have been slowly increasing since the original Hatch Waxman Act in 1984, as shown in Figure 29.

Figure 29: Impact of the Hatch Waxman Act since its 1984 introduction



Source: Federal commission into generic drug entry DATAMONITOR

EU

Encouraging the substitution of generics for branded products has been a common method of cost containment across Europe, and is a key factor driving the growth of generics usage. The introduction of lower priced generics from accession countries (Czech Republic, Cyprus, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia and Slovenia) has provided increased incentives for Western European governments to implement additional measures that promote widespread generic substitution and therefore reduce healthcare costs. This is well illustrated by Portugal and Sweden, who encouraging generic substitution by allowing patients to opt for branded drugs as long as they pay the differential cost.

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505667

PTX0098-00092
CIPLA LTD. EXHIBIT 2021 PAGE 92

Generic drug manufacturers have argued that the system for generic drug entry in the EU falls short of the US, Canadian and Indian systems wherein generic drugs can be marketed as soon as patents expire. This is called the Bolar system in the US, and generic drug manufacturers are seeking to have a similar system adopted in Europe.

Japan

The generics market in Japan accounts for a lower proportion of the total pharmaceutical market than in the US or Europe due to a number of factors:

- strong brand loyalty among Japanese physicians;
- reliability and quality concerns;
- annual generic drug listing;
- pricing policy maintains relatively high generic prices.

Another constraint on the market is that generic drugs can only be listed in the reimbursement tariff once a year, in July. Therefore if a drug is patent protected until August, it will be safe from generic competition until July the following year, essentially providing the drug with a further 12 months of exclusivity.

The fact that generic drug prices are lower than branded pharmaceuticals can dissuade pharmacies and physicians from prescribing and dispensing generics. The difference between the purchase prices of pharmaceuticals set by wholesalers and the reimbursement price set by the government, known as Yakkasa, is a key source of income for medical institutions. However, as generic drugs have lower prices, wholesalers are less inclined to provide discounts and thus prescribing and dispensing these drugs does not yield the same profits. The government has been attempting to reduce Yakkasa, as it will not only increase the prescription volume of lower cost generic drugs, but will also reduce the overall prescription rate. The main drive to achieve this is through the separation of prescribing and dispensing, so that physicians will no longer benefit from prescribing more expensive drugs.

A clear draw exists from Japan for products whose US and EU patent protection has expired. The prevalence of AR is the second highest in the world with approximately 25 million sufferers. Therefore antihistamine and corticosteroid producers would be wise to take advantage of this. Schering-Plough launched Claritin in Japan in September 2002, and has a marketing agreement with Shionogi. This drug has been very successful in the Japanese market, with 2003 sales of $94m, only one year after launch.

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505668

PTX0098-00093
CIPLA LTD. EXHIBIT 2021 PAGE 93

Case study two – Variation in degree of country-specific generic erosion for antihistamines and corticosteroids

This case study investigates the differing impacts of patent expiry in the seven countries investigated by Datamonitor. Claritin was a blockbuster antihistamine, whose patent has now expired in all seven markets. The impact in the US is the focus of analysis, with comparative assessments made with the five EU countries and Japan. This comparison also drives the assumptions made for future patent expiries in the forecasting model.

US

Antihistamine

Claritin lost its patent protection in December 2002, and suffered considerably from generic competition in this market as a result.

Table 31 shows the fall in both sales and volume of the Claritin brand and the overall loratadine molecule, following the launch of generics in Q1 2003. This impact actually began six months prior to patent expiry in the US predominantly due to wholesale stocking activity. Eight generic are available in the US, as of December 2003, according to IMS data, and create the sales and volume generic totals.

Table 31: Impact of patent expiry on volume and sales of loratadine, Q4 2002–Q4 2003[3]

	SU[1]	Sales[2]
Brand (Claritin)	-82.4	-92
Molecule (Loratadine)	-68.3	-88

1 = SU (standard units) as defined by IMS Health that one dose is equivalent to one SU

2 = Percent of US$ sales (ex-manufacturer)

3 = 13 months of data from December to December

Source: MIDAS Sales Data, IMS Health, April 2004, Copyright ©, reprinted with permission

ims™ DATAMONITOR

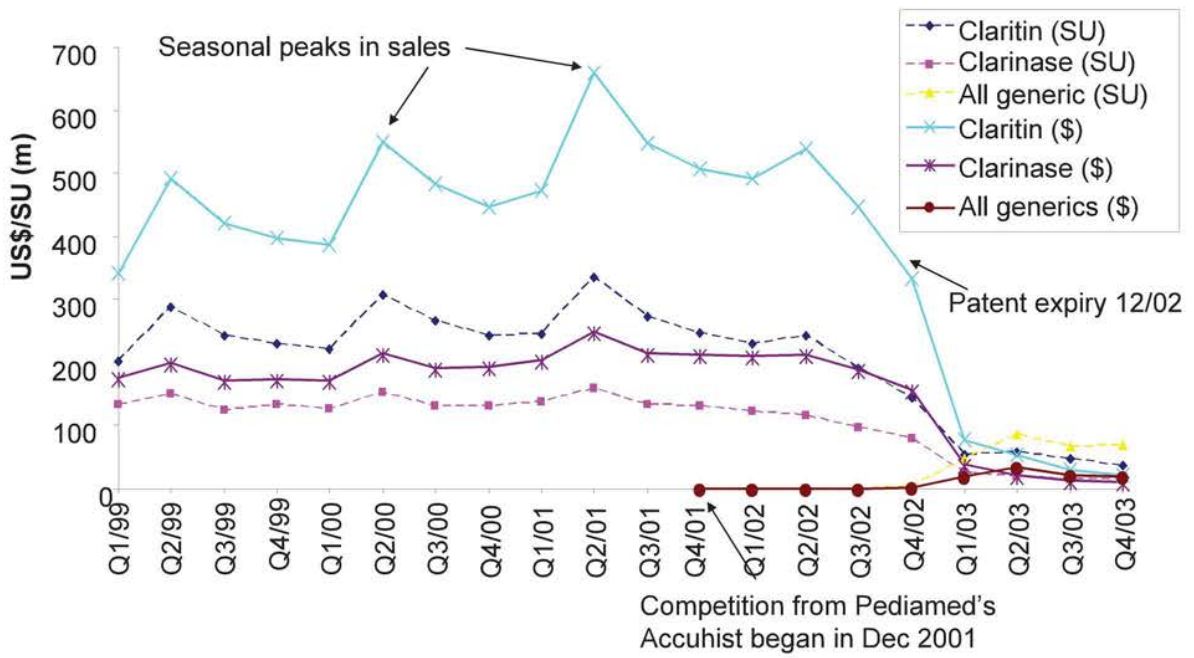
Figure 30 illustrates the trend in both SU and US$ sales by quarter in the period leading up to, and following, patent expiry.

This report is a licensed product and is not to be photocopied

MEDA_APTX03505669

PTX0098-00094
CIPLA LTD. EXHIBIT 2021 PAGE 94

Figure 30: US quarterly sales of loratadine franchise US$ (m), and SU (m), 1999–2003



SU= Standard Units, the number of "dose units" sold. It is determined by taking the number of counting units sold and dividing them by the standard unit factor which is the smallest common dose of a product as defined by IMS Health.

Source: Datamonitor; MIDAS Sales Data, IMS Health, April 2004, Copyright ©, reprinted with permission; Dolphin, August 2004, Copyright Thomson Scientific.

ims™ DATAMONITOR

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

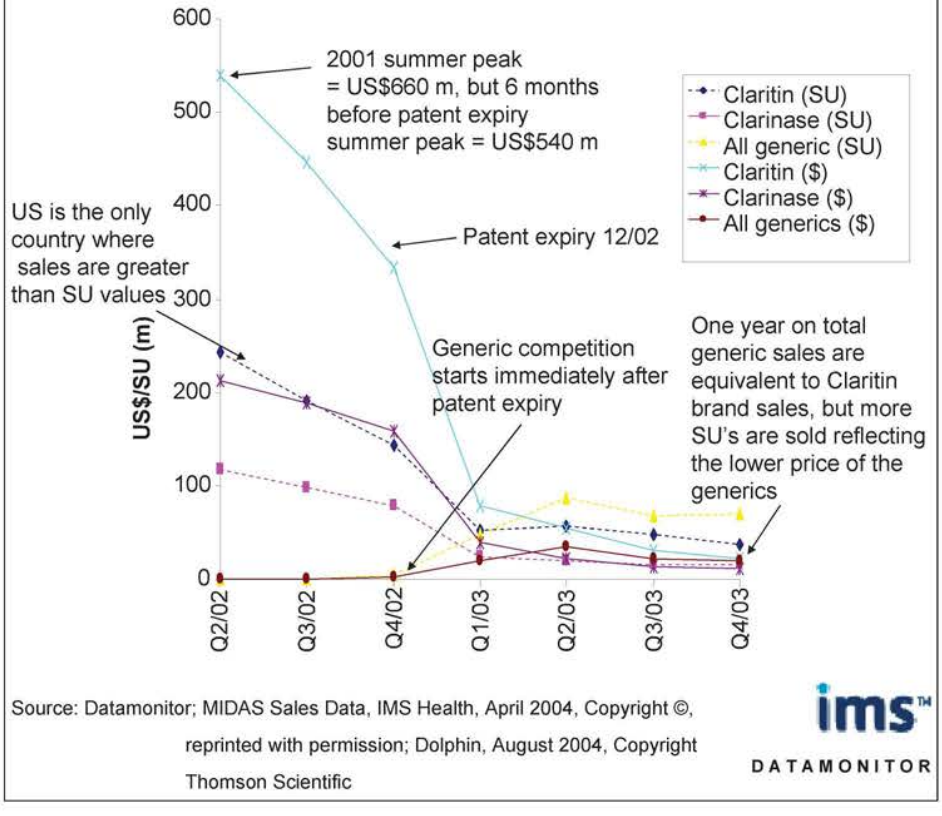
PTX0098-00095

MEDA_APTX03505670

CIPLA LTD. EXHIBIT 2021 PAGE 95

Figure 31 expands on the immediate period, pre and post patent expiry.

Figure 31: US quarterly sales of loratadine franchise US$ (m), and SU (m)), Q2 2002–Q4 2003



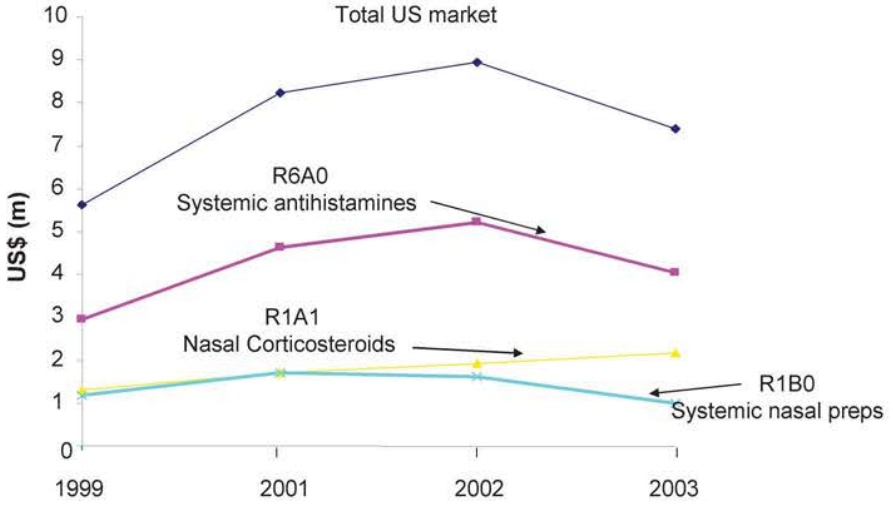
Source: Datamonitor; MIDAS Sales Data, IMS Health, April 2004, Copyright ©, reprinted with permission; Dolphin, August 2004, Copyright Thomson Scientific

ims™ DATAMONITOR

This report is a licensed product and is not to be photocopied

Figure 32 shows the effect of the Claritin patent expiry on the other AC classes in the allergic rhinitis market.

Figure 32: US annual sales of the allergic rhinitis market by AC class, US$ (billion), 1999–03



Source: Datamonitor; MIDAS Sales Data, IMS Health, April 2004,

Copyright ©, reprinted with permission

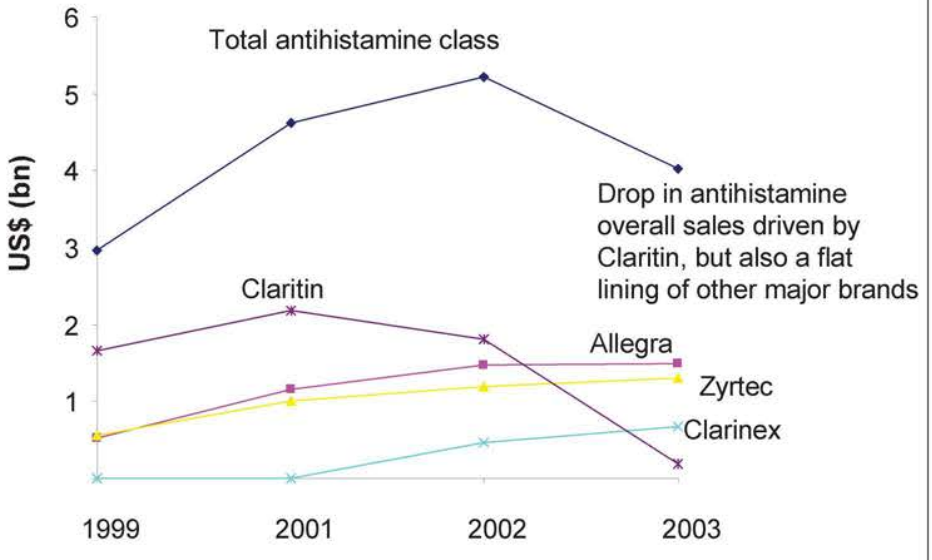
The drop in the value of the US allergic rhinitis market, as defined by Datamonitor, is driven by the fall in both the systemic antihistamine class and the systemic nasal preparations, which includes Clarinase (loratadine + pseudoephedrine). However, the impact of this drop appears to be negligible on the corticosteroid class, where a shift from steroids to the cheaper (and more easily available due to OTC status) loratadine may have been expected.

The fall in systemic antihistamine sales is obviously driven by the Claritin patent expiry, but also by a flat-lining in the sales of major rival brands such as Allegra and Zyrtec, as can be seen in Figure 33. This indicates the extent of the shift of patients from their branded antihistamine to generic loratadine.

MEDA_APTX03505672

PTX0098-00097
CIPLA LTD. EXHIBIT 2021 PAGE 97

Figure 33: US annual sales of the antihistamine class and key brands, US$ (billion), 1999–2003



Source: Datamonitor; MIDAS Sales Data, IMS Health, April 2004, Copyright ©, reprinted with permission; Dolphin, August 2004, Copyright Thomson Scientific.

ims™ DATAMONITOR

Nasal corticosteroid

Budesonide is a common corticosteroid whose primary product patent held by AstraZeneca expired in 1992. However the allergic rhinitis formulation of the product, Rhinocort, appears to be protected by a product delivery patent listed in the Orange Book to expire in October 2017. This patent covers the metered nasal spray mechanism of Rhinocort. Another formulation patent covers the aqueous formulation of budesonide used in this product. As a result no generic are available on the US market, as infringement of these complex delivery mechanisms is difficult to avoid.

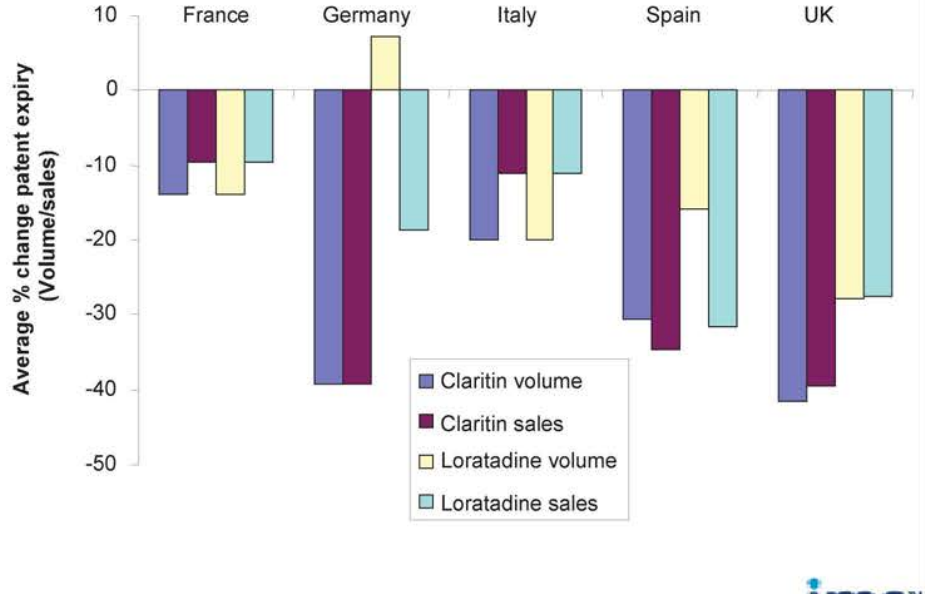
However, this varies in some markets as explained in the relevant sections below.

This report is a licensed product and is not to be photocopied

EU

The impact of patent expiry varies widely across the EU, indicated in Figure 34, depending on differing generic penetration and market circumstances. Each country impact is explored in more depth in the following sections.

Figure 34: Comparison of impacts of patent expiry on volume and value of the Claritin brand and total loratadine molecule, five EU countries



Source: Datamonitor; MIDAS Medical Data, IMS Health, April 2004, Copyright ©, reprinted with permission

ims™ DATAMONITOR

France

Antihistamine

The impact of patent expiry was much reduced in France compared to the US, and no generic competition is recorded by IMS sales.

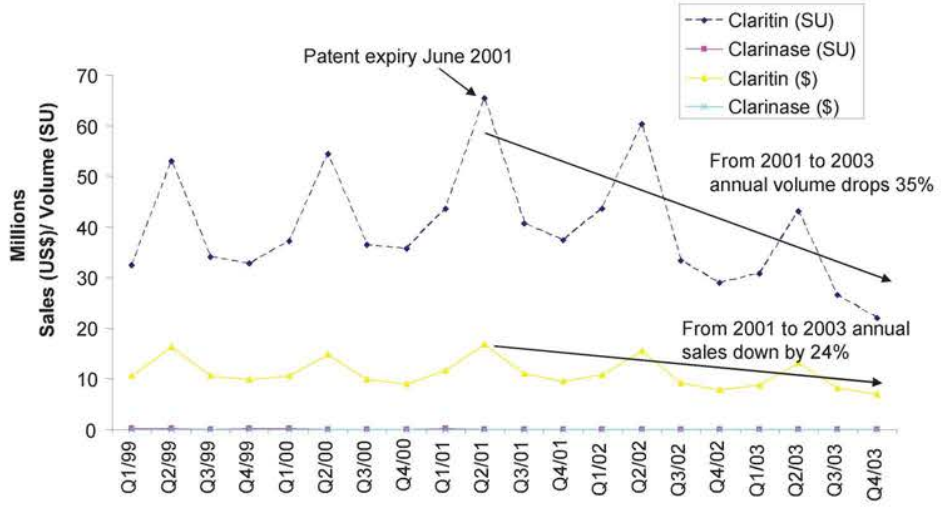
Two and a half years after expiry the volume of Claritin has decreased by 34.6 % and the sales by 24% in France. The impact on Clarinase is negligible in comparison as this product has not been particularly successful here.

This report is a licensed product and is not to be photocopied

MEDA_APTX03505674

PTX0098-00099
CIPLA LTD. EXHIBIT 2021 PAGE 99

Figure 35: French quarterly sales of loratadine franchise US$ (m) and SU (m), 1999–2003



Source: Datamonitor; MIDAS Sales Data, IMS Health, April 2004, Copyright ©, reprinted with permission; Dolphin, August 2004, Copyright Thomson Scientific

ims™

DATAMONITOR

Nasal corticosteroid

Rhinocort was launched in June 2000 in France and, in parallel with antihistamine generic competition, no generics are available for Rhinocort in France.

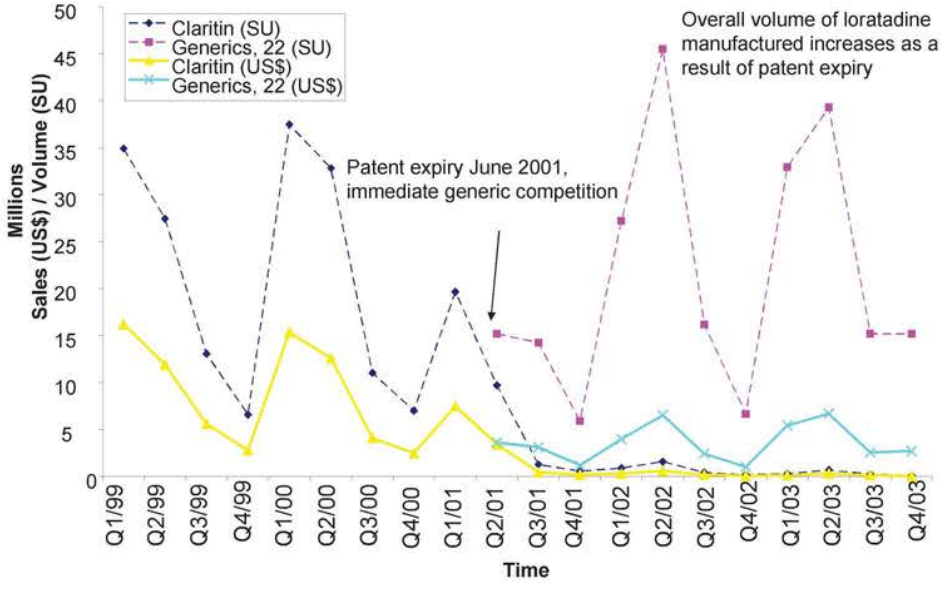
Germany

Antihistamine

Generic competition is fierce in Germany, with 22 generic currently available. Impact occurred immediately and has resulted in a 98% decrease in both Claritin brand volume and sales since patent expiry in June 2001. However, Germany is the only country that shows an increase in the volume of loratadine. This is due to the large number of generic molecules flooding onto this market at a cheaper price.

This report is a licensed product and is not to be photocopied

Figure 36: German quarterly sales of loratadine, US$ (m) and SU (m), 1999–2003



Source: Datamonitor; MIDAS Sales Data, IMS Health, April 2004, Copyright ©, reprinted with permission; Dolphin, August 2004, Copyright Thomson Scientific

ims™ DATAMONITOR

Nasal corticosteroid

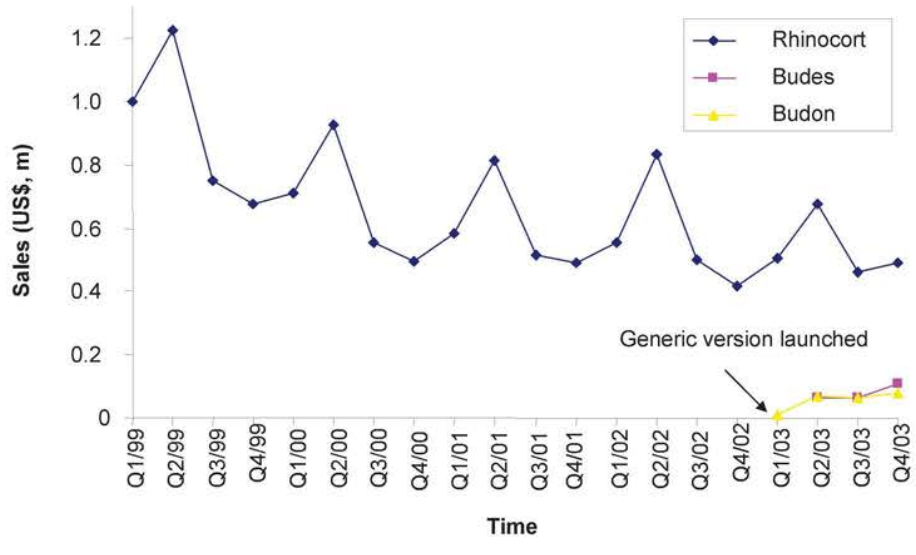
Germany shows slight generic erosion, although the date at which this started does not correspond to any patent expiry, and is more likely to be due to a breakthrough in the generic delivery mechanism research.

This report is a licensed product and is not to be photocopied

MEDA_APTX03505676

PTX0098-00101
CIPLA LTD. EXHIBIT 2021 PAGE 101

Figure 37: German quarterly sales of budesonide US$(m), 1999–2003



Source: Datamonitor; MIDAS Sales Data, IMS Health, April 2004, Copyright ©, reprinted with permission; Dolphin, August 2004, Copyright Thomson Scientific

ims™ DATAMONITOR

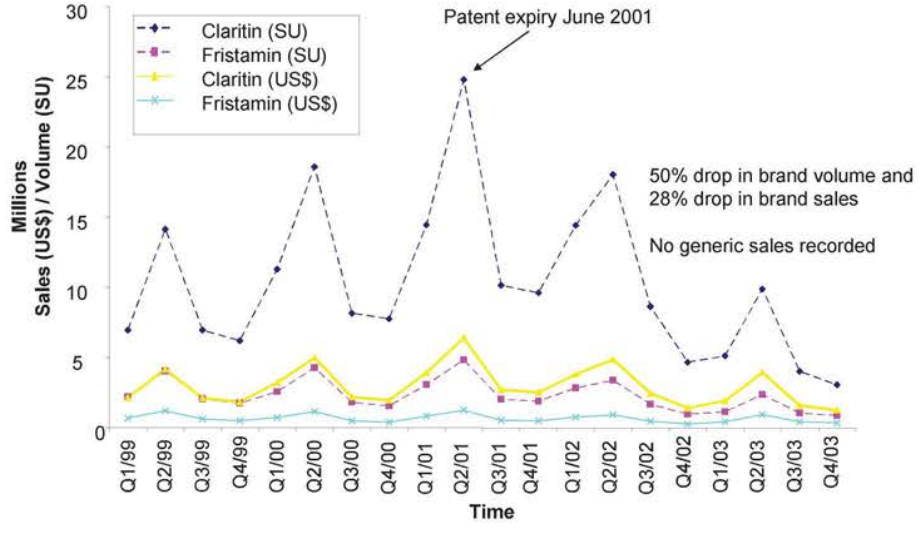
Italy

Antihistamine

Loratadine is marketed under a number of brand names in Italy, the largest sales going to Claritin, followed by Fristamin. This is due to licensing deals made by Schering-Plough with local companies, such as Firma in the case of Fristamin. This split is maintained in the graph below to show the effect of patent expiry of different brand names of the same product is also relatively small in this market. A drop of 50% in all brand volume occurred over 2.5 years after patent expiry, and no generics are recorded in the IMS data. As can be seen in Figure 37, both brand names suffered a drop in sales and volume, although this strategy of multiple brands may have helped to reduce this impact, as little space in this market for other versions.

This report is a licensed product and is not to be photocopied

Figure 38: Italian quarterly sales of loratadine US$ (m) and SU (m), 1999–2003



Source: Datamonitor; MIDAS Sales Data, IMS Health, April 2004, Copyright ©, reprinted with permission; Dolphin, August 2004, Copyright Thomson Scientific

ims™

DATAMONITOR

Nasal corticosteroids

Aircort is marketed by Italchimici in Italy, and can clearly be seen Figure 39, to be outselling the Rhinocort brand.

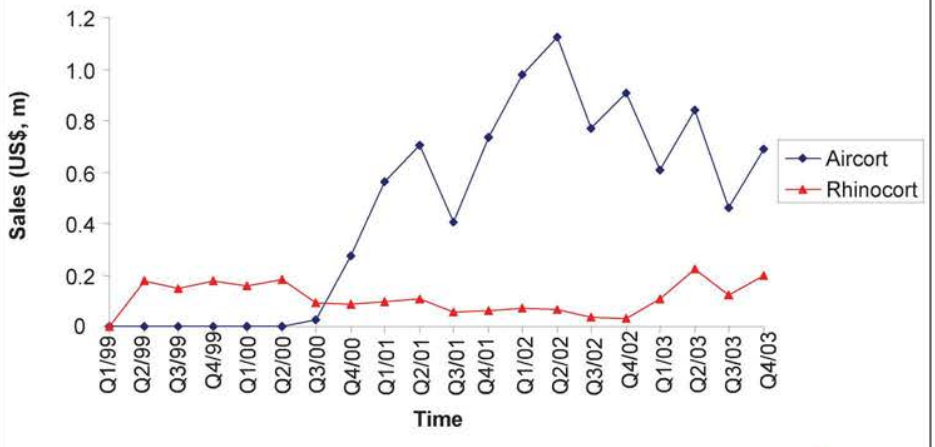
© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505678

PTX0098-00103
CIPLA LTD. EXHIBIT 2021 PAGE 103

Figure 39: Italian quarterly sales of budesonide, US$(m), 1999–2003



Source: Datamonitor; MIDAS Sales Data, IMS Health, April 2004,

Copyright ©, reprinted with permission

ims™

DATAMONITOR

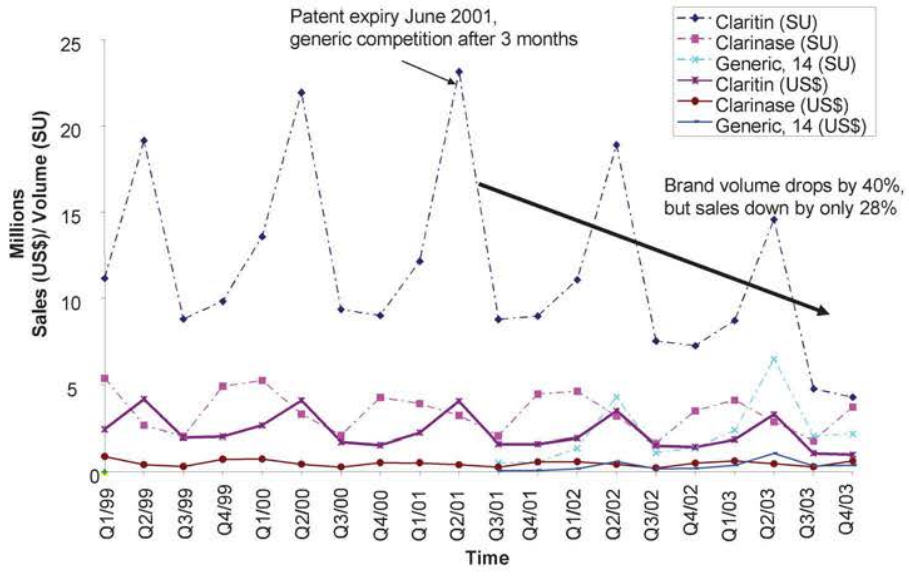
This report is a licensed product and is not to be photocopied

Spain

Antihistamine

Figure 40 shows the comparatively smaller impact of the Claritin patent expiry in the Spanish market.

Figure 40: Spanish quarterly sales of loratadine US$ (m) and SU (m), 1999–2003



Source: Datamonitor; MIDAS Sales Data, IMS Health, April 2004, Copyright ©, reprinted with permission; Dolphin, August 2004, Copyright Thomson Scientific

ims™ DATAMONITOR

Despite a relatively large number of generic loratadine products, 14, on the Spanish market, the impact on Claritin has only been a 28% drop in sales. This has occurred in the 2.5 years since expiry.

Nasal corticosteroids

© Datamonitor (Published 09/2004)

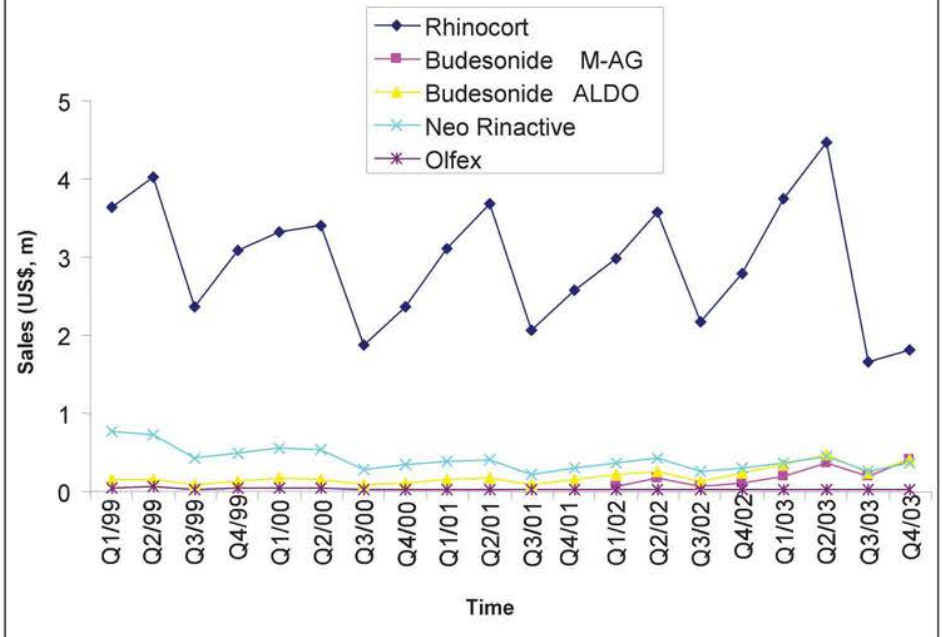
This report is a licensed product and is not to be photocopied

MEDA_APTX03505680

PTX0098-00105
CIPLA LTD. EXHIBIT 2021 PAGE 105

Four generic versions of nasal budesonide exist in the Spanish market, but as with the loratadine, they have little impact on the Rhinocort original branded version.

Figure 41: Spanish quarterly sales of budesonide, US$(m), 1999–2003



ALDO= Aldo Union
M-AG = Merck Genericos

Source: Datamonitor; MIDAS Sales Data, IMS Health, April 2004,

Copyright ©, reprinted with permission

ims™ DATAMONITOR

MEDA_APTX03505681

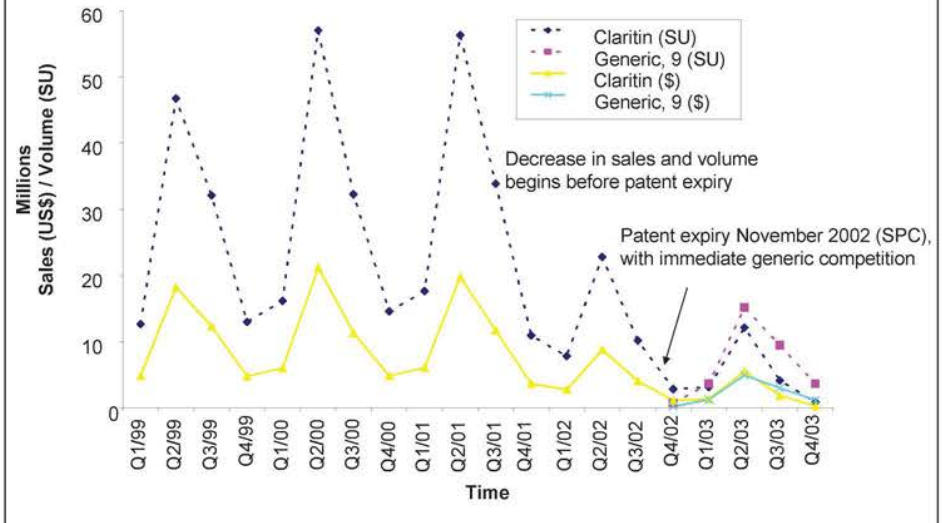
PTX0098-00106
CIPLA LTD. EXHIBIT 2021 PAGE 106

UK

Antihistamine

The UK healthcare system favors the cheaper generic versions of branded drugs, therefore, as shown in Figure 42, the impact is large with an 83% drop in Claritin volume.

Figure 42: UK quarterly sales of loratadine US$ (m) and SU (m), 1999–2003



Source: Datamonitor; MIDAS Sales Data, IMS Health, April 2004, Copyright ©, reprinted with permission; Dolphin, August 2004, Copyright Thomson Scientific

ims™

DATAMONITOR

The UK also showed a slight drop even before the patent expiry, as sales decreased in anticipation of the generic version. This is comparable, although not as dramatic, to the situation that occurred in the US, with a drop in sales occurring up to six months before Claritin patent expiry.

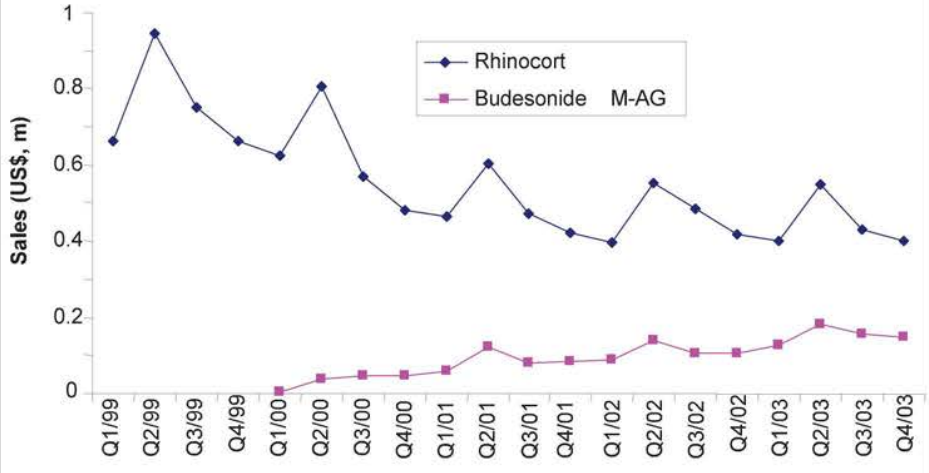
MEDA_APTX03505682

PTX0098-00107
CIPLA LTD. EXHIBIT 2021 PAGE 107

Nasal corticosteriod

The UK generic budesonide has been slowly eroding Rhinocort sales since its launch in Q2 2000. The generic sales are forecast to exceed Rhinocort by 2008, if uptake continues at this rate.

Figure 43: UK quarterly sales of budesonide, US$(m), 1999–2003



M-AG = Merck Genericos

Source: Datamonitor; MIDAS Sales Data, IMS Health, April 2004,

Copyright ©, reprinted with permission

ims™ DATAMONITOR

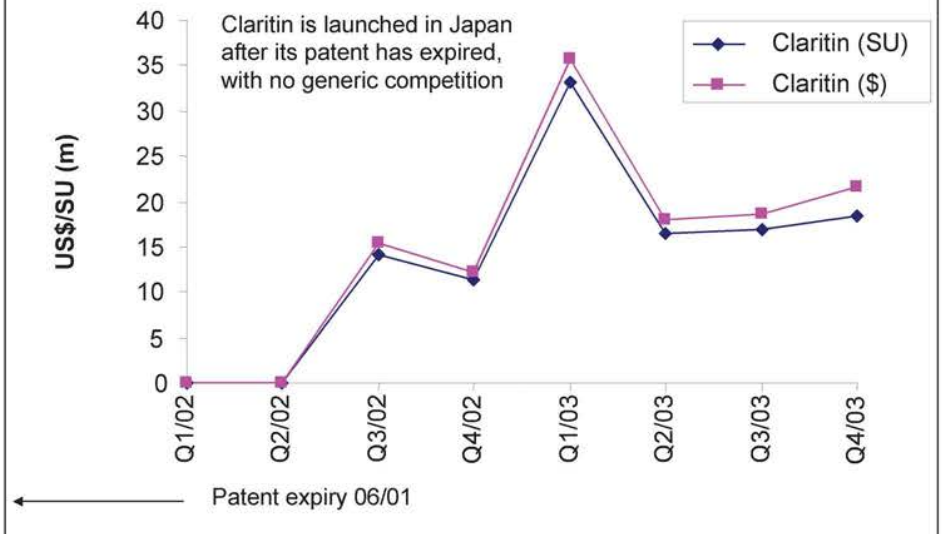
MEDA_APTX03505683

PTX0098-00108
CIPLA LTD. EXHIBIT 2021 PAGE 108

Japan

Claritin was launched in Japan in 2002, after the Japanese product patent expiry in June 2001. General interest and combination component patents exist after this point but the primary patent is taken to be the 2001. Therefore the effect of patent expiry cannot be assessed using this example. As can be seen by Figure 44, Claritin sales and volume is increasing and no generics are currently available.

Figure 44: Impact of Japanese patent expiry on loratadine US$ (m) and SU (m), Q1 1999–Q4 2003



Source: Datamonitor; MIDAS Sales Data, IMS Health, April 2004, Copyright ©, reprinted with permission; Dolphin, August 2004, Copyright Thomson Scientific

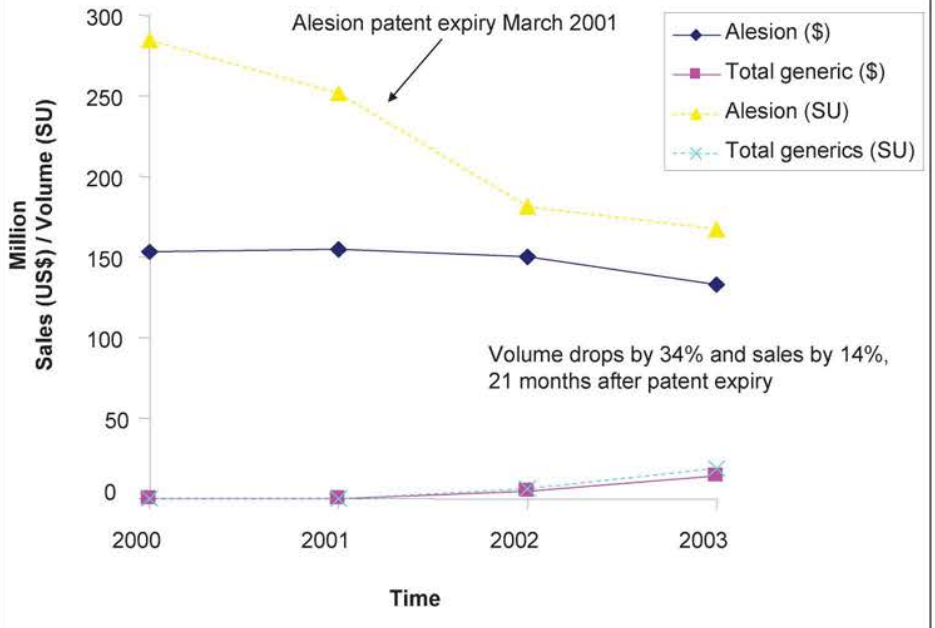
ims™ DATAMONITOR

The top-selling antihistamine in Japan is Alesion (epinastine), with sales in 2003 of $166.5m. Patent expiry occurred in March 2001 and generic competition has eroded sales from $284.3m in 2000. The impact of this patent expiry is investigated below as an explanation of antihistamine patent expiry for this particular market.

Total sales for generic versions of epinastine in Japan were $18m in 2003, only 10% of total molecule sales, although this figure is predicted to slowly increase. Therefore the impact of patent expiry is relatively small in Japan, closer to the impacts seen in France and Italy than the US. This reflects the general attitude among Japanese prescribers against generic substitutes.

This report is a licensed product and is not to be photocopied

Figure 45: Alesion (epinastine) Japanese patent expiry, US$ (m) and SU (m), 2000-2003



Source: Datamonitor; MIDAS Sales Data, IMS Health, April 2004, Copyright ©, reprinted with permission; Dolphin, August 2004, Copyright Thomson Scientific

ims™ DATAMONITOR

"Another influencing factor is the economy since many people now have less time and money which forces them to take over-the-counter medicines rather than to visit a doctor." – Japanese opinion leader

This report is a licensed product and is not to be photocopied

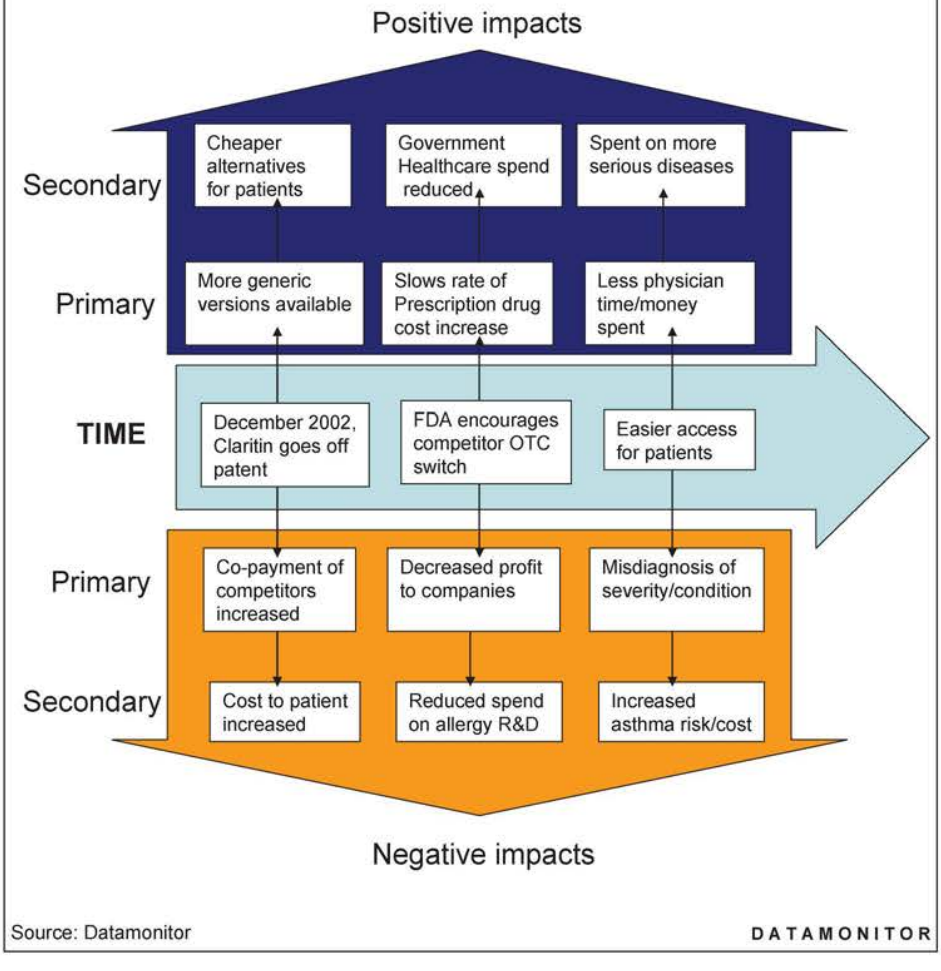
MEDA_APTX03505685

PTX0098-00110
CIPLA LTD. EXHIBIT 2021 PAGE 110

Case study three – Impact of Rx to OTC switches in the US allergic rhinitis market

This case study focuses on the effects and changing regulations in the switch of treatments, particularly antihistamines, to an over-the-counter status in the US market.

Figure 46: Positive and negative impacts of switching from RX to OTC for stakeholders in the US allergic rhinitis market



According to the FDA, one of its objectives under its new budget is "to become more proactive in recommending key potential prescription-to-OTC switches that could

This report is a licensed product and is not to be photocopied

MEDA_APTX03505686

PTX0098-00111
CIPLA LTD. EXHIBIT 2021 PAGE 111

result in further consumer empowerment in self-medication as well as provide an expedient way to significantly reduce consumer healthcare costs for certain ailments."

> *"I think antihistamines are much safer than 98% of the other stuff we prescribe. So I don't see any reason for them not to go OTC."* – US opinion leader

The FDA's goal is to increase Rx-to-OTC switches by 50% on average, but not on an annual basis (DHHS 2004 US Budget) To accomplish this, the agency has allocated $1m to the expansion of the over-the-counter division.

> *"I think once patents expire, it is highly likely that all the antihistamines that we currently prescribe will go OTC. In fact, they are much safer than the ones that are already OTC."* – US opinion leader

This has been driven predominantly by the new FDA chairman, Mark McClellan, who has made very clear his position on increasing the use of both generic and OTC drugs.

Marketing strategy and patient demand

An effective marketing and advertising strategy for a new OTC drug will 'sell it' to the uninsured patient, who was previously unaware and/or unable to obtain the drug. It should also drive the switching of a number of patients using competitor drugs.

However, in practice, insured patients will be paying more for their original prescription drugs. This is due to revised co-payments on competitor drugs, pushing them into higher co-payment tiers in the majority of insurance schemes. Patients will in turn put pressure on physicians to prescribe cheaper alternatives.

Managed care organizations and insurance companies

Almost 43 million people in the US—15% of the population—do not have basic healthcare coverage. If these people are allergy sufferers, then they will be better off as a result of the OTC switch of Claritin, but this is no consolation to the remaining 85% who may now need to pay more for their preferred rhinitis medication.

> *"Yes, there are two sides to antihistamine OTC status, they are certainly safe and it would certainly decrease overall healthcare costs. However, for those who do have health insurance, then it becomes much cheaper for them to have it covered under their*

This report is a licensed product and is not to be photocopied

plan but it can only be a prescription item in that case." – US opinion leader

According to WellPoint, this cost shift to patients will increase his company's bottom line by about $90m per year. They are now asking the FDA to switch the next generation of non-sedating antihistamines, starting with Clarinex, to OTC status. Kaiser's position is also that these drugs should be sold over the counter. They claim the drug companies can make more money as long as these drugs remain available by prescription only. Blue Cross of California has made an unprecedented request to the FDA to allow drugs such as Claritin, Allegra and Zyrtec to be sold without a prescription.

The dangers of this practice include not just "self-medicating" but also "un-medicating" due to an inability to afford medications once they are removed from an insurance plan. De-listing these medications may also prompt state Medicaid plans to drop the drugs from their formularies as well.

"If antihistamines don't seem to help it may be because they have sinus disease or viral illness and there is a potential misdiagnosis." – US opinion leader

However, the availability of different brand names for the same drug may cause problems for some.

"The biggest concern that I run into in my practice is that now that there is more than one OTC Loratadine product, we have Alavert and Claritin – patients often don't realize that they're the same drug, and so they will try one and if it doesn't work they will try the other brand. On a few occasions, I've had patients take one in the morning and the other one at night and they don't realize that they are basically doubling up on the same drug and now you're into doses that can cause side effects." – US opinion leader

Pricing strategies and co-payments

Figure 47 shows some examples of insurance co-pays from the leading insurance companies in the US. Level 3 represents the highest tier of co-pay, and none of the leading brands are in the level 1 tier.

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505688

PTX0098-00113
CIPLA LTD. EXHIBIT 2021 PAGE 113

Figure 47: Insurance formulary status for antihistamines

	Aetna [1]	Humana [2]	Wellpoint [3]	United Health [4]	Harvard Pilgrim [5]	Cigna [6]
Allegra	3	3	3	3	2	3
Allegra D	3	3	3	3	2	3
Clarinex	3	3	3	2	3	3
Flonase	-	2	3	3	2	2
Nasacort	-	2	3	2	2	3
Nasonex	-	-	2	2	2	3
Rhinocort	-	2	3	2	2	2
Zyrtec	3	3	-	2	3	3
Zyrtec D	3	3	-	2	3	3

3 = Highest tier co-may (US $30-40/Rx)
2 = Middle tier co-pay (US $15-20/Rx)
- = Not available/applicable

Source: Various websites, Sept 2004
1 = www.aetna.com/formulary
2 = http://apps.humana.com/prescription_benefits_and_services
3 = www.wellpoint.com
4 = www.unitedhealthcare.com
5=http://www.harvardpilgrim.org/portal/page?_pageid=213,38489&_dad=portal&_schema=PORTAL
6 = https://secure.cigna.com/cgi-bin/health/sdrug_list.cgi

DATAMONITOR

Clear discrepancies can be seen in the amount of money a patient is expected to pay for the same brand in different formularies. These changes created initial confusion with switching of patients depending on company co-pays, but this has now

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505689

PTX0098-00114
CIPLA LTD. EXHIBIT 2021 PAGE 114

stabilized. However, the patent expiries of Allegra and Zyrtec may produce similar issues in the future.

> *"Initially, when Claritin went OTC, a lot of people suddenly couldn't get their prescriptions refilled, so we were very frustrated and we wasted a lot of time faxing and filling out forms. It's less of a problem now that patients realize what their insurance company covers."* – US opinion leader

Doubling of co-payments has been found to be associated with a reduction in the use of antihistamines by 44% according to research published in *JAMA* in May this year (Goldmann *et al.*, 2004). Other classes that were taken intermittently to treat symptoms, such as NSAIDs, were equally sensitive to co-payment changes.

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505690

PTX0098-00115
CIPLA LTD. EXHIBIT 2021 PAGE 115

Case study four – Physician specialty

Definition of allergic rhinitis prescriptions

Prescription audit data from the IMS prescribing insight database is used to further analyze drug treatment of the following International Classification of Diseases, version 10 (ICD-10) diagnoses:

- J300: vasomotor allergic rhinitis;
- J302: allergic rhinitis – pollen;
- J302: other seasonal allergic rhinitis;
- J303: other allergic rhinitis;
- J304: allergic rhinitis unspecified;
- J310: chronic rhinitis.

As can be seen, this does not include diagnosis commonly associated with allergic rhinitis such as sinusitis and nasopharyngitis, which may be treated using similar therapies.

Physician specialty

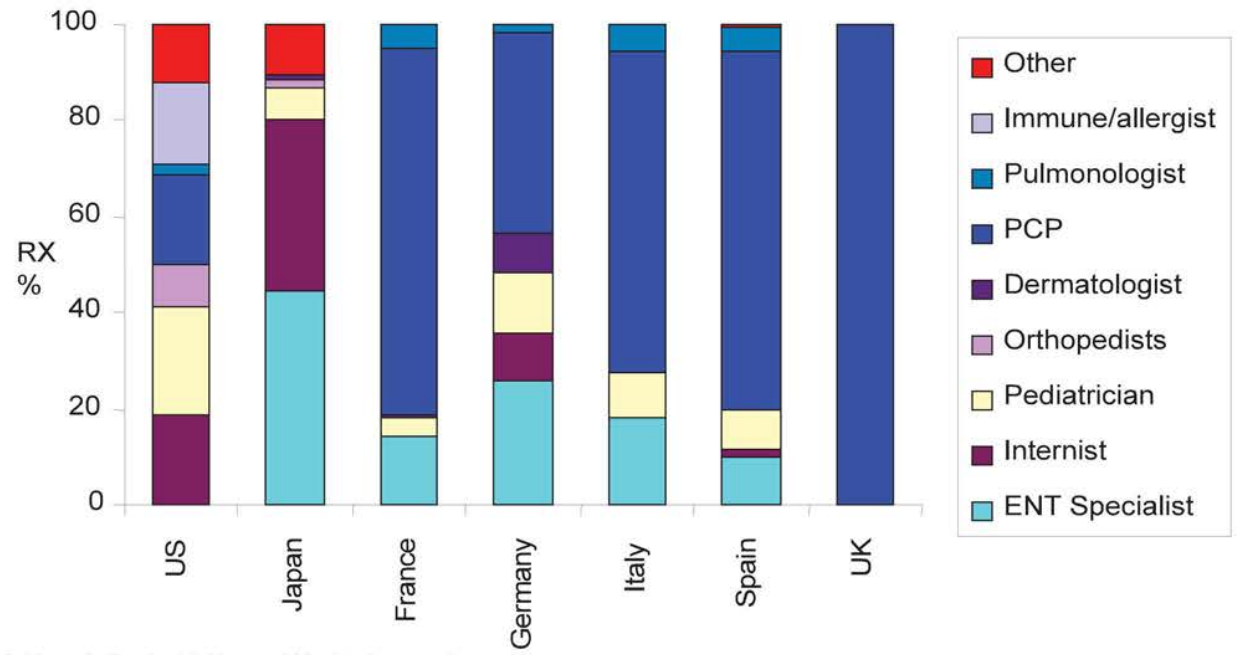
Figure 48 shows the physician types that most commonly treat allergic rhinitis. The physician most likely to prescribe allergic rhinitis treatments should be the target specialty area for advertising and detailing. These specialties vary over the seven major markets, with the US, Japan and Germany showing a wider range of physicians treating allergic rhinitis patients, compared to the other EU countries.

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505691

PTX0098-00116
CIPLA LTD. EXHIBIT 2021 PAGE 116

Figure 48: Physicians treating allergic rhinitis[1], specialty and country (%), 2003



1= For definition of allergic rhinitis see ICD-10 classes above

Source: Prescribing Insights Data, IMS Health, April 2004, Copyright ©, reprinted with permission

ims™ DATAMONITOR

PTX0098-00117

MEDA_APTX03505692

CIPLA LTD. EXHIBIT 2021 PAGE 117

Table 32 shows the percentage breakdown of physician specialists by country.

Table 32: Physicians treating allergic rhinitis, specialty and country (RX %), 2003

	US	Japan	France	Germany	Italy	Spain	UK
ENT specialist	0.00	44.56	14.14	26.01	18.38	9.92	0.00
Internist	18.42	35.56	0.00	9.57	0.00	1.46	0.00
Pediatrician	23.00	6.74	3.98	12.81	9.00	8.14	0.00
Orthopedists	8.42	1.51	0.00	0.00	0.00	0.00	0.00
Dermatologist	0.00	1.17	0.37	8.33	0.00	0.00	0.00
GP	19.10	0.02	76.43	41.65	66.98	75.16	100.00
Pulmonologist	1.80	0.00	5.00	1.54	5.52	4.96	0.00
Immune/allergist	17.43	0.00	0.00	0.00	0.00	0.00	0.00
Other	11.82	10.44	0.07	0.10	0.12	0.36	0.00

Source: Datamonitor; Prescribing Insights Data, IMS Health, April 2004,

Copyright ©, reprinted with permission

ims™ DATAMONITOR

The UK healthcare system means that all patients initially go to their GP. Referral is very rare for allergic rhinitis, as there are very few practicing specialists in this field.

> *"It's not very well set up in the UK because allergy is a very small specialty here. The Professional Allergy Society are trying to do something about this and there is a House of Commons select committee, but the situation is that there are very few allergists and its mostly GPs prescribing."* – UK opinion leader

However, the other six countries show variation in the type of physician prescribing treatments for an allergic rhinitis diagnosis. The two largest markets in terms of sales and prevalence have the largest range of treating physicians for allergic rhinitis.

In the US, more specialists exist and patients have a larger choice as to who they want to consult. This creates a more competitive environment among physicians, and patient demand becomes an important factor in prescribing patterns.

> *"With a greater focus on specialty medicine in the US, it makes it more challenging for the drug companies; they have many more healthcare professionals to target versus the UK where the*

This report is a licensed product and is not to be photocopied

generalist predominates. Typically companies seem to target allergy, immunology and pediatricians." – US opinion leader

"Unlike Germany, ENT is really separate from allergy in the US. Companies have got to target them separately. There's little interchange between allergists and ENT." – German opinion leader

Japan also shows a wide range of specialties, but has the lowest proportion of GPs. According to opinion leader research, GPs in Japan usually specializes in internal medicine, pediatrics or surgery. When they decide to work as a GP, they brush up other areas to receive a wide range of patients. The service offered also influences patients in the Japanese market.

"Sometimes patients come to an internist because there are a larger number of internists than ENT doctors. ENT doctors also have less time with their patients and patients prefer to come to internists if they want more explanation. ENT doctors must see about 100 patients per day while internists see about 40 patients per day." – Japanese opinion leader

Germany seems closer to the US than the rest of the EU in terms of prescribing specialties. Less than half of allergic rhinitis patients are treated by a GP.

"Basically it is a historical development in Germany, so allergists always were dermatologists 20–30 years ago and then allergy was becoming increasingly important for pediatric patients, so a lot of pediatricians now became like me, allergists." – German opinion leader

The remaining three EU countries—France, Italy and Spain—have very similar prescribing patterns. All three have over three quarters of allergic rhinitis patients treated by GPs. ENT specialists and pediatricians follow.

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

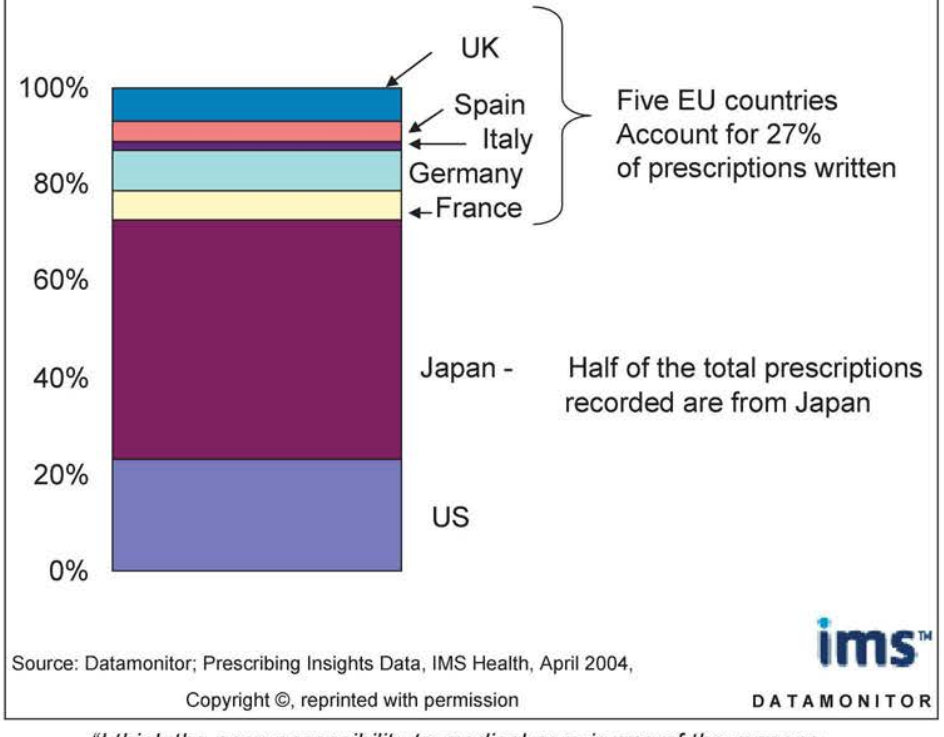
MEDA_APTX03505694

PTX0098-00119
CIPLA LTD. EXHIBIT 2021 PAGE 119

Prescription numbers caveat

The data in Figure 48 is based on the total number of prescriptions written in each country, which should be taken into account when considering the validity of this data. Japan accounts for over 50% of the prescriptions written for allergic rhinitis globally, whereas the US, by far the greater population, only accounts for 23% of global prescriptions.

Figure 49: Global prescription volume (RX) comparison, by country (%), 2003



Source: Datamonitor; Prescribing Insights Data, IMS Health, April 2004,

Copyright ©, reprinted with permission

> *"I think the easy accessibility to medical care is one of the reasons why many patients, even the mildest cases come to visit doctors. Many also say that they feel safer to come to doctors to get prescriptions than to buy drugs over the counter."* – Japanese opinion leader

If the Japanese visit doctors more regularly prescriptions in Japan may be for a shorter time, accounting for the difference in actual number, but this should not affect the proportion split by physician type compared by country.

MEDA_APTX03505695

PTX0098-00120
CIPLA LTD. EXHIBIT 2021 PAGE 120

APPENDIX A – INTERVIEW TRANSCRIPTS

Opinion leader biographies

- Dr Eckard Hamelmann is a Research Associate at the Clinic of Pediatrics -Focus on Pneumology and Immunology, Charité-Virchow Hospital, Berlin since 1997, and is Head of the Respiratory Infections and Asthma work-group.

- Bruce Bochner is Professor of Medicine at the Johns Hopkins Asthma and Allergy Center, Baltimore, US.* He completed his fellowship training in the Division of Clinical Immunology of the Department of Medicine at the Johns Hopkins University School of Medicine, and stayed to join the faculty in 1988. Professor Bochner is a Fellow of the American Academy of Allergy, Asthma and Immunology and a member of the American Association of Immunologists and the American Society for Clinical Investigation. *Participation by Professor Bochner does not constitute or imply endorsement by the Johns Hopkins University, the Johns Hopkins Hospital, or the Johns Hopkins Health System.

- William Henderson is a Professor in Department of Medicine, University of Washington, Seattle. He is head of the Allergy Section at the Department of Medicine and Director of the Allergy/Immunology Fellowship Training Program, University of Washington, Seattle, WA. Prof. Henderson was elected to the Board of Directors of the American Academy of Allergy, Asthma and Immunology in 2000.

- Professor Barry Kay is Head of the Department of Allergy and Clinical Immunology, National Heart & Lung Institute, Faculty of Medicine, Imperial College London, and Consultant Physician, Royal Brompton NHS Trust, London. He is in charge of a research team investigating molecular and cellular mechanisms in allergy and asthma, funded by the Medical Research Council, the Wellcome Trust, and the National Asthma Campaign.

- Michiko Haida is Head of the Division of Allergy and Respiratory Diseases, Department of Internal Medicine at Hanzomon Hospital, Tokyo, Japan, and is Vice Director and administrator of the same institution. Dr Haida also works in the Department of Respiratory Internal Medicine at the University of Tokyo Hospital, Tokyo, Japan.

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505696

PTX0098-00121
CIPLA LTD. EXHIBIT 2021 PAGE 121

US opinion leader

Patient demographics

- **Epidemiology numbers and trends.**
  I would guess in the US it's somewhere around 20-30%. I've heard higher numbers and I've heard lower numbers, but that's probably close.

- **Awareness of increasing prevalence. Would you say this is due to allergy awareness?**
  To a small extent. I think some of the increase is real and we are starting to see it in other countries as they are becoming more industrialised, for example in China there is an increase of allergic disease in the last decade. So, I do think some of the increase is real, but it's so hard to prove cause and effect. There is a correlation with asthma increases and average body weight increases in the US. It doesn't mean that gaining weight gives you allergies, it's just that people have implicated sedentary lifestyles and other types of co-factors.

- **Drop in prescription numbers in age range 20-29 in US, Japan but not EU. Can you think of any reasons for this, is it a medical based issue or possibly social factors?**
  From the pediatric side, in terms of the numbers of patients that are feeding that age group, we're not seeing a drop in the frequency of their disease. So, it's not as though one would have predicted this. So I don't have a good explanation.

- **Country variation in treating doctor specialties. In the US, allergic rhinitis seems to be treated by pediatricians more often than in other countries. I haven't seen any evidence showing that the prevalence is that much higher in the US among that age range.**
  I think in the US most people take their children to pediatricians rather than primary care general practitioners or internists. It may simply represent the pattern by which people seek care for any childhood disease rather than any allergy-related reason. I don't think pediatricians do anything any differently in the US, I just think that more children are treated by pediatricians in the US compared to other countries. But I guess you would have to look at another illness. If you looked at prescriptions for, say, otitis media, you would probably find that most of it is also coming from pediatricians. There is some increased level of awareness among pediatricians but I do feel it's simply the system.

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505697

PTX0098-00122
CIPLA LTD. EXHIBIT 2021 PAGE 122

More kids are treated that way and kids account for a sizeable percentage of the prescriptions for allergic rhinitis.

I would also say that the number of different specialties treating allergic rhinitis is just due to the way patients are seen and treated here in the US. I would not be surprised if you had a similar graph of where people seek medical care. I don't think they are over treating or under treating in any particular category, I think it's more based on who is seeing these patients. If you look at the UK it's completely different. I think that is just the way care is provided in each country.

Antihistamines

- **Differentiation of efficacy, including Inhanced Chemical Entities (ICE) such as desloratadine and levocetirizine. In your opinion, which is the best antihistamine currently available?**

  Among the prescription antihistamines, some of the old antihistamines are the best antihistamines for worsening conditions.

  However, among the current prescription antihistamines - focusing on Clarinex versus Allegra versus Zyrtec – in my opinion Zyrtec is the most potent of the three, Allegra second and Clarinex third. In my opinion, there is absolutely no difference between Clarinex and Claritin in terms of its efficacy. However, their efficacy in allergic rhinitis is not all that different, but as for their efficacy in urticaria, I do see more of a difference in the same rank order that I mentioned to you. For allergic rhinitis, and I would really say allergic rhino-conjunctivitis because they get ocular benefits as well, the differences are relatively subtle but I think Zyrtec is the best of the three, and the differences between Allegra, Claritin or Clarinex are more subtle. I do know that Claritin and Clarinex are better antihistamines at higher than the recommended dose, but at higher than the recommended dose one has sedation side effects. So the dose that was chosen for marketing in the US is in the middle of the dose response curve in terms of efficacy. So that tells you that it hasn't maxed out its clinical potency at the recommended dose but it's a dose that is chosen because it is better tolerated.

  Do you think that prescribing doctors see a difference between ICE's, for example the difference between Clarinex and Claritin, (levocetirizine and cetirizine)?

  No, I do not, not at all. I haven't prescribed levocetirizine. We don't have that available in the US, but from what I've seen I don't see any real difference. I think the only difference

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505698

PTX0098-00123
CIPLA LTD. EXHIBIT 2021 PAGE 123

is that you give a smaller dose because you're giving a fully effective drug. Perhaps it's off the topic but I would say the same thing for albuterol and levoalbuterol for asthma, I don't see any real difference, I think it's all hype and marketing.

- **Over the counter use of antihistamines. Do you think that all of them should be available OTC?**

  I do, yes. I think once patents expire, it is highly likely that all the antihistamines that we currently prescribe will go OTC. In fact, they are much safer than the ones that are already OTC and we can prescribe things like diphenhydramine or Benadryl with greater side effects profiles than any of the ones that we currently prescribe that are non-sedating or minimally sedating. So I think once you see patents expiring, you will see them all go OTC, and you will see all the generics following.

  So there is no real reason for these drugs to be prescription only, from a medical point of view.

  No, I think they are much safer than 98% of the other stuff we prescribe. So I don't see any reason for them not to go OTC.

- **Self-diagnosis or misdiagnosis. Do you think that the switch of loratadine to OTC in 2002 has led to better self diagnosis or a possibility of misdiagnosis of allergic rhinitis?**

  It gives patients a very simple option for mild to moderate disease management which I'm perfectly fine with. In my clinic, people who come just for refills for Claritin are really a wasting their time and my time. On the other hand, if antihistamines don't seem to help, it may be because they have sinus disease or viral illness and there is a potential misdiagnosis. The biggest concern that I run into in my practice is that now that there is more than one OTC loratadine product, we have Alavert and Claritin – patients often don't realize that they're the same drug, and so they will try one and if it doesn't work they will try the other brand and that won't work either! On a few occasions, I've had patients take one in the morning and the other one at night and they don't realize that they are basically doubling up on the same drug and now you're into doses that can cause side effects. So that's potentially harmful.

- **Pre-certification for US insurance companies.**

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505699

PTX0098-00124
CIPLA LTD. EXHIBIT 2021 PAGE 124

It was hard initially when Claritin went OTC and a lot of people suddenly couldn't get their prescriptions refilled, so we were very frustrated and we wasted a lot of time faxing and filling out forms. It's less of a problem now that patients either realize what their insurance company covers, or the insurance companies have relaxed some of their criteria. It perhaps pops up once a month now whereas it was popping up several times a week earlier

I think we see it now mostly with new patients who have never tested the waters before. We had a flurry because we had this huge backlog of all our existing patients who suddenly couldn't get their Allegra or whatever filled. So that was a huge flood that hit us right at the beginning. Now that has settled down, it just happens every now and then in some new patients who didn't realize that they couldn't get those meds.

Corticosteroids

- **Differentiation of efficacy.**
  For example, Flonase, has the highest sales in the US; do you think this is the best option for allergic rhinitis?

  I think for run of the mill allergic rhinitis, all the intra-nasal antihistamines work and work reasonably. It boils down to the older preparations being recommended twice a day versus some of the newer preparations being once a day. That is a key feature. Secondly, Flonase in my practice is not the most popular because a lot of patients feel it's too much liquid and they don't like the scent. I actually end up using a lot more Nasacort and Rhinocort which are scent-free.

  The one thing that a lot of my patients miss is a propellant nasal spray. They are all currently off the market, so we only have aqueous preparations available. Nasacort is about to come out with an HFA propellant for intra-nasal use and I think that will be popular because a lot of patients don't like the feel of a liquid spray. It sort of drips to the back of their throat. I think potency-wise, the differences are pretty subtle. The older nasal steroids like beclomethasone and triamcinolone are not quite as potent as budesonide or mometasone or fluticasone.

- **Side effect balance. What about the side effects issues, just general steroid side effects compared to antihistamines, how much do you think this affects prescribing of these?**

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505700

PTX0098-00125
CIPLA LTD. EXHIBIT 2021 PAGE 125

Some of the high potency nasal steroids, especially in the drier winter months, will cause nose bleeds and we sometimes have to change to one of the lower potency ones. How patients tolerate the smell or the liquid is more of a preference issue rather than a side effect. I really don't see much in the way of nasal irritation. I've never seen a nasal perforation, the only thing I run into on occasion is nose bleeds. We usually just reduce the dose or we go to one of the older intra-nasal steroids if that occurs.

Brand Specific opinions

- **Claritin (loratadine) – effect of patent expiry in the US on AR treatment?**
  I think the biggest issues are the two we have already discussed. You can now get a decent non-sedating antihistamine without having to see your doctor.

  So do you see fewer allergic rhinitis patients?

  I do. I think that is one issue. The second is because patients are paying directly out of pocket for this medication, they're more likely to use this medication more judiciously in terms of maybe I will take every other day instead of every day because I see the cost directly hit me next time I have to go back to the pharmacy. But I don't have any problem with that. Unlike asthma, you don't feel like you really do yourself any harm by under treating. It's just that you deal with some level of symptoms that you are going to be comfortable with.

- **Singulair (montelukast) – efficacy?**
  In my personal opinion, Singulair is the least effective of all the allergic rhinitis medicines that are out there. That includes antihistamines, nasal steroids, decongestants, and even intra-nasal antihistamines like azelastine. So when I use Singulair I use it mainly for its effects on congestion and I also sometimes use Singulair – it's interesting, because of insurance reasons, they won't cover antihistamines but they will cover Singulair which is really foolish because Singulair is much more expensive, but a lot of insurance plans will cover Singulair. It's very silly but that's the game, so some patients say my insurance company won't pay for any antihistamine, so I have to go out and get Clarytin, is there anything else you can give me? And so if they don't want to use a nasal spray, I'll have them try Singulair and that will be covered. But it's not as effective as anything else that is out there.

  How important do you think is the fact that it treats both asthma and allergic rhinitis in prescribing?

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505701

PTX0098-00126
CIPLA LTD. EXHIBIT 2021 PAGE 126

I think that's good, I think this whole one airway, one disease concept has some validity. And so it can be useful in that situation, but if I'm just seeing somebody for run-of -the-mill allergic rhinitis, that's not the group that I would go to.

- **Xolair (omalizumab) – cost?**
  Xolair is an interesting, exciting drug that is way too expensive for the treatment of allergic rhinitis. The only way that you can get at this one is what you just said about Singulair, the one airway/ one disease – I might be able to take somebody who has asthma and allergic rhinitis, and give them a single drug. It's just that the cost makes it so prohibitive. And in my opinion, they kind of screwed up the allergic rhinitis studies that they did because they didn't adequately appreciate the fact that Xolair takes several months to really kick in, to fully effect mast cells in tissues. So they were hoping, because of the cost, that they can just give you a dose before the season and a dose during the season and make it a lot less expensive that way. But the effects of the drug don't kick in quick enough, so you really do need to use it for many months. And the only way you are going to get it for rhinitis is if you can justify the expense by treating asthma. Theoretically, it ought to work beautifully for allergic rhinitis and for the ocular symptoms as well.

Combinations with decongestants

- **Allegra-D (fexofenadine, pseudoephedrine)**
- **Clarinase (loratadine, pseudoephedrine)**
- **Zyrtec-D (cetirizine, pseudoephedrine)**
  Do you think these formulations are really useful, or a company ploy to extend patent life?

  I tend not to prescribe fixed combinations, primarily because I would rather patients have the option of taking their decongestants on a PRN basis rather than in fixed combination. So I usually have patients get prescriptions of antihistamine and then just get OTC preparations of pseudoepedrine just to be used as needed. I don't like the side effects of the pseudoepedrine such asagitation, the caffeine-like side effects, and difficulties with sleeping. Some men have difficulties with urination and some people have a nervousness. A lot of patients like taking a decongestant in the morning but not in the evening, so I tend to steer clear of the fixed combination drugs and I agree with what you said, that it's more of a patent ploy.

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505702

PTX0098-00127
CIPLA LTD. EXHIBIT 2021 PAGE 127

Future challenges in Allergic rhinitis

- **Opportunities for allergic rhinitis treatment manufacturers in the US. What do you think the future challenges of allergic rhinitis are likely to be?**

  I think we've got a couple of areas that I am excited about. We still need better decongestants. Pseudoepedrine is essentially the only one on the market now in the US. I have seen some data recently suggesting that prostaglandin D, which is released by mast cells, is a cause of nasal congestion and it's recently been identified that there is a specific prostaglandin receptor called DP in the blood vessels and they are very highly expressed in the nose. So there are companies such as Merck and others that are developing DP receptor antagonists. I'm very optimistic about that. I don't know whether they will be given orally or intra-nasally, I don't know enough about the drugs. But I think that's a wonderful opportunity, whether it be that one or other kinds of decongestants.

  And I'm still also optimistic about the future development of mast cells stabilizing drugs, Cromolyn has been around for a long time, it's not particularly effective – it didn't even make it on your list here even though it's available OTC. We tend to only use it in very small children or maybe during pregnancy if somebody is worried about medication side effects. But there are other companies out there developing other mast cell stabilizing drugs, especially those that inhibit IgE receptor signal transduction pathways. So there are companies that are developing inhibitors of some of the immediate signal transduction proteins in cells that translate the signal from IgE receptor cross linking to degranulation response. One of the key signal transduction proteins in that pathway is a molecule called SYK and there are companies like RIGEL that are developing SYK inhibitors and they have tested one in man as an intra-nasal spray. These are potentially toxic drugs because that SYK molecule is also important for other cells besides mast cells. It is hoped that if it used topically you can get the anti-mast cell effects to occur hopefully without the systemic side effects. Whether or not it will be efficacious – I think it's only in phase I, so they're just getting started. But I think that's an interesting approach.

  So those are the two main issues and the other thing that I would add is that I still think that we might be able to develop a safer, more effective immunotherapy. Probably the most enticing data that I have seen in the last few years have been DNA-based allergen vaccines. They have the potential of turning off allergic responses with just maybe half a dozen or so injections, so it's more like a vaccine.

  It's more of a cure than just treating symptoms.

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505703

PTX0098-00128
CIPLA LTD. EXHIBIT 2021 PAGE 128

Exactly. You just get a couple of shots and you are done. It's not like you have to be on shots for 3-5 years. Then the last I'll mention is oral immunotherapy. It seems to be popular in Europe, especially in Italy; and I'm slowly but surely learning more about it. I was highly skeptical of its efficacy initially. I thought it didn't make any sense whatsoever. But for a time, there has been a lot more data to suggest that if you eat enough ragweed, or if you eat enough cat allergen or whatever, you actually suppress the allergic response. So that bears keeping in mind because there seems to be some efficacy there.

German opinion leader

Patient demographics

- **What would you estimate the prevalence of allergic rhinitis to be in Germany?**
  I am a pediatric allergist, so we see a lot of allergic rhinitis, we have a multi-center allergy cohort with five different clinical centers which is now up to the age of 13, and which started from newborns, and the all time prevalence of the allergic rhinitis was 22%.

- **How do you think that compares with the rest of Europe?**
  I think the UK is very similar or more, in Sweden and Scandinavian countries is at least as high as it is in Germany, but in Southern Europe it is lower, Spain and Italy and Greece and so forth.

- **Do you think there is an increasing awareness of allergic rhinitis?**
  I think definitely amongst the physicians, allergies and allergic rhinitis is definitely a major concern now and if people come with a runny blocked nose, it is more often that the physicians think about the diagnosis and I think this is pretty similar with the patients as well. So I think yes, the awareness is increasing as well.

  There is a lot of information about allergies in the newspapers, TV, I think it is not basically the companies, but it is more the public awareness, public media.

- **German pediatric prescription levels**
  I think definitely it is high, so I think the numbers are correct. Germany is an industrialized country, we have low family numbers and only 1.7 children on average in a German family and the day care is considerably late in Germany, compared to other countries. So this may be one reason why incidences are higher than in southern European countries, I

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505704

PTX0098-00129
CIPLA LTD. EXHIBIT 2021 PAGE 129

mean that is the hygiene hypothesis. It is a one million dollar question, but this is the only thing we can think about.

- **There is a dip between the ages of 20 to 29 and that happens across most of the developed countries, US, Japan and the UK, but not in the rest of the EU, can you think of any reason for that?**
  There is a dip in the prevalence between 20 and 30 yes, I see it from the numbers, but of course we stop seeing patients when they are the age of 20, so that is the problem hat we normally do not follow. I mean certainly we have a decrease in the number of allergic symptoms anywhere in allergic disease, in the age range of 15 – 20. That is true for asthma, dermatitis, allergic rhinitis as well. So this decrease is just due to the adolescents, so that the patients grow out of their disease and the later increase that you see from 20 – 30, I would not know how to explain this. I mean we don't see this for the other diseases, like atopic dermatitis, this is rather decreasing or even stable in the population.

- **Large number of prescriptions from pediatricians and dermatologists in Germany.**
  Yes, basically it is a historical development, so allergists always were dermatologists 20 – 30 years ago and then the allergy was becoming increasingly important for pediatric patients, so a lot of pediatricians now became like me, allergists. So now, normally children with an allergic problem, asthma or allergic rhinitis are treated by a pediatric allergist and when they have atopic dermatitis, they go to the dermatologist. We don't have a real allergist sub-speciality like America for example, so you are either a dermatologist or pediatrician in the first line and then you have a sub-speciality in allergology.

Antihistamines

- **What you would consider to be the most effective antihistamine on the market at the moment?**
  At the moment I think the best drugs would be Xusal and Aerus which is the trade name in Germany which is desloratadine and levocetirizine, and I think fexofenadine is pretty similar, but I have less experience with this and we normally prescribe the former two. I think the desloratadine is probably best, they all have the same sort of efficacy, the desloratadine may have a little bit of advantage due to even less sedating side effects, compared to the levocetirizine.

This report is a licensed product and is not to be photocopied

MEDA_APTX03505705

PTX0098-00130
CIPLA LTD. EXHIBIT 2021 PAGE 130

- **How much of an advantage do you think these have over the metabolite molecular, so loratadine and cetirizine?**
  I think it is more an advantage on paper. I mean some patients have concerns with the sedating side effects with the older forms, with cetirizine and so on. So they complained a little bit about sedating effects, sleepiness and so on. I think this is a little bit less now. In terms of efficacy, the patients do not see a big difference there, but at least from the pharmacological raw data, you would suggest that you would have better efficacy and you have a little bit longer efficacy, I mean in terms of hours of effect.

- **Over the counter use of antihistamines in Germany.**
  It is mostly cetirizine and there is as least five or six companies with their own pill now, because it is off patent now. In Germany, anyway, the situation has changed so that cetirizine is not prescribable any more, so the insurance companies won't pay for it any more, and this is a new change in Germany since last year. So if something has not been prescribed by a doctor, it will not be covered by the insurance company any more, so people buy a lot of the off label medications, over the counter medications, but it is not covered by insurance. But the newer drugs like the desloratadine or levocetirizine can still get reimbursed by the insurance, even though they are much more expensive.

  It is not only that they get off patent, but the German health system also changed, in terms of reimbursement.

- **Did you notice a drop in the number of allergy patients, did you notice that people went and used this over the counter medicine instead?**
  No, not at all. I mean, we are a big hospital so we always have too many patients, but even the normal physicians, the allergists outside, I think they don't see a drop now.

  In Germany, it is very different to the US. Normally people don't go to the drug store, buy the medication and be happy. I think most people still go first to the doctors.

- **Do you think there is any possibility of misdiagnosis, now this is available over the counter?**
  Oh yes, sure. I think so. I mean definitely there is differential diagnosis to allergic rhinitis, I mean not every runny nose is allergic rhinitis, so of course there is a misdiagnosis if patients just buy the antihistamines right, but as I said, in Germany, most people won't do that. There is still a big belief in the skills of doctors, so most people see a doctor first and then they get treated.

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505706

PTX0098-00131
CIPLA LTD. EXHIBIT 2021 PAGE 131

Corticosteroids

- **In Germany, Nasonex has the highest sales for allergic rhinitis, would you say that this is the best corticosteroid there is?**

  I think it is the best because it has the highest affinity to the receptor; it has the advantage of a 24 hour efficacy. You just have to take it once a day, which is great for the patient. It has the highest lipophilia and so the bio-efficacy just in the organ where you treat is the highest with the mometasone. The only disadvantage is that some patients have the feeling that taking the mometasone gives them a little bit of an itch or they complain that it hurts them a little bit.

  Now, in a number of other countries, it is fluticasone that is the most popular, is there any reason why that hasn't taken off so much in Germany?

  We use quite a bit of Flutide Nasal, which is fluticasone, so we prescribe it quite a bit. It is basically for the patients who don't like to get the mometasone, who complain about the itchiness after taking it. I always switch to fluticasone and I think the best reason to take mometasone is that you really only need to take it once, so the time kinetics is advantageous and the affinity to the receptor just is still higher for mometasone, so I think if you really compare the two molecules, you would go with the mometasone. I mean, there is no reason why you should take fluticasone, only may be pricing. I would take it when patients are having discomfort with the mometasone, then I would switch.

- **Do you think that the Nasonex patent expiry in 2005 will have much of an effect in Germany?**

  For the company yes, definitely. I think yes it is similar with cetirizine, I think that people then will buy it and a lot of companies will bring it on the market. I'm pretty sure. We have a lot of cheaper generic companies and with the new prescribing system, things have changed a lot and I think there will be a lot of changes then, price reductions and so on.

- **How much do you think that steroidal side effects affect physicians' prescribing habits?**

  I think that is a big problem in Germany. A lot of patients, especially the pediatric patients or better the mothers are concerned about using steroids and it is not really based on data or on side effects that are measurable, it is just a bit of steroid phobia. So, I think in Germany that is a problem and that there is a lot of work that we have to do with the patients to convince them that steroids are rather good drugs and that the side effects

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505707

PTX0098-00132
CIPLA LTD. EXHIBIT 2021 PAGE 132

are minimal to zero when you have the topical steroids in these kinds of concentrations. To add, a lot of physicians use this kind of public fear of steroids and they convince their patients rather to "go with Mother Nature" and not to use any steroids, so of course, there is a fraction of physicians who have it in their marketing strategy not to use steroids.

I am pretty convinced that if you use topical steroids in the amounts that are normally used with the mometasone or the fluticasone, it is rather safe, the data are pretty obvious. You don't have any serious side effects and if anything, you have a little bit of a decrease in the growth, which will be taken up again when you stop the steroids.

Combinations with Decongestants

I think the idea to add a decongestant is not really great, if it is really an allergic rhinitis, I think the main treatment should be a topical steroid, because it definitely covers most, or all of the nasal symptoms including the nasal obstruction very good and better than an antihistamine. So, if you really have nasal symptoms only or mainly, I would go with a topical steroid and if you have ocular symptoms as well, then I would add a systemic antihistamine, but I think the decongestant is not really necessary if you go with a topical steroid. So basically I wouldn't see a big marketing chance for this, I think it is the wrong way to treat allergic rhinitis. It has no anti-inflammatory effect, it is just a decongestant.

Future Challenges in allergic rhinitis

The last question is a very open ended one. I just wanted to know what your thoughts are on the major unmet needs within allergic rhinitis treatments.

I think allergic rhinitis is basically of all the allergic diseases, the best treatable and treated disease, definitely. I mean 80-90% of the patients are pretty happy if you treat them with systemic antihistamines, with or without topical steroids. I mean they have really very, very few symptoms. The problem with allergic rhinitis is that we still have the feeling that having allergic rhinitis is increasing the chance of having allergic asthma as well, so stopping the change from the upper to the lower airways is one thing that is definitely in our minds, so the prevention of getting allergic asthma in patients that have or will have allergic rhinitis, that is one unmet need.

Second unmet need would be to have a really causal treatment. We have these specific immunotherapies for those patients who for example have birch sensitization, birch allergy, and it works in 70-80% of the patients if they just have an allergic rhinitis, so this

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505708

PTX0098-00133
CIPLA LTD. EXHIBIT 2021 PAGE 133

is quite good. But if you have a polysensitized patient, house dust mite and animals and so on, then it is becoming more complex. We have studied these patients in an interventional trial and treated with a combination of anti-IgE and immunotherapy and we had quite good results with that approach, but it is very expensive of course, so it is not a standard protocol. So, the unmet need is to find something that really not only treats the symptoms, but treats the disease.

So, what do you think about Singulair?

Singulair is definitely less effective than steroids and less effective than antihistamines, it's more or less on the level of the chromones and I think it is third line medication for allergic rhinitis and I don't see a big advantage of the drug, no. Most people who just use anti-leukotrienes are not happy, they are not treated well.

I think if you have exercise induced asthma and you have allergic asthma and only, mild intermittent or mild persistent asthma, then you can give it a try with a leukotriene antagonist, but for allergic rhinitis, I don't see the case where you should start with it.

END OF INTERVIEW.

US opinion leader

Patient demographics

- **Epidemiology numbers and trends. What would you estimate the US prevalence of allergic rhinitis to be?**
  ~ 10-15%.

  How do you think that compares to other countries?

  Probably it's similar to Western countries, I think the general thought has been that the prevalence is on the increase.

- **Awareness of increasing prevalence. Do you think this increase in awareness is due to allergy awareness or a general increase in the disease?**
  It looks like it's a combination of both, the awareness is certainly increasing with more studies on this problem, but also as people are staying more indoors with greater

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505709

PTX0098-00134
CIPLA LTD. EXHIBIT 2021 PAGE 134

exposure to indoor allergens (dust mites, animals, cockroaches), are less active this is contributing to the problem.

- **The US has a steadier number of prescriptions over the last three years,**
  Yes, this is by managed care so I think a lot of that creates a homogeneity just with coverage. Probably some of that is since Claritin became over the counter, and that probably cut down on the number of prescriptions, instead of increasing like in Japan or the other countries.
  The overall total seemed to have decreased in 2002, do you think that's basically down to Claritin? Probably due to going over to OTC status. I think there has been less advertising too by the drug companies, and greater restrictions on their marketing to health care professionals because of revised FDA guidelines. Most companies didn't have any new products to be introduced in this period, so I think they probably haven't been detailing the products to the doctors as much. That's why the numbers have been flat.

- **Drop in prescription numbers in age range 20-29 in US, Japan but not EU. That's in the table on the second page that I sent to you. Does this drop relate to a medical basis or do you think social factors are more likely to explain it?**
  I think that's primarily to healthcare coverage, most US jobs have fewer health benefits. So, it would be the age group that has been the hardest hit with unemployment, the recent college graduates not finding jobs and when they do find a job it doesn't have the health benefits that most positions would have had previously. So if the prescriptions aren't covered, the patients would not be seeking a doctor.

  That explains why when it gets to 30-39, the prescriptions jump.

  Yes, they likely have better healthcare coverage than the younger group. So I think that's primarily economic.

- **Pattern of first time/repeat prescriptions. For example, the US shows 60% of prescriptions are first time drug use and this is compared for example to the EU which is only about 48% and Japan which is even less, can you think of any reasons that is, particularly in the US?**
  It looks like poor compliance, not getting them refilled.

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505710

PTX0098-00135
CIPLA LTD. EXHIBIT 2021 PAGE 135

It's one of two possibilities then, not getting them refilled or likely to try new drugs. It's hard to say. I mean looking at the antihistamines and the nasal steroids, the question is do we have more options than you in Europe, that would be one possibility I guess. I don't know that. Are you more restricted there with regards to one drug per class in the treatment plans? Is it just greater freedom of US physicians to prescribe medications

I guess it would depend on the health plans though, if you have a health plan that says if you have rhinitis you have got to use cetirizine or something another drug first.

Aside from that, I guess people might be coming in for prescription but wouldn't be able to afford it on the repeat, maybe go to OTC, go back to Claritin. Or maybe there is poorer compliance in the US, I know that has been a problem regarding inhaled steroid use, there is a much higher initial prescription rate than repeat refills. So maybe it's due to poorer compliance.

Why do patients not follow up, particularly with steroids?

I think one thing is that there has been a lot of Press against steroids, people get confused about them with anabolic steroids, and so they are reluctant to use them over a long term. I mean when their symptoms have peaked, they don't use them in follow up or maybe if they have seasonal rhinitis, I think there are just concerns over the long term safety.

- **Country variation in treating doctor specialities.**
  There has certainly been more attention to the burden of allergic disease in early childhood, I think that's one group that has the attention of researchers and pharmaceutical companies. There has been a big focus of the drug companies on pediatricians and primary care physicians with regard to detailing the products. So I think that probably reflects marketing and also a lot of scientific articles focusing on the high incidence of rhinitis in childhood, or allergic diseases in general. So for me, that wasn't surprising, that was just reflecting all the market trends, the big companies focusing on the pediatricians and family practitioners.

  With a greater focus on specialty medicine in the US, it makes it more challenging for the drug companies, they have a lot more health care professionals to target versus the UK where the generalist predominants. Typically they seem to target allergy, immunology and pediatricians.

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505711

PTX0098-00136
CIPLA LTD. EXHIBIT 2021 PAGE 136

Yes, because they figure they get a lot of referrals so internists, general practitioners and pediatricians and so they see what they are doing – and they are also giving talks to community physicians, so they are getting guidance from them there. And the ENT is really separate from allergy in the US.. They've got to target them separately. There's little interchange between allergists and ENT – amongst themselves, other than like referrals for surgery. And then the pediatricians, they're taking care of so many they are just targeting that group too.

Antihistamines

- **Differentiation of efficacy, including Inhanced Chemical Entities (ICE) such as desloratadine and levocetirizine. In your opinion, what would you say is the best antihistamine currently available?**

  For potency of the non–sedating antihistamines, we generally prefer cetirizine. So it's probably the most potent but it does have a slight sedation compared to placebo, a couple of percent; so some people cannot tolerate that and would prefer Allegra. But overall there is not much difference in the comparative studies of efficacy in allergic rhinitis, comparing between loratadine, fexofenadine, cetirizine. Desloratadine doesn't appear to have any greater efficacy than loratadine so that is why it hasn't gained much acceptance on the market.

  Do you think doctors see that for what it is, it's just a metabolite?

  Yes, and also I think they haven't noted anything in their practice, any benefits for the cost. In antihistamines, you have some that are very cheap OTC, particularly in some of the big discount pharmaceutical drugstores. And then you've got something that is many times more expensive, which doesn't mean that there could be some new ones that might have some advantages in terms of potency, but this will have to be shown in clinical studies for this to have a major impact.

- **Over the counter use of antihistamines. Do you think that all should be available OTC?**

  Yes, there are two sides of that, they are certainly safe and would certainly decrease overall healthcare costs. However, many people have their medications covered by their health plan, those who do have health insurance, then it becomes much cheaper for them to have it covered under their plan but it can only be a prescription item in that

This report is a licensed product and is not to be photocopied

MEDA_APTX03505712

PTX0098-00137
CIPLA LTD. EXHIBIT 2021 PAGE 137

case. So then if they have out of pocket expense they are less likely to pay for that. To be consistent, I think you would have to have them all over the counter.

Aventis claim that Allegra needs to be prescription only.

I think it's very safe, I would think it's not with regards to safety concerns – the only problem is that the drug companies have got to recoup their costs for development of it.

Yes, it's marketing and recouping their financial – but not regards to safety, they should probably all be over the counter, like loratadine is.

- **Pre-certification for US insurance companies. How much of an issue is pre-certification of these prescription antihistamines for the US physicians now?**
  Yes, that's a big problem because often you will have to write several different antihistamines and not knowing which one will be covered by the health plan. You know at the first visit. And then sometimes you have to show that they have failed OTC plus another one before you can prescribe the third one so there is a lot of back and forth between the insurance companies and the doctors' offices before you finally settle on a prescription. It might take letters detailing why you need one versus another. Sometimes, no matter what you do you fail, but for the most time you can get the one that you intended but it may take some effort to do it.

  But there are some health cooperatives who have one of the whole class in their formulary, so if you are part of their system, that way you can't get one of the other ones, they just won't be available, other than out of pocket expense I guess.

  Do you think there is a better way of doing this?

  Well, if they had more of a general health insurance I guess, probably like in the UK or Canada, coverage across the board for medications, but it's all down to the insurer in the US.

  What do you think the impact of patent expiry would have on Allegra in the US market?

  I guess there would be a lot less presence of Aventis, unless they come up with an alternative one. I guess the one hope for some of these is that they've got these separate drugs– where you take the different isomer of the antihistamine, if that could be shown

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505713

PTX0098-00138
CIPLA LTD. EXHIBIT 2021 PAGE 138

that the active part of it has greater efficacy, then that would make it extend the patent life of the new compound. So I think it would be just like Schering where they ran into their trouble when loratadine went over the counter, they had a big drop in revenue. So just economically, there won't be the detailing, you would see a further drop in prescriptions I would think if they are not doing that active role to try and sell their product, there is going to be a slippage in the prescription rate. So there could be a big drop in the whole market there, a big impact on the company.

Cetirizine (Zyrtec) is due to go off patent in 2007, another big drug, what additional impact will this have?

Yes, so there will be less sponsorship of physician education courses and they just won't be detailing. Presumably they've got other products they are positioning to replace it, but the trouble if they go OTC it's going to be hard – there's not going to be an economic incentive to bring out new products, because they'll be unlikely to recoup its cost, especially if these new products go OTC too, like desloratadine. So there are some big legal battles ahead, it's hard to predict how the battle will turn out.

There are also changes in the administration as regards to whether the Democrats win and who is going to be Head of the new FDA. Someone could push a greater movement to OTC, with the decreased healthcare costs. It looks like the trend of the FDA is to move to OTC whenever possible.

Corticosteroids

- **In the US, Flonase (fluticasone) has the highest sales. Do you think this is the best steroid option for allergic rhinitis?**

  The safety profile of mometasone (Nasonex) is superior to fluticasone. But comparative studies haven't shown any difference in efficacy between the products. It just means that there may be less systemic absorption with mometasone. So we tend to use it frequently There is a new potential for new products there, like ciclesonide if that becomes available. The long term use of steroids in patients, cataract formation or systemic absorption – so one that would show to have a respiratory safety profile, then that could rapidly gain market share. There's more juggling of positioning there in the nasal steroids side, if you have got a better nasal steroid product, it would probably go right to the top whereas with antihistamines it's hard to show much difference between them, since they are all safe for the most part.

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505714

PTX0098-00139
CIPLA LTD. EXHIBIT 2021 PAGE 139

Brand Specific opinions

- **Claritin (loratadine) – effect of patent expiry in the US on AR treatment?**
  Yes, I guess a lot more people became self treating, it was heavily promoted at the drugstore level and in the Press and television, the generic version of it.

  Do you think there are any drawbacks to self medication for AR?

  The main thing is just not seeking attention as regards to other options, you know like the use of nasal steroids or immunotherapy, avoidance immunotherapy, things that mask like sinusitis, problems with that. I think that would be the major problem with misdiagnosis. One would not be seeking the triggers, not understanding more about the disease.

  You could look at it in the opposite way too, the greater access to the population that may not be covered by healthcare plans and can afford them – some of them are quite inexpensive now, so it's quite a bit cheaper. So maybe in a way – what have you seen as regards the generic numbers? Is there a way to estimate the number of purchases of the generic medications?

  Presumably because the prescriptions are flat, but overall use of antihistamines may have increased, the prevalence has increased.

  So you would estimate that the actual use of loratadine has gone up since patent expiry?

  Yes, I think the prescription side has just shifted over to Allegra and Zyrtec, but there are many people who were just as well maintained on Claritin that are probably just continuing to take it now OTC.

- **Singulair (montelukast)**
  Most physicians think it's pretty weak, particularly for allergic rhinitis control of nasal congestion when compare to nasal steroids. A marketing area that could help them position the drug is the theory of the one airway, "one pill treating both the nose and the lungs.

  If that could be got over effectively to the physician population, that would help build market share.

  Do you think the dual action could be a target area for other companies to follow?

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505715

PTX0098-00140
CIPLA LTD. EXHIBIT 2021 PAGE 140

Yes, because in general physicians are more concerned about asthma, it's considered a more serious disease. So if you can get their attention, to control their asthma symptoms and if you have a bi-product that is also controlling rhinitis, then it makes them happy but they would be more focused on the asthma control. The drug company, it doesn't matter to them as long as they are prescribing the medication.

- **Xolair (omalizumab).**

  Do you think it will ever be prescribed for AR?

I think the cost would prohibit that because you can't even get a patient to use it for their asthma symptoms, when they have severe asthma and hospitalizations. In general, most insurers cover it at 80% level, so 20% of $20,000-40,000/year is a lot of money, people just can't afford that when they've got all their other medications they're taking too. So that's been a real problem. But I guess the question too is its efficacy. Whether it's potent enough and there is enough of a reduction in IgE levels to warrant that cost. I mean the theory is great, but if it's got this moderate efficacy and price, plus you would have limited availability, probably all the allergic rhinitis patient population would benefit from it if you could afford it, but then you wouldn't have enough of it to treat all that number of people or it would be way too expensive. So the economics are driving that drug, if it was a small molecule or something that was cheap and blocking that, then that would be a different situation. If you had that approach, that could be a cornerstone of all treatment for allergic disease, because of the importance of IgE.

Combinations with decongestants

- **Allegra-D (fexofenadine, pseudoephedrine)**
- **Clarinase (loratadine, pseudoephedrine)**
- **Zyrtec-D (cetirizine, pseudoephedrine)**

  There are a number available in the US at the moment, do you think these formulations are useful or possibly a company attempt to extend this patent life issue?

Yes, mainly I think to get another drug in their portfolio, because Sudafed by itself is cheap, even though a lot of people are limited anyway by the side effects of the decongestant part, having jitteriness or interfering with their sleep and also the risk of increasing blood pressure. So that's the main problem there, essentially adding bad side

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505716

PTX0098-00141
CIPLA LTD. EXHIBIT 2021 PAGE 141

effects to a very safe medication, the antihistamine part. I think it's an attempt to increase their number of products, increase the patent life.

Future challenges in Allergic rhinitis

- **Top three challenges.**

  A safer steroid because steroids are the most effective for controlling nasal congestion, it would be likely that a better steroid would gain market acceptance and increase potentially overall use in the market place. Since people are concerned about safety issues, that would never be OTC, so that would always be a place where the drug companies could detail the physicians and focus on that. I think there is a potential there for new products, like ciclesonide or something else. Perhaps something that could be safely used in children without any impact on growth let's say over a long period of time. And you could have one that would be a lifelong treatment.

  It's hard to know how much protective a new antihistamine could be, a new generation, other than the isomer – these compounds, if the isomer of them would add, somehow counteracting benefits, there is some potential there.

  And others would be new approaches, one would be a small molecule version of the anti-IgE approach, blocking the mass cell degranulation but not a monoclonal antibody type of treatment, that's going to be way too expensive unless there are some breakthroughs that makes that cost competitive, which is hard to believe currently. Others would be immunomodulators, anything to block the IgE process, things that would down regulate things like a better immunotherapy, like the cat peptide vaccine approach, something like that to prevent someone from developing symptoms. Also DNA vaccinations, that are immunomodulators, that would be a wide-open approach for future treatments. Something to treat in early childhood and abort the asthmatic immune response would be beneficial

END OF INTERVIEW.

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505717

PTX0098-00142
CIPLA LTD. EXHIBIT 2021 PAGE 142

UK opinion leader

Patient demographics

- **Epidemiology in the UK**
  About 30% of people who are skin test positive, may have allergic rhinitis but I doubt whether that number really have symptoms which require medication. Allergic rhinitis is seasonal and perennial, it is certainly scientifically better to break it down in these groups for marketing as the approach must be slightly different.

- **Would you say the increase in prevalence was down to an increasing awareness?**
  Yes, a greater awareness in part. A possible factor is this question of the combination of allergens with diesel fumes, making them more allergenic. However, I don't think the pollen counts have varied all that much.

  The hygiene hypothesis is terribly complex and it is something which is multi-system based and cannot be looked at over a two or three year period. It would have to be a 20 or 30 year period, or even more.

- **IMS data showed a drop in prescription numbers in the age range between 20 and 29, particularly in the US and Japan and also in the UK, but not in other countries in the EU.**
  It is very, very easy here to get virtually everything OTC, and that is the line of least resistance. People who suffer from hayfever, tend to be more affluent and middle class people. They have busy jobs or can't be bothered to go to GPs, and if they can get a quick fix from a chemist, that is the least line of resistance. I think that is the way hayfever in this country is dealt with and that is the policy of the government. We don't have any allergy specialists, so we will just make everything available OTC and we make the pharmacists the allergy specialists.

  However, under that age range and then above that age range the prescriptions increase.

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505718

PTX0098-00143
CIPLA LTD. EXHIBIT 2021 PAGE 143

It may be that people above that age range don't realize that there are so many things available OTC, that message hasn't got through to them. Below that age range, there are probably parental influences.

If it was legal to advertise here in the UK, I think people would be amazed at the things you can get over the counter, particularly fluticasone for example.

- **Treating doctor specialities.**
  It's not very well set up in the UK because allergy is a very small specialist here. The Professional Allergy Society are trying to do something about it and there is a House of Commons select committee, but the situation is that there are very few allergists, its mostly GP's prescribing. All these different numbers that you give here, for country by country, that reflects the local, traditional and historical prescribing practices. This dictates the strength of allergy as a specialty within a country, for instance, it has always been big in the United States and Canada, it has always been zero in the UK. I suppose I am slightly surprised there is not a bit more allergy prescribing on the continent of Europe.

  They are also very aware of allergy in Japan. They are a very affluent society and they don't want the inconvenience, they have high pollen counts, they have a slightly different pollen flora, but the Japanese grasses are pretty allergenic. Of course they also have huge urban sprawl, which again, with the pollution allergen complex may be a factor. The Japanese were the first people to describe this.

  Pediatrician trends, particularly in the US.

  Perception is so much different in the United States. If you have health insurance, you've got an entrée into any specialist you want, no waiting, you go to your center, you can take your kid along to a pediatrician for almost anything. Whereas here, getting an appointment for a consultant pediatrician can take weeks and who is going to take a child along for hayfever to a consultant pediatrician?

Antihistamines

- **Which in your opinion would be the best antihistamine currently available in the UK?**
  I don't think you can say really which is the best one, because it is well known that there is quite a patient variation in response to antihistamines, but we don't really understand

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505719

PTX0098-00144
CIPLA LTD. EXHIBIT 2021 PAGE 144

the reasons for that. For instance, in chronic urticaria people often rotate antihistamines because there seems to be some refractoriness. The only thing that is important is the vast difference between the new generation antihistamines and the old non selective antihistamines, (e.g. chlorphenamine and clemastine), all of which were sedative, interacted with alcohol, or potentially, impaired driving performance, they were also poor antihistamines because they had poor receptor binding for the H1 receptor. There is really not much to say between all the new antihistamines. They talk about second and third generation, but the third generation aren't novel steps.

Do you think doctors see any difference between things like levocetirizine for example and the desloratadine that has been introduced?

Well, levocetirizine is an isomer of cetirizine, so that is no big breakthrough, desloratadine is a metabolite of loratadine and fexofenadine is another so called third generation and that is also a metabolite of terfenadine. They are not a different class structurally but there is huge marketing behind them. What they have got is the potential cardio toxic effects of the second generation. Not all second-generation antihistamines are cardio toxic, but they are all 'tarred with the same brush''. You just can't have anything that is remotely cardio toxic in an OTC preparation.

- **Do you think the majority of antihistamines should be OTC?**
  All OTC treatments just have to go through the hurdles, or it is just a matter of time. It has to be under prescription in the UK for a number of years before it becomes OTC. Antihistamines which aren't OTC at the moment, like fexofenadine, will be over the counter in due course.

  So, with all these drugs available OTC these days, what are the implications in terms of managing this disease?

  On the one hand, that sensible advice from a pharmacist is probably all that is required for the vast majority of sufferers with mild intermittent, mild persistent or even moderate persistent symptoms, so going to the GP is probably a waste of time for the majority of people with hayfever. As for it interfering with asthma, I don't know that that is so. If people have an appreciable asthmatic component, then they are going to go to their GP who is going to add in an inhaled steroid.

This report is a licensed product and is not to be photocopied

MEDA_APTX03505720

PTX0098-00145
CIPLA LTD. EXHIBIT 2021 PAGE 145

Corticosteroids

- **At the moment Flixonase is by far the highest sales in the UK, would you say this was the best product?**
  It is a useful product; but I myself am quite fond of mometasone, Nasonex, because that allows one to titrate up and down, and also the studies on mometasone are very convincing. I don't particularly like beclomethasone, I think it is a weaker one, you have to use it more frequently.

  Do you think that the marketing power of GSK for example, would have a lot to do with the success of Flixonase?

  Of yes, the marketing is such a confounding factor when it comes to real scientific evidence of efficacy that it is very difficult to know. The one who shouts the loudest gets the sales.

- **Is there a gap in the UK market for antihistamine/decongestant combinations?**
  It is difficult to say - it is complicated as there are already a number of things you can get over the counter, you haven't for instance mentioned the topical antihistamines, azelastine and levocabastine. Introduce yet another treatment, a combination with decongestants, and you have another layer of complexity for the vendor and the purchaser in a market which is already pretty free OTC.

  The science behind it is good, the only issue is that I've never prescribed topical decongestants or recommend them. I don't think they are really necessary if you can get judicious treatment with antihistamines and corticosteroids, and I don't like the rebound phenomenon, in effect people abuse them.

- **Claritin (Loratadine) now it is off patent. What do you think the affect of this going off patent in the UK has been on allergic rhinitis treatment?**
  Well the main effect is that Schering Plough aren't giving any fellowships now for people to go to meetings!

  Is allergic rhinitis better treated now that this is available – cheaper?

  I am not sure about that, all the tablets are OTC, they are all about £1.00 each, but I haven't seen any signs of a huge drop in price.

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505721

PTX0098-00146
CIPLA LTD. EXHIBIT 2021 PAGE 146

I suppose there will be more competition and therefore they may be putting the price down. There isn't much to choose between cetirizine, loratadine, desloratadine or fexofenadine, so they are all going to fight each other.

Future Challenges in allergic rhinitis

I think the main thing is more effective vaccines really. Going for a cure, rather than symptomatic treatment is next, and I think that progress is being made in that area. (T-cell peptide approach, the CPG ISS approach, recombinant allergens)

Antihistamines have probably got several years, maybe 10 or 20 years. But I don't think the vaccinations will obviate the need for antihistamines, but they will make drug usage less.

I don't think there are going to be a lot of changes over the next few years. We are going to maintain a status quo.

END OF INTERVIEW

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505722

PTX0098-00147
CIPLA LTD. EXHIBIT 2021 PAGE 147

APPENDIX B

Bibliography

Epidemiology

Azpiri A, Alonso E, Gamboa PM, Jauregui I, Antepara I, Fernandez E, Fernandez de Corres L, Audicana M, Munox D, Escobar A. Prevalence of pollinosis in the Basque Country. Allergy, 1999; 54(10): 1100-1105

Burney P, Chinn S, Jarvis D, Luczynska C, Lai E. Variations in prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey. Eur Resp, 1996; 9: 687-695

Charpin D, Raherison C, Dutau H, Taytard A. Epidemiology of respiratory allergies: current data. Rev Mal Respir, 2000; 17 (1) pt2: 139-58

Crown WH, Olufade A, Smith MW, Nathan R. Seasonal versus perennial allergic rhinitis: drug and medical resource use patterns. Value Health, 2003; 6(4):448-56

Dykewicz, Fineman, Skoner *et al.* Joint task force practice parameters on diagnosis and management of rhinitis. 1998

Leynaert B, Neukirch C, Kony S, Guenegou A, Bosquet J, Aubier M, Neukirch F. Association between asthma and rhinitis according to atopic sensitization in a population-based survey. J Allergy Clin Immunol, 1999; 113(1): 86-93.

McCrory et al, 2003

Mosges R, Epidemiology of allergic diseases. University of Cologne, 1995

Nakamura A, Asai T, Yoshida K, Baba K, Nakae K. Allergic rhinitis epidemiology in Japan. Nippon Jibiinkoka Gakkai Kaiho, 2002, 105(3): 215-24

Olivieri M, Verlato G, Corsico A, Lo Cascio V, Bugiani M, Marinoni A, de MarcoR, (Italian ECRHS group). Prevalence and features of allergic rhinitis in Italy. Allergy, 2002; 57(7): 600

Okuda M, Epidemiology of Japanese ceder pollinosis throughout Japan. Ann Allergy Asthma Immunol, 2003; 91(3): 288-96

Pearce et al, 2000. Comparison of asthma prevalence in the ISAAC and the ECRHS. Eur Respir J, 2000; 16: 420-426

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505723

PTX0098-00148
CIPLA LTD. EXHIBIT 2021 PAGE 148

Summary Health Statistics for US Adults: National Healt Interview Survey, 2001 – CDC website

Sibbald B, Rink E. Epidemiology of seasonal and perennial rhinitis: clinical presentation and medical history. Thorax, 1991; 46(12): 895-901

Verlato G, et al; Is the prevalence of adult asthma and allergic rhinitis still increasing? Results of an Italian study. J Allergy Clin Immunol, 2003; 111(6): 1232-8

Clinical trial data

Condemi J, Schulz R, Lim J. Triamcinolone acetonide aqueous nasal spray versus loratadine in seasonal allergic rhinitis: efficacy and quality of life. *Ann Allergy Asthma Immunol*. 2000 May; 84(5):533-8

Daniel K.C. Lee, Caroline E. Bates, Graeme P. Currie, Brian J. Lipworth. Comparative in vivo bioactivity of modern H_1-antihistamines on AMP challenge in atopic asthma. *Journal of Allergy and Clinical Immunology*. February 2003, (1), 111:2

Drouin M, Yang WH, Bertrand B, Van Cauwenberge P, Clement P, Dalby K, Karnell R, Ernst TM, Herbert J, Karlsson G, Luciuk G, Mazza J. Once daily mometasone furoate aqueous nasal spray is as effective as twice daily eclomethasone dipropionate for treating perennial allergic rhinitis patients. *Annals of Allergy Asthma and Immunology* 1996,77:2 (153-160)

Friedrich Horak, Ursula P. Stübner, Rene Zieglmayer, Alan G. Harris. Effect of desloratadine versus placebo on nasal airflow and subjective measures of nasal obstruction in subjects with grass pollen–induced allergic rhinitis in an allergen-exposure unit. *Journal of Allergy and Clinical Immunology* June 2002, 1, 109 (6)

Graft D, Aaronson D, Chervinsky P, Kaiser H, Melamed J, Pedinoff A, Rosen JP, Schenkel EJ, Vandewalker ML, Keim A, Jensen PK, Nolop K, Mesarina WICKIB A placebo- and active-controlled randomized trial of prophylactic treatment of seasonal allergic rhinitis with mometasone furoate aqueous nasal spray. *Journal of Allergy and Clinical Immunology* 1996, 98:4 (724-731)

Hebert JR, Nolop K, Lutsky BN. Once-daily mometasone furoate aqueous nasal spray (Nasonex) in seasonal allergic rhinitis: an active- and placebo-controlled study. *Allergy* 1996, 51:8 (569-576)

Jankowski R, Bonfils P, Castillo L, Gilain L, Prades JM, Strunski V. Once-daily dose of budenoside aqueous nasal spray 128g is efficacious primary treatment with rapid onset in nasal polyps. *Journal of Allergy and Clinical Immunology* 1999,103:1

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505724

PTX0098-00149
CIPLA LTD. EXHIBIT 2021 PAGE 149

Linden M, Svensson C, Andersson E, Andersson M, Greiff L, Persson CGA Acute effect of topical budesonide on nasal mucosal GM-CSF and IL-5 after allergen challenge in allergic rhinitis Journal of Allergy and Clinical Immunology 1999, 103:1 (Abs 959)

Meltzer EO, Weiler JM, Widlitz MD.J Comparative outdoor study of the efficacy, onset and duration of action, and safety of cetirizine, loratadine, and placebo for seasonal allergic rhinitis. *Allergy Clin Immunol*. 1996 Feb;97(2):617-26.

Meltzer EO, Prenner BM, Nayak A, *et al.* Efficacy and tolerability of once-daily 5mg desloratadine, an H1-receptor antagonist, in patients with seasonal allergic rhinitis. *Clin Drug Invest* 2001

Molkhou P, Billardon M, Jouan AM, Fondarai J. Multicenter study on the efficacy of Zyrtec (Cetirizine) in the treatment of perennial allergic rhinitis in 875 adolescents. *Allerg Immunol (Paris).* 1996 Jan;28(1):19-24.

Leynadier F, Mees K, Arendt C, Pinelli ME. Efficacy and safety of levocetirizine in seasonal allergic rhinitis. *Acta Otorhinolaryngol Belg*. 2001;55(4):305-12.

Paul J. Bryce, PhD, Raif Geha, MD, Hans C. Oettgen, MD, PhD Desloratadine inhibits allergen-induced airway inflammation and bronchial hyperresponsiveness and alters T-cell responses in murine models of asthma. *Journal of Allergy and Clinical Immunology.* July 2003 • 112 (1)

Salmun LM, Lorber R, Danzig M, *et al.* Efficacy and safety of desloratadine in seasonal allergic rhinitis (abstract 1123). *J Allergy Clin Immunol* 2000; 104

Scadding GK, Lund VJ, Jacques LA, Richards DH. A placebo-controlled study of fluticasone propionate aqueous nasal spray and beclomethasone dipropionate in perennial rhinitis: efficacy in allergic and non-allergic perennial rhinitis. *Clin Exp Allergy.* 1995 Aug; 25(8):737-43.

Other

Goldmann D, Jotce G, Escarce J, Pace J, Solomon M, Laouri M, Landsman P, Teutsch S. Pharmacy benefits and the use of drugs by the chronically ill. JAMA, 2004; 291(19): 2344

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505725

PTX0098-00150
CIPLA LTD. EXHIBIT 2021 PAGE 150

Report methodology

For more information on Datamonitor Healthcare's primary and secondary research methodology please refer to the Methodology Document, available from your account manager.

Japanese market data

The Japan market value and volume numbers, for the period 2000-03, presented in this report are estimates derived from the IMS Pacific Rim regional total. Therefore, they may not correlate exactly with those numbers reported for Japan in the IMS MIDAS audit.

Standard units

'Standard units' are used to describe the number of standard dose units sold. It is determined by taking the smallest number of counting units (the number of tablets, milliliters of liquid, grams of ointment) sold divided by the standard unit factor. This 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. Therefore, standard units is equal to total volume of a drug prescribed (e.g. in mg) divided by the smallest common dose of a product form.

However, if there are a number of dosage forms (for example 5mg, 10mg ,20mg) and the 5mg dosage form is the most commonly prescribed, standard units will be worked out based on the 5mg dosage form. This might result in a higher number of standard units being calculated than was, in reality, consumed. Variations in dosing frequency are not accounted for when using this measure. As such, all standard units values and measures should be considered with this in mind, and may represent the highest possible prescribed volume of a drug.

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505726

PTX0098-00151
CIPLA LTD. EXHIBIT 2021 PAGE 151

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;
- Oncology;
- Women's Health;
- 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;

© Datamonitor (Published 09/2004)
This report is a licensed product and is not to be photocopied

MEDA_APTX03505727

PTX0098-00152
CIPLA LTD. EXHIBIT 2021 PAGE 152

- Forecasting and modeling.

Datamonitor Healthcare's research and analysis methodologies

For detailed information about Datamonitor Healthcare's research and analysis methodologies, go to www.datamonitor.com/healthcare/methodology.

Datamonitor Healthcare's therapy area capabilities

Datamonitor's therapy area team offers both customized and syndicated analysis across a wide range of therapeutic areas. Within Datamonitor Healthcare's six therapy area teams, analysis is produced in the following sectors:

- cardiovascular disease;
- endocrinology;
- gastrointestinal disorders;
- infectious disease;
- musculoskeletal disease;
- neurology;
- oncology;
- pain management;
- psychiatry;
- respiratory disease;
- women's health.

© Datamonitor (Published 09/2004)

This report is a licensed product and is not to be photocopied

MEDA_APTX03505728

PTX0098-00153
CIPLA LTD. EXHIBIT 2021 PAGE 153

Disclaimer

All Rights Reserved.

No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the publisher, Datamonitor plc.

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.

MEDA_APTX03505729

PTX0098-00154
CIPLA LTD. EXHIBIT 2021 PAGE 154