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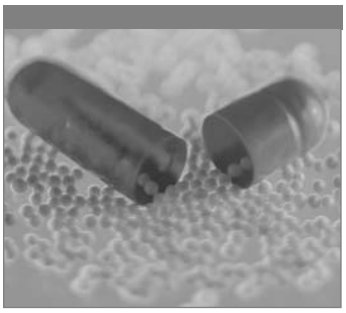

HEALTHCARE

THE DIABETES MARKET OUTLOOK:

Market analysis of future growth and leading players by sector

By Gayle Hamilton

Gayle Hamilton

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- The type 1 diabetic population is relatively small and is also not expected to grow significantly in the coming years.
- Type 2 diabetes is now at epidemic levels with approximately 30.3m type 2 diabetics in the US and Europe in 2003, and this figure is projected to rise to 41.5m in 2012.
- Drivers for growth in type 2 diabetes are the increasing age demographic, as type 2 diabetes is formed later in life, and an escalation in rates of obesity, a key risk factor. In 1999-2000 the NHANES survey reported that 64% of US are overweight or obese.
- Diagnosis rates for type 2 diabetes range from 58% in the US and Germany to just 41% in the UK. These low diagnosis rates are because the disease symptoms are often asymptomatic, especially in the early stages.
- In 2003 the FDA announced a plan to apply a fast-track process to new diabetes drugs, due its epidemic nature.
- Prescribing of insulin to type 2 diabetics as a first line of treatment is low, varying from 16% in France to 28% in Germany. Recent evidence has suggested the use of insulin earlier in the treatment of type 2 patients is advantageous, so insulin prescribing is expected to increase further. The launch of non-invasive insulins will also increase insulin use amongst type 2 diabetics.

Global diabetes market analysis

- The US/European diabetes market totaled $10.4bn in 2003, an increase of 183% from 1999 total sales. The current growth drivers of this market are the insulins, thiazolodinediones (TZDs) and combination therapies.

- The largest drug class in 2003 was the TZDs with $3.1bn in US/European sales. This drug class also recorded impressive growth with a compound annual growth rate (CAGR) 1999-2003 of 36.3%. Although the TZDs are popular in the US, this is not the case in Europe, where insulins have the largest share of the market.

- The US/European insulin market has grown by a CAGR 1999-2003 of 17.4%, and in 2003 totaled $3.9bn. This growth is due to increased insulin treatment of type 2 patients, and the launch of fast-acting and long-acting insulin analogs.

- Combination therapies recorded the highest growth from 1999-2003 with a CAGR of 94.3%. Combination therapy is proving increasing popular as many of the antidiabetic drugs have different and complimentary modes of action.

- Future growth drivers include the non-invasive insulins, the dual peroxisome proliferator activator receptor (PPAR) agonists and the glucagon-like peptide-1 (GLP-1) agonist/dipeptidyl peptidase-IV (DDP-IV) inhibitor compounds.

- The key unmet need in the insulin market is an alternative delivery mechanism to subcutaneous injection. Pills, mouth sprays, inhalers and patches are some of the novel mechanisms being tested. The inhalable insulins, Exubera and AERx insulin diabetes management system (iDMS), are likely to be the first to market.

- The dual PPAR agonists have blockbuster potential for treating both diabetes and heart disease. Two compounds in phase III trials are Bristol-Myers Squibb (BMS)/Merck's Muraglitazar, and AstraZeneca's Galida.

- The GLP-1 agonists/DPP-IV inhibitors are related compounds that will treat type 2 diabetes without the risk of hypoglycemia or weight gain. Many companies, including Novo Nordisk and Eli Lilly, have these drugs in development.

Insulin market analysis

- The US/European insulin market totaled $3.9bn in 2003, with a CAGR 1999-2003 of 17.4%.
- The fast-acting insulins hold the largest share of the market at $1.3bn and have also shown strong growth due to the launch of insulin analogs Humalog and NovoLog.
- The long-acting insulins have shown the strongest growth since 1999 with a CAGR of 108%. This has resulted from the launch of Aventis' Lantus in 2001, and is set to grow further with Novo Nordisk's Levemir launched in 2004.
- Humalog was the leading US/European insulin brand in 2003 with sales accounting for 27.7% of the market. In the US Humalog had sales of $753m.
- Lantus has gained a 14.6% US/European market share since launch in 2001. However, its US success has not been mirrored as yet in the European markets.
- NovoLin's US/European market share has declined from 1999 to 2003, now holding 23.1% of the market. However, this drug remains the leading insulin brand in Europe, and has been largely unaffected there by the launch of Humalog.
- Humulin was the leading US/European antidiabetic until 2002. Sales of this product have suffered from the introduction of fast-acting analog, Humalog, with Eli Lilly moving patients from Humulin to the newer treatment.
- NovoLog has not shown strong sales to date, but as Novo Nordisk switches patients from NovoLin to the newer NovoLog then its sales should rise, especially in Europe.
- Eli Lilly is the leading insulin company in the US with a 62.2% market share in 2003, but this share has declined from 82.2% in 1999. Aventis, and to a lesser degree, Novo Nordisk have captured Lilly's lost share. In the European markets Novo Nordisk is the leading player, accounting for 46.6% of sales in 2003, and Lilly (25.3%) and Aventis (19.6%) have had relatively flat growth in the last five years.

Oral antidiabetic (OAD) market analysis

- Sales of OADs totaled $6.5bn in 2003, an average increase over 5 years of 16.0%. This growth has mirrored the increasing population of type 2 diabetics.

- TZDs is the largest class of OADs, accounting for 48.9% of US/European sales in 2003. Growth in this area is due to the success of this class in the US, but the TZDs are not as popular in Europe after the withdrawal of Rezulin in 1999. Actos is the leading US/European TZD with a 53% market share to Avandia's 42.4%.

- Sales of biguanides have declined overall and dropped behind TZDs in recent years. The market has also changed significantly since the US patent expiry of BMS/Merck KGaA's Glucophage in 2001. In 2000 Glucophage accounted for 96.2% of US/European sales in this class and was the leading OAD. However, due to generic competition and strong sales of Glucophage XR (extended release), in 2003 this figure had dropped to 36% of total sales.

- The sulfonylurea class is heavily genericized and holds a 17.2% US/European OAD market share. Glucotrol XL is the leading drug in the US but lost patent protection in 2003, so sales are expected to decline due to generic competition. Amaryl from Aventis has shown strong growth over the last five years and is now the leading US/European sulfonylurea with 36.0% of the market.

- BMS and GlaxoSmithKline (GSK) have developed single-pill combination therapies to take advantage of the complementarity of different OAD classes and to extend product life-cycles.

- Both the alpha glucose inhibitors (AGIs) and the prandial glucose regulators (PGRs) have had poor uptake, perhaps because of their late entry onto the market.

- Takeda and GSK are the leading companies involved in OADs, both selling TZDs. Takeda is the top company with a market share of 25.9%, although this comes from sales of just one product, Actos. GSK has 23.0% of the market from sales of two products, Avandia and Avandamet.

Leading players in the diabetes market

- The insulin market is dominated by Eli Lilly, Novo Nordisk and Sanofi-Aventis, while in the OAD market Takeda, GSK and BMS are the key players.

- Eli Lilly is the leader in the US insulin market, with its Humulin and Humalog range of products. The most promising projects in Eli Lilly's pipeline are Exenatide (a GLP-1 compound) expected for launch in 2005, and an inhalable insulin, AIR, although it will most likely be third to market behind Exubera and AER iDMS.

- Novo Nordisk is the leader in the European insulin markets, holding a 46.6% market share in 2003. The company has also increased its US share to 20.5%. Novo Nordisk's R&D pipeline is very strong and includes AERx iDMS, an inhalable insulin expected to be launched in 2007.

- Sanofi-Aventis has a 17.2% share of the US insulin market (through Lantus sales) and 19.6% in Europe, and is also a key player in the OAD market through sales of Amaryl. Sanofi-Aventis has a number of products in development, most notably Exubera (with Pfizer/Nektar), likely to be the first inhalable insulin to market.

- Takeda is the leading company in the OAD market but its sales are expected to decline when Actos loses patent in 2006, and generic competition enters the market. Takeda has five compounds in development although none are expected to reach the market before 2008.

- GSK recorded 2003 sales of $1.5bn for Avandia and Avandamet. GSK plans to launch Avandaryl (Avandia + Amaryl) in 2004, but besides this, GSK's late-stage diabetes pipeline is thin. However, GSK has several projects in phase I trials.

- BMS's diabetes sales have declined significantly in recent years due to the US patent expiry of Glucophage. BMS's diabetes pipeline has been built through in-licensing. The most promising drug in the pipeline is Muraglitazar, a dual PPAR agonist in phase III trials, and it is the most advanced compound of its type in development. PPAR agonists are expected to have blockbuster potential.

CHAPTER 1

Epidemiology analysis

Chapter 1 Epidemiology analysis

Summary

- Type 2 diabetics account for approximately 90 to 95% of the total diabetic population.
- The type 1 diabetic population is relatively small and is also not expected to grow significantly in the coming years.
- Type 2 diabetes is now at epidemic levels with approximately 30.3m type 2 diabetics in the US and Europe in 2003, and this figure is projected to rise to 41.5m in 2012.
- Drivers for growth in type 2 diabetes are the increasing age demographic, as type 2 diabetes is formed later in life, and an escalation in rates of obesity, a key risk factor. In 1999-2000 the NHANES survey reported that 64% of US are overweight or obese.
- Diagnosis rates for type 2 diabetes range from 58% in the US and Germany to just 41% in the UK. These low diagnosis rates are because the disease symptoms are often asymptomatic, especially in the early stages.
- In 2003 the FDA announced a plan to apply a fast-track process to new diabetes drugs, due its epidemic nature.
- Prescribing of insulin to type 2 diabetics as a first line of treatment is low, varying from 16% in France to 28% in Germany. Recent evidence has suggested the use of insulin earlier in the treatment of type 2 patients is advantageous, so insulin prescribing is expected to increase further. The launch of non-invasive insulins will also increase insulin use amongst type 2 diabetics.

Introduction

This chapter provides a disease description of type 1 and type 2 diabetes, defining the differences between the conditions and briefly outlining the treatment options available. This is followed by estimated current and future prevalence rates of type 1 and type 2 diabetes in the US and the five major European markets. The chapter will then look at the treatment patterns in each of these countries, particularly in the prescribing of insulin and thiazolidinediones (TZDs) in type 2 patients.

Disease description

Diabetes mellitus is a chronic metabolic disorder that is caused by a failure of the body to produce insulin, in the case of type 1 diabetes, or by an inability of the body to respond adequately to circulating insulin – type 2 diabetes.

In healthy individuals, the insulin secreted by the pancreas increases the ability of tissue to absorb blood glucose. A resulting disruption of insulin function results in the high levels of blood glucose that is commonly associated with diabetic patients. High blood glucose or hyperglycemia is one of main problems arising from diabetes and can lead to the development of debilitating macro- and microvascular complications.

Type 1 diabetes

Type 1 diabetes, previously known as insulin-dependent diabetes mellitus (IDDM), occurs most often in children or young adults and accounts for 5–10% of the diagnosed diabetes patient population. Type 1 is thought to be the result of an autoimmune attack on the body's own pancreatic islet beta-cells, resulting in failure of the pancreas to produce an adequate amount of insulin to aid glucose absorption. The causes of

autoimmune attacks are not known but are thought to be influenced by environmental factors such as exposure to viruses or antigens.

Currently, type 1 patients must have daily injections of insulin, and failure to do so results in diabetic ketoacidosis, a potentially life-threatening complication. The key disadvantage of insulin therapy is its injected mode of administration that is inconvenient and unpopular with patients. For this reason, optimum level of control may not be achieved as full compliance can be a major concern and patients may be reluctant to make significant lifestyle changes to adhere fully to insulin therapy. Another significant disadvantage to insulin therapy is the associated gain in weight that, given the association and possible contribution obesity has to the development of diabetes, is a particularly unwanted side effect.

In recent years, the introduction of different forms of insulin has meant that patients have a choice in terms of the speed of onset, peak time and duration of action of the insulin they administer. In addition, advances in drug delivery devices, such as pre-filled pens and pump therapy, have lead to greater convenience for patients requiring multiple daily insulin injections. Despite this, it is still difficult for diabetic patients to gauge exactly how much insulin to inject, and most insulin-treated patients are required to conduct frequent blood glucose monitoring (up to four times a day), which can also be unpleasant and inconvenient.

In the near future, non-invasive insulins will provide patients with more convenient drug delivery options. Researchers are also looking at islet cell transplantation and stem cell therapy as possible cures for type 1 diabetes, eliminating the need for exogenous insulin.

Type 2 diabetes

Type 2 diabetes, previously called non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes, accounts for 90–95% of diagnosed diabetes cases worldwide and typically develops in middle-aged adults. Unlike type 1 patients, pancreatic beta-cells in type 2 patients are able to produce insulin. However, there is an inability of tissue to respond to the effects of the insulin, which ultimately results in high levels of blood glucose. This decreased response to insulin is also referred to as insulin resistance.

Increased levels of calories consumed and the higher frequency of meals that are associated with Western diets are thought to cause this type 2 diabetes adaption of the body's insulin response. The end result is a decreased sensitivity of the body's cells to the effects of insulin, which in turn leads to higher insulin production to compensate and achieve a normal blood glucose level. This ever-increasing positive feedback loop results in a pancreatic 'burn-out' or an inability to produce enough insulin to maintain a normal blood glucose level. While this disease process is significantly different than the natural history seen in type 1 diabetes, both conditions result in elevated blood glucose levels.

There is a wide range of treatment options available for type 2 diabetics. Depending on the severity of symptoms, some patients are able to control their diabetes through a strict diet and exercise program, although it is likely that oral antidiabetic (OAD) drugs will be required. There are a number of different types of OADs used to treat type 2 diabetes, each having a different mode of action and side-effect profile. Insulin is another treatment option, most often reserved for later lines of therapy. Type 2 patients typically have normal to elevated insulin production, as it is the use of insulin that is disrupted in these patients. Thus, on average, the insulin dose required in type 2 patients is significantly higher since the underlying insulin resistance is overcome by a greater insulin load.

Current and future prevalence of diabetes

Type 2 diabetics make up approximately 90 to 95% of the total diabetes population. Thus the type 1 diabetic population is relatively small, and in fact is also relatively stable in terms of growth. It is the type 2 diabetes population that has driven growth in the diabetes market over the last five years, and this trend is expected to continue over the forecast period. Table 1.1 illustrates this increase with 41.5 million people projected to be type 2 diabetic by 2012, compared to a 2003 figure of 30.3 million.

Table 1.1: Prevalence of Type 2 diabetes (m), 2003-2012

	2003	2004	2006	2008	2010	2012	CAGR (%) 2003-2012
US	16.8	17.3	18.7	20.1	21.6	23.2	3.7
France	2.4	2.5	2.6	2.8	3.0	3.1	3.0
Germany	3.5	3.6	3.8	4.1	4.4	4.8	3.7
Italy	3.4	3.5	3.8	4.1	4.4	4.7	3.7
Spain	2.0	2.1	2.2	2.3	2.5	2.6	3.0
UK	2.2	2.3	2.5	2.6	2.8	3.1	3.7
Total	**30.3**	**31.3**	**33.6**	**36.0**	**38.7**	**41.5**	**3.5**

Source: WHO; Gale, 2002; Janka, 2002; Business Insights

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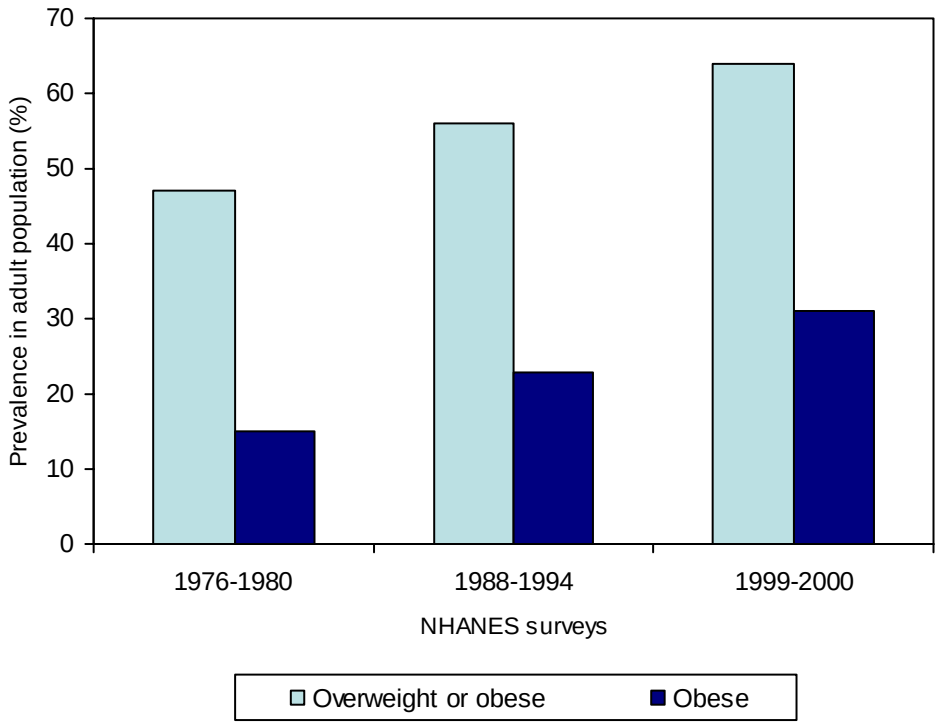
The drivers for growth in the type 2 patient population include the aging demographic and the escalation in rates of obesity, which is a key risk factor for developing type 2 diabetes. The proportion of diagnosed patients, currently estimated to be 50%, will also continue to rise in proportion with the rising overall prevalence, meaning that the market for antidiabetic drugs will grow faster and larger as a result.

People with a body mass index (BMI) in the obese category have a five fold greater risk of developing diabetes than those individuals classed as neither overweight nor obese.

As illustrated in Figure 1.1 the incidence of overweight and obese individuals in the US has increased significantly in the last 25 years, such that in 1999-2000 64% of US adults were either overweight or obese. Type 2 diabetes is not the only consequence of obesity, with many patients also developing other chronic cardiovascular complications, including hypertension and dyslipidemia.

Figure 1.1: Prevalence of obese and overweight adults in US, 1976-2000



Prevalence is age-adjusted

Adults defined as aged > 20

Source: NHANES II, III and IV; Business Insights

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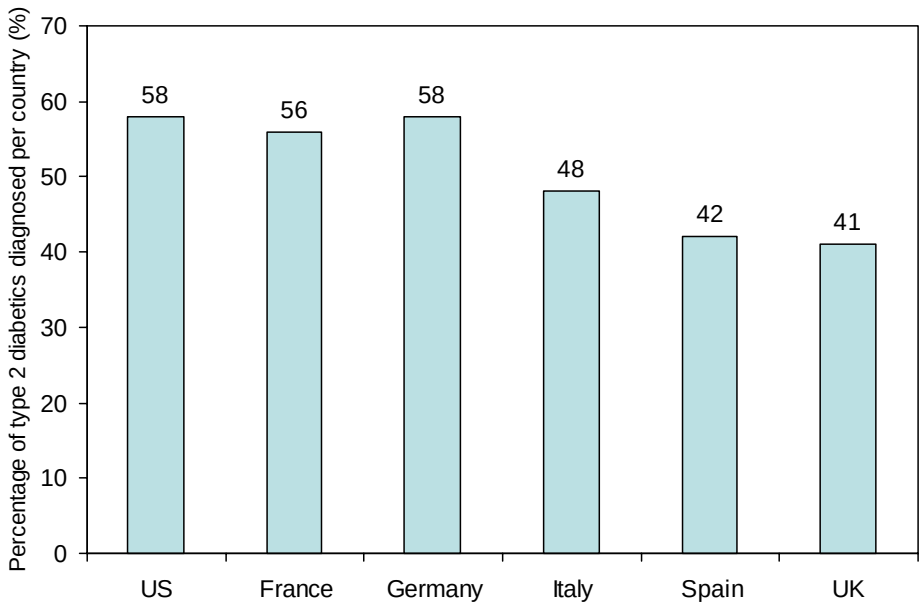
Diagnosis

Unlike type 1 diabetes, where symptoms cannot be ignored, type 2 diabetes can often be asymptomatic, particularly in the early stages of the disease, and therefore this condition can go undetected for years. Figure 1.2 shows that the estimated proportion of type 2 diabetics diagnosed across the six markets covered is fairly consistent, ranging from 41% of patients in the UK to 58% in the US and Germany.

Figure 1.2: Proportion of type 2 diabetics diagnosed, 2003



Source: Business Insights, Type 2 Diabetes Insight Physician Survey (Q1.1) Business Insights Ltd

The length of time from disease onset to diagnosis can sometimes be several years, during which time the microvascular complications associated with diabetes may begin to develop.

Fast-track review for diabetes drugs

Due to the epidemic nature of obesity and type 2 diabetes the FDA announced in 2003 a plan to apply a fast-track review process to new drugs for such diseases. The fast-track reviewal process is normally reserved for drugs for life-threatening diseases such as terminal cancer and AIDS, with low survival expectations and no other treatment options available.

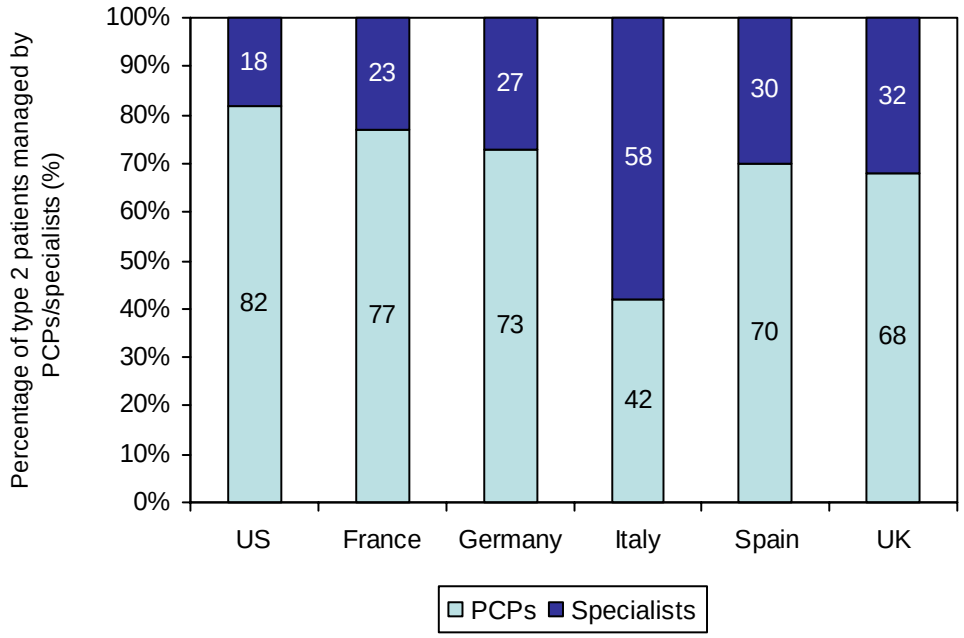
Diabetes drugs that are fast-tracked will be able to win licenses based on preliminary indicators such as glucose levels or weight loss, instead of waiting for completion of lengthy phase III trials. However, there is scepticism of this FDA plan because of its handling of Pfizer/Aventis/Nektar's diabetes drug, Rezulin. This drug was given priority status – one tier down from accelerated approval – by the FDA when it was approved by the FDA in 1998, but was the subject of a highly publicized recall in 2000 amid links to liver toxicity.

This accelerated approval process can cut clinical trial time by over a year, and final approval time by the FDA by six months or more. Thus in total if a drug is fast-tracked by the FDA it will reach market between 18 months and 2 years ahead of schedule. This is a valuable incentive for pharmaceutical companies developing drugs as this will enable fast-tracked drugs to have more time on the market under patent exclusivity that those years being spent in clinical trials or approval time.

Current and future treatment patterns

Figure 1.3 shows the estimated breakdown of the management of type 2 diabetes by physician type – primary care physician (PCP) or specialist. In the US 82% of diagnosed type 2 patients are treated by a PCP, whilst in the five major European markets this figure varies from 77% in France down to 42% in Italy.

Figure 1.3: Management of type 2 diabetes by physician type, 2003



PCP = Primary Care Physician

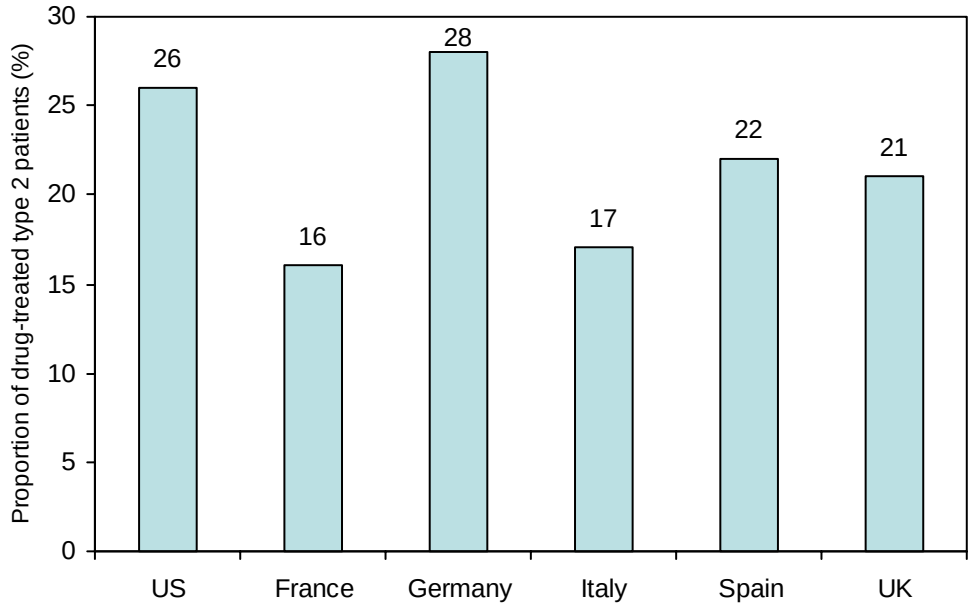
Source: Business Insights, Type 2 Diabetes Insight Physician Survey (Q1.3) Business Insights Ltd

Insulin prescribing

Patients with type 2 diabetes are generally referred to a specialist when blood glucose levels are poorly controlled by a combination of oral antidiabetics (OADs) and more intensive treatment is needed or the patient requires insulin therapy. Due to the complexity of the insulin regimens and the time it takes the physician to educate the patient on the use of this type of therapy, many PCPs remain reluctant to initiate insulin in type 2 diabetics.

The majority of patients in the six markets analysed are treated by PCPs, with the exception of Italy, as shown in Figure 1.3. One consequence of this is that the prescribing of insulin as a first line therapy is low. The percentage of type 2 patients on insulin therapy ranges from 13% in France to 28% in Germany (Figure 1.4).

Figure 1.4: Proportion of drug treated type 2 diabetics treated with insulin in monotherapy or combination, 2003



Source: Business Insights, Physician Survey

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Despite the low proportion of patients currently on insulin, changes to treatment guidelines – such as the 1997 revisions to the American Diabetes Association (ADA) guidelines specifying a target HbA1c goal of <7.0% - have meant that physicians are now required to prescribe more aggressive therapies to control blood glucose, the result of which is an increase in the use of insulin in type 2 diabetes patients. The benefits obtained from improving glycemic control are now well documented and a number of clinical trials have shown that the risk of developing diabetic complications is reduced if glycemic control is maintained at target levels. However, this evidence to support tight glycemic control has only been available since 1998 and, as a result, many physicians still believe insulin therapy to be detrimental in the treatment of type 2 diabetes.

More patients receive insulin as a second or third line therapy than at first line. This reflects the general trend among physicians and patients that insulin is a therapy of last resort in the treatment of type 2 diabetes. However, as well as increased prescribing of insulin, evidence also suggests that initiating insulin therapy earlier can help to correct underlying pathogenic abnormalities associated with type 2 diabetes, namely insulin resistance and impaired glucose secretion. In addition, the consequent improvement in glycemic control can result in fewer long-term complications.

TZD prescribing

The failure of alternative therapies to provide adequate glycemic control is also a major factor for the increase in insulin prescribing for type 2 diabetics, although this is less true in the US where the TZD oral antidiabetics, Actos and Avandia, are the diabetes market leaders. The TZDs have thus far had little market penetration in Europe, but following both Actos and Avandia receiving full EU marketing approval in September 2003, the prescribing of this drug should increase. However, many European physicians remain sceptical about the TZDs after the withdrawal of Pfizer's Rezulin.

Rezulin was the first TZD to be launched in 1997, but was voluntarily withdrawn in the UK by GSK, the European licensee, in 1997 and was never launched in other EU countries, due to cases of severe liver toxicity. However, despite withdrawal in the UK,

Rezulin remained very popular with physicians in the US, who saw the drug as fulfilling many of the unmet needs in the treatment of type 2 diabetes and felt that the benefits of treatment outweighed the potential risks. However, in March 2000, Rezulin was also withdrawn from the US market by Warner Lambert (now part of Pfizer) following a request by the FDA and, in the same month, Sankyo withdrew the product in Japan. The presence of two competitors, Avandia and Actos, that were not associated with problems of liver toxicity, rendered it unethical to prescribe Rezulin.

Table 1.2 shows the continued dominance of TZDs in the US diabetes market, while in Europe, market penetration is small.

Table 1.2: US and European* Sales by Drug Class ($m), 2002-2003

	2002	2003	Growth (%) 2002-2003	CAGR (%) 1999-2003
US				
Insulins	1,865	2,280	22.3	18.4
TZDs	2,529	3,039	20.2	34.9
SUs	679	732	37.9	2.5
BGs	1,222	969	24.2	-6.2
Comb (SU+BG)	410	506	12.6	---
AGIs	36	39	39.6	-1.7
Other OADs	196	220	6.0	25.7
Others	2	1	31.3	---
US Total	**6,940**	**7787**	**12.2**	**17.2**
Europe*				
Insulins	1,191	1,586	33.2	16.0
TZDs	79	133	68.4	---
SUs	315	380	20.8	5.1
BGs	160	220	37.9	17.2
Comb (SU+BG)	34	42	24.2	2.4
AGIs	99	111	12.6	-4.0
Other OADs	63	88	39.6	77.8
Others	54	58	6.0	-6.3
Europe* Total	**1,995**	**2,619**	**31.3**	**13.9**

* France, Germany, Italy, Spain, UK

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CHAPTER 2

Global diabetes market analysis

Chapter 2 Global diabetes market analysis

Summary

- The US/European diabetes market totaled $10.4bn in 2003, an increase of 183% from 1999 total sales. The current growth drivers of this market are the insulins, thiazolodinediones (TZDs) and combination therapies.
- The largest drug class in 2003 was the TZDs with $3.1bn in US/European sales. This drug class also recorded impressive growth with a compound annual growth rate (CAGR) 1999-2003 of 36.3%. Although the TZDs are popular in the US, this is not the case in Europe, where insulins have the largest share of the market.
- The US/European insulin market has grown by a CAGR 1999-2003 of 17.4%, and in 2003 totaled $3.9bn. This growth is due to increased insulin treatment of type 2 patients, and the launch of fast-acting and long-acting insulin analogs.
- Combination therapies recorded the highest growth from 1999-2003 with a CAGR of 94.3%. Combination therapy is proving increasing popular as many of the antidiabetic drugs have different and complimentary modes of action.
- Future growth drivers include the non-invasive insulins, the dual peroxisome proliferator activator receptor (PPAR) agonists and the glucagon-like peptide-1 (GLP-1) agonist/dipeptidyl peptidase-IV (DDP-IV) inhibitor compounds.
- The key unmet need in the insulin market is an alternative delivery mechanism to subcutaneous injection. Pills, mouth sprays, inhalers and patches are some of the novel mechanisms being tested. The inhalable insulins, Exubera and AERx insulin diabetes management system (iDMS), are likely to be the first to market.
- The dual PPAR agonists have blockbuster potential for treating both diabetes and heart disease. Two compounds in phase III trials are Bristol Myers-Squibb (BMS)/Merck's Muraglitazar, and AstraZeneca's Galida.
- The GLP-1 agonists/DPP-IV inhibitors are related compounds that will treat type 2 diabetes without the risk of hypoglycemia or weight gain. Many companies, including Novo Nordisk and Eli Lilly, have these drugs in development.

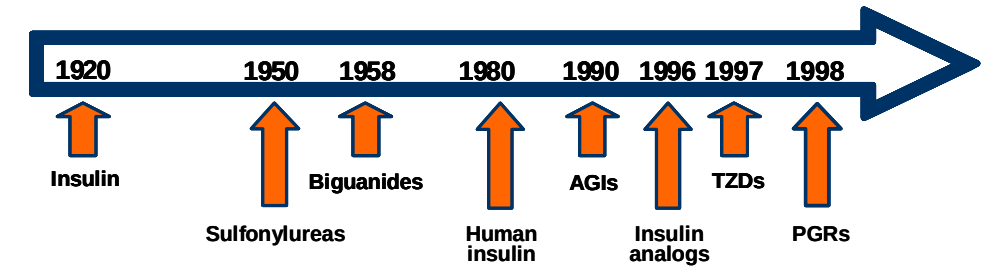
Introduction

This chapter reviews the current and future growth drivers in the diabetes market, highlighting the therapies in development that will shape the market in the future.

History of antidiabetic drugs

Insulin is the oldest class of antidiabetic drug, and remains the only drug available for treating type I diabetics as these patients have the inability to produce insulin, and thus no breakdown of glucose occurs in the body without an external source of insulin. The sulfonylureas and biguanides (both OADs) became available in 1950 and 1958 respectively, before human insulin became the first recombinant DNA product on the market in the 1980s. The 1990s was a period of great development in the diabetes market with three new classes of anti-diabetic drugs in addition to insulin analogs being launched – the alpha glucose inhibitors (AGIs), TZDs, and prandial glucose regulators (PGRs) – (Figure 2.5).

Figure 2.5: Development timeline for antidiabetic drug classes, 1920-2004



Source: Business Insights

Business Insights Ltd

Current growth drivers

Human insulin remains a major growth driver in the antidiabetics market, in particular the long acting and fast acting insulin analogs launched in recent years, with CAGR rates 1999-2003 of 108% (long acting) and 26.9% (short acting). Within the OAD market, the TZDs and combined sulfonylurea and biguanide drugs are driving growth. TZDs sales alone in 2003 accounted for 30.5% of total antidiabetic sales in the six major markets analysed. The PGR class has also shown strong growth over the 5 year period but still accounts for a relatively small proportion of the total market. The main resistor to growth in the OAD market is the biguanide class, with metformin now heavily genericized. 2003 sales in this class dropped to just 53% of their 2001 value.

Table 2.3: US/European* sales category totals ($m), 2002-2003

	2002	2003	Growth (%) 2002-2003	CAGR (%) 1999-2003
OADs:				
Sulfonylureas (SU)	994	1,112	12.0	3.3
Biguanides (BG)	1,382	1,189	-13.9	-3.5
Combined SU + BG	444	548	23.6	94.3
TZDs	2,608	3,172	21.6	36.3
AGIs	135	151	11.4	-3.4
PGRs & other OADs	260	308	18.8	33.5
Total OADs	**5,822**	**6,481**	**11.3**	**16.0**
Insulins:				
Human (Fast acting)	972	1,298	33.6	26.9
Human (Intermediate acting)	642	672	4.7	1.9
Human (Int + Fast acting)	1,069	1,245	16.5	13.1
Human (Int + Long acting)	35	32	-7.9	-8.1
Human (Long acting)	284	545	91.5	108.0
Animal Insulin	16	14	-12.3	-26.9
Insulin Devices	38	60	57.9	21.3
Total Insulins	**3,056**	**3,866**	**26.5**	**17.4**
Others	56	59	4.4	-5.9
Total	**8,934**	**10,406**	**16.5**	**16.3**

* France, Germany, Italy, Spain, UK

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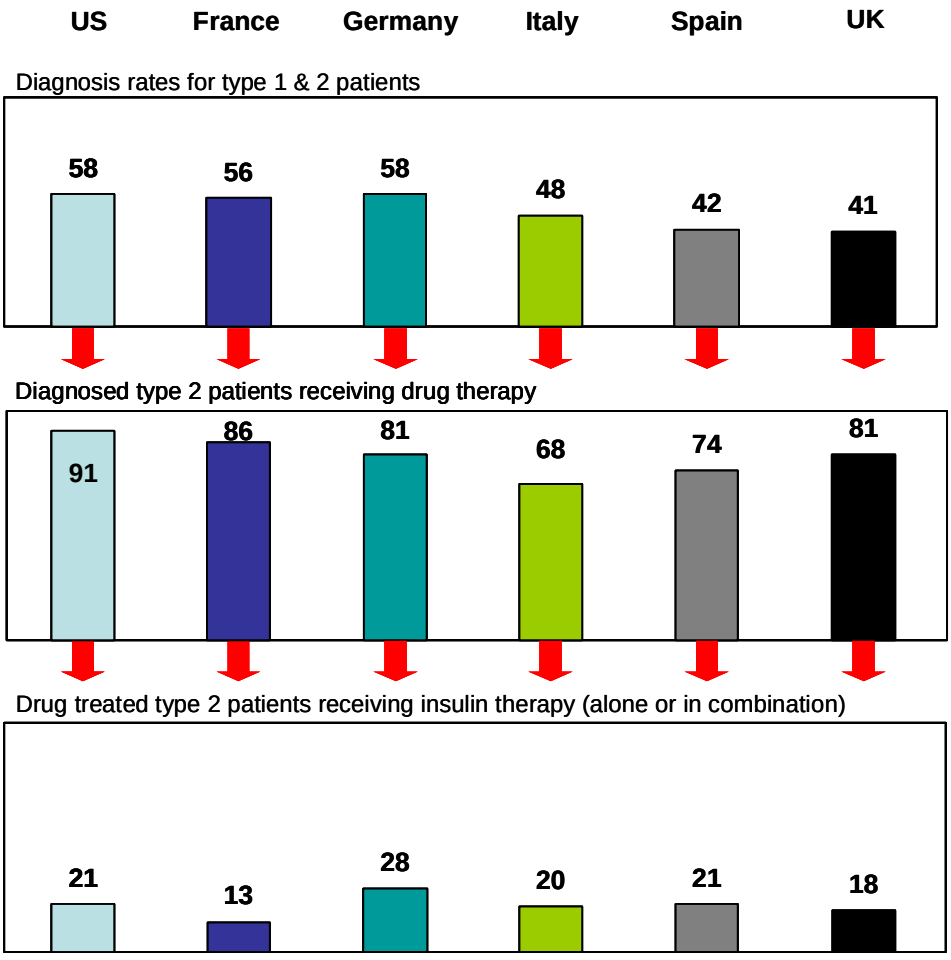
Insulins

Insulin continues to be a successful class of antidiabetic because:

- It is the only drug indicated for the management of hyperglycemia in patients with type 1 diabetes and many patients will be prescribed more than one type of insulin, such as a rapid-acting insulin with a long-acting insulin;
- it is increasingly being prescribed to treat type 2 patients, particularly in later lines of therapy and in combination with OADs.

Figure 2.6: Overview of diagnosis rates, treatment rates and insulin prescribing trends in six major markets, 2003



Source: Business Insights, Physician Survey (Q1.1, Q1.8, Q2.1 and Q3.1) Business Insights Ltd

Figure 2.6 provides an overview of diagnosis rates, treatment rates and insulin prescribing trends for type 2 diabetics in 2003. In the US and in Germany more than a quarter of drug-treated type 2 patients received insulin therapy either alone or as a combination, while rates in France in Italy were just 16 and 17 per cent, respectively. This illustrates that there is still much room for growth in the insulin market, especially with the non-invasive insulin delivery methods being developed.

TZDs

The TZD class, the first drug of which was launched in 1997, is the other main growth driver of the antidiabetic market. Takeda/Eli Lilly's Actos and GlaxoSmithKline's (GSK) Avandia are the leaders in this class, and also account for a major proportion of sales in the total antidiabetic market. The class has been successful because:

- It is the first class of OADs to treat the underlying cause of type 2 diabetes, cellular insulin resistance;
- many of the unpleasant side-effects, such as hypoglycemia, seen with other OAD classes are not seen with TZDs;
- TZDs require only once-daily dozing, which is becoming an essential criterion for a successful OAD drug.

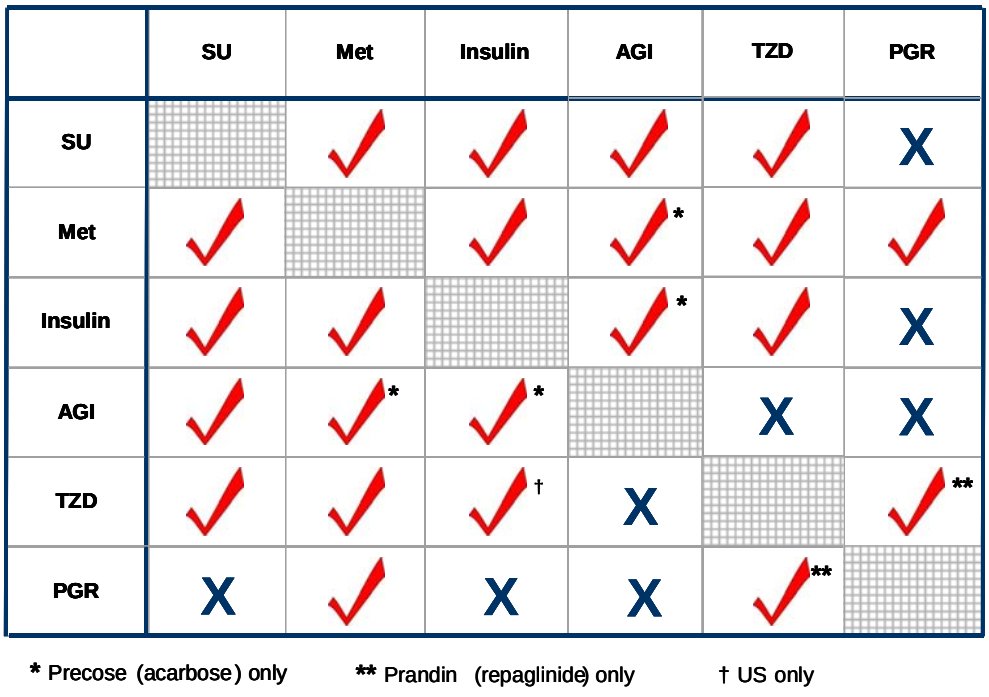
In fact, in 2003 the TZDs had sales accounting for 30.5% of the combined US and Europe antidiabetics market. For the TZD class, it is important to note that sales of TZDs have continued to rise, despite the withdrawal of Pfizer's Rezulin (troglitazone) in March 2000 due to problems of severe liver toxicity. 2003 sales of TZDs in the US and Europe reached $3.17bn. The majority of these sales were in the US, where Rezulin was a popular treatment until its withdrawal and by which time alternatives Actos and Avandia were available, which helps to explain why this class has continued to be popular in the US.

Combination therapies

Combination therapy can refer to being treated with two or more separate antidiabetic drugs at the same time, or by a single-pill combination drug.

The use of combination therapy within type 2 diabetes is common, as many of the antidiabetics have different and complimentary mechanisms of action. Combination therapy has become an increasingly recognized treatment regimen for type 2 diabetes, as monotherapy with sulfonylureas, metformin or insulin often fails to maintain glucose levels over time. Figure 2.7 shows the numerous approved combinations of antidiabetic drugs for type 2 diabetics.

Figure 2.7: Approved combination therapies for type 2 diabetes, 2003



Met: metformin

Source: Business Insights

Business Insights Ltd

As a response to the increased use of combination therapy, Bristol-Myers Squibb (BMS) and GSK have developed single pill combination formulations. The sales figures in Table 2.3 show a category for single-pill combined sulfonylurea and biguanide drugs, however there are some additional single-pill combination drugs on the market from GSK, based on their successful TZD drug Avandia.

One reason for companies such as GSK and BMS developing these single-pill formulations is for life cycle management purposes, as their branded monotherapies come off patent and lose market share to generics companies. Currently marketed or soon to be marketed single pill combination therapies include:

- BMS's Glucovance (glyburide + metformin), which was launched in the US in August 2000 but lost patent protection in 2002;
- BMS's Metaglip (glipizide + metformin), which was launched in the US in November 2002. Oral tablets for the treatment of type 2 diabetes;
- GSK's Avandamet (Avandia + metformin), which was launched in the US in November 2002 and approved in the EU in October 2003;
- GSK's Avandaryl (Avandia + sulfonylurea), which was submitted for regulatory approval in 2003, with expected submission in the EU in 2004;
- GSK's Avandamet XR (Avandia + metformin ER). This compound in currently in phase I clinical trials, and an NDA is expected to be filed in 2005.

Future growth drivers

The combined type 1 and type 2 diabetes mellitus population in the six major markets analysed is projected to grow from 39.4m in 2003 to 49.4m in 2010, a 25.4% growth rate. This is due to the increasing population of type 2 diabetics, which currently represents approximately 90 to 95% of the total diabetic population. The number of type 2 patients is increasing as a result of the aging of the population, obesity and related diabetes risk factors.

In the context of this growth in the patient population, diabetes disease management is set to change dramatically. The developments that will be covered in this report are:

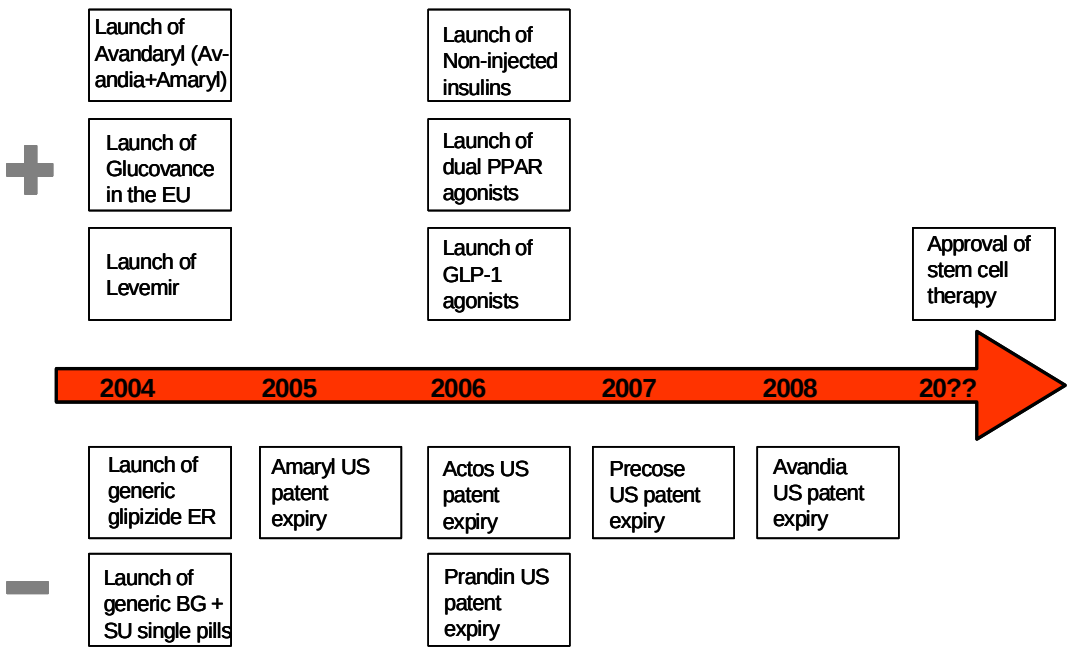
- Non-invasive insulins: In the $4 billion insulin market, the arrival of inhaled and oral insulins, as well as insulin patches, will offer greater flexibility and options for both type 1 and type 2 patients;
- dual/pan peroxisome proliferators activator receptor (PPAR) agonists: These are an exciting new class of drugs with blockbuster potential as they have shown to control both blood sugar and cholesterol before these conditions become serious;
- glucagon-like peptide-1 (GLP-1) agonists/dipeptidyl peptidase-IV (DPP-IV) inhibitors: These are thought to represent a significant advance in the treatment of type II patients and could represent an alternative to insulin therapy;
- amylinomimetic agents: Symlin is the first alternative to insulin treatment for type I diabetics for 80 years, but safety concerns continue to delay its progress and could affect uptake of this product.

These changes in diabetes management will improve patient compliance and help to slow disease progression, and are charted in Figure 2.8.

There are some additional treatments in development although these are much further from commercialization and thus will merely be mentioned in this report. These are:

- Islet transplantation for patients with type 1 diabetes: Current islet transplantation technology requires use of immunosuppressant drugs for life, so the future of this type of treatment will be dependent on the approval of stem cell research;
- autoantigen vaccination in human type 1 newly diagnosed diabetes mellitus: Early vaccination of type 1 patients is being investigated using a synthetic, metabolically inactive form of insulin designed to prevent pancreatic ß-cell destruction.

Figure 2.8: Positive and negative developments influencing the antidiabetics market, 2004 & forwards



BG: biguanide (metformin)

Source: Business Insights

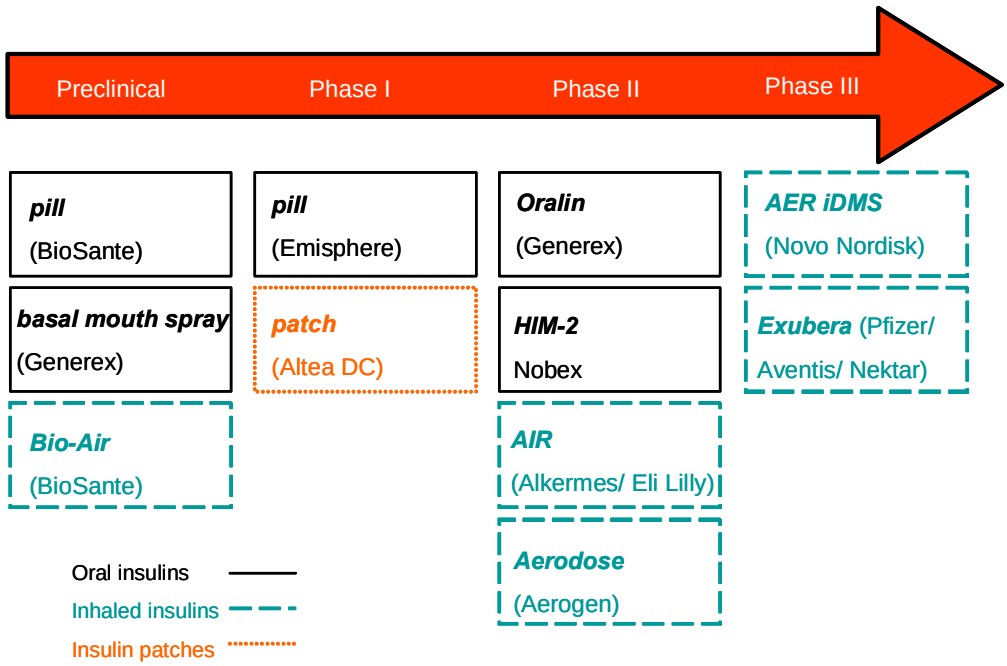
Business Insights Ltd

Non-injected insulin

The key unmet need in the diabetes market is a novel delivery mechanism for insulin, which is currently administered by subcutaneous injection. Developing a drug delivery technology to meet this need is one of the most pressing concerns for companies involved in diabetes R&D because of the large type 2 diabetic population.

The anticipated arrival of novel oral and inhaled insulin, and insulin patches would increase the appeal of insulin to physicians and patients in the growing type 2 market and potentially increase the use of insulin therapy. Therefore, the development of a non-invasive insulin therapy with minimal side-effects should have a dramatic impact on the type 2 market. Given the current efficacy and safety of insulin therapy, any new insulin compound will need to demonstrate at least an equivalent safety profile to gain traction in the market. The first non-injected insulins, Exubera and AERx insulin diabetes management system (iDMS), are expected to reach the market in 2006 (Figure 2.9).

Figure 2.9: Overview of the non-invasive insulin pipeline, 2004



Source: Business Insights

Business Insights Ltd

Inhaled insulins

Most inhaled insulins are being developed as a replacement for short-acting agents such as Novo Nordisk's NovoLog or Lilly's Humalog. Unlike most other inhaled medications, which act locally in the respiratory system, inhaled insulin is absorbed into the bloodstream where it has systemic effects in the body. While this mode of delivery has potentially the shortest time to onset compared to the other classes, it currently has the most issues surrounding its potential safety.

Within the inhaled insulin class, there are five compounds in Phase II or later in development, and these projects involve the major players in the insulin market, Novo Nordisk, Aventis and Eli Lilly. Of these three inhaled insulins, Novo Nordisk's AERx

iDMS is expected to become the market leader due to its novel inhalation device, and the safety concerns of Exubera.

- Exubera (Nektar Therapeutics/Pfizer/Sanofi-Aventis): Likely to be first to market of the non-invasive insulins, although this drug has been severely delayed due to a fatal case of pulmonary fibrosis. Exubera initially completed Phase III trials in 2001, but it was not until March 2004, after additional safety studies had been carried out, that European Medicines Evaluation Agency (EMEA) accepted the filing of a marketing authorization application for Exubera;

- AERx iDMS (Aradigm/Novo Nordisk): Expected to be the second non-invasive insulin to market in 2006. AERx iDMS has the advantage of its superior inhalation device over other competing products. AERx iDMS employs an active breath control mechanism to release the insulin at the optimum moment, and also records the inhaler use, thus aiding physician monitoring. No major safety issues have been reported with AERx iDMS so far;

- AIR (Alkermes/Eli Lilly): Likely to be the third in this class to market. The AIR systems works by relatively large, low-density drug particles being inhaled into the lungs with high efficiency from simple inhalers. It will be a simpler delivery device than AERx iDMS which may be an advantage from a patient convenience point of view, but dosing consistency may be compromised.

Oral insulins

Similar to inhaled insulins, oral insulins are being developed to compete with short-acting agents. Patient potential for inhaled products would be threatened by the oral insulins, which could prove to be more popular and more successful than the inhalation products. However, several of the pharmaceutical companies that were developing oral insulins have now returned the products to their originators (during 2003, Eli Lilly returned Oralin to Generex, GSK returned its product to Nobex, and an undisclosed partner exited its deal with Emisphere). As a consequence there is now a high degree of uncertainty surrounding launch of oral insulins.

- Oralin (Generex Biotechnology Corporation): This drug is a mouth spray currently in Phase II trials with Generex, with expected launch in 2007. Oralin was partnered for development with Eli Lilly in 2000 but this agreement was terminated in May 2003, which may indicate that Eli Lilly has either found a better oral insulin candidate or is not confident of Oralin's success. Generex is also trialing a long-acting basal formulation of this drug, although it is currently only in pre-clinical testing.

- HIM2 (Nobex Corporation): This drug is a pill formulation that was partnered with GlaxoSmithKline, but GSK has now terminated the agreement, returning all rights to the originator, Nobex.

Insulin patches

Most forms of insulin in development are fast-acting, but the insulin patch is a novel delivery mechanism being developed for long-acting basal insulins. An insulin patch is currently in phase I trials with Altea Development Corporation, and it is expected that the patch would last either 12 or 24 hours.

Dual PPAR agonists

The competition to develop drugs that target more than one of the cellular signals called peroxisome proliferation activation receptors (PPARs) is one of the most heated contests in the drug industry. These medicines work by affecting switches in cells, called PPARs, which control the entry of sugar, fat and cholesterol into these cells. These drugs could control both cholesterol and blood sugar before more serious conditions develop. Some existing diabetes drugs – the TZDs – work by affecting one PPAR (there are several switches), but by affecting these switches in combination, researchers hope that they can modify the risk factors for both diabetes and heart disease. Dual PPAR agonists thus have blockbuster potential in market where type 2 diabetes, heart disease and obesity are increasing.

Unfortunately, two recent dual PPAR agonist compounds – one by Merck and one by Novo Nordisk – faltered after causing cancer in laboratory animals and as a consequence the FDA now requires companies to perform extra pre-clinical trials of dual PPAR agonists. Among those remaining, AstraZeneca's Galida is in late-stage trials, trailing an effort by BMS and Merck. In addition, Eli Lilly, GlaxoSmithKline, Amgen and Pfizer are all working on similar drugs.

- Muraglitazar (BMS/Merck): This is the most advanced PPAR in development, and could be submitted to the FDA for regulatory approval as soon as the end of 2004. In April 2004 BMS signed a deal with rival Merck on April 28th to co-develop and co-market Muraglitazar, after Merck's rival drug caused cancer in rats;

- Galida (AstraZeneca): Is expected to be the second PPAR drug to market. AstraZeneca had previously stated that this drug would be launched soon after the BMS/Merck compound, however in October 2004 AstraZeneca announced that development of Galida had been delayed by a year.

GLP-1 agonists and DPP IV inhibitors

Another key therapeutic approach in development in several companies is with the related compounds, dipeptidyl peptidase (DPP) IV inhibitors and the glucagon-like peptide-1 (GLP-1) agonists. GLP-1 lowers blood glucose in type 2 diabetes patients with the unique advantage that glucose-lowering ceases when blood glucose gets into the normal range, as both effects on insulin and glucagon release are glucose-dependent. DDP-IV in the body degrades GLP-1 so several companies are also developing DDP-IV inhibitors to stop this process and maintain or increase GLP-1 levels. As a consequence, it is possible to treat diabetes effectively without simultaneously running a risk of inducing hypoglycemia. At the same time the patient's ability to manage weight is improved, which is a side effect with some current treatments of type 2 diabetes.

GLP-1 agonists

The glucose-dependent action of GLP-1 has the advantage of reducing the need for glucose monitoring in diabetes patients, and also reducing the risk of hypoglycemia, which is an unwanted side effect of many anti-diabetes medications. In addition, unlike the DPP-IV inhibitors, a GLP-1 analog can theoretically be dosed up to produce any required level in the body. Exenatide is the most advanced GLP-1 compound, with Novo's Liraglutide (NN2211) expected to begin Phase III trials in the second half of 2004, and ConjuChem's DAC:GLP-1 in Phase II development.

- Exenatide (Amylin/Eli Lilly): This was submitted for regulatory review in Q3 2004, and is the most advanced of the GLP-1 agonists in development. Amylin has demonstrated efficacy and tolerability in patients controlling their diabetes with exercise and diet, OADs and insulin, which indicates that the compound has a wide patient potential. Furthermore, although Exenatide is injectable, it may represent a useful substitute for insulin in type 2 patients as, unlike insulin, it is not associated with weight gain.

- Exenatide LAR (Amylin/Alkermes): A long-acting release (LAR) version of Exenatide is being developed and is currently in Phase II clinical trials. In May 2000,

Amylin signed an agreement with Alkermes utilizing Alkermes' injectable sustained release drug delivery technology, known as Medisorb. This technology is patented and approved by the FDA. The companies are aiming to develop a formulation that would allow once-a-week to once-a-month administration of Exenatide for the treatment of type 2 diabetes.

- Liraglutide NN2211 (Novo Nordisk): Novo Nordisk is currently developing Liraglutide (NN2211), a GLP-1 agonist. Phase II trials of NN2211 have been concluded, with Phase III trials expected to commence mid-2004, and possible launch in 2007. As part of the Phase III studies, the company intends to investigate the drug's effect on beta cell preservation, which has been observed in animal models.

DPP IV inhibitors

A key advantage of DPP-IV drugs is that they are expected to control blood sugar only when it is too high, cutting the risk of hypoglycemia. Another advantage of the DPP-IV inhibitors is their oral method of administration compared to GLP-1 analogs which have to be injected. Novartis leads the pack with LAF237, while Merck is close behind with MK-0431 and BMS has a DPP-IV inhibitor in mid-stage trials.

- LAF237 (Novartis): Novartis began Phase III trials of LAF 237 as both a monotherapy and in combination with metformin in January 2004 in order to aim for a 2006 filing. Clinical results so far have indicated a significant dose dependant reduction in HbA1c, both alone and as an additive to metformin therapy.

- MK-0431 (Merck): Merck expects to begin late stage trials in 2004 of MK-0431 and seek approval in mid-2006. It is expected that Merck's drug will also cause weight loss in diabetics but the company has released less data than Novartis.

Amylinomimetic agents

Symlin (pramlintide) is a synthetic version of the human hormone, amylin. It is the first (and currently only) member of a new class of therapeutic medications known as amylinomimetic agents, or amylin receptor agonists. In clinical studies, Symlin has shown improvements in blood glucose control in people treated with insulin alone, or insulin plus one or more oral medications, without causing a weight increase. Weight gain is one cause of type 2 diabetes, so a medication that increases weight only exacerbates this condition. Symlin is an injectable product candidate intended for the treatment of patients with type 1 diabetes and insulin-using patients with type 2 diabetes. This target population currently has limited therapeutic options. Replacement of insulin alone, the current therapy, cannot replace amylin's actions nor can insulin normalize post-meal glucagon concentrations.

In December 2000, Amylin submitted an application to the FDA in the US and, although an approval letter was granted October 2001, the FDA requested additional data from clinical trials. Following completion of a seven-month dose titration study and other smaller trials, the company submitted an NDA amendment in June 2003 and received a second approvable letter in December 2003, again requesting additional clinical data. Discussions are underway with the FDA to identify specific requirements for approval. Submissions to the EMEA in the EU, and in Switzerland have also since been withdrawn. Given the continued safety concerns of the regulatory authorities, its launch date and expected uptake are unclear.

CHAPTER 3

Insulin market analysis

Chapter 3 Insulin market analysis

Summary

- The US/European insulin market totaled $3.9bn in 2003, with a CAGR 1999-2003 of 17.4%.
- The fast-acting insulins hold the largest share of the market at $1.3bn and have also shown strong growth due to the launch of insulin analogs Humalog and NovoLog.
- The long-acting insulins have shown the strongest growth since 1999 with a CAGR of 108%. This has resulted from the launch of Aventis' Lantus in 2001, and is set to grow further with Novo Nordisk's Levemir launched in 2004.
- Humalog was the leading US/European insulin brand in 2003 with sales accounting for 27.7% of the market. In the US Humalog had sales of $753m.
- Lantus has gained a 14.6% US/European market share since launch in 2001. However, its US success has not been mirrored as yet in the European markets.
- NovoLin's US/European market share has declined from 1999 to 2003, now holding 23.1% of the market. However, this drug remains the leading insulin brand in Europe, and has been largely unaffected there by the launch of Humalog.
- Humulin was the leading US/European antidiabetic until 2002. Sales of this product have suffered from the introduction of fast-acting analog, Humalog, with Eli Lilly moving patients from Humulin to the newer treatment.
- NovoLog has not shown strong sales to date, but as Novo Nordisk switches patients from NovoLin to the newer NovoLog then its sales should rise, especially in Europe.
- Eli Lilly is the leading insulin company in the US with a 62.2% market share in 2003, but this share has declined from 82.2% in 1999. Aventis, and to a lesser degree, Novo Nordisk have captured Lilly's lost share. In the European markets Novo Nordisk is the leading player, accounting for 46.6% of sales in 2003, and Lilly (25.3%) and Aventis (19.6%) have had relatively flat growth in the last five years.

Introduction

This chapter will look at company market share in the US and Europe as well as giving sales figures and profiles for the leading insulin brands in the past five years.

Insulin is the only drug available to treat patients with type 1 diabetes. This is because these patients lack the ability to produce any insulin themselves, and thus need to take an external source of insulin in order to break down glucose. There is also an increasing trend towards the use of insulin to treat type 2 patients, possibly as a second- or third-line response and in combination with OADs. The first recorded use of insulin to treat diabetes was in 1922, where insulin was purified from a bovine source. Now, through the advent of recombinant DNA technology, it is relatively inexpensive to produce the highly purified human insulin that is used to treat diabetic patients. This also vastly reduces the risk of an immune response which was a problem with previous non-human insulin preparations.

Insulin categories and sales

A variety of human insulin preparations are now available which vary in their onset time and length of action:

- Human insulins and analogs, *fast-acting:* includes human soluble insulin (neutral insulin) and insulin lispro;
- Human insulins and analogs, *intermediate-acting*: includes neutral protamine Hagedorn/human isophane insulin (NPH) and human amorphous insulin zinc suspension (semi-lente);
- Human insulins and analogs, *intermediate-acting combined with fast-acting*: includes combinations of human NPH with neutral insulin (biphasic isophane insulin);

- Human insulins and analogs, *intermediate-acting combined with long-acting*: includes fixed combinations of human crystalline insulin suspension 70% with human amorphous insulin zinc suspension 30% (lente);
- Human insulins and analogs, *long-acting*: includes human crystalline insulin zinc suspension (ultra-lente);
- Other human insulins.

There are also animal insulins available, which were used prior to the human insulins being widely available, and a growing market for insulin devices (CAGR 1999-2003 of 21.3%).

Table 3.4 shows sales figures for each insulin class over the past five years. The long acting insulins have increased market share significantly with the launch of Aventis' Lantus and now Novo Nordisk's Levemir. The fast acting insulins also grew during this five-year period with the launch of Humalog and NovoLog, and in 2003 were the highest selling insulin class. The fast-acting insulin market and insulin devices market are also likely to grow significantly in the future with the development of oral and inhaled insulin formulations.

Table 3.4: US/European* Sales of insulins by category ($m), 2002-2003

	2002	2003	Growth (%) 2002-2003	CAGR (%) 1999-2003
***Human insulins*:**				
Fast acting	972	1,298	33.5	26.9
Intermediate & fast acting	1,069	1,245	16.5	13.1
Intermediate acting	642	672	4.7	1.9
Long acting	284	545	91.5	108.0
Intermediate & long acting	35	32	-7.9	-8.1
Insulin devices	38	60	57.9	21.3
Animal insulins	16	14	-12.3	-26.9
Total	**3,056**	**3,866**	**26.5**	**17.4**

* France, Germany, Italy, Spain, UK

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Company market share

Eli Lilly, Novo Nordisk and Aventis (now Sanofi-Aventis) are the key players in the insulin market (Table 3.5). Eli Lilly continues to dominate the US market with a 62.2% market share in 2003, although this share has diminished from previous years when the company held more than 80% of the US market. Aventis with its long acting insulin, Lantus, and to a lesser extent Novo Nordisk, have captured Lilly's lost share to achieve increased US sales figures in 2003 – 17.2% for Aventis and 20.5% for Novo Nordisk. Novo Nordisk has identified an increased share of the US market as the way to grow its business, and has increased US sales force numbers, tailored its products to the US market, and signed a distribution agreement with US giant Wal-Mart.

In Europe, Novo Nordisk is the market leader with a 46.6% share in 2003, while Eli Lilly has a 25.3% share, although figures for both these companies have dropped slightly in the last few years. As in the US, Aventis has increased its share of the market in Europe in 2003 to 19.6%.

Table 3.5: Insulin market share by company and territory (%), 2002-2003

	2002	2003	Growth (%) 2002-2003	CAGR (%) 1999-2003
US				
Eli Lilly	71.2	62.2	6.8	10.5
Novo Nordisk	17.7	20.5	42.0	22.7
Aventis	11.1	17.2	89.2	---
Europe*				
Novo Nordisk	47.7	46.6	30.1	13.1
Eli Lilly	27.5	25.3	22.9	15.9
Aventis	16.7	19.6	56.6	17.3
US/Europe*				
Eli Lilly	54.2	47.1	10.0	11.5
Novo Nordisk	29.4	31.2	34.5	16.4
Aventis	13.3	18.2	73.2	43.8

*France, Germany, Italy, Spain, UK

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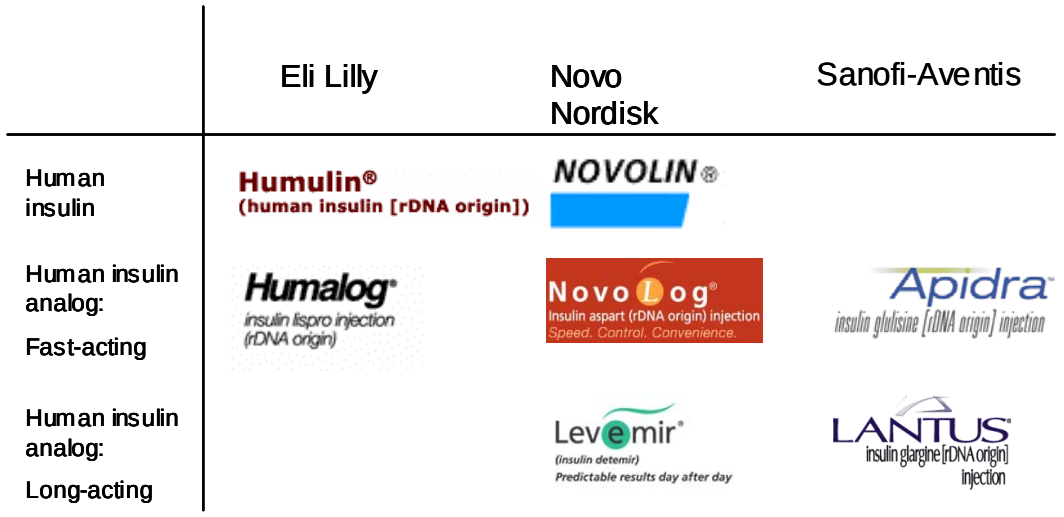
Brand market share and sales

Eli Lilly and Novo Nordisk have two successful brands ranges - NovoLin and NovoLog for Novo Nordisk, and Humulin and Humalog for Eli Lilly – which along with Aventis's Lantus are the leading insulin products (Figure 3.10). Levemir and Apidra are products launched in 2004.

Figure 3.10: Insulin brands by company and type, 2004



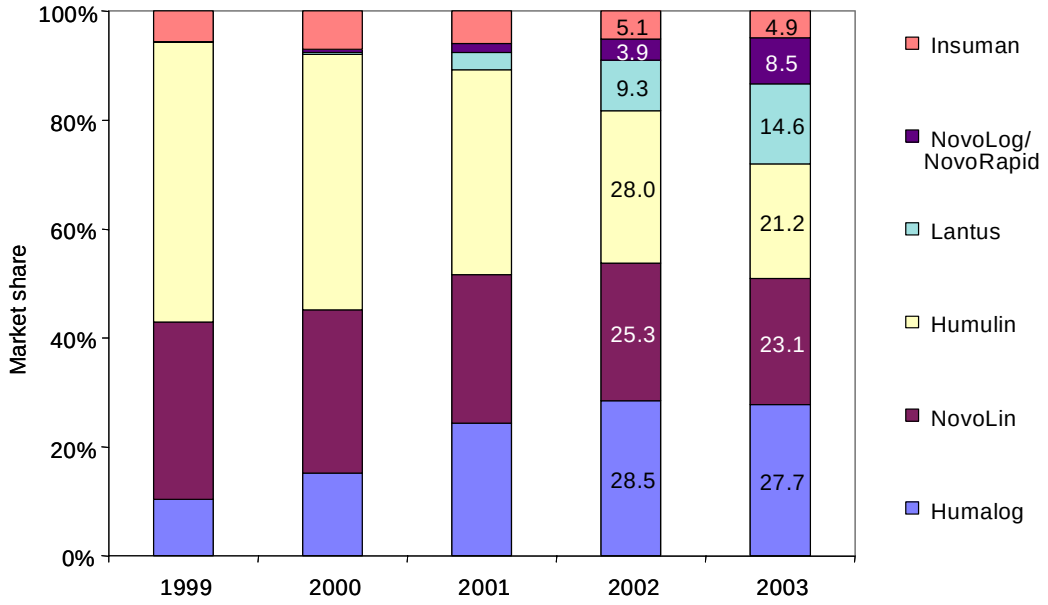
Source: Business Insights

Business Insights Ltd

The fast-acting insulins, Humalog and NovoLog/NovoRapid have grown every year between 1999 and 2003, as has long-acting insulin, Lantus. Humalog is now the highest selling insulin product in the combined US/European market. As a result, during the same period Humulin and NovoLin have seen their market share decline.

Figure 3.11 gives the US/European market share held by each leading insulin brand.

Figure 3.11: US/European* market share of leading insulins (%), 1999-2003



* France, Germany, Italy, Spain, UK

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Sales of Novo Nordisk's and Eli Lilly's insulin products have traditionally been separated by geography, with Novo Nordisk being dominant in the European market and Eli Lilly dominant in the US market.

In the US the two top products are Eli Lilly's Humalog and Humulin, with Lantus also having grown significantly since launch in 2001. However, in each of the five major European markets Novo Nordisk's NovoLin is the highest selling insulin, and sales in this area have been largely unaffected by the launch of Humalog. With the recent launch of Novo Nordisk's NovoLin, it is expected that patients will be switched from NovoLin to fast-acting insulin analog, NovoLog. It can also be concluded from these sales figures that Lantus has not been as successful in Europe than in the US. In Europe Lantus lags behind both Novo Nordisk's and Eli Lilly's products.

Table 3.6: Sales of leading insulins by country ($m), 2002-2003

	2002	2003	Growth (%) 2002-2003	CAGR (%) 1999-2003
US				
Humalog	615	753	22.4	59.1
Humulin	710	663	-6.6	-4.9
Lantus	207	391	89.2	---
NovoLin	277	295	6.5	10.1
NovoLog/NovoRapid	49	167	238.3	---
Total	**1,859**	**2,270**	**22.1**	**19.1**
France				
NovoLin	43	58	35.3	10.0
Humalog	29	39	34.6	61.7
NovoLog/NovoRapid	3	13	350.6	---
Lantus	0	9	---	---
Insuman	4	6	35.2	20.2
Total	**79**	**124**	57.6	**26.8**
Germany				
NovoLin	154	206	33.4	9.4
Insuman	138	168	22.2	15.8
Humalog	86	112	28.9	30.2
Lantus	52	92	74.9	---
NovoLog/NovoRapid	39	69	78.2	233.1
Total	**470**	**647**	**37.6**	**23.6**
Italy				
NovoLin	50	61	21.3	14.4
Humulin	33	46	39.6	11.2
Humalog	16	20	28.1	36.4
NovoLog/NovoRapid	4	6	65.8	---
Lantus	0	1	---	---
Total	**103**	**134**	**31.1**	**17.2**
Spain				
NovoLin	63	79	25.0	12.0
Humalog	19	26	35.6	103.8
Humulin	15	17	12.4	4.6
NovoLog/NovoRapid	1	9	805.7	---
Lantus	0	0	---	---
Total	**99**	**132**	**33.0**	**18.8**
UK				
NovoLin	127	131	3.8	8.8
Humalog	38	47	22.2	45.6
NovoLog/NovoRapid	15	40	161.9	326.5
Humulin	34	35	3.6	-0.4
Lantus	3	32	832.6	---
Total	**1218**	**286**	**31.3**	**19.6**

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Human Insulins

The human insulin products, Humulin and NovoLin, come in a variety of formulations and have dominated the insulin markets in the US and Europe since launch. Humulin was the first human insulin on the market in 1982, and prior to this type 1 diabetics injected animal-derived insulins.

In recent years these human insulins have come under threat from newer insulin analog products with fast-acting or long-acting properties.

Brand analysis

Table 3.7 shows the two human insulin brands that will be profiled in this report, Humulin and NovoLin. Both products were launched in the 1980's and their patents have since expired.

Table 3.7: Branded human insulins

US brand	Generic	Marketing Company	First global launch date	US patent expiry	Alternative brand names
Humulin	Human insulin	Eli Lilly	1982 (US 1994)	Expired	Humulin N, Humulin L, Humulin U, Humulin R, Humulin Mix
NovoLin	Human insulin	Novo Nordisk	1988	Expired	Actrapid, Insulatard, Mixtard, Actraphane, Protaphane

Source: Business Insights

Business Insights Ltd

Humulin (human insulin)

Humulin was the first human insulin product to be launched, reaching the market in 1982. It was also the world's first biotechnology product using recombinant DNA technology, and was originally developed by Genentech. The brand includes several formulations of recombinant human insulin (with different durations of action and onset times) available in different delivery formats. Products within the range include: Humulin

L, Humulin R, Humulin U, Humulin 50/50 and Humulin 70/30, all of which are available within pen delivery systems. A SWOT analysis of Humulin is shown in Figure 3.12.

Despite the broad product range and growing patient population, Humulin sales have declined by an average 4% from 1999 to 2003. These sales are expected to decline further as Lilly pushes the switch of patients from Humulin to Humalog, and also as a result of increased competition from Novo Nordisk's and Aventis's insulin analog products, NovoLog and Lantus. Despite this, in 2003 Humulin maintained a 29.2% share of the US insulin market, although in Europe, where the insulin market is more advanced, this figure was just 8.9%. The arrival of non-injected forms of insulin on the market in 2005 or 2006 will further impact Humulin's sales.

Figure 3.12: Humulin SWOT analysis

Humulin®
(human insulin [rDNA origin])

Strengths	Weaknesses
• Suitable for injection with a variety of devices • Therapy is well established in the market in the US • Supported by the marketing strength of Eli Lilly	• Injection drug delivery • Poorer presence in the EU than Novo Nordisk's insulin products
Opportunities	**Threats**
• Increased use of insulin in type 2 diabetics • Cost-efficiency advantages over newer insulins	• Launch of oral and inhaled insulins • Competition from Novo Nordisk's insulin products • Competition from longer-acting insulins

Source: Business Insights

Business Insights Ltd

NovoLin (human insulin)

NovoLin is a collection of short-acting soluble human insulins developed and marketed by Novo Nordisk. There are four NovoLin products, which vary in their onset, peak and duration. The NovoLin brands compete directly with the equivalent Humulin brands. NovoLin cartridges can be used with Novo Nordisk's pen injection system, NovoPen, which is the company's leading pen delivery system.

NovoLin remains the leading insulin brand in Europe with 38% of the market in 2003, but this brand is growing slower than the newer insulin brands, Humalog, NovoLog and Lantus, and is likely to continue to lose its market share over the coming years (SWOT analysis Figure 3.13). In the US NovoLin had lower sales than both Eli Lilly brands, Humalog and Humulin, and again market share is expected to decline in this market.

Figure 3.13: NovoLin SWOT analysis

NOVOLIN®

Strengths	Weaknesses
• Suitable for injection with a variety of devices • Therapy is well established in non-US markets • Supported by the marketing strength of Novo Nordisk	• Injection drug delivery formulation • Poorer presence in the US than Eli Lilly's insulin products • Drug requires more frequent daily administration than longer-acting insulins
Opportunities	**Threats**
• Increased use of insulin in type 2 diabetes • Expansion into the large US market	• Launch of oral and inhaled insulins • Competition from Eli Lilly's insulin products • Competition from longer-acting insulins that offer greater convenience for the patient

Source: Business Insights

Business Insights Ltd

Fast-acting human insulin analogs

The fast-acting insulins have a faster onset and shorter duration of action than regular human insulin. These products have proved popular because they can be taken immediately prior to a meal rather that one hour before as is required when using regular human insulin.

Brand analysis

There are now three fast-acting human insulin analogs on the market. Table 3.8 shows the first to launch was Eli Lilly's Humalog in 1996, followed by Novo Nordisk's NovoLog/NovoRapid in 2001. A recent addition to the fast-acting insulin analog market is Apidra, launched in 2004 by Sanofi-Aventis.

Table 3.8: Branded fast-acting human insulin analogs

US brand	Generic	Marketing Company	First global launch date	US patent expiry	Alternative brand names
Humalog	Insulin lispro	Eli Lilly	1996	2013	n/a
NovoLog	Insulin aspart	Novo Nordisk	2001	2014	NovoRapid
Apidra	Insulin glulizine	Sanofi-Aventis	2004	2018	n/a

Source: Business Insights

Business Insights Ltd

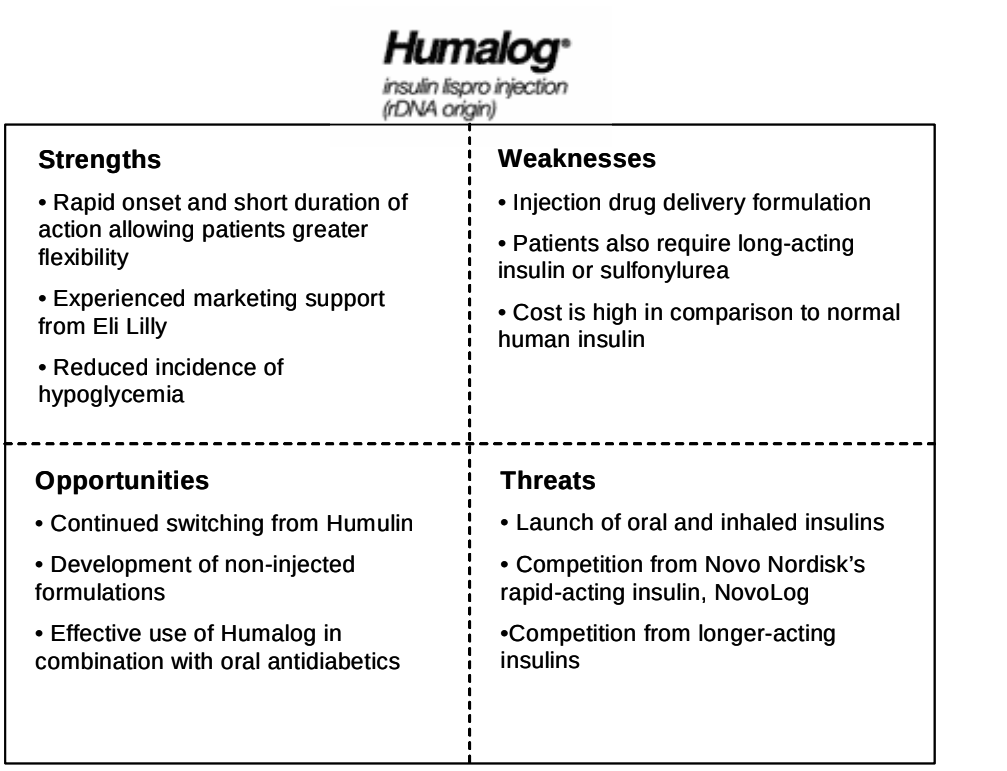
Humalog (insulin lispro)

Humalog is a fast-acting analog of recombinant human insulin, engineered by switching the position of two of the amino acids in the protein chain. The result of this manipulation is that the analog is absorbed more rapidly and has a shorter plasma half-life than the naturally occurring hormone. One of the benefits of Humalog is that the drug can be injected by the patient directly before a meal rather than up to an hour beforehand, which is a requirement of standard insulin therapy. This represents a major advance in patient convenience, as it removes the need to assess far in advance, what

and when a patient will eat. Studies have shown that a large proportion of patients do not comply with this requirement, and so use of Humalog could reduce the costs of patient non-compliance, and increase the efficacy of the drug as a result.

Lilly has expanded its product range by launching Humalog mixtures which combine the long-acting and short-acting features of insulin in analog form. Humalog is currently the best selling insulin brand in the combined US and European market, having overtaken Lilly's other insulin product, Humulin, in 2002. In the US market alone Humalog has 33.2% of the market, while in Europe where Novo Nordisk is the dominant insulin provider, Humalog has a lesser share at 27.0%. This share is likely to be threatened further by Novo Nordisk's own short-acting insulin analog, NovoLog, which was launched in September 2001, and has shown high growth rates. Sales will also be impacted by the launch of inhaled and oral insulins from 2005 or 2006.

Figure 3.14: Humalog SWOT analysis



Source: Business Insights

Business Insights Ltd

NovoLog (insulin aspart)

NovoLog (insulin aspart) is a rapid-acting human insulin analog that was approved in the EU in late 1999 (where is it branded NovoRapid) and in the US in June 2000. Due to its fast onset of action (twice as fast as regular insulin) and short duration of action, it is effective in controlling post-prandial glycemia and has a flexible dosing regimen. Patients can start eating five to 10 minutes after dosing with insulin aspart compared to 30 minutes with regular insulin. However, these properties mean that NovoLog should normally be administered in combination with intermediate or long-acting insulin and an injection of NovoLog should be immediately followed by a meal. A SWOT analysis of NovoLog is shown in Figure 3.15.

Figure 3.15: NovoLog SWOT analysis

NovoLog®
Insulin aspart (rDNA origin) injection
Speed. Control. Convenience.

Strengths	Weaknesses
• Effective in controlling post-prandial glycemia due to rapid onset of action and short duration • Approved for use in pump therapy and with FlexPen •Exceptional marketing support from Novo Nordisk	• Injection drug delivery formulation • Needs to be administered in combination with intermediate or long-acting insulin • Dosing flexibility results in greater responsibility for the patient to manage their diabetes
Opportunities	**Threats**
• Increased use with pump therapy in type 1 patients • Establishment of cost-efficacy advantages over IV regular insulin in the acute care setting	• Competition from Eli Lilly's Humalog, which has been on the market since 1996 • Launch of oral and inhaled insulins • Competition from longer-acting insulins • Approval of other insulins for use with pump therapy

Source: Business Insights

Business Insights Ltd

Novo Nordisk announced in September 2001 at the annual meeting of the European Association for the Study of Diabetes (EASD) that the EMEA approved NovoRapid for pump therapy, also known as continuous subcutaneous insulin infusion (CSII). Pump therapy is prescribed to patients that need to intensively control their blood glucose levels. The external device provides a continuous infusion of insulin throughout the day and doses can be increased before meals, according to the individual patients' needs. In particular, in type 2 patients this delivery device offers greater convenience for a more intensive insulin treatment. NovoLog is the only insulin analog currently indicated for use in insulin pumps, although Humalog (insulin lispro) is also commonly used off label in pump therapy. NovoLog is also indicated for use with Novo Nordisk's FlexPen, its most advanced prefilled, disposable insulin pen device.

NovoLog still lags behind Novo's other brand NovoLin, and Eli Lilly's Humulin and Humalog due to its late entry onto the market.

Apidra (insulin glulisine)

Sanofi-Aventis's Apidra is a fast-acting insulin analog for the treatment of hyperglycemia in people with type 1 and type 2 diabetes. It has a faster onset of action and shorter duration of action than regular human insulin, and is intended to cover mealtime 'spikes' in blood sugar level.

The FDA approved Apidra in the US in March 2004, ahead of its EU approval on October 1st 2004. The drug will be in direct competition with Novo Nordisk's NovoLog and Lilly's Humalog. Advantages of Apidra are its flexible mealtime dosing and its pump application. This drug is important to Sanofi-Aventis in helping it to build a global presence in the insulin market, and the company intends to market it together with Lantus, its successful long-acting insulin.

A SWOT analysis for Apidra is shown in Figure 3.16.

Figure 3.16: Apidra SWOT analysis

Apidra™
insulin glulisine [rDNA origin] injection

Strengths	Weaknesses
• Rapid onset and short duration of action, allowing patients greater flexibility • Pump application • Aventis has strong presence in both US and EU for insulins	• Later onto the market than Humalog or NovoLog • Dosing flexibility results in greater responsibility for the patient to manage their diabetes • Rival Novo Nordisk has greater presence in EU, and Eli Lilly has greater presence in US
Opportunities	**Threats**
• Co-marketing with successful basal insulin, Lantus • Development of non-injected formulations	• Launch of oral or inhaled insulins • Competition from Humalog and NovoLog • Competition from longer-acting insulins

Source: Business Insights

Business Insights Ltd

Long-acting insulin analogs

The long-acting insulin analogs are designed to produce a steady release of insulin throughout a 24 hour period, without peak effect. These insulins require only once-daily administration but patients usually have to take short-acting insulins or OADs as well.

Brand analysis

Table 3.9 details the long-acting human insulin analogs on the market – Sanofi-Aventis's Lantus and Novo Nordisk's Levemir. Currently the market is dominated by Lantus which was launched in 2000, and it has seen rapid uptake in the US. Levemir has only recently been launched but has the backing of Novo Nordisk.

Table 3.9: Branded long-acting human insulin analogs

US brand	Generic	Marketing Company	First global launch date	US patent expiry	Alternative brand names
Lantus	Insulin glargine	Sanofi-Aventis	2000	2015	n/a
Levemir	Insulin detemir	Novo Nordisk	2004	n/a	n/a

n/a: not available/not applicable

Source: Business Insights

Business Insights Ltd

Lantus (insulin glargine)

Lantus (glargine insulin) is a human insulin analog that was approved for the treatment of type 1 diabetes in adults and children and type 2 in adults, and a SWOT analysis for the product is shown in Figure 3.17. This product is formulated so that insulin precipitates into tissues and is then released slowly. This results in delayed absorption and the possibility of once-daily administration. Unlike intermediate-acting insulin, Lantus is very slowly released into the body with no pronounced 'peak of action' that can lead to hypoglycemia. Two other formulations of Lantus with different rates of release are being investigated. Lantus was launched in Germany in mid 2000, and

achieved European sales of $32m in 2001. Lantus was then launched in the US in May 2001, where it demonstrated a rapid uptake. The drug was launched in France in August 2003 and gained approval in Japan in October 2003. In 2003 Lantus achieved sales totalling $526m.

Roll-out in the major markets is nearing completion and means that this agent was well-established before Novo Nordisk's new long-acting insulin, Levemir (insulin detemir) was launched in 2004. This is particularly important in the EU where Novo Nordisk has considerably more expertise in the insulin market than Sanofi-Aventis.

Figure 3.17: Lantus SWOT analysis

LANTUS
insulin glargine [rDNA origin]
injection

Strengths	Weaknesses
• 24 hour basal insulin coverage with a once daily administered dose • Reduced incidence of hypoglycemia • Indicated for both type 1 patients >6 years and type 2 patients • Flexible administration improves patient satisfaction	• May need to be prescribed in combination with short-acting insulins or OADs •Injection delivery formulation • Launched late into the market where Eli Lilly and Novo Nordisk are already well established
Opportunities	**Threats**
• Greater use in combination with OADs • Greater use in type 2 patients • Indications in niche diabtetic populations, such as the obese • Promotion of favorable effects on lipid profile and weight control • Launch in additional markets ahead of Novo Nordisk's Levemir	• Launch of non-invasive insulins • Competition from fast-acting insulins for the treatment of type 2 diabetes • Competition from other once-daily insulins, i.e. Levemir (insulin detemir) • Availability of cheaper insulins

Source: Business Insights

Business Insights Ltd

Levemir (insulin detemir)

Levemir is a long-acting injection insulin from Novo Nordisk, to rival Aventis's Lantus. Novo Nordisk was a granted marketing authorization in the EU for the drug in June 2004, which completes its insulin analog portfolio in Europe, giving the company a major marketing advantage. Levemir also received an approval letter from the FDA in October 2003, but the FDA requested that Novo Nordisk address certain clinical issues and provide additional information before US marketing approval is granted. Levemir has been shown in clinical trials to provide an improved basal insulin profile without a peak effect and with less day-to-day variation than insulin glargine (Sanofi-Aventis' Lantus) and NPH insulin. Levemir has also shown to have a lower risk of hypoglycemia, and no weight gain versus NPH and Lantus.

Figure 3.18: Levemir SWOT analysis

Levemir®
(insulin detemir)
Predictable results day after day

Strengths	Weaknesses
• Improved basal insulin profile without a peak effect and less day-to-day variation than Lantus • Lower risk of hypoglycemia, and no weight gain •Marketing strength of Novo Nordisk •Available with pen delivery	• May need to be prescribed in combination with short-acting insulins or OADs • Injection delivery formulation • Launched late onto the market where Lantus is already well established •FDA has requested more information before marketing approval is granted
Opportunities	**Threats**
• Promotion of favorable basal insulin profile and weight control over Lantus • Novo Nordisk can market its now complete insulin porfolio in Europe • Target use in the large type 2 patient population • Target obese patients because of weight control properties	• Launch of non-invasive insulins • Competition from short-acting insulins in the treatment of type 2 diabetes • Competition from Aventis's Lantus which is already well established in the market • Availability of cheaper insulins

Source: Business Insights

Business Insights Ltd

Levemir will face competition from other long-acting insulins, in particular Sanofi-Aventis' Lantus (insulin glargine), launched in 2001. The arrival of non-invasive insulins is another possible threat, although sales of long-acting insulins are not expected to be affected to the same extent as regular and rapid acting insulins.

CHAPTER 4

Oral antidiabetic (OAD) market analysis

Chapter 4 Oral antidiabetic (OAD) market analysis

Summary

- Sales of OADs totaled $6.5bn in 2003, an average increase over 5 years of 16.0%. This growth has mirrored the increasing population of type 2 diabetics.
- TZDs is the largest class of OADs, accounting for 48.9% of US/European sales in 2003. Growth in this area is due to the success of this class in the US, but the TZDs are not as popular in Europe after the withdrawal of Rezulin in 1999. Actos is the leading US/European TZD with a 53% market share to Avandia's 42.4%.
- Sales of biguanides have declined overall and dropped behind TZDs in recent years. The market has also changed significantly since the US patent expiry of BMS/Merck KGaA's Glucophage in 2001. In 2000 Glucophage accounted for 96.2% of US/European sales in this class and was the leading OAD. However, due to generic competition and strong sales of Glucophage XR (extended release), in 2003 this figure had dropped to 36% of total sales.
- The sulfonylurea class is heavily genericized and holds a 17.2% US/European OAD market share. Glucotrol XL is the leading drug in the US but lost patent protection in 2003, so sales are expected to decline due to generic competition. Amaryl from Aventis has shown strong growth over the last five years and is now the leading US/European sulfonylurea with 36.0% of the market.
- BMS and GlaxoSmithKline (GSK) have developed single-pill combination therapies to take advantage of the complementarity of different OAD classes and to extend product life-cycles.
- Both the alpha glucose inhibitors (AGIs) and the prandial glucose regulators (PGRs) have had poor uptake, perhaps because of their late entry onto the market.
- Takeda and GSK are the leading companies involved in OADs, both selling TZDs. Takeda is the top company with a market share of 25.9%, although this comes from sales of just one product, Actos. GSK has 23.0% of the market from sales of two products, Avandia and Avandamet.

Introduction

Oral antidiabetic (OAD) drugs are used to treat patients with type 2 diabetes. For type 1 diabetics OAD treatment is not an option, and insulin must be injected to break down blood glucose. There are a large number of OADs available, each with a different mode of action. It is also common to for type 2 diabetics to be treated with two or more OADs at once, as many have complimentary modes of action. This chapter describes the major marketed drugs and competitive dynamics of each of the OAD classes.

OAD categories and sales

Within the oral antidiabetics market there are five classes of drugs:

- Sulfonylureas;
- Biguanides;
- Thiazolodinediones (TZDs);
- Alpha glucose inhibitors (AGIs);
- Other oral antidiabetics (such as the prandial glucose regulators (PGRs)).

The sulfonylureas and biguanides are the oldest classes of OAD and are now both heavily genericized. Newer classes of drugs are the TZDs, AGIs and PGRs, although of these three only the TZDs have been successful with the two highest selling antidiabetic drugs being in this category.

Table 4.10 lists the generic and branded names of all the marketed OADs available, detailing dose frequency and level. The drugs performing better in today's market are those with once-daily dosing that improve patient compliance, such as the TZDs.

Table 4.10: Frequency and level of dose of OADs

Generic name	Proprietary name	Dose frequency (max single dose)	Daily dose
Sulophonylureas:			
Glibenclamide	Semi-Daonil, Daonil, Euglucon	Daily	2.5-15 mg (15 mg)
Gliclazide	Diamicron,	1-2 times daily	40-80 mg (160 mg)
	Diamicron 30 mg MR	Daily	30-120 mg (120 mg)
Glimepiride	Amaryl	Daily	1-6 mg (4 mg)
Glipizide	Glibenese, Minodiab	1-3 times daily	2.5-40 mg (15 mg)
Biguanides:			
Metformin	Glucophage	1-3 times daily	500 mg-3g (1 g)
TZDs:			
Rosiglitazone	Avandia	Daily	4-8 mg (8 mg)
Pioglitazone	Actos	Daily	15-30 mg (30 mg)
AGIs:			
Acarbose	Glucobay	1-3 times daily	50-600 mg (200 mg)
PGRs:			
Nateglinide	Starlix	With each meal	60-540 mg (180 mg)
Repaglinide	NovoNorm/Prandin	With each meal	0.5-16 mg (4 mg)

Source: Diabetes and Primary Care, June 2003 Business Insights Ltd

In 2003 the TZD class had sales accounting for 48.9% of the total US/European OAD market, growing from 25.7% in 1999 (Table 4.11). This market share has been obtained at the expense of the older biguanide and sulfonylurea classes. The TZDs are popular because they treat the underlying cause of diabetes and require only once-daily dozing.

Table 4.11: US/European* OAD category market share (%), 2002-2003

	2002	2003	Growth (%) 2002-2003	CAGR (%) 1999-2003
TZDs	44.8	48.9	21.6	36.3
Biguanides (BG)	23.7	18.4	-13.9	-3.5
Sulfonylureas (SU)	17.1	17.2	12.0	3.3
Combined SU+BG	7.6	8.5	23.6	94.3
Other OADs	4.5	4.8	18.8	33.5
AGIs	2.3	2.3	11.4	-3.4

* France, Germany, Italy, Spain, UK

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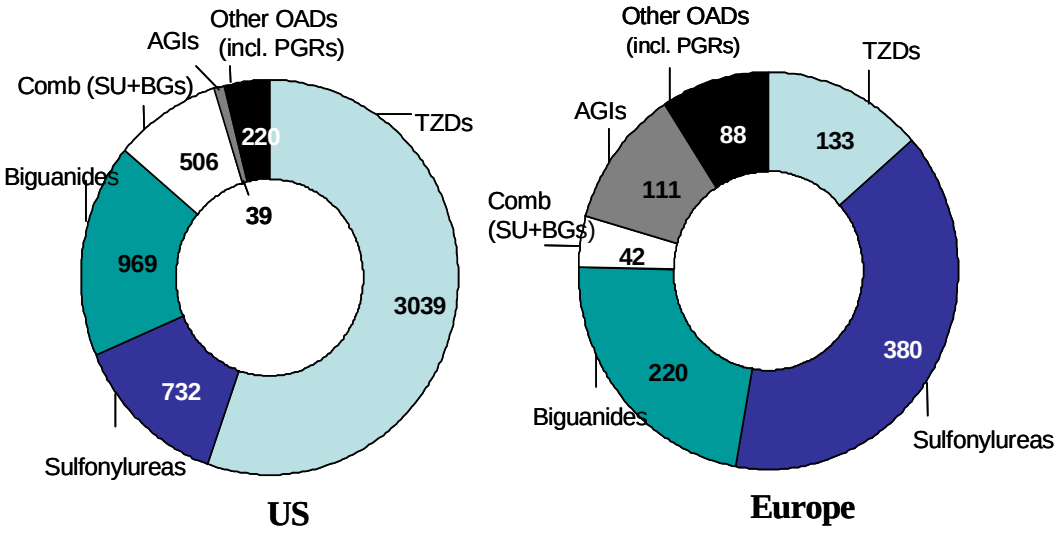
However, it is only in the US where the TZDs have proved to be popular, while in Europe their market penetration has been low due to continuing concerns over safety of this class following the Rezulin withdrawal in 1999 (Figure 4.19).

Figure 4.19: Sales of OAD categories in Europe* and US ($m), 2003



* France, Germany, Italy, Spain, UK

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Company market share

The leading companies in the OAD market are those marketing the popular TZDs – Takeda (Actos) and GSK (Avandia). From Actos sales alone, Takeda was the market leader in 2003 with a 25.9% share, and with sales of Avandia and Avandamet GSK had 23.0% of the total OAD market. During this five year period from 1999 to 2003 BMS has seen its market share fall from a high of 39.8% in 2001 to just 17.1% in 2003. This decline has primarily been due to the patent expiry of Glucophage in 2002 and the entry of generic competition onto the market.

Table 4.12: US/European* OAD Market Share by Company (%), 2002-2003

	2002	2003	Growth (%) 2002-2003	CAGR (%) 1999-2003
Takeda	24.3	25.9	18.6	132.7
GlaxoSmithKline	20.5	23.0	24.8	85.5
BMS	21.5	17.1	-11.5	-3.0
Aventis	6.1	6.8	24.3	14.1
Pfizer	6.7	6.1	0.5	-23.3
Novo Nordisk	2.7	2.8	12.4	16.6
Novartis	2.3	2.3	14.0	50.0
Merck KGaA	1.5	1.9	38.8	11.8
Teva	2.0	1.7	-8.0	9.7
Bayer	1.6	1.5	10.6	-8.7
Others	10.8	11.0	1.9	---

* France, Germany, Italy, Spain, UK

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Sulfonylurea products

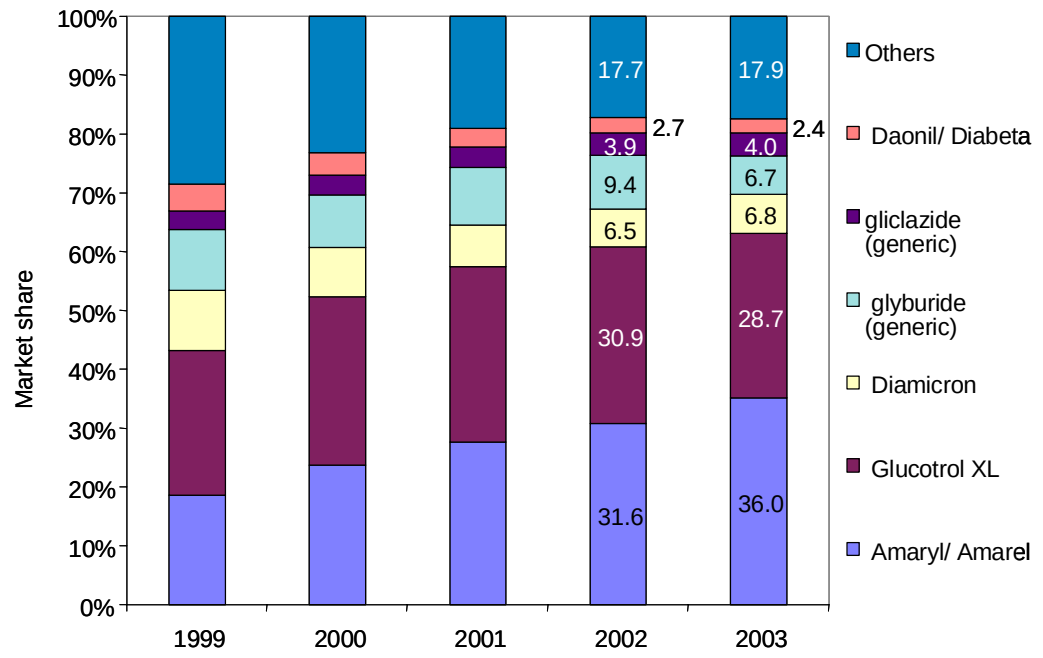
Sulfonylureas are the oldest class of OAD, the first drug of this class having been launched in the 1950s. Sulfonylureas act by stimulating the production of insulin from the pancreas by binding to receptors on the insulin-producing cells in the islet of Langerhans. The newer sulfonylureas only require a single daily dose, therefore increasing patient compliance, and the wide range of sulfonylureas available with different durations of action provides flexibility in prescribing.

The majority of sulfonylureas are now highly genericized and they are facing increasing competition from newer agents, such as the TZDs, which offer greater efficacy and reduced side-effects. Sulfonylureas should be used with caution in the elderly and in patients with impaired liver or kidney function, which can severely limit the use of this class as many patients that suffer from type 2 diabetes are over the age of 60 years. Moreover, sulfonylureas can cause weight gain unlike the biguanide class.

Brand market share and sales

Amaryl from Aventis (now Sanofi-Aventis) and Pfizer's Glucotrol XL are the two leading sulfonylureas on the market (Figure 4.20). Amaryl has gained market share from 1999 to 2003 to now hold 36% of the US/European sulfonylurea market, while Glucotrol XL has kept a steady market share during this same period of between 25.8% and 30.9%.

Figure 4.20: Global* market share of leading sulfonylureas (%), 1999-2003



* US, France, Germany, Italy, Spain, UK

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Many of the older sulfonylureas are highly genericized as shown by market shares among the leading brands. Glucotrol XL lost patent protection in 2003, and there is now a generic version of this drug (glipizide ER), so sales in subsequent years of Glucotrol XL are likely to decrease significantly. This will also be true of Amaryl when its patent protection expires in 2005.

There are some notable differences in the sulfonylurea markets in the six countries analyzed, summarized in Table 4.13. In the US Glucotrol XL is the market leader with sales of $319m in 2003, with second-ranked Amaryl having sales of $249m. There is also a significant presence of generics in the US with glyburide, glipizide and glipizide ER having the largest share. The sales of generic glipizide ER, launched in 2003, are

expected to rise in the coming years and have a major impact on the sales of the branded Glucotrol XL.

Table 4.13: Sales of leading sulfonylureas by country ($m), 2002-2003

	2002	2003	Growth (%) 2002-2003	CAGR (%) 1999-2003
US				
Glucotrol XL	307	319	4.0	6.1
Amaryl/Amarel	195	249	27.3	22.5
glyburide (generic)	105	83	-21.0	-13.6
glipizide (generic)	23	21	-7.8	-13.7
glipizide ER (generic)	0	21	---	---
Total	**679**	**732**	**7.8**	**2.5**
France				
Diamicron	45	55	23.0	-7.9
Amaryl/Amarel	28	37	30.1	17.8
Daonil/Diabeta	15	17	14.2	-0.7
Gliclazide (generic)	14	18	28.6	---
Total	**108**	**131**	**22.0**	**2.0**
Germany				
Amaryl/Amarel	56	72	28.6	13.6
Total	**74**	**92**	**24.9**	**5.5**
Italy				
Amaryl/Amarel	7	10	46.0	61.4
Diamicron	11	9	-12.4	-14.6
gliclazide (generic)	6	9	86.4	---
Solosa	3	6	100.0	97.6
Total	**34**	**42**	**23.3**	**8.9**
Spain				
Amaryl/Amarel	17	22	26.6	13.2
Roname	5	8	50.5	---
Diamicron	6	8	25.6	6.7
Daonil/Diabeta	5	5	8.0	-4.4
Total	**39**	**49**	**25.4**	**10.8**
UK				
gliclazide (generic)	40	46	15.0	6.4
Amaryl/Amarel	9	9	1.6	64.2
Total	**60**	**65**	**8.8**	**5.4**

Source: IMS Health, Copyright ©, reprinted with permission; Business Insights Business Insights Ltd

In Germany, Italy and Spain Amaryl is the leading sulfonylurea. Indeed in Germany sales of Amaryl accounted for 78% of total sales in this class. This product has shown strong growth in each of the six markets analyzed with compound annual growth rates from 1999 to 2003 ranging from 13.2% in Spain to 64.2% in the UK. However, when its patent expires in 2005 and generics enter the market, its sales are expected to fall.

Other sulfonylureas with good sales in the Europe markets are Diamicron, the leading product in France, and also popular in Italy and Spain, and generic gliclazide in the UK which accounts for 71% of the market. Glucotrol XL, in contrast to its success in the US, is not among the leading sulfonylureas in any of the European countries analyzed.

Brand analysis

Table 4.14 provides information on launch dates and patent expiries of the leading branded sulfonylureas. Amaryl (glimepiride) and Glucotrol XL (glipizide) were the two highest selling sulfonylureas globally in 2003, and these two products are profiled in this report.

Table 4.14: Branded sulfonylureas

US brand	Generic	Marketing company	First global launch date	US patent expiry
Amaryl	glimepiride	Aventis	1996	2005
Glucotrol XL	glipizide	Pfizer	1994	2003
Daonil/Diabeta	glyburide	Aventis	1984	Expired in 1995
Diamicron	gliclazide	Servier	n/a	Expired in 1993
Euglucon	glyburide	Yamanouchi	n/a	Expired
Micronase	glyburide	Pharmacia	1984	Expired in 1994
Glucotrol	glipizide	Pfizer	1984	Expired in 1994

n/a = not available

Source: Business Insights

Business Insights Ltd

Amaryl (glimepriride)

Amaryl (glimepiride) is an oral once-daily sulfonylurea for the treatment of type 2 diabetes. It was first launched in 1996 and is now available in more than 60 countries, including Japan. Amaryl has achieved good sales since its launch in 1996, however, its patent expiry in 2005 will reduce its sales as generics enter the market. Sanofi-Aventis is trying to expand its patent protection with additional indications and formulations.

The success of Amaryl over older sulphonylureas is related to its novel mechanism of action - it binds to a different receptor in the pancreas than the older sulphonylureas - which results in reduced incidence of hypoglycemia. In addition, the drug's once-daily formulation has improved patient compliance. Amaryl is also the only sulphonylurea to be indicated for use as a monotherapy, and in combination with insulin and metformin.

Figure 4.21: Amaryl SWOT analysis

Amaryl® glimepiride TABLETS

Strengths	Weaknesses
• Extended release formulation and once-daily administration • Patent protected in the US until 2005 with marketing strength of Aventis •Approved for use in combination with insulin, metformin, AGIs and TZDs • Efficacy advantages over glyburide and weight neutralizing/ reducing effects	• Old class of OADs that faces increasing competition from newer OADs, i.e. TZDs • Aventis preferentially promoting newer products, such as Lantus
Opportunities	**Threats**
• Co-marketing opportunities with Aventis's insulin products • Increasing prevalence of type 2 diabetes • Pediatric indication, extending patent protection by six months • Promotion to obese diabetics	• Increasing use of insulin in type 2 diabetics • Generic competition from older sulfonylureas • Competition from Glucotrol XL and generic glipizide extended release

Source: Business Insights

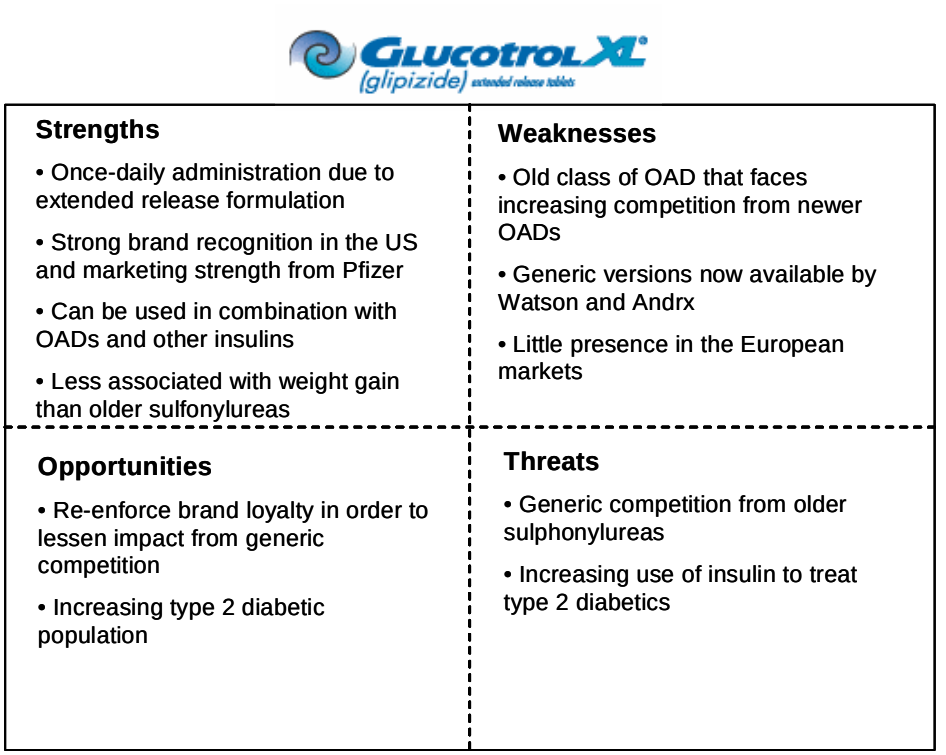
Business Insights Ltd

Glucotrol XL (glipizide)

Glucotrol XL (extended release glipizide) is a once-daily sulfonylurea medication launched by Pfizer in 1994, the same year that the patent for Glucotrol expired, allowing Pfizer to maintain its strong presence in the diabetes market. One advantage of Glucotrol XL over its parent, Glucotrol, is that it provides effective glycemic control over a 24-hour period with a single daily dose. Additionally, it is independent of pH and gastrointestinal motility, and uses Alza's oral osmotic pump technology.

Until 2000 Glucotrol XL was the top selling sulphonylurea, based on its large sales in the US, although the product has little presence in the major European markets.. Despite the fact that Sanofi-Aventis' Amaryl (glimepiride) has now become the sulphonylurea market leader, Glucotrol XL still dominates the US market. Generic versions are now available from Watson Pharmaceuticals and Andrx Corporation.

Figure 4.22: Glucotrol XL SWOT analysis



Source: Business Insights

Business Insights Ltd

Biguanide products

The biguanide class is the second oldest OAD class of drugs and is comprised mainly of metformin. The biguanide class of drugs act to lower blood glucose levels by decreasing hepatic glucose production, decreasing intestinal absorption of glucose and improving the insulin sensitivity of target cells.

As biguanides do not cause excess insulin release, the incidence of hypoglycemic attacks are reduced and, due to the high level of genericization, this class of drugs are relatively inexpensive compared to other OADs, such as TZDs. Moreover, biguanides are associated with weight loss rather than weight gain and, as obesity plays a key role in the development of type 2 diabetes, any drug that helps decrease weight is advantageous in the treatment of this condition.

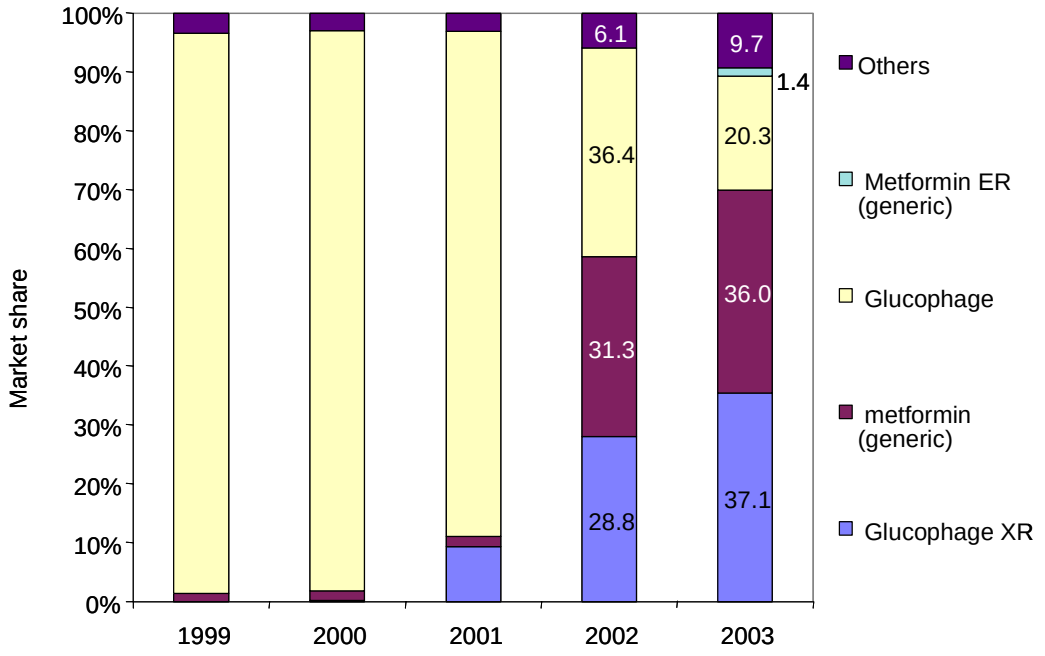
However, although cheaper than many other OADs, biguanides usually require more frequent administration, which can reduce patient compliance and thus decrease the effectiveness of the therapy. In addition, biguanides are unsuitable for patients with renal impairment and have a tendency to exert gastrointestinal side effects. As a result, newer OADs like the TZDs and combination therapies have seized much of the market share of biguanides.

Brand market share and sales

Figure 4.23 shows the US/European market shares of the leading biguanides from 1999 to 2003. The highest selling product, Glucophage XR, is marketed by BMS and is an extended release version of the older Glucophage. This product has grown significantly since launch in 2000 to hold a 37.1% biguanide market share in 2003. During the same period, however, sales of Glucophage have declined from a 96.2% market share in 2000 to just 20.3% in 2003. This is the result of the entry of generic versions of Glucophage (metformin) entering the market following patent expiry. Generic metformin sales in 2003 accounted for 36% of the US/European market. With Glucophage XR having also

lost patent in 2003, it is expected that generic metformin extended release will capture a large proportion of its market share in the coming years.

Figure 4.23: Global* market share of leading biguanides, 1999-2003



* US, France, Germany, Italy, Spain, UK

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The US market is by far the largest market for biguanides, and so trends in this market are reflected in the global market – Glucophage XR is the leading product, and generic metformin has captured much of Glucophage's sales.

In the five European markets analyzed generic metformin and Glucophage (marketed by Merck KGaA in Europe) are most popular. The extended release biguanides have yet to make an impact in these markets.

Table 4.15: Sales of leading biguanides by country ($m), 2002-2003

	2002	2003	Growth (%) 2002-2003	CAGR (%) 1999-2003
US				
Glucophage XR	398	441	10.7	---
Metformin	379	349	-7.7	---
Glucophage	445	163	-63.5	-40.0
Metformin ER	0	17	---	---
Total	**1,222**	**969**	**20.7**	**-6.2**
France				
Glucophage	35	45	29.0	4.2
Metformin	15	23	46.7	54.9
Stagid	8	10	23.2	7.3
Total	**59**	**78**	**32.3**	**11.7**
Germany				
Metformin	16	25	53.5	49.5
Glucophage	11	17	55.4	0.9
Total	**54**	**74**	**36.6**	**13.1**
Italy				
Glucophage	10	15	56.1	42.3
Metforal	4	7	61.9	52.9
Metbay	1	1	29.9	18.9
Metformin	0	1	---	---
Total	**14**	**23**	**61.9**	**44.9**
Spain				
Dianben	7	12	64.9	37.4
Metformin	1	0	-34.9	---
Total	**8**	**12**	**57.2**	**36.2**
UK				
Metformin	22	30	36.9	33.3
Glucophage	1	1	-17.7	-15.2
Total	**24**	**32**	**33.7**	**27.6**

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Brand analysis

Table 4.16 lists the two leading branded biguanides. Glucophage XR is now the top selling product but due to its patent expiry in 2003 sales are expected to decline significantly in subsequent years.

Table 4.16: Branded biguanides

US brand	Generic	Marketing company	First global launch date	US patent expiry	Alternative brand names
Glucophage	metformin	BMS / genericized Merck KGaA	1958	2002	Highly
Glucophage XR	metformin extended release	BMS	2000	Exclusivity Oct 2003	n/a

n/a = not applicable

Source: Business Insights

Business Insights Ltd

Glucophage & Glucophage XR (metformin)

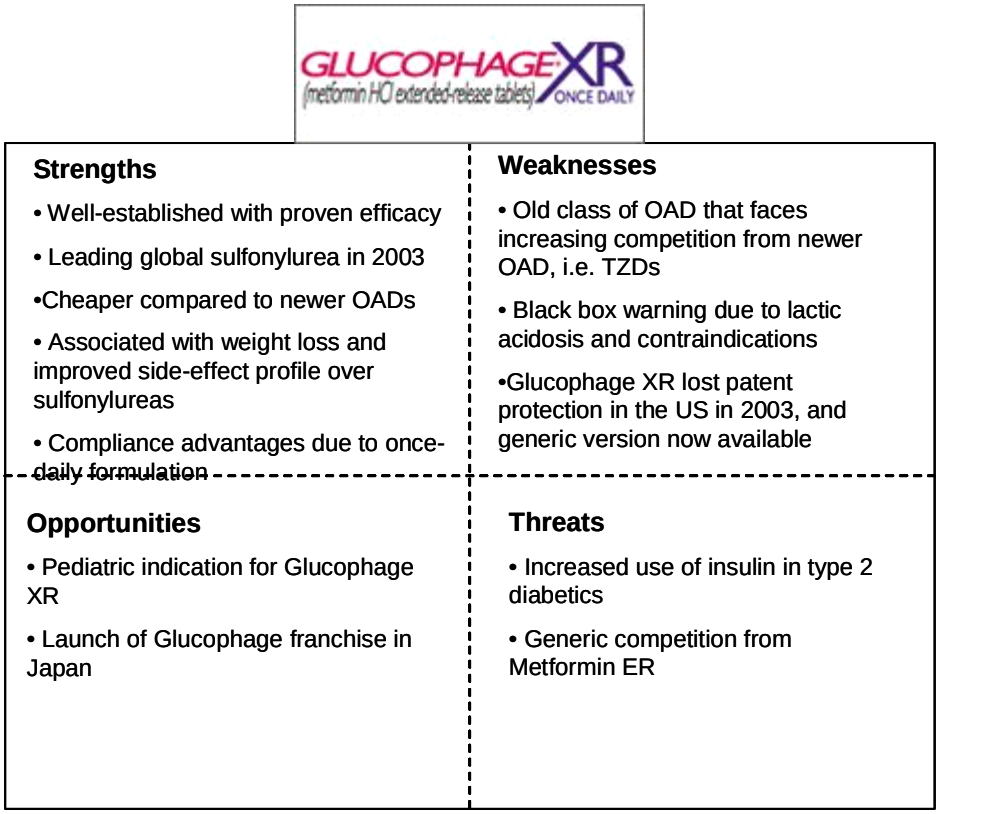
Glucophage is an oral biguanide agent used in the treatment of type 2 diabetes. This drug is used either as a first-line monotherapy or in combination with existing drugs when glucose levels are not sufficiently reduced. Glucophage works to slow glucose production and also increase its peripheral utilization, which is dependent on residual production of insulin by the pancreas. Merck KGaA originally developed the drug, which was first launched in 1958, and markets Glucophage primarily within Europe, while BMS has in-licensed the US marketing rights.

Glucophage lost patent protection in European countries in 1997, but in the US, BMS was granted an extension on marketing exclusivity for Glucophage until September 2000. Following its European patent expiry and anticipating it in the US, Merck KGaA and BMS collaborated to reformulate Glucophage, hoping to protect revenues against generic competition. Merck KGaA and BMS gained approval of a combination of

metformin and glyburide, marketed as Glucovance in Europe and the US (and profiled under combination therapies), in addition to a once-daily formulation, Glucophage XR.

Glucophage XR is a once-daily formulation that offers compliance advantages compared with the conventional formulation, which requires twice or three times daily dosing. Glucophage XR is targeted at patients who require metformin monotherapy or who take metformin in combination with other oral anti-diabetic agents. In clinical trials with more than 1,200 patients, Glucophage XR was shown to be comparable to Glucophage in lowering patients' blood sugar levels. Glucophage XR was introduced to the US market in January 2001, but the generic version was available just two years later in October 2003. It is likely that BMS will see its sales of Glucophage XR decline in much the same way as its Glucophage sales. Currently Andrx has generic versions of both metformin products.

Figure 4.24: Glucophage XR SWOT analysis



Source: Business Insights

Business Insights Ltd

Combined sulfonylurea & biguanide products (and other combination therapies)

The use of combination therapy within type 2 diabetes is increasingly common, as many of the antidiabetic drug classes have different and complimentary mechanisms of action. Combination therapy is usually used in second or third line therapy as monotherapy with sulfonylureas, metformin or insulin often fails to maintain glucose levels over time (Table 4.17).

Despite the recommendations against combination therapy at first line, the physician survey data reveals that 15–25% of drug-treated patients across the six major markets analysed do receive combination therapy at first line. The use of combination therapy at first line is usually reserved for patients with very significant disease progression or for patients that have developed diabetic complications at the time of the diagnosis.

Table 4.17: Proportion of patients receiving monotherapy versus combination therapy treatment (%), 2003

	US	France	Germany	Italy	Spain	UK
First-line therapy						
Monotherapy	75	85	79	82	81	75
Combination therapy	25	15	21	18	19	25
Second-line therapy						
Monotherapy	57	21	34	30	30	28
Combination therapy	43	79	66	70	70	72
Third-line therapy and beyond						
Monotherapy	7	7	28	4	22	23
Combination therapy	93	93	72	96	78	77

Source: Business Insights, Type 2 Diabetes Insight Physician Survey (Q2.3) Business Insights Ltd

Sulfonylurea + biguanide single-pill combination drugs

As a response to the increased use of combination therapy, several companies have developed single pill combination formulations. In the combined sulfonylurea plus biguanide class the dominant drug is Glucovance marketed by BMS, and part of the Glucophage franchise. In the six markets analyzed Glucovance had total sales of $0.5bn in 2003. Metaglip was also launched by BMS in 2002, but has had little impact to date in terms of sales, despite a high growth rate from 2002 to 2003. Glucovance is profiled in this report.

Table 4.18: US/European* sales of sulfonylurea + biguanide single-pills ($m), 1999-2003

Brand Name	Marketing company	2002	2003	Growth (%) 2002-2003	CAGR (%) 1999-2003
Glucovance	BMS	404	479	18.5	---
Metaglip	BMS	5	27	397.0	---
Glibomet	Menarini	16	21	27.5	4.2
Others		19	21	10.5	---
Total		**444**	**548**	**23.4**	**---**

* France, Germany, Italy, Spain, UK

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Glucovance (glyburide + metformin)

Glucovance was launched in the US in August 2000 and was the first drug to offer patients the two most widely prescribed OADs combined in one tablet. The key advantage of Glucovance over existing biguanides is that, as a combined pill, it reduces the number of pills a patient needs to take each day, thereby improving patient compliance. On the other hand, the disadvantage of any single pill combination therapy is that physicians lose the flexibility to individually titrate doses. However, as diabetic type 2 patients will commonly be prescribed combination therapy and may also be receiving therapy for other conditions, such as hypertension and dyslipidemia, patient

compliance is one of the key unmet needs in the management of diabetes and therapies that offer improvements in this respect have significant potential.

In clinical trials of Glucovance the combined pill has been shown to be more effective in treating type 2 diabetes than the two components prescribed separately.

Additionally, in October 2002, BMS announced that the US FDA had approved Glucovance for use in combination with TZDs. The new indication specifies that a TZD can be added when inadequate glycemic control has been achieved with Glucovance and diet and exercise.

Figure 4.25: Glucovance SWOT analysis

Strengths	Weaknesses
• Glucophage franchise well established • Single pill combination treatment aids patient compliance • Associated with weight loss and improved side-effect profile over sulfonylureas • Complementary action of 2 different OADs	• Single-pill formulation means a fixed-dose of each drug administered • Combines old classes of OAD that face increasing competition from newer OADs, i.e. TZDs •Glucophage lost patent protection in the US in April 2002, so separate prescribing of glyburide and metformin cheaper
Opportunities	**Threats**
• Pediatric indication GLucovance • Launch of Glucophage franchise in Japan • Launch of Glucovance in non-US markets	• Increased use of insulin in type 2 diabetics • Generic competition from generic single pill combination • Uptake of other single pill combinations with metformin

Source: Business Insights

Business Insights Ltd

TZD + other OAD single-pill combination therapies

GSK has developed two single-pill combination therapies based on its successful TZD drug Avandia.

- Avandamet (Avandia + metformin), which was launched in the US in November 2002 and approved in the EU in October 2003;
- Avandaryl (Avandia + sulfonylurea), which was submitted for regulatory approval in 2003, with expected submission in the EU in 2004.

GSK is also developing Avandamet XR, which is again based on Avanida but with an extended release version of metformin. Although this product is only in early stage trials GSK expects to submit an NDA in 2005.

Avandamet is profiled in this report under TZD products, and sales figures for the drug are also given in this section.

Thiazolidinedione (TZD) products

The TZDs (also known as glitazones or insulin sensitizers) represent one of the newest classes of OAD and the first class of drugs to be developed that target the underlying cause of type 2 diabetes, cellular insulin resistance. The TZDs produce their anti-hyperglycemic effect by enhancing certain actions of insulin – increasing insulin-dependent glucose disposal and decreasing hepatic glucose output. TZDs specifically act on a peroxisome proliferator activator receptor (PPAR) gamma that controls a number of transcription factors. The PPAR-gamma subtype activated by TZDs is involved in the regulation of lipid and glucose metabolism. In addition, there is considerable evidence to suggest that the mechanism of action may have protective effects: studies performed in rodents suggest that PPAR-gamma agonists protect against islet cell degeneration and this finding supports the potential benefits of TZDs in metabolic syndrome and type 2 prevention.

The fact that these agents treat the underlying pathology of the disease means that they offer distinct advantages over other OADs as their pharmacological effects do not lead to hypoglycemia and TZDs enable the body to use its own insulin more effectively. Additionally, the TZDs only require once-daily dosing, a characteristic that is becoming a prerequisite within the OAD market.

However, the downside to the TZD class for patients is the associated dose-related weight gain. Additionally, the fact that these drugs command a price premium over other classes of OADs, many of which are highly genericized, is a downside to TZD use by payer/provider organizations. Recent studies have also suggested that the TZDs exacerbate congestive heart failure (CHF) and pulmonary edema, particularly when used in combination with insulin.

Brand market share and sales

Pfizer/GSK/Sankyo's Rezulin (troglitazone) was the first TZD to market in 1997. However the drug was withdrawn in March 2000 from the US because of serious adverse safety events. Sales of Rezulin were still high in 1999 in the US although the drug had been publicly associated with liver toxicity before its withdrawal. Rezulin was briefly available in the UK (marketed by GSK) before being withdrawn, and was never launched in other EU countries.

GSK's Avandia (rosiglitazone) and it major rival, Takeda/Eli Lilly's Actos (pioglitazone), were launched in 1999. In the US they have successfully overcome the initial stigma associated with the class following the Rezulin withdrawal, and the TZD class now represents 39% of the total diabetes market, more than the entire insulin class.

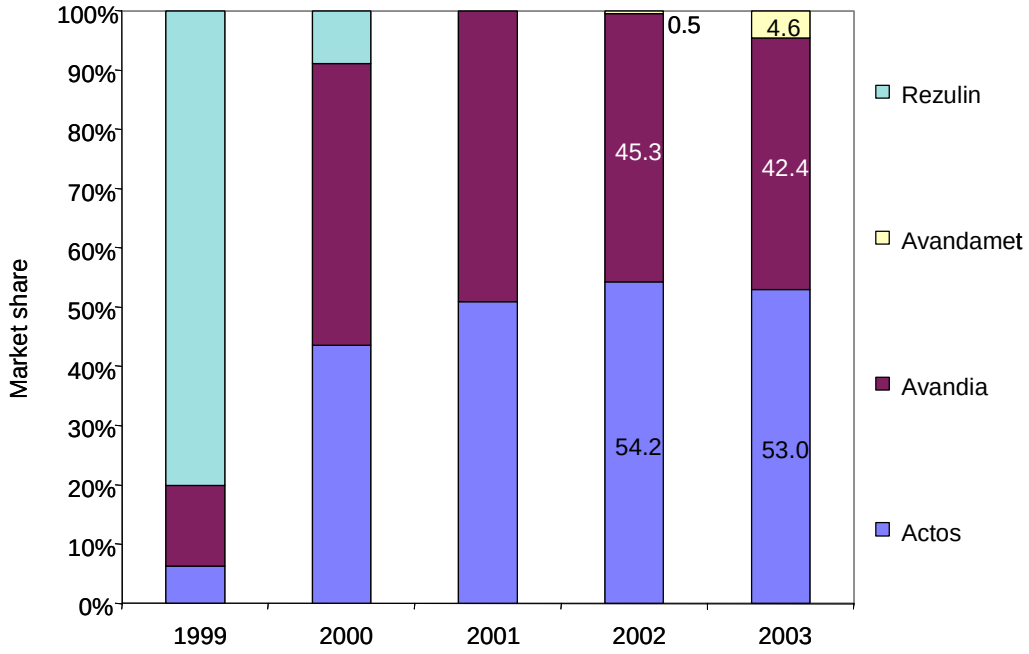
However, in Europe the uptake of TZDs has been markedly slow – only a 5.1% share in 2003, with half of these sales in the UK alone. This is due to concern by patients and physicians about the TZD class in light of the Rezulin withdrawal, and due to the larger insulin market in Europe compared to the US.

GSK has also had approval for a combination single pill of Avandia with metformin, launched as Avandamet in 2003.

Actos is the highest selling TZD with 53% of the TZD market. It overtook sales of rival Avandia in 2001, with Avandia now holding a 42.4% share. The table also illustrates that Rezulin had over 80% the TZD market before its withdrawal over safety concerns.

Figure 4.26 shows the US/European market shares of the leading TZDs, 1999 to 2003.

Figure 4.26: US/European* market share of leading TZDs (%), 1999-2003



* France, Germany, Italy, Spain, UK

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TZDs are the leading antidiabetic class in the US, with sales of $3 billion in 2003. This is in stark contrast to the situation in Europe, where TZDs have had little impact in many countries, most notably France, Italy and Spain. This can be explained partly by lingering doubts over TZDs due to Rezulin's withdrawal from the UK in 1999 which meant this drug was never launched in other European countries. Also, the market for insulins in proportion to OADs is larger in Europe than in the US, and Actos only received full EU approval in 2003.

Table 4.19: Sales of leading TZDs by country ($m), 2002-2003

	2002	2003	Growth (%) 2002-2003	CAGR (%) 1999-2003
US				
Actos	1,386	1,631	17.7	131.1
Avandia	1,131	1,263	11.7	78.0
Avandamet	12	144	1,078.4	---
Rezulin	0	0	-100.0	---
Total	**2,529**	**3,039**	**20.2**	**34.9**
France				
Actos	1	3	464.4	---
Avandia	0	3	1,552.7	---
Total	**1**	**5**	**726.2**	**---**
Germany				
Actos	18	27	51.8	---
Avandia	18	23	24.6	---
Avandamet	0	0	---	---
Total	**36**	**50**	**38.5**	**---**
Italy				
Avandia	1	1	100.4	---
Actos	0	1	68.4	---
Total	**1**	**2**	**88.7**	**---**
Spain				
Avandia	3	7	130.2	---
Actos	1	6	360.2	---
Total	**4**	**12**	**198.5**	**---**
UK				
Avandia	28	48	68.3	---
Actos	9	16	77.4	---
Avandamet	0	0	---	---
Total	**37**	**64**	**70.9**	**---**

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Brand analysis

Table 4.20 provides information on the available TZDs. Following the withdrawal of Pfizer/GSK/Sankyo's Rezulin (troglitazone), Actos, Avandia and single-pill combination drug Avandamet are the only TZDs currently on the market.

Table 4.20: Branded TZDs

US brand	Generic	Marketing company	First global launch date	US patent expiry
Actos	pioglitazone	Takeda/Eli Lilly	1999	2006
Avandia	rosiglitazone	GSK	1999	2008
Avandamet	rosiglitazone + metformin	GSK	2002	2008*

* Patent expiry dependent on success of GSK upholding reformulation patent extensions – could run until 2015.

Source: Business Insights

Business Insights Ltd

Drug analysis

Actos (pioglitazone)

Actos (pioglitazone) was developed by Takeda and is licensed to Eli Lilly for co-promotion in the US, where it was launched in August 1999. Following launch in the US, Actos gained approval in Japan in December 1999 and in the EU in October 2000. In the US from launch, Actos has been approved for use as a monotherapy and for use in combination with a sulfonylurea, metformin and insulin. In the EU, Actos received EU approval for use as a monotherapy in patients unable to tolerate metformin in June 2003, and later as an oral combination treatment in type 2 diabetes patients with either metformin or sulphonylurea. In addition, Actos was approved for use in combination with alpha glucosidase inhibitors in Japan in June 2002.

Importantly, none of the toxic side effects that were associated with Rezulin have been seen in patients treated with Actos. Additionally, Actos has been found to significantly reduce blood glucose levels, decrease mean triglyceride levels and increase mean HDL

levels in both monotherapy and in combination with sulfonylureas, metformin or insulin. In contrast, no significant changes in mean total cholesterol or mean LDL or 'bad' cholesterol levels were seen with Actos either as a monotherapy or combination.

Actos is the leading US/European TZD, with strong sales in the US. This drug also achieved high sales in Japan, whereas Avandia was not due for launch there until 2004 at the earliest. Therefore, since Actos was launched in Japan at the end of 1999, Takeda has gained invaluable time in establishing this agent in this market before the launch of any direct competitors. In addition, the licensing agreement with Eli Lilly has strengthened the marketing expertise in the US and has enabled Actos to compete more aggressively with GSK's Avandia (rosiglitazone). Combined US revenues for Actos in 2003 were $1.6bn, with Takeda recording the majority of these sales.

Figure 4.27: Actos SWOT analysis

actos®
pioglitazone HCl

Strengths	Weaknesses
• Once-daily administration and novel mechanism of action • Good marketing strength of Takeda and Eli Lilly • Was highest selling diabetes drug in 2003 • Superior benefits on lipid profiles to Avandia	• Concerns over long-term effects of hepatic function with the TZDs • Can cause weight gain in some type 2 patients • TZDs shown to increase the risk of congestive heart failure and pulmonary edema
Opportunities	**Threats**
• Development of single pill combination with metformin or a sulfonylurea • Increased promotion in Europe where Avandia is the leading TZD	• Competition from Avandia, Avandamet and new TZDs • Launch of dual PPAR agonists that have superior benefits on lipid profiles • Patent expiry in 2006 • Competition from cheaper generic OADs, e.g. metformin

Source: Business Insights

Business Insights Ltd

Avandia (rosiglitazone)

Avandia (rosiglitazone) was launched by GSK in the US in June 1999, beating Actos by 2 months. Avandia was also approved in the EU in June 2000, although this was after an initial rejection in 1999, and an application was filed for approval in Japan in December 2001. However, in order to increase the potential of Avandia in Japan, Sankyo obtained joint sales rights from GSK in January 2003 to market Avandia, which is expected for launch there at some point in 2004. Avandia is indicated for the treatment of type 2 diabetes either as a monotherapy or in combination with metformin, sold both generically and by BMS as Glucophage.

In clinical trials, Avandia has been shown to increase insulin sensitivity and beta-cell function. By targeting insulin resistance, Avandia has a beneficial impact on many of the metabolic risk factors (including microalbuminuria, endothelial dysfunction, hypertension and dyslipidemia) that predispose patients to cardiovascular disease. In addition, due to its complimentary mechanism of action to metformin and sulfonylureas, Avandia has been shown in a number of clinical trials to deliver enhanced glycemic control in high-risk patients when used in combination therapy. However Avandia is associated with weight gain when used alone and in combination with a sulfonylurea, metformin or insulin, and there has also been a concern over heart and liver failure after 32 patients filed a lawsuit in the US in 2003.

Avandia has performed well in the US market, but this has not been matched in the European and Japanese market, where there is much more concern by regulators and physicians of the safety of TZDs following the withdrawal of Rezulin. GSK has also specifically targeted Hispanic populations, which have both a high risk of type 2 diabetes and account for an increasing proportion of the US market.

Figure 4.28: Avandia SWOT analysis

Strengths	Weaknesses
• Market leader in Europe • Once-daily administration and novel mechanism of action • Available in single-pill combination with metformin (Avandamet) • 2nd highest selling diabetes drug in 2003	• Concerns over long-term effects on hepatic function with TZDs • Inferior lipid profile to Actos • Can cause weight gain in some type 2 patients •TZDs show to increase the risk of congestive heart failure and pulmonary edema
Opportunities	**Threats**
• Launch in Japan by Sankyo in 2004 • Positive results from DREAM trial in 2007 • Increased promotion in US	• Competition from Actos and new TZDs • Launch of dual PPAR agonists that have superior benefits on lipid profiles • Competition from cheaper generic OADs, e.g. metformin • Launch of generic pioglitazone in 2006, and US patent expiry of Avandia in 2008 •Product liability suit launched in US

Source: Business Insights

Business Insights Ltd

Avandamet (rosiglitazone + metformin)

GSK developed a single pill combination of these two commonly prescribed antidiabetic agents, which has been branded Avandamet and was approved in the US in October 2002. Avandamet is indicated as an adjunct to diet and exercise to improve blood glucose control in patients with type 2 diabetes who are already treated with Avandia and metformin as two separate medications or who are not adequately controlled on metformin alone.

Launch of Avandamet, and development of Avandaryl and Avandamet XR, represent an important life cycle management program for the Avandia franchise. GSK has beaten

Takeda and Eli Lilly in this respect as Actos is not available as yet in a single pill combination form.

In the six markets analysed in 2003 Avandamet held 4.6% of the TZD market.

Figure 4.29: Avandamet SWOT analysis

Avandamet™
rosiglitazone maleate/metformin HCl

Strengths	Weaknesses
• Part of GSK's successful Avandia franchise • The only single-pill combination therapy available with a TZD • Single-pill combination improves patient compliance • Complimentary actions of two differents types of OAD	• Single-pill formulation means a fixed-dose of each drug administered • Associated with weight gain • Concerns over long-term effects on hepatic function with TZDs • TZDs shown to increase the risk of congestive heart failure and pulmonary edema
Opportunities	**Threats**
• Avandamet XR (extended release) in pre-clinical trials • Avandia franchise expanding with launch of Avandaryl • Increase market share before a single-pill combination form of Actos becomes available	• Competition from new drug classes such as the dual PPAR agonists • Competition from generics when Avandia and Actos come off patent • Competition should a single-pill combination of Actos and metformin become available

Source: Business Insights

Business Insights Ltd

Alpha glucosidase inhibitor (AGI) products

Since the launch of the biguanides in the 1950s, the AGIs were the first of the new oral drug classes to reach the diabetes market in 1990. AGIs work by slowing down the digestion and absorption of ingested carbohydrates through the small intestine, which in turn decreases the exaggerated rise in blood glucose levels that occurs following meals in diabetic patients (post-prandial hyperglycemia). As a result, there is a decrease in HbA1c levels and a reduction in the risk of long-term microvascular complications. Unlike sulfonylureas, AGIs are not associated with hypoglycemia and do not cause hyperinsulinemia or weight gain.

Disadvantages of alpha-glucoside inhibitors are a less favorable gastrointestinal (GI) side-effect profile, including nausea, flatulence, abdominal pain and hepatotoxicity, which are dose-related, and it can take months to effectively titrate doses. In addition, there is a lack of efficacy when AGIs are administered as a monotherapy, which is why they are often prescribed in combination with a sulfonylurea or insulin. However, when used with these agents there is an increased risk of hypoglycemia and, owing to their ability to delay the absorption of complex sugars, patients being treated with an AGI and insulin need to take oral glucose tablets or gel to treat symptoms of hypoglycemia. AGIs are generally taken three times a day at the start of a meal, which can cause patient compliance problems.

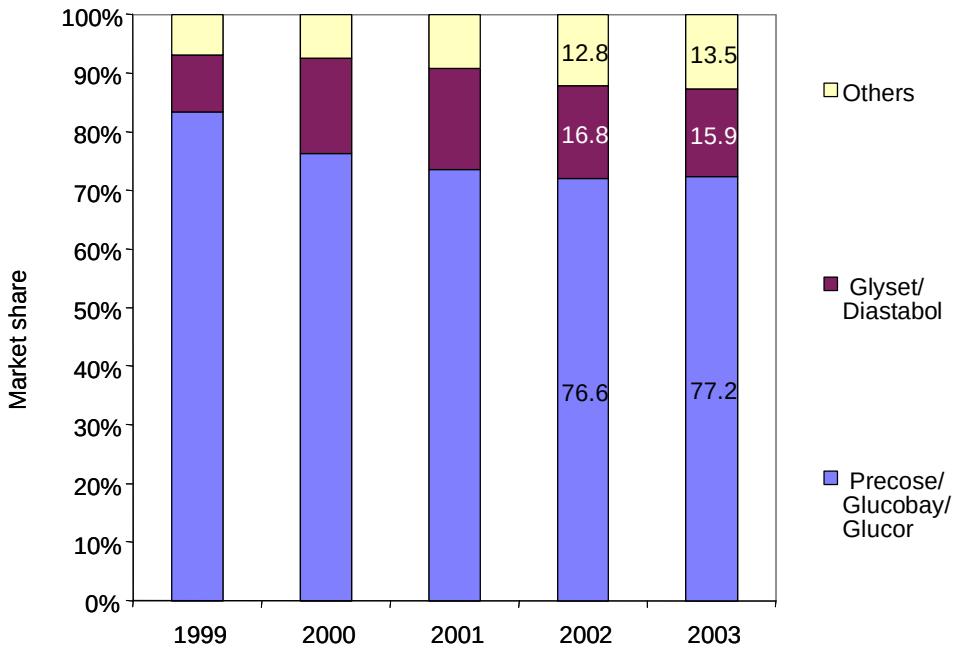
Brand market share and sales

Since the introduction of Precose in 1990, two other AGIs have been launched, Takeda's Basen (voglibose) in Japan in 1994 and Bayer's Glyset (miglitol), which was out-licensed to Pharmacia & Upjohn (now Pfizer), in the US and Sanofi (now Sanofi-Aventis) in the EU in 1996 where it is marketed as Diastabol. AGIs are not a popular class of drugs in the US and Europe, but have been successful in Japan where the

success of Takeda's Basen clearly demonstrates rapid uptake of AGIs in the Japanese market.

As illustrated in Figure 4.30, in the six markets analysed Precose and Glyset are the leading AGIs. Basen is not featured in these sales tables as this product has not been launched in the US or Europe. Precose has maintained its dominant position over Glyset in the last five years, with 77.2% of the AGI market in 2003.

Figure 4.30: US/European* market share of leading AGIs (%), 1999-2003



* France, Germany, Italy, Spain, UK

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The AGI class of antidiabetic drugs is more popular in France, Germany and Spain than in the US, Italy and the UK. Sales recorded in $m were similar in the US, France, Germany and Spain despite the large difference in total diabetes market size. Again, as in the US, Precose is the most popular AGI in each of the five European markets analyzed.

Table 4.21: Sales of leading AGIs by country ($m), 2002-2003

	2002	2003	Growth (%) 2002-2003	CAGR (%) 1999-2003
US				
Precose/Glucobay/Glucor	26	28	5.7	-6.7
Glyset/Diastabol	10	12	14.7	19.6
Total	**36**	**39**	**8.2**	**-1.7**
France				
Precose/Glucobay/Glucor	28	33	18.0	2.3
Glyset/Diastabol	3	3	3.4	4.6
Total	**31**	**36**	**16.5**	**2.5**
Germany				
Precose/Glucobay/Glucor	27	30	12.0	-11.5
Glyset/Diastabol	5	5	-4.7	-5.9
Total	**32**	**35**	**9.5**	**-10.8**
Italy				
Precose/Glucobay/Glucor	5	6	13.1	0.8
Glicobase	0	0	-8.1	-13.4
Total	**6**	**7**	**11.7**	**-0.3**
Spain				
Precose/Glucobay/Glucor	13	16	18.4	-2.5
Glumida	6	7	15.6	-5.6
Glyset/Diastabol	4	4	-2.5	12.8
Plumarol	2	3	16.9	---
Total	**26**	**30**	**14.2**	**0.8**
UK				
Precose/Glucobay/Glucor	4	3	-4.2	-16.3
Total	**4**	**3**	**-4.2**	**-16.3**

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Brand analysis

Table 4.22 shows the launch dates and patent expiries of the leading branded AGIs. Basen is included in this table as although no sales figures are provided it is the dominant product in Japan. Each of these three products is profiled in this report.

Table 4.22: Branded AGIs

US brand	Generic	Marketing company	First global launch date	US patent expiry
Precose	acarbose	Bayer	1990	2007
Basen	voglibose	Takeda	1994	n/a
Glyset	miglitol	Pfizer/Sanofi	1996	2009

n/a = not applicable

Source: Business Insights

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Precose/Glucobay (acarbose)

The first AGI to reach the market was Bayer's Precose (acarbose), which was first launched in Germany in 1990 and has since been launched throughout the EU, Latin America and Japan (1993) under the brand names Glucobay, Glucor and Prandase. The FDA granted approval in the US in 1996.

As a monotherapy, Precose is indicated as an adjunct to diet to lower blood glucose in patients with type 2 diabetes whose hyperglycemia has not been adequately controlled with diet alone. Precose is also indicated for use in combination with a sulfonylurea when diet plus either acarbose or a sulfonylurea have not resulted in adequate glycemic control. In addition, the FDA approved the use of Precose in combination with insulin or metformin in the US in November 1998.

Precose is the market leading AGI in each of the six markets analysed, but the AGI class as a whole represents only 2.3% of the total oral antidiabetic market.

Figure 4.31: Precose/Glucobay SWOT analysis

Strengths	Weaknesses
• Leading AGI in the US and EU • AGIs not associated with weight gain or hypoglycemia • Can be used in combination with a sulfonylurea, metformin or insulin	• Low efficacy in comparison to other OADs • Compliance issues due to 3 times daily dosing • AGI class associated with GI side-effects that can discourage use
Opportunities	**Threats**
• Increased use in combination with insulin following expansion of type 2 diabetes managed with insulin	• Competition from Basen in Japan • Competition from generic OADs, e.g. metformin • Uptake of newer, more efficacious OADs

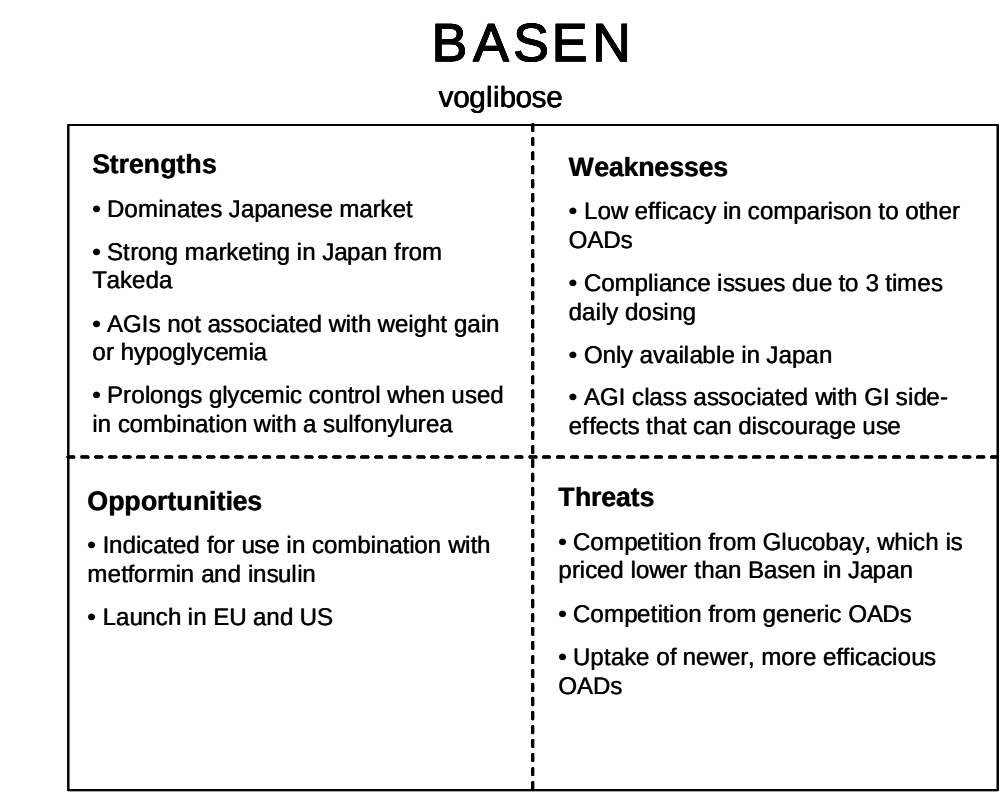
Source: Business Insights

Business Insights Ltd

Basen (voglibose)

Basen was developed by Takeda and launched in Japan in 1994 one year after the launch of Bayer's Glucobay (acarbose) in this market. Despite being launched at a higher price to Glucobay, Basen has proved extremely successful in Japan due to the popularity of this class of drugs in this market and the strong marketing support from Takeda.

Figure 4.32: Basen SWOT analysis



Source: Business Insights

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Glyset/Diastabol (miglitol)

Pharmacia & Upjohn Inc. (now part of Pfizer) was granted marketing rights to Bayer's miglitol in the United States, Canada, Australia, and New Zealand under the trade name Glyset. Sanofi (now Sanofi-Aventis) holds the European rights to miglitol and it is branded Diastabol in the EU. Bayer recently granted Sanwa Kagaku the Japanese development rights to the product. Glyset/Diastabol has not shown strong sales since its launch in 1996, mirroring other products in its class in the US and Europe, probably because of their late entry onto the market.

Other OAD products (the prandial glucose regulators)

Prandial glucose regulators (PGR), which were launched in 1998, are the newest class of drugs in the diabetes market and, like sulfonylureas, these agents stimulate insulin release from the pancreas. However PGRs act through a different receptor to that of the sulfonylureas and only stimulate insulin release in the presence of glucose. In addition, PGRs exhibit a quick onset and short duration of action, the effect of which is concentrated around meal times.

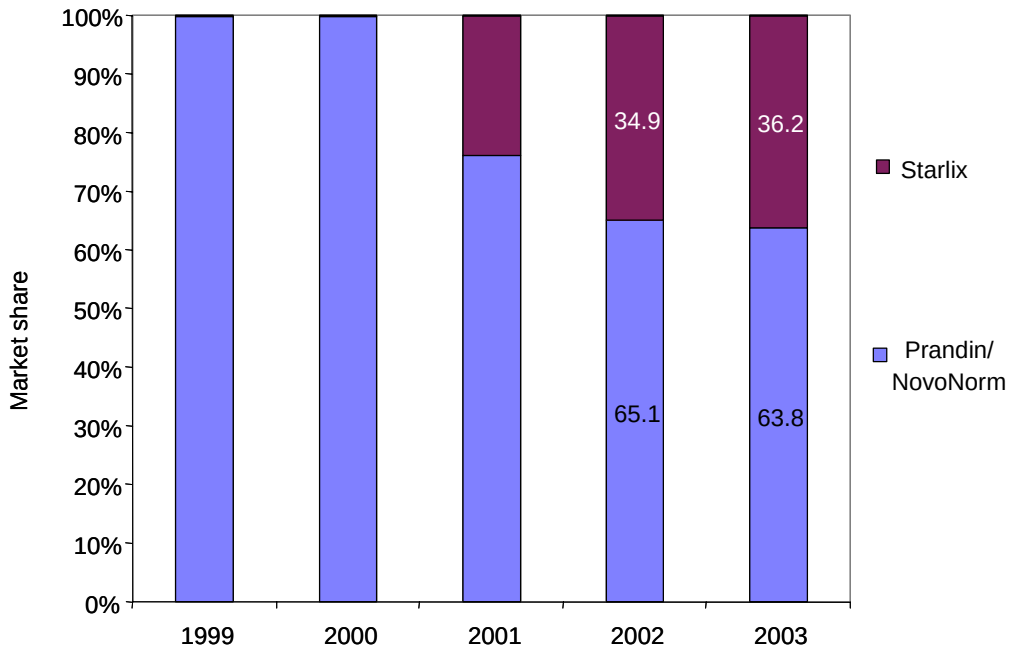
The advantage of the action of PGRs is that the risk of hypoglycemia is vastly reduced, although the disadvantage is that they require multiple daily dosing (i.e. with each meal), which can reduce compliance. Furthermore, these agents are more expensive than the highly genericized sulfonylureas in a majority of the major pharmaceutical markets.

Brand market shares and sales

The first PGR to enter the market was Novo Nordisk's repaglinide, which was launched in 1998 and is marketed under the brand name Prandin in the US and NovoNorm in the EU. In January 2001 Novartis received marketing approval from the FDA for its version of nateglinide, branded Starlix, for the treatment of type 2 diabetes as both a monotherapy and in combination with metformin for patients whose blood glucose has not been controlled by diet and exercise. This was followed in 1999 by the launch of nateglinide in Japan, which is sold as Starsis by Yamanouchi and as Fastic by HMR Nippon.

From its 99% US/European market share in 1999 and 2000, Prandin has lost some of it market share to Starlix following its launch in 2001. However, Prandin was still the market leader in 2003 with 63.8%. There is no generic competition on the market as yet with Prandin patent protected until 2006 and Starlix until 2012.

Figure 4.33: US/European* market share of leading PGRs (%), 1999-2003



* France, Germany, Italy, Spain, UK

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NovoNorm (Prandin's European name) is also the leading PGR in each of the five European markets analyzed – France, Germany, Italy, Spain and UK. In France and Italy Starlix has not been launched. Overall, the PGR class does not record high sales compared other OAD classes.

Table 4.23: Sales of leading PGRs by country (%), 2002-2003

	2002	2003	Growth (%) 2002-2003	CAGR (%) 1999-2003
US				
Prandin/NovoNorm	116	123	5.8	8.6
Starlix	80	97	20.9	---
Total	**196**	**220**	**12.0**	**25.7**
Germany				
Prandin/Novonorm	20	26	31.8	39.1
Starlix	7	11	42.1	---
Total	**27**	**37**	**34.6**	**51.4**
France				
Prandin/Novonorm	14	19	35.6	---
Total	**14**	**19**	**35.9**	**244.2**
Spain				
Prandin/Novonorm	10	17	69.3	170.3
Starlix	1	1	36.1	---
Total	**11**	**18**	**66.2**	**175.7**
Italy				
Prandin/Novonorm	6	9	56.7	125.2
Total	**6**	**9**	**56.7**	**125.2**
UK				
Prandin/Novonorm	3	3	-21.0	25.5
Starlix	2	2	37.5	---
Total	**5**	**5**	**-1.3**	**47.0**

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Brand analysis

There are two prandial glucose regulators currently on the market, both of which are still under patent in the US. These two products are Novo Nordisk's Prandin/NovoNorm, and Starlix, licensed to Novartis outside of Japan. Prandin was the first of these PGRs to be launch in 1998 but its patent is due to expire in 2006, at which point sales of this product will suffer from generic competition. Starlix was second to market but it is patent protected in the US until 2012, although sales will still suffer should generic forms of Prandin be launched.

Table 4.24 lists these branded PGRs along with launch and US patent expiry dates.

Table 4.24: Branded PGRs

US brand	Generic	Marketing companies	First global launch date	US patent expiry
Prandin/NovoNorm	repaglinide	Novo Nordisk	1998	2006
Starlix	nateglinide	Yamanouchi /HMR Nippon /Novartis	1999	2012

Source: Business Insights

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Prandin/NovoNorm (repaglinide)

Prandin (repaglinide) was the first PGR to be approved, and was launched in the US in 1998. Prandin was developed by Boehringer Ingelheim and was out-licensed to Novo Nordisk for worldwide development and marketing. Outside of the US the drug is called NovoNorm. Novo Nordisk and Fournier Pharma announced in April 2003 that they had signed an agreement to co-market repaglinide in the EU. Novo Nordisk will market the product under the brand name NovoNorm, while Fournier Pharma will market the PGR under the US brand name Prandin. Fournier Pharma is expected to give Novo Nordisk access the general practioner area where most prescriptions for OADs are made, as Novo Nordisk's experience has been largely restricted to the specialist injectable insulins market rather then the OAD market.

The key advantage of repaglinide is that it allows patients to vary their meal times. Prandin is only minimally excreted by the kidney, making it advantageous for diabetic patients with decreased kidney function. According to the National Kidney Foundation, almost all patients with type 1 diabetes develop some evidence of functional change in the kidneys two to five years after diagnosis. About 30–40% progress to more serious kidney disease, usually within 10–30 years. The course of type 2 diabetes is less well defined but is believed to follow a similar course, except that it occurs at an older age.

A SWOT analysis of the drug is shown in Figure 4.34.

Figure 4.34: Prandin/NovoNorm SWOT analysis

Strengths	Weaknesses
• Reached market before Starlix, and is cheaper and has greater efficacy when used with metformin than Starlix • Safe for use in patients with renal failure • Prandin allows patients to vary mealtimes • Can be used in combination with metforming and TZDs	• PGR class latest to market • PGRs shown poor uptake to date • Novo Nordisk preferentially marketing its insulin portfolio • Requires 3 times daily dozing
Opportunities	**Threats**
• Increased marketing support in the EU following co-marketing agreement with Fournier Pharma • Promotion as PGR of choice in patients receiving metformin •Development of single pill combination of Prandin and metformin	• Competition from Starlix • Competition from other OADs and generics • Patent expiry in 2006 in the US and subsequent launch of generics

Source: Business Insights

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In 2002, Prandin was approved for use in combination therapy with GSK's Avandia (rosiglitazone) or Takeda/Lilly's Actos (pioglitazone), both of which are insulin sensitizers. Prandin, an insulin secretagog, rapidly stimulates insulin secretion whereas insulin sensitizers primarily improve the body's response to the hormone. Recent studies support a combination approach showing that among patients previously poorly controlled with monotherapy with either a sulfonylurea or metformin, the combination of Prandin with a sensitizer resulted in better blood glucose control than monotherapy with either of these agents alone.

Overall, the clinical trials carried out on Prandin demonstrate the drug to offer type 2 diabetics a more advantageous therapy than many of the older OADs. However, the

PGR class has not performed particularly well, and it is likely that these drugs have suffered from their relatively late arrival on the market and lack of strong promotion. The competition in the OAD market intensified with the US launch of generic versions of metformin, the most commonly used OAD, in January 2002 following the US patent expiry of Glucophag, marketed in the US by BMS.

Starlix (nateglinide)

Starlix (nateglinide) was developed by the Japan-based Ajinomoto Company, which licensed the product to Yamanouchi and Sankyo where it was launched in Japan in 1999 under the brand names, Starsis and Fastic, respectively. Outside of Japan, Starlix was licensed to Novartis and the product was approved in 2001 in most of the major EU markets, with the exception of France and Italy, where it is also co-marketed with Merck KGaA. Starlix was approved in December 2000 in the US.

Figure 4.35: Starlix SWOT analysis

Strengths	Weaknesses
• Protected by derivative patents in the US until 2012 • Good marketing support in Japan • Safe for use in patients with renal failure as drug is not excreted through the kidneys	• AGI class latest to market and has shown relatively poor uptake to date • Lower efficacy when used in combination with metformin than Prandin • Requires 3 times daily dosing • Priced higher than Prandin
Opportunities	**Threats**
• Launch in additional markets, including France and Italy • Approval for use in combination with TZDs • Positive results from NAVIGATOR trial supporting use in the prevention of type 2 diabetes	• Competition from Prandin •Competition from other OAD classes •Competition from generic repaglinide in the US from 2005 • Main product patents expire in 2006, even though derivative patents run until 2012

Source: Business Insights

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Although Starlix is protected by derivative patents until 2012, the main product patents expire in Europe and the US in March 2006. Therefore the product may be threatened by generic competition from this date if the derivative patents are overturned. Starlix may also be impacted by the entry of generic versions of Prandin, which may enter the European market in early 2005 after its main product patents expire in December 2004.

CHAPTER 5

Leading players in the diabetes market

Chapter 5 Leading players in the diabetes market

Summary

- The insulin market is dominated by Eli Lilly, Novo Nordisk and Sanofi-Aventis, while in the OAD market Takeda, GSK and BMS are the key players.
- Eli Lilly is the leader in the US insulin market, with its Humulin and Humalog range of products. The most promising projects in Eli Lilly's pipeline are Exenatide (a GLP-1 compound) expected for launch in 2005, and an inhalable insulin, AIR, although it will most likely be third to market behind Exubera and AIR iDMS.
- Novo Nordisk is the leader in the European insulin markets, holding a 46.6% market share in 2003. The company has also increased its US share to 20.5%. Novo Nordisk's R&D pipeline is very strong and includes AERx iDMS, an inhalable insulin expected to be launched in 2007.
- Sanofi-Aventis has a 17.2% share of the US insulin market (through Lantus sales) and 19.6% in Europe, and is also a key player in the OAD market through sales of Amaryl. Sanofi-Aventis has a number of products in development, most notably Exubera (with Pfizer/Nektar), likely to be the first inhalable insulin to market.
- Takeda is the leading company in the OAD market but its sales are expected to decline when Actos loses patent in 2006, and generic competition enters the market. Takeda has five compounds in development although none are expected to reach the market before 2008.
- GSK recorded 2003 sales of $1.5bn for Avandia and Avandamet. GSK plans to launch Avandaryl (Avandia + Amaryl) in 2004, but besides this, GSK's late-stage diabetes pipeline is thin. However, GSK has several projects in phase I trials.
- BMS's diabetes sales have declined significantly in recent years due to the US patent expiry of Glucophage. BMS's diabetes pipeline has been built through in-licensing. The most promising drug in the pipeline is Muraglitazar, a dual PPAR agonist in phase III trials, and it is the most advanced compound of its type in development. PPAR agonists are expected to have blockbuster potential.

Introduction

Chapter 3 will provide an overview of the diabetes portfolios of the leading players in the diabetes market, assessing both those products currently marketed and those in R&D. The companies that will be profiled in this report are listed in Table 5.25.

Table 5.25: US/European* diabetes market share by company (%), 2002-2003

	2002	2003	Growth (%) 2002-2003	CAGR (%) 1999-2003
Lilly	18.5	17.6	10.2	11.6
Takeda	15.8	16.1	18.6	132.7
GlaxoSmithKline	13.4	14.3	24.8	85.5
Novo Nordisk	11.8	13.3	31.1	16.4
Aventis (now Sanofi-Aventis)	8.5	11.0	50.4	28.1
Bristol-Myers Squibb	14.0	10.7	-11.5	-3.0
Pfizer	4.4	3.8	0.5	-23.3
Novartis	1.5	1.5	13.2	49.0
Merck KGaA	1.0	1.2	38.4	10.6
Others	11.0	10.6	-3.6	---

* France, Germany, Italy, Spain, UK

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The analysis will also look at how important each company's diabetes portfolio is for the company revenue as a whole, and how they are shaping themselves for the future in terms of their R&D pipeline.

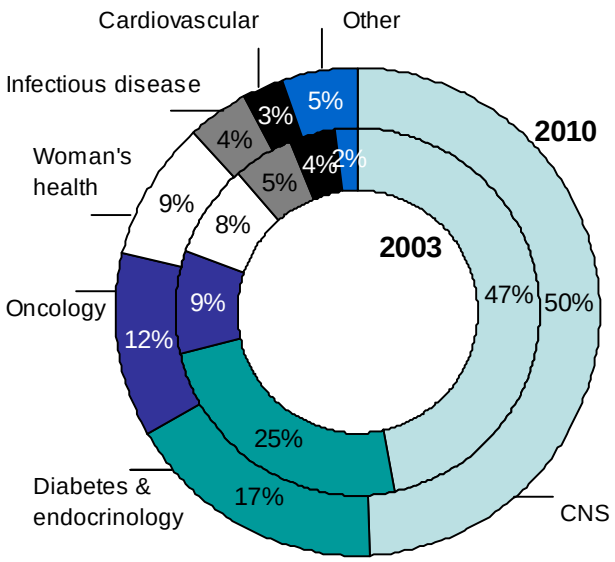
The company profiles will start by assessing the three major companies in the insulin market – Eli Lilly, Novo Nordisk and Sanofi-Aventis. This will be followed by analysis of the major companies in the OAD market – Takeda, GSK and BMS, along with Pfizer, Novartis and Merck KGaA.

Eli Lilly

Therapeutic focus

Eli Lilly's largest franchise is the central nervous system (CNS) with 47% of 2003 sales coming from this area (Figure 5.36), and this is set to continue through the forecast period to 2010, when half of all sales are projected to come from this franchise. The diabetes and endocrinology franchise, Lilly's second largest focus in terms of sales, is projected to decline from a 25% share in 2003 to 17% in 2010. Other areas such as oncology and woman's health will see an increase through this period as Lilly tries to broaden its therapeutic focus rather than relying on its largest two for sales.

Figure 5.36: Eli Lilly's therapeutic focus, 2003-2010



Source: Company reports & information; Business Insights

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Insulin market share

Eli Lilly has the advantage in the diabetes market of being the leading company in the US. The US market is both the largest volume and highest value diabetes market globally, with high price premiums being paid for novel, branded products. An additional advantage of US market leadership is that there is a high degree of physician loyalty in this therapy area, meaning that new diabetes products from Eli Lilly should have high market penetration. However, the OAD market is by far the largest segment of the US diabetes market, yet Eli Lilly's has just one marketed OAD, Actos, which is co-marketed with Takeda (Takeda receives the majority of US sales of this product). Eli Lilly also has just one OAD in development, compared to Novo Nordisk's five. Expanding its diabetes portfolio to include more OADs would boost its growth and reduce reliance on a single segment of the market.

Table 5.26: US Insulin Market Share by Company (%), 2002-2003

	2002	2003	Growth (%) 2002-2003	CAGR (%) 1999-2003
Lilly	71.2	62.2	6.8	10.4
Novo Nordisk	17.7	20.5	42.0	22.7
Aventis	11.1	17.2	89.2	---

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Europe, in contrast, is the most attractive market for insulin as the market is larger in proportion to the diabetic population size. However, the penetration of Lilly's diabetes products in the US is not mirrored in Europe or Japan where Novo Nordisk is the dominant company. Alliances with companies in these markets would help Eli Lilly gain more revenue from its insulin dominated pipeline in these areas.

Marketed products

Lilly's diabetes portfolio is very strong with two insulin products, Humulin and Humalog, and Actos, an OAD in-licensed from Takeda and co-promoted in the US. However, Takeda receives the majority of Actos revenue and the co-promotion deal ends in September 2006. Increased uptake Humalog is currently driving the growth of Lilly's diabetes portfolio.

Table 5.27: US/European* sales of Eli Lilly's marketed diabetes portfolio ($m), 2002-2003

Brand	Drug class	US patent expiry	2002	2003
Humulin	human insulin	2001	824	798
Humalog	human insulin	2014	804	997
Actos	TZD	2006	6	1
Iletin	animal insulin	Expired	3	2
Other diabetes		20	28	
Total			**1,657**	**1,826**

* France, Germany, Italy, Spain, UK

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R&D pipeline

Eli Lilly currently has five compounds in development for the treatment of diabetes, each of which has high revenue potential. A sixth compound, the oral antidiabetic Oralin, has been terminated and the rights returned to Generex in May 2003.

Exenatide is expected to be the first of these pipeline products to be launched in 2005, and is currently in the registration phase with the US FDA. Global sales of Exenatide are expected to reach $316m in 2007, and $730m by 2010.

Table 5.28 shows the expected launch year of each of Lilly's development compounds, as well as forecast sales for 2007 and 2010.

Table 5.28: Projected sales of Eli Lilly's diabetes R&D pipeline ($m), 2007 & 2010

Brand	Generic	Stage	2007	2010	Launch year
Exenatide	synthetic exendin 4	Registration	316	730	2005
Ruboxistaurin	n/a	Phase III	150	360	2006
Pulmonary insulin	n/a	Phase II	n/l	161	2008
LY-818	n/a	Phase III	n/l	n/l	>2010
LY-929	n/a	Phase I	n/l	n/l	>2010
Oralin	n/a	Terminated	n/l	n/l	n/a

n/a = not applicable; n/l = not launched

Source: Company reported information; IDdb, August 2004, Copyright Thomson Scientific; Business Insights

Exenatide (synthetic exendin-4)

The natural hormone GLP-1 (glucagon-like peptide-1) has a major effect in enhancing the release of insulin in response to a glucose stimulus and coincidentally suppressing secretion of glucagon. As a result, injections of this hormone lower blood glucose levels in both type 1 and type 2 diabetes patients. Exenatide (AC2993), from Amylin, is one of a new class of compounds that have similar action to GLP-1. In clinical trials Exenatide has been shown to reduce blood glucose levels in patients where other drugs have failed to do so.

In September 2002, Lilly and Amylin announced that they had signed a global agreement to collaborate on the development and commercialization of AC2993. Lilly previously had its own GLP-1 analog in development, but this project is thought to have been terminated in favor of Amylin's compound. AC2993 is currently under regulatory review in the US, after submission in Q2 2004, and launch is expected in the second half of 2005.

The drug will be in competition with several other compounds in development, including Novartis' LAF-237, a compound (DPP-IV inhibitor) which inhibits the breakdown of GLP-1 resulting in raised endogenous GLP-1 levels. This is in contrast to Lilly's product which, as a GLP-1 analog, can theoretically be dosed up to produce any desired level in the body. The DPP-IV inhibitors have an oral method of administration that will give such compounds an added advantage over GLP-1 products that require injection administration. Novo Nordisk has a similar GLP-1 product to Lilly's, NN-2211, which is currently in Phase II development.

Ruboxistaurin

Lilly's investigational protein kinase C beta (PKC beta) inhibitor is being studied as a possible treatment for multiple diabetic microvascular complications, including diabetic retinopathy and diabetic peripheral neuropathy. Lilly anticipates submission at some point in 2004, depending on successful phase III results. In Japan Ruboxistaurin will be co-developed and co-marketed with Takeda.

Pulmonary insulin (AIR)

Inhaled insulin fulfills one of the key unmet needs in the diabetes market, with many type 2 patients put off from switching to insulin therapy due to the lack of alternative to injection delivery. In April 2001 Alkermes and Lilly signed a broad, mutually exclusive agreement to develop inhaled formulations of insulin, including short- and long-acting forms and other potential products for the treatment of diabetes based on Alkermes' AIR pulmonary drug delivery system.

However, there have been concerns over the safety and efficacy of inhaled insulin devices. Exubera, an inhaled insulin from Pfizer and Aventis, has been linked with pulmonary fibrosis, and a less serious side effect seen in clinical trials of inhaled insulins is a mild to moderate cough. However, on August 10 2004, Alkermes announced that Lilly had made a decision to continue funding the pulmonary insulin project following favorable clinical data. The product is now in phase II clinical trials.

Should this product eventually reach the market, competition will come from other inhaled insulins in development – Exubera, expected to be the first inhaled insulin to market, and Aradigm/Novo Nordisk's AERx Diabetes management system, which is also expected to beat AIR to the market by launching in 2007. In addition, oral insulins represent a threat to inhaled products, should they reach market, although three of the most advanced oral insulins in development have recently been returned to their originators by big pharma partners.

Oralin

Oralin (US)/Oralgen (Canada) is currently in Phase II trials in Canada for type 1 and 2 diabetes with Generex Biotechnology Corporation. Following a September 2000 agreement, Generex partnered with Eli Lilly for the development of the product in the US. However, in May 2003, it was announced that Generex and Lilly had agreed to end their development and license agreement for Oralin.

LY-818 (naveglitazar)

LY-818 is a PPAR agonist and was in-licensed from Ligand Pharmaceuticals in April 2002. Lilly is developing the once-daily drug as a potential treatment for type 2 diabetes and began phase III studies in March 2004. Lilly has another compound of this type in phase I development, also in-licensed from Ligand: LY-929, which is being developed for the treatment of type 2 diabetes, metabolic diseases and dyslipidemias.

The development of naveglitazar has been delayed for up to two years, as a result of safety concerns surrounding the PPAR agonist class that were raised by the FDA. The FDA has introduced guidelines calling for any company testing a PPAR compound in humans for longer than six months to carry out two years of cancer studies in mice or rats prior to human trials. An FDA review of some PPAR drug data in rodents has raised concerns that compounds in the class might cause cancer. Launch of this compound is now not expected until after 2010, and the negative publicity surrounding this class of drugs, as well as the delayed launch of the products, is expected to have downgraded the potential of the drug.

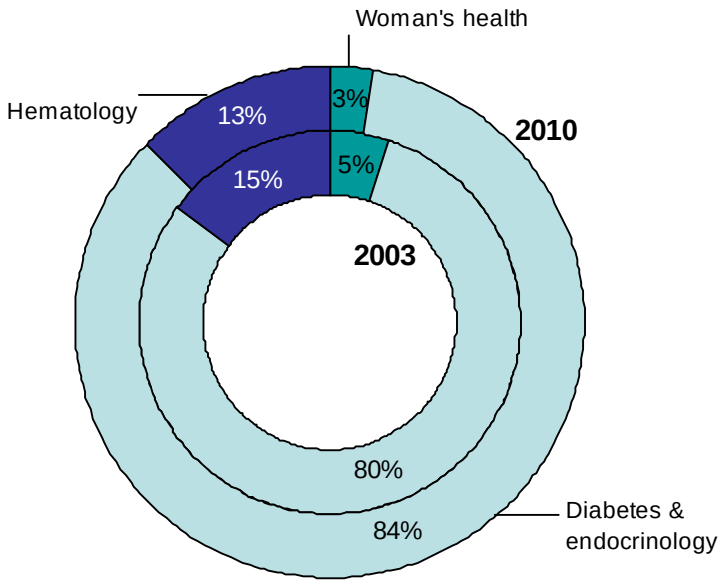
Novo Nordisk

Therapeutic focus

Novo Nordisk has three therapy area franchises, of which diabetes and endocrinology is by far the largest, accounting for 80% of the company's total sales in 2003. This focus is set to continue through the forecast period, as illustrated in Figure 5.37.

The company has thus far focused primarily on the insulin market, but several of the seven development products are oral anti-diabetics (OADs). This illustrates Novo Nordisk's efforts to broaden its portfolio in diabetes, and in particular target the large US market for OADs.

Figure 5.37: Novo Nordisk's therapeutic focus, 2003 and 2010



Source: Company reports & information; Business Insights

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Insulin market share

Novo Nordisk is the European leader in the insulin market, commanding a 46.6% share of the European insulin market in 2003. Novo Nordisk has also historically had a strong presence in Japan. This trend is set to continue with a strong diabetes pipeline, and a high degree of patient and physician loyalty in this therapy area.

Table 5.29: European* insulin market share by company (%), 2002-2003

	2002	2003	Growth (%) 2002-2003	CAGR (%) 1999-2003
Novo Nordisk	47.7	46.6	30.1	13.1
Lilly	27.5	25.3	22.9	15.9
Aventis	16.7	19.6	56.6	17.3

* France, Germany, Italy, Spain, UK

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In the US Novo Nordisk trails Eli Lilly in terms of insulin sales but Novo Nordisk has identified greater penetration of the US market as the way to drive growth. Its diabetes products have been specially tailored to the US market, and the company has significantly expanded its sales force in this area. The most important event, however, is its marketing deal with Wal-Mart, which is expected to increase sales and the company's visibility in the US.

Additionally the company has strengthened its presence in Latin America, where 12m people are believed to have diabetes, by acquiring the Brazilian diabetes specialist Biobras in 2002.

Marketed products

As can be expected for a company heavily dependent on its diabetes and endocrinology franchise, Novo Nordisk's marketed portfolio for diabetes is very strong (Table 5.30).

Table 5.30: US/European* sales of Novo Nordisk's marketed diabetes portfolio ($m), 2002-2003

Brand	Drug class	2002	2003
NovoLin	human insulin	715	831
NovoNorm/Prandin	PGR	159	179
NovoRapid/NovoLog	human insulin	111	304
NovoMix 30	human insulin	3	15
Levemir	human insulin	0	0
Other diabetes		69	58
Total		**1,057**	**1,387**

* France, Germany, Italy, Spain, UK

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NovoLin remains the company's primary diabetes product, despite the fact that it has been on the market since 1988. The growth in sales of this brand has sbeen maintained by the variety of products available within the brand and the increasing patient population. Since the 2001 launch of NovoLog, the rapid onset injection insulin analog, it is expected that patients on NovoLin will be switched to NovoLog, and this erosion will intensify with the roll-out of Novo's other analogs, NovoMix and Levemir – a long-acting insulin analog.

The main threat to the future sales of Novo Nordisk's brands is Eli Lilly and Aventis insulins, although the geographical separation of Lilly and Novo Nordisk sales has thus far protected Novo's brands from losing out to Lilly to some degree. The newer inhaled and oral insulin products currently in development by several companies are expected to impact the future sales of these injectable insulins, with the rapid-acting insulins most

likely to be affected. However, Novo Nordisk is currently developing its own inhaled insulin product, AERx iDMS.

R&D pipeline

Novo Nordisk's diabetes and endocrinology franchise is the only area in which the company is expected to launch novel pipeline products until 2010. The company is expanding into the OAD market in addition to its retained focus on insulins. The lack of an oral insulin had been seen as a weakness in Novo Nordisk's pipeline, but the recent setbacks to development of oral products, with several major diabetes players returning rights of in-licensed candidates to their originators, puts Novo Nordisk back at the head of the race to commercialize a non-invasive method of insulin delivery with AERx iDMS.

Table 5.31: Projected sales of Novo Nordisk's diabetes R&D pipeline ($m), 2007 & 2010

Brand	Generic	Stage	2007	2010	Launch year
NovoMix 50 & 70	insulin aspart	Phase III	70	126	2004
AERx iDMS	human insulin	Phase III	100	776	2007
NN2344	balaglitazone	Phase II	15	45	2007
NN2211 (GLP-1)	liraglutide	Phase II	200	602	2007
NN344	insulin analog	Phase I	n/l	n/l	>2010
NN2501	n/a	Phase I	n/l	n/l	>2010
NN622	ragaglitazar	Terminated	n/a	n/a	n/a

n/a, n/l: not applicable/available, not launched

Source: Company Reported Information; IDdb, August 2004, Copyright Thomson Scientific; Business Insights

NovoMix 50 and 70 (NN1185): Injectable insulin formulations

These two products are premixed formulations of the rapid-acting insulin analog, insulin aspart. Injecting three times each day with these products will provide greater glycemic control without increasing the risk of hypoglycemia. In July 2004 Novo Nordisk filed for marketing approval of NovoMix 50 and NovoMix 70 in Europe as well as for NovoMix 50 in Japan. NovoMix 50 and NovoMix 70 are completing the Novo Nordisk

portfolio of premix insulin analogues (includes NovoMix 30) that provides a mix of both rapid-acting and intermediate-acting insulin effect. Upon approval, Novo Nordisk will be the only company providing the patients with a wide range of premix insulin analogues.

AERx iDMS (NN1998): An inhaled insulin

The AERx insulin Diabetes Management System (AERx iDMS) is an insulin inhalation system that is being developed for use in type 1 and type 2 diabetics for glycemic control. It meets the key unmet need in the diabetes market, which is for a non-invasive method of insulin delivery, and thus the patient potential for AERx is large. AERx is differentiated from other inhalation devices in development because of its inhaler technology, which employs active breath control to deliver insulin at the optimum time and records inhaler use for physicians.

Aradigm originally developed the drug and entered a worldwide collaboration agreement with Novo Nordisk in June 1998. Phase III trials of AERx were initiated in September 2002 after successful Phase II trials found that AERx iDMS achieved the same level of glycemic control in type II diabetics as intensive multiple injection therapy.

Launch of AERx is expected in 2006 and it is likely to be the second inhaled insulin to market behind Exubera. However, promising clinical data and greater ease-of-use compared to Exubera, as well as Exubera's well publicised safety concerns, should help AERx iDMS to become the leading non-invasive insulin.

Liraglutide (NN2211)

NN2211 is a stable analog of the natural hormone GLP-1 (glucagon-like peptide-1), which enhances the release of insulin in response to a glucose stimulus. Injections of GLP-1 work to lower blood glucose levels, and so its potential in diabetes therapy is being investigated. Phase II trials have concluded with phase III to be initiated in mid-2004 and a possible launch in 2007.

The glucose-dependent action of GLP-1 has the advantage of reducing the need for glucose monitoring in diabetes patients, and also reducing the risk of hypoglycaemia, which is an unwanted side effect of many anti-diabetes medications. It also improves the patient's ability to manage weight, a very important problem during current treatment of type 2 diabetes.

During preclinical testing, Liraglutide (NN2211) increased the ß-cell mass in animal models of type 2 diabetes leading to speculations about its potential ß-cell regeneration capacity.

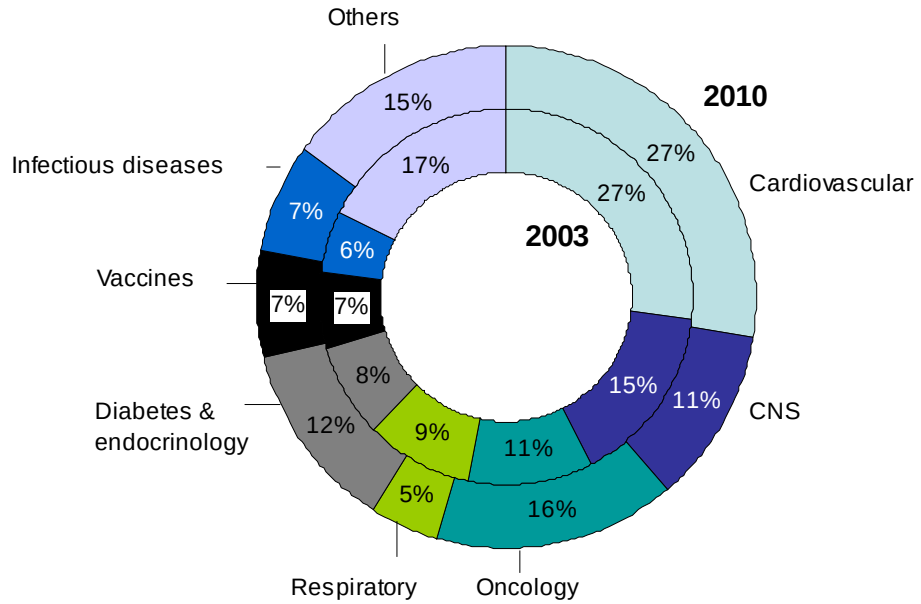
Potential competition for Novo Nordisk's GLP-1 analog is Amylin/Eli Lilly's GLP-1 analog, Exenatide (AC-2993), which was submitted for regulatory review in Q2 2004. Novartis' Phase II project LAF-237 will be another competitor to NN2211. LAF-237 is a compound belonging to the dipeptidyl peptidase IV inhibitor (DPP-IV) class that inhibits the breakdown of GLP-1, resulting in raised endogenous GLP-1 levels. This is in contrast to Novo Nordisk's product which, as a GLP-1 analog, can theoretically be dosed up to produce any desired level in the body. According to Novartis, LAF-237 will be filed for regulatory approval in 2006. A key advantage the DPP-IV inhibitors are expected to have over GLP-1 analogs is their oral method of administration.

Sanofi-Aventis

Therapeutic focus

Figure 5.38 illustrates breakdown in terms of sales of Sanofi-Aventis' franchises in 2003 and forecast sales in 2010. For 2003, Aventis sales and Sanofi sales have been combined.

Figure 5.38: Sanofi-Aventis' therapeutic focus, 2003 & 2010



Source: Company reports & information; Business Insights

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The three therapy areas where Sanofi and Aventis are both active are cardiovascular, CNS and oncology. Not surprisingly, these three areas were the largest in 2003 and most important therapeutic areas for the new company, with cardiovascular standing out as the largest franchise. Cardiovascular was the leading franchise for both companies before the merger. The smaller four franchises—respiratory, diabetes & endocrinology, vaccines and infectious diseases—are derived mainly from Aventis, with Sanofi contributing some pipeline products. At this early stage it is unclear if Sanofi-Aventis

will retain an interest in all of these areas, or if it will withdraw from some markets to avoid stretching resources too thinly.

Sanofi-Aventis' diabetes & endocrinology franchise benefits from Aventis' established insulin and diabetes portfolio and the promising obesity development compounds from Sanofi. This therapy area is expected to overtake CNS to become the third largest franchise in 2010. It should be noted that the future growth of this franchise is high risk, as both Exubera and Acomplia are unproven R&D drugs and there are potential safety concerns about Exubera.

Insulin and OAD market shares

With the launch of long-acting insulin, Lantus, in 2001 and now the approval of rapid-acting insulin, Apidra, Sanofi-Aventis is beginning to compete with Novo Nordisk and Eli Lilly, the leading insulin companies. In just three years Aventis captured a 17.2% of the US insulin market, mostly at the expense of Lilly, and its sales of Amaryl rank it fourth in the combined US and Europe OAD market. Additionally, Aventis' recent merger with Sanofi-Synthélabo is likely to result in increased marketing of their products in Europe in particular, which will intensify competition with Novo Nordisk. Aventis' investment in diabetes in recent years also made the company an attractive licensing partner for Pfizer/Nektar Therapeutics' Exubera (inhaled insulin).

Sanofi-Aventis' diabetes & endocrinology marketed portfolio comes almost entirely from Aventis. Although Amaryl has been the company's leading drug up until 2003, it is the high profile launch and fast uptake of long acting insulin, Lantus that has helped the company to build a reputation as a leading diabetes company. Lantus has grown by over 100% over a one-year period, 2002 to 2003.

Table 5.32 shows the sales figures for Sanofi-Aventis' marketed products for 2002 and 2003.

Table 5.32: US/European* sales of Sanofi-Aventis' marketed diabetes portfolio ($m), 2002-2003

Brand	Generic	US patent expiry	2002	2003
Lantus	insulin glargine	2014	263	526
Amaryl	glimepiride	2005	314	399
Insuman	human insulin	n/a	143	175
Other diabetes	n/a	n/a	55	57
Total			**775**	**1,157**

* France, Germany, Italy, Spain, UK; n/a: not available

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R&D pipeline

Sanofi-Aventis has few early-stage pipeline diabetes products following the termination of DiaPep277 in 2004, with the company instead focusing on its pipeline products for obesity. Sanofi-Aventis's late stage pipeline carries high risk because of the uncertainty surrounding clinical safety data of inhaled insulin Exubera, and thus its successful launch. The company has however just had approval for Apidra, a fast-acting insulin to rival NovoLog and Humalog, and this provides an ideal partner drug for Lantus, the long acting basal insulin. Another recent approval in August 2004 for Sanofi-Aventis is its OptiClik pen system to rival those of Eli Lilly and Novo Nordisk.

Table 5.33: Projected sales of Sanofi-Aventis' diabetes R&D pipeline ($m), 2003 & 2010

Brand/code	Generic	Stage	2007	2010	Launch year
Apidra	glulisine	Approved	222	403	2004
Exubera	inhalable insulin	Phase III	260	548	2005
DiaPep277	n/a	Terminated	n/l	n/l	n/a

Source: Business Insights, company reported data information Business Insights Ltd

Apidra, profiled earlier in the report, and Exubera have significant sales potential as highlighted with 2010 forecasts of $403m and $548m respectively.

Exubera

Exubera is an inhaled insulin formulation which is being developed in collaboration with Pfizer and Nektar Therapeutics for the treatment of type 1 and type 2 diabetes. While initial Phase III trials of Exubera were completed in July 2001, there has been significant health concerns stemming from a case of pulmonary fibrosis in a patient treated with Exubera, which delayed the drug's development while additional safety data was collected. Pulmonary fibrosis is a condition in which the tissue of the lung becomes scarred and, depending on the severity, can progress to heart failure or even death. However, after a two year safety study, Pfizer and Aventis announced in March 2004 that the European Medicines Evaluation Agency (EMEA) had accepted the filing of a marketing authorization application for Exubera, but in May 2004 it was believed that European experts assessing this marketing application had stated that Exubera was "not licensable at this time".

Exubera has a large patient potential given the high patient demand in both type 1 and type 2 diabetes for a less invasive delivery of insulin. Furthermore, patients are very excited at the rapid uptake of inhaled insulin as it reduces the burden of timing insulin administration and meal times. Exubera is expected to be the first inhalable insulin to market, although there are several competing products in late-stage development.

AERx iDMS, being developed by Novo Nordisk and currently in Phase III trials, is also an inhaled insulin product. Although Exubera will beat it to market, AERx has active breath control, enabling insulin to be delivered at the optimum moment, and can record insulin use facilitating physician monitoring. Another rival product is Eli Lilly/Alkermes' AIR pulmonary drug delivery system, which has the advantage of utilizing a small, convenient delivery device, can deliver a wide range of drug doses, and has the potential to provide sustained-release drug delivery.

DiaPep277

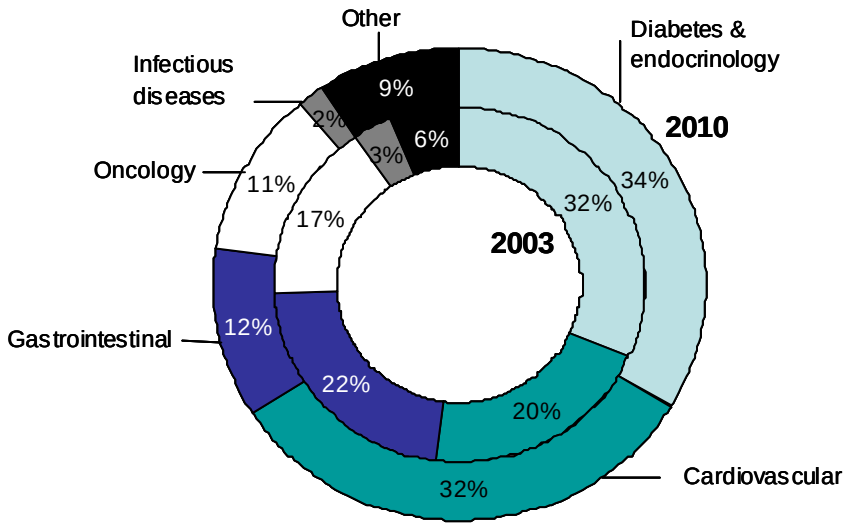
DiaPep277 was designed to stop the attack and destruction of healthy beta cells, an event that occurs in type 1 diabetes. The drug could thus be described as a diabetes vaccine. DiaPep277 was in phase II development with Peptor for the treatment of type 1 diabetics, and Aventis had in-licensed the marketing rights to the drug in August 2002. However, in May 2004 Aventis announced that this program had been terminated, stating that the project no longer met corporate business priority criteria.

Takeda

Therapeutic focus

Takeda focuses on five major therapy areas: diabetes and endocrinology, cardiovascular, gastrointestinal, oncology, and infectious diseases (Figure 5.39). The diabetes and endocrinology franchise generated the highest sales in 2003 with 32%, and by 2010 this is expected to rise to 34%. Its cardiovascular drugs are forecast to contribute 32% of total sales in 2010, with gastrointestinal 22%.

Figure 5.39: Takeda's therapeutic focus, 2003 & 2010



Source: Company reports & information; Business Insights

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OAD market share

Takeda is the leading company in terms of sales of OADs, with a 25.9% share of the market in the six countries analysed in 2003 – US, France, Germany, Italy, Spain and UK. For the whole diabetes market, including insulin products, Takeda is second-ranked behind Eli Lilly, with a market share of 16.1% in 2003. The growth in Takeda's market share has been rapid, with the company only holding a 1.0% share in 1999, and is due solely to sales of Actos which was launched in 1999.

The majority of Takeda sales, however, are in Japan and these figures are not included in this analysis. In recent years Takeda's strategy has been to expand sales outside of Japan, firstly in the US and then more recently in the EU. In Europe, Takeda has already gained full control of most of its subsidiaries, and in the US has established a strong wholly owned subsidiary in Takeda Products North America (TPNA). Basen and Glufast, Takeda's other diabetes products are only currently available in Japan, where Basen has proved to be very successful.

Marketed products

Table 5.34 lists Takeda's marketed diabetes products, although Basen and Glufast are only available in Japan so the sales figures in the six markets analyzed are zero.

Table 5.34: US/European* sales of Takeda's marketed diabetes portfolio ($m), 2002-2003

Brand	Generic	US patent expiry	2002	2003
Actos	pioglitazone hydrochloride	2006	1,414	1,677
Basen	voglibose	n/a	0	0
Glufast	mitiglinide	n/a	0	0
Other diabetes			0	0
Total			**1,414**	**1,677**

* France, Germany, Italy, Spain, UK; n/a: not available

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Actos has been a highly successful product for Takeda since its launch in 1999 and in 2003 was the highest selling antidiabetic globally. Takeda markets Actos globally, co-marketing it in the US through Takeda Pharmaceuticals North America with Eli Lilly.

R&D pipeline

Takeda has five products in its diabetes pipeline, although none of these products are expected to reach the market during the forecast period.

Table 5.35: Projected sales of Takeda's diabetes R&D pipeline ($m), 2007 & 2010

Brand/code	Stage	2007	2010	Launch year
TAK-559	Phase III	n/l	321	2008
TAK-428	Phase II	n/l	n/l	> 2010
TAK-654	Phase II	n/l	n/l	>2010
Actos + metformin	n/a	n/a	n/a	n/a
ATL-962	n/a	n/a	n/a	>2010

n/l = not launched; n/a = not available/not applicable

Source: Company reported information; IDdb, August 2004, Copyright Thomson Scientific; Business Insights

Actos/metformin combination

On 8 January 2004, Andrx and Takeda jointly announced that they had entered into an agreement to develop and market a combination product consisting of Takeda's Actos (pioglitazone) and Andrx's Fortamet (metformin extended release), each of which is administered once-a-day for the treatment of type 2 diabetes. Once approved, the combination product will be manufactured by Andrx, and exclusive marketing rights worldwide will be held by Takeda.

ATL-962

Alizyme is currently developing ATL-962 in Europe as an agent to treat obesity and obesity-associated diabetes. It is designed to cause weight loss by reducing the digestion and thus the absorption of fat from the diet. Takeda has acquired the exclusive rights to develop and market ATL-962 in Japan.

TAK-559

TAK-559 is an insulin resistance-decreasing drug. It controls blood glucose levels by improving the insulin resistance in liver and peripheral tissues. It is expected to be less likely than TZD compounds to produce unfavorable reactions such as weight gain and edema. This compound is currently in phase III trials in the US and Europe and phase I studies in Japan.

TAK-654

TAK-654, like TAK-559, is also an insulin sensitizer and is less likely to cause weight gain and edema than the TZDs. It is in phase II trials in the US and Europe, and phase I studies in Japan.

TAK-428

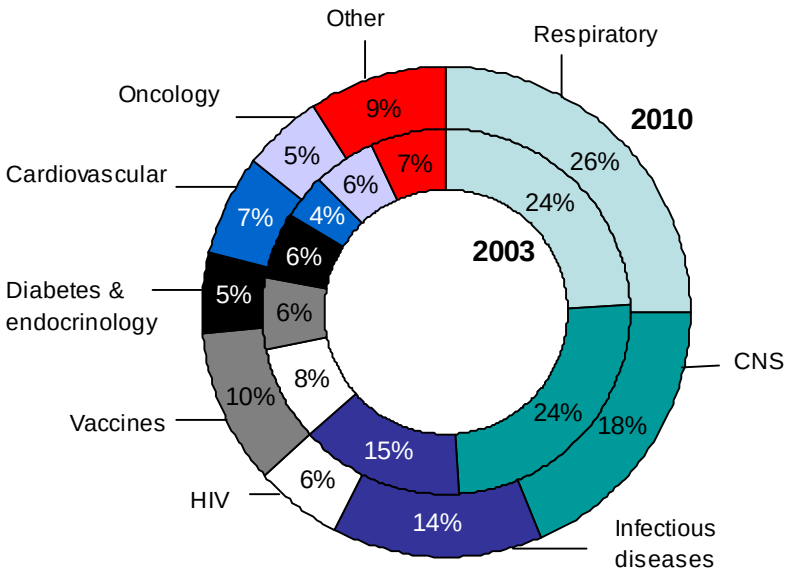
TAK-428 is a neurotrophic factor production accelerator that is thought to aid the repair and regeneration of peripheral nerve tissues damaged by diabetes mellitus. It is in phase II trials in the EU and US.

GlaxoSmithKline

Therapeutic focus

GSK has a broad therapeutic focus, comprising eight major franchises. Of these eight, the respiratory and CNS franchises are the largest, as shown in Figure 5.40. Diabetes is one of the newest major franchises for GSK, although currently the company has just two major products on the market, the TZD Avandia and the single-pill combination therapy Avandamet (Avandia + metformin) which was launched in 2002. The diabetes franchise is expected to decline slightly until 2010 due to a gap in GSK's late-stage pipeline in this area.

Figure 5.40: GSK's therapeutic focus, 2003 & 2010



Source: Company reports & information; Business Insights

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OAD market share

Sales of these Avandia and Avandamet now give GSK sales in Europe and the US totalling $1.5bn, and rank the company second in terms of sales of OADs and third in the total diabetes market globally. In 2004 the company filed for approval for an additional combination therapy Avandaryl (Avandia + sulfonylurea). A further combination therapy, Avandamet XR (extended release) is also currently in development.

Marketed products

Table 5.36 lists the marketed products for GSK. Avandia generates the second highest sales on the diabetes market in the US and Europe, accounting for 12.9% of total sales. This single product sales figure is even more impressive considering 94% of Avandia's sales were in the US market alone. Avandia's major competitor is Eli Lilly's Actos. In 2006 Actos comes off patent in the US and this will significantly impact Avandia sales with patients more likely to be prescribed the cheaper generic Actos compared to Avandia, even though Avandia's patent runs until 2008. Further threats are newer classes of OADs in development, such as the dual PPAR agonists, and inhaled and oral insulins.

Table 5.36: US/European* sales of GSK's marketed diabetes portfolio, 2002-2003

Brand	Generic	US patent expiry	2002	2003
Avandia	rosiglitazone	2008	1,181	1,345
Avandamet	rosiglitazone + metformin	2008*	12	145
Other diabetes			0	0
Total			**1,193**	**1,489**

* France, Germany, Italy, Spain, UK
** Patent expiry dependent on success of GSK upholding reformulation patent extensions – could run until 2015

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R&D pipeline

The diabetes franchise has been identified as a key growth driver for GSK, with the portfolio being primarily supported by in-licensing. GSK currently has a large number of early stage projects but has a significant gap in its late stage pipeline, with the termination of HIM-2. This will need to be filled by a further increase in in-licensing activity in order that GSK fully capitalizes on the good start it has made in the diabetes market with Avandia and Avandamet, and soon to be launched Avandaryl. Table 5.37 lists GSK's diabetes R&D pipeline, and demonstrates the company's focus on developing this therapy area. Projected sales for Avandaryl are not given, due to the uncertainty of patent expiry dates. The main product patent on Avandia expires in 2008 but GSK are aiming to extend this for Avandamet and Avandaryl until as late as 2015, which would affect future sales of this product.

Table 5.37: GSK's diabetes R&D pipeline, 2003

Brand/code	Stage	Launch year
Avandaryl	Submitted	2004
677954	Phase II	>2010
427353	Phase I	>2010
815541	Phase I	>2010
823093	Phase I	>2010
869682	Phase I	>2010
Avandamet XR	Phase I	>2005
HIM 2	Terminated	n/a

n/a = not applicable, n/l = not launched

Source: Business Insights, company reported data, IDdb, Copyright Thompson Scientific, Biospace

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Avandaryl

GSK expects to launch its third product in the Avandia franchise for the treatment of type 2 diabetes in the second half of 2004. Avandaryl is a single-pill fixed dose combination of Avandia and Sanofi-Aventis' Amaryl, the leading sulfonylurea in the six markets analyzed in 2003 with 36% market share. The NDA for this product was filed

in October 2003 and approval by the FDA is expected in late 2004. Additionally, MAA filing in Europe is expected at some point in 2004.

This product is expected to perform well in the market on the back of the successes of Avandia and Avandamet, although this is dependent on a patent extension for reformulation past the Avandia patent expiry of 2008. The launch of this product is important for GSK in the continued life cycle management of the Avandia franchise, as most of the rest of its diabetes R&D portfolio are still in early phase trials.

Avandamet XR

This drug is a combination of Avandia and metformin extended release. Although it is currently only in early stage trials GSK expects to file an NDA in 2005.

HIM-2

HIM-2, developed by Nobex Corporation, is an orally-active recombinant human insulin currently in phase II trials. The insulin for HIM-2 has been modified to make it resistant to enzymatic degradation in the gastrointestinal tract and has greater bioavailability for increased absorption. In May 2002 Nobex entered into a partnership with GSK for the development of HIM-2, however GSK has since returned the rights to this compound to Nobex.

677954

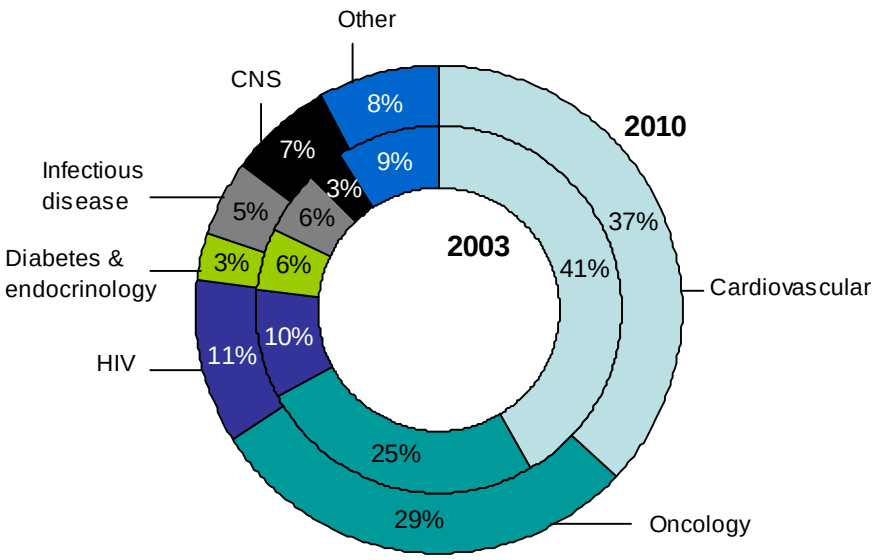
677954 is a PPAR (peroxisome proliferator activator receptor) pan agonist, which GSK is currently investigating for the potential treatment of type 2 diabetes. This product is in phase II trials, and at the company's R&D day in December 2003 strong preclinical data was presented.

Bristol-Myers Squibb

Therapeutic focus

BMS focuses on ten therapeutic areas with cardiovascular and oncology the largest, as shown in Figure 5.41. In 2003 the diabetes franchise accounted for 5.5% of company sales, but this is expected to decrease by 2010 to 3% due to the demise of its Glucophage-based products.

Figure 5.41: BMS's changing therapeutic focus, 2003-2010



Source: Company reports & information; Business Insights

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OAD market share

BMS's sales in diabetes come entirely from the US market where it promotes Merck KGaA's Glucophage family of products. In 2003 these sales were $1.1bn, accounting for 20.2% of the US OAD market, placing BMS third behind Takeda and GSK (Table 5.38). While these companies – Takeda and GSK – have seen their share of the market rise significantly in the last 5 years with the launch of their TZD products, BMS's share has declined significantly from a high of 44.8% in 2000 to less than half that value in 2003. This decline is due to the loss of patent of Glucophage in the US 2002.

Table 5.38: US OAD Market Share by Company (%), 2002-2003

	2002	2003	Growth (%) 2002-2003	CAGR (%) 1999-2003
Takeda	27.3	29.6	17.7	131.1
GSK	22.5	25.6	23.2	82.9
BMS	24.7	20.2	-11.5	-3.0
Pfizer	7.6	7.0	0.5	-23.5
Aventis	4.0	4.6	25.1	17.4
Novartis	2.2	2.3	11.1	50.4
Novo Nordisk	2.3	2.2	5.8	8.6
Teva	2.2	1.9	-9.4	8.4
Andrx	1.8	1.6	-5.3	---
Ivax Corporation	0.5	0.7	37.6	68.3

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Marketed products

BMS's diabetes and endocrinology franchise is derived entirely from the Glucophage family of products, listed in Table 5.39. The franchise suffered an 11.5% decline in sales in the US in 2003, and is now valued at $1.1bn. The drop in value from 2001 is even more striking when sales totalled $2.343bn, and resulted from the entry of generic competition in the US to Glucophage in 2002. The other products in BMS's portfolio grew during 2003, but it was the decline of Glucophage, licensed from Merck KGaA for sale in the US, which had the most significant effect.

The further loss of patent protection on the follow-up products, Glucovance, Glucophage XR and Metaglip (due in 2005) means that sales are expected to drop further over the coming years.

Table 5.39: US/European* sales of BMS's diabetes portfolio, 2002-2003

Brand	Generic	Patent expiry	2002	2003
Glucovance	metformin + glyburide	Expired	404	479
Glucophage XR	metformin	Expired	398	441
Glucophage	metformin	Expired	445	163
Metaglip	metformin + glipizide	2005	5	27
Other diabetes			0	0
Total			**1,253**	**1,110**

* France, Germany, Italy, Spain, UK

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R&D pipeline

In order to maintain its presence as a leading company in the diabetes market, BMS has built its early stage pipeline through in-licensing. Basulin and inhaled insulin are two such compounds that have been in-licensed by BMS (Table 5.40).

Table 5.40: Projected sales of BMS's diabetes R&D pipeline ($m), 2007 & 2010

Brand	Generic	Stage	2007	2010	Launch year
Muraglitazar	Dual PPAR alpha/gamma antagonist	Phase III	178	514	2006
Basulin		Phase II	0	0	>2010
Inhaled insulin		Phase I	0	0	>2010

Source: Company reported data, IDdb, Copyright Thompson Scientific, Biospace Business Insights Ltd

In addition, BMS has formed a licensing agreement with Merck & Co. for the joint development and marketing of the company's promising phase III compound, Muraglitazar. This deal was formed in order for BMS to expand its sales and marketing resource, and fits BMS's new corporate strategy of focusing on specialty markets, allowing the company to reduce its spend on its primary care sales force and operate a smaller, more focused sales force targeting specialist physicians.

Muraglitazar

Muraglitazar is a PPAR agonist that is currently in phase III clinical trials for the treatment of type 2 diabetes. PPAR agonists work by affecting switches in a cell that control the entry of sugar, fat and cholesterol into cells. The 'switches' that control this process are the peroxisome proliferator activator receptors. These types of drugs are expected to have blockbuster potential because of their potential applications in both diabetes and cardiovascular diseases, although safety concerns have caused the FDA to insist on extra pre-clinical trials for this class.

In April 2004 BMS signed an agreement with Merck & Co. for co-development and commercialization of Muraglitazar. Filing of this product in the US is expected by the end of 2004, with launch at some point in 2006. Muraglitazar is the most advanced PPAR agonist in development, ahead of Galida by AstraZeneca, which has suffered a setback with its development delayed by a year.

Basulin

Basulin is a once-daily injectable controlled release formulation of insulin. This compound was in-licensed from Flamel in August 2003 and is currently in phase II trials. Basulin was originally licensed to Novo Nordisk but this agreement was terminated in March 2002, with Novo Nordisk focusing on the launch of Levemir, also a long-acting injectable insulin.

Basulin will compete directly with Aventis's Lantus and Novo Nordisk's Levemir for market share, and due to its late arrival on the market it will be difficult for Basulin to achieve significant market penetration.

Inhaled Insulin

In September 2003, BMS in-licensed the worldwide exclusive rights to QDose's inhaled insulin. The drug is currently in phase I trials. Under the terms of the agreement, BMS will lead development, manufacturing and commercialization with the support of QDose.

The inhaled insulin is a pulmonary formulation of fast-acting insulin combining expertise in formulation and particle engineering technologies with novel dry powder inhaler and filling capabilities.

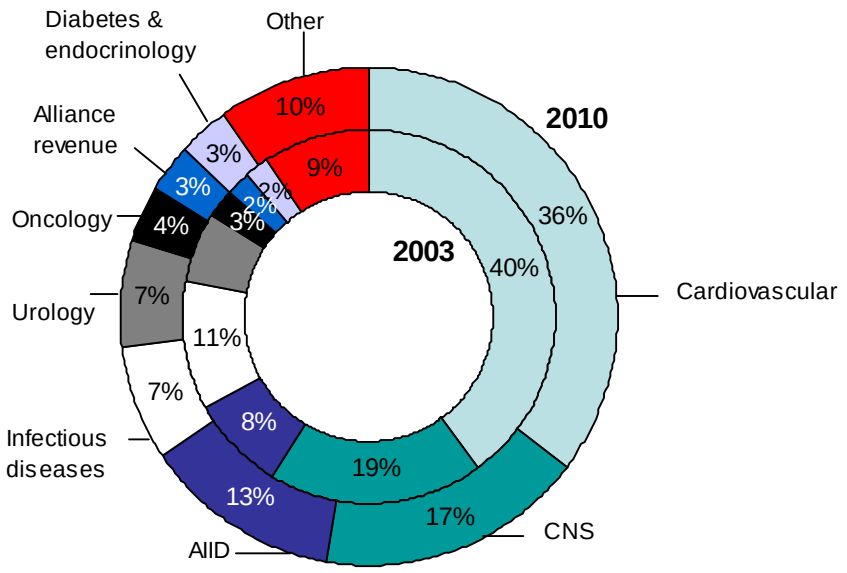
Competition in the inhaled insulin market will come from Pfizer/Aventis's Exubera and AERx iDMS from Novo Nordisk, which are both in late stage development.

Pfizer

Therapeutic focus

Pfizer has a broad therapeutic focus, with its major franchises being cardiovascular, CNS, arthritis, immune and inflammatory disorders, and infectious diseases. Its diabetes and endocrinology franchise comprised just 2.2% of sales in 2003, although this is forecast to increase to 3.4% by 2010 (Figure 5.42).

Figure 5.42: Pfizer's changing therapeutic focus, 2003-10



Source: Company reports & information; Business Insights

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Marketed products

In the six markets analysed Pfizer was ranked sixth with sales accounting for 3.8% of the total diabetes market in 2003. Its one major product in the diabetes market is Glucotrol XL, the leading sulfonylurea in the US with 2003 sales of $319. This product has little presence in the European markets but maintains a 28.7% share overall due to

its US sales. Glucotrol XL lost patent protection in the US in 2003 and thus will come under increasing pressure from generics. Consequently, its sales are expected to decline over the coming years.

R&D pipeline

Pfizer's late-stage diabetes R&D pipeline has just one product, Exubera, an inhaled insulin. Pfizer is also in the early stages of developing a PPAR agonist, although this will be beaten to market by BMS's Muraglitazar and AstraZeneca's Galida.

Exubera

Exubera is an inhaled insulin formulation being co-developed by Pfizer, Aventis and Nektar Therapeutics. This product is being developed for type 1 and 2 diabetic patients who require both a long-acting insulin product to maintain baseline insulin levels and a short-acting product to prevent hyperglycemia when eating. The inhalation system involves the use of insulin as a dry powder in a handheld inhalation device that converts the insulin powder particles into an aerosol cloud, without the use of propellants. Phase III trials of Exubera were completed in 2001 but delays have occurred in the filing of this product because a diabetic patient who received the experimental therapy was diagnosed with pulmonary fibrosis, a condition that scars the lungs and eventually leads to death. However, in March 2004, Pfizer and Aventis announced that the European Medicines Evaluation Agency (EMEA) had accepted the filing of a marketing authorization application for Exubera. The companies are still thought to be in discussions with the FDA over an appropriate US filing date.

Exubera is expected to be the first inhaled insulin product to market, beating closest rival Novo Nordisk's AERx iDMS. However, AERx has the advantage over Exubera of employing active breath control, helping patients to control their breathing and dispense the dose at the correct moment. In addition, AERx has not seen any of the safety concerns associated with Exubera. As the market for inhaled insulins is expected to be large – both type 1 and type 2 patients – Pfizer expects Exubera to be a major growth driver of its diabetes and endocrinology franchise.

Novartis

Therapeutic focus

Novartis has five therapeutic franchises – cardiovascular, oncology, arthritis, immune and inflammatory disorders (AIID), CNS and infectious diseases. Products which fell outside of Novartis' key therapies accounted for 8.5% of the company's sales in 2003. Diabetes is one of Novartis' non-key therapy areas.

Marketed products

Starlix is a prandial glucose regulator (PGR) and is Novartis's first and only diabetes drug. It was first launched in Japan in 1999, with approval following in the US in December 2000 and in the EU in April 2001. In 2003 Starlix held a 36.2% share of the PGR market in the six countries analysed, with the remaining 63.8% of sales from Novo Nordisk's Prandin/NovoNorm. The PGRs have had relatively low market penetration to date, with sales accounting for 4.8% of total OAD sales in 2003.

R&D pipeline

LAF237

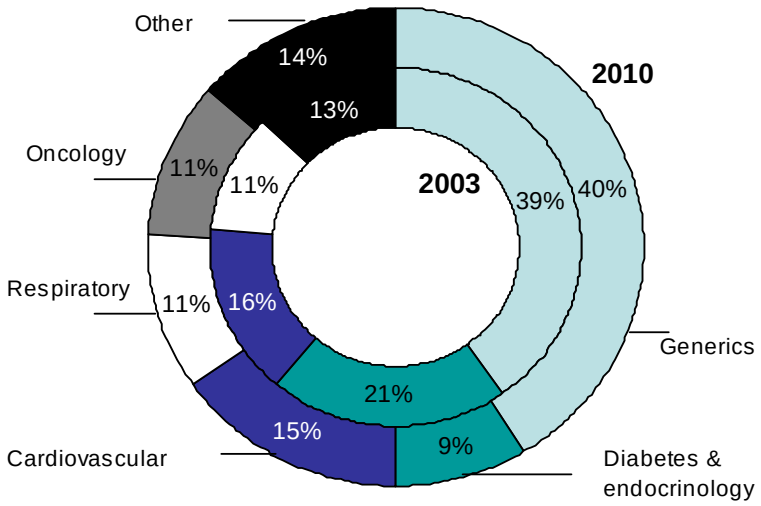
LAF237 is a dipeptidyl-peptidase IV (DPP IV) inhibitor in phase III trials for the treatment of type II diabetes. The drug is one a new generation of oral treatments for diabetes, and in studies conducted to date has shown a promising effect on fasting glucose and HbA1c (glycosylated hemoglobin), in addition to lowering prandial glucose. This drug is being trialed both as a monotherapy and in combination with metformin, and Novartis is aiming for a 2006 filing. Competition in this area comes from Merck & Co. and its MK-0431 development compound, also expected to be launched in 2006. Additionally, there are several companies developing GLP-1 compounds. Exenatide is the most advanced, having been submitted by Amylin/Eli Lilly, and Novo Nordisk's Liraglutide is currently in phase III trials.

Merck KGaA

Therapeutic focus

Outside of generics, Merck KGaA focuses on five therapeutic areas, as illustrated in Figure 5.43. Of these franchises, diabetes and endocrinology was the largest in 2003, contributing to 21% of total sales. However, this percentage is forecast to decline by 2010 to 9% with Merck KGaA expanding an oncology franchise. Merck KGaA's diabetes and endocrinology area is dominated by the Glucophage family of products.

Figure 5.43: Merck KGaA's changing therapeutic focus, 2003 & 2010



Source: Company reports & information; Business Insights

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Marketed products

Merck KGaA's diabetes products consist of Glucophage, Glucophage XR and Glucovance. Glucophage was the company's best selling drug in 2003 and Merck KGaA has also recorded a royalty line on this product from Bristol-Myers Squibb (BMS), to whom it out-licensed the Glucophage family for sale in the US market. Sales have dropped since the loss of patent protection in the US in 2002 and other markets since

1997, but this has been off-set to some extent by the launch of enhanced preparations Glucophage XR and Glucovance. Merck KGaA has also been co-promoting Novartis's Starlix in Europe since 2000. Sales of Merck KGaA's diabetes products are expected to continue to decline over the coming years due to generic competition.

R&D pipeline

Merck KGaA has a lack of diabetes R&D compounds in late-stage development after it terminated the four most advanced projects in the first quarter of 2003, and as a result this will reduce the diabetes & endocrinology franchise's value to the company. Merck KGaA has described the discontinuation of the diabetes projects as a strategic move to focus clinical development resources even more strongly on its oncology pipeline, and overcome the disappointments found in the diabetes research. An opportunity for Merck KGaA may be to in-license novel late-stage oral antidiabetics from small US biopharmaceutical companies that Merck can introduce to the European markets, where it has a strong reputation in the field.

Table 5.41: Projected sales of Merck KGaA's diabetes R&D pipeline ($m), 2007 & 2010

Brand	Indication	Stage	2007	2010	Launch year
Fenofibrate/metformin	Metabolic disorders; insulin resistance; obesity; dyslipidemia	Phase II	n/l	n/l	>2010
Obesity/diabetes targets	Diabetes; obesity	Preclinical	n/l	n/l	>2010
Metabolic disease therapy	Metabolic disorders	Discovery	n/l	n/l	>2010
EML-16257	Type 2 diabetes; insulin resistance	Phase II	n/a	n/a	Discontinued
EML-4156	Type 2 diabetes; dyslipidemia	Phase II	n/a	n/a	Discontinued
EML-336	Type 2 diabetes	Phase II	n/a	n/a	Discontinued
IDD-676 (lidorestat)	Peripheral neuropathy	Phase II	n/a	n/a	Discontinued

Source: Company reported information; IDdb, Copyright Thomson Scientific Business Insights Ltd

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