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EDITORIAL

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The market in diabetes

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Marketing diabetes

There are two dimensions to each new treatment for diabetes. The first is the impact it will have upon glucose control, measured in terms such as clinical trial outcomes, risk vs benefit, patient satisfaction and cost. The other dimension, rarely considered in clinical journals, is that of the market place. Diabetes has been a major driver of the worldwide pharmaceutical market over the past 10 years, and this sector has grown at an annual rate of just below 20%, from US$3.8 billion in 1995 to US$17.8 billion in 2005. Growth in the diabetes market remained at a solid double-digit level even when growth of the world pharma market slowed from 11% in 2002 to 5% in 2005 [1]. Diabetes is common—and rapidly becoming more so—and current therapies are only partially effective in controlling glucose levels and preventing late complications. It is therefore expected to remain one of the most attractive growth areas in the global pharmaceutical market.

This was not always the case, for 10 years ago the market in diabetes was limited to insulin, sulfonylureas and metformin, medications that were well established, largely generic and relatively inexpensive. In contrast, the past decade has seen the introduction of a wide range of new therapies that have varied in their clinical and commercial success but have invariably been more expensive than the previously available options (Fig. 1). This article will describe how the market has changed over the past 10 years and will consider how it might change over the next 5 years. Readers should note that market analysis draws together information from a variety of sources, including IMS Health (http://www.ims-global.com/globalinsights.htm, last accessed in November 2005), data provided by the pharmaceutical companies, and other sources of information; thus, in many cases the standard citation format cannot be supplied for such estimates.

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The market in oral agents, 1995–2005

Oddly enough, the market surge over the past decade was initially driven by the entry of metformin into the US market. The USA, which saw sales of US$200 billion on prescription drugs in 2002, accounts for about 50% of the global market, and is thus the dominant force within it. First introduced in France in 1968, metformin has been used around the world for decades, mostly as an inexpensive generic; it was, however, banned from the USA in 1977 because of concerns about the risk of lactic acidosis with its sister drug, phenformin.

Metformin was treated as a new drug when approval was finally granted by the US Food and Drug Administration (FDA) in 1994. Launched by Bristol-Myers Squibb under the brand name Glucophage, it soon became a blockbuster, with sales of US$2 billion in 2001, the final year before generic entries. This launch, together with the introduction of troglitazone in 1997 (it was withdrawn in 2000) and of two further glitazones in 1999, largely drove the diabetes market between 1995 and 2001 (Fig. 2). Growth slowed when metformin generics entered the USA following loss of market exclusivity in 2001, although Bristol-Myers secured some further market share by ‘evergreening’, a process by which patent-protected drugs are altered, reformulated and repackaged as they come to the end of their patent lives. Priced at four times the price of branded Glucophage [1], the glitazones are expected to generate sales of US$4 billion in 2005. Even so, rosiglitazone (Avandia) and pioglitazone (Actos) were less successful

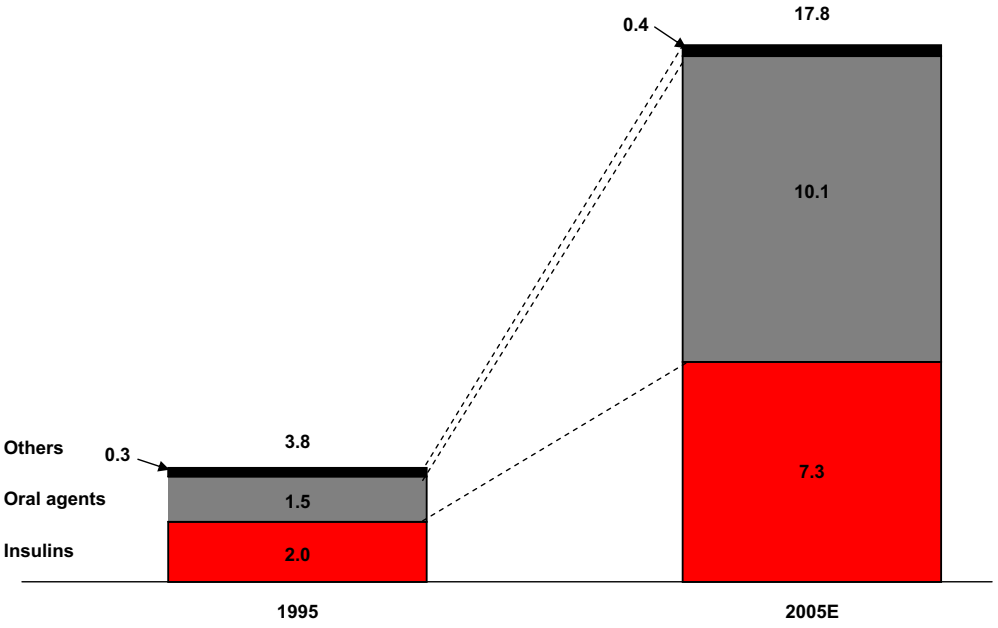

Fig. 1 The global diabetes market (US$ in billions), 1995–2005. The figure for 2005 represents an estimate. Sources: IMS, company data, Bear Stearns estimates

than originally anticipated, especially in Europe, where they account for some 5% of oral antihyperglycaemic use, as against ~20% in the USA [2]. The growth in market share of metformin and the glitazones has been matched by a reduction in the use of the less costly sulfonylureas, while the newer short-acting insulin secretagogues (e.g. repaglinide) failed to capture a significant share of the market.

Sales of oral therapies for type 2 diabetes have risen for three reasons. The first is the increase in the prevalence of diabetes, currently estimated at around 5–6% per year. Another element has been the more aggressive treatment of type 2 diabetes in response to publication of the results of the UK Prospective Diabetes Study (UKPDS) and increasingly demanding guidelines for glycaemic control. As a result, some 70% of patients in the USA are on two oral agents for diabetes, and 10% are on three. More intensive therapy is thought to have contributed a further 6–7% of market growth, and the remaining 7–8% can be attributed to the use of newer, more expensive patent-protected products.

The market in insulin, 1995–2005

The market in insulin grew relatively slowly during the 1990s. Outside the USA, volume growth of 5–6% was largely the result of the increasing prevalence of the condition, lowered thresholds for the use of insulin, and a trend towards more intensive therapies. In the USA, volume growth, as measured by prescriptions, appeared not to increase over this period, partly because human insulin was largely sold over the counter and does not feature in the estimate. The introduction of metformin and troglitazone

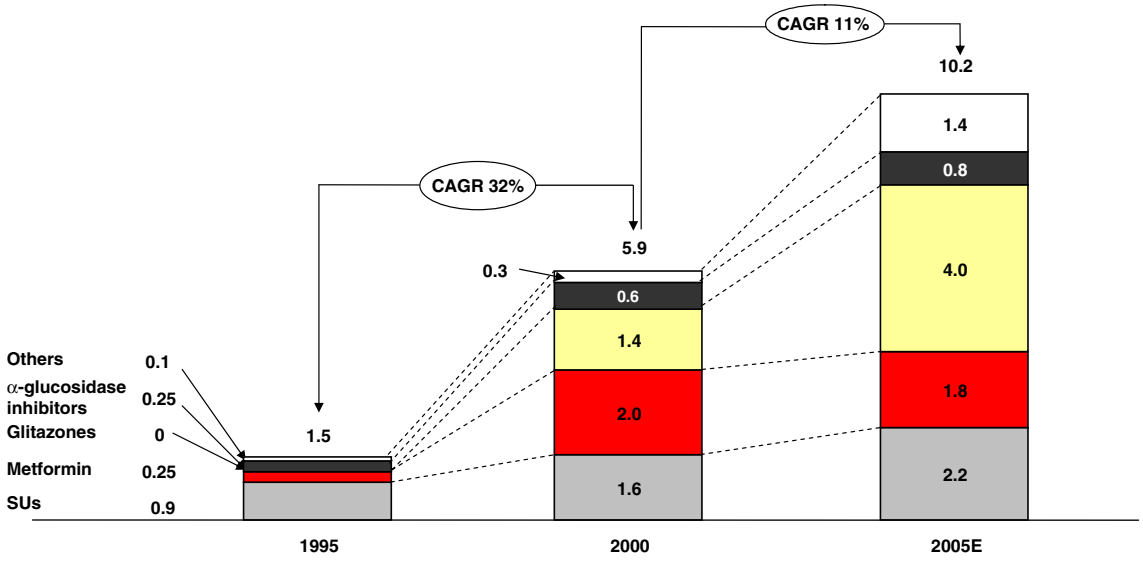

Fig. 2 The global diabetes market (US$ in billions) for oral agents in 1995, 2000 and 2005. The figure for 2005 represents an estimate. *SU* Sulfonylureas, *CAGR* compound annual growth rate. Sources: IMS, company data, Bear Stearns estimates

may also have slowed the uptake of insulin treatment for type 2 diabetes in the USA. Sales began to accelerate with the launch of Humalog in 1996 and Novorapid in 1999, further boosted by the introduction of Lantus in 2001 (Fig. 3). Lantus, marketed as a 'peakless insulin', enjoyed rapid success and looks set to achieve peak sales well in excess of US$2 billion; Detemir, another long-acting analogue, has been launched in Europe but has yet to reach the USA. Insulin growth rates in US dollars have been boosted by the increased use of pens. These devices, considered a routine part of therapy in Europe, Japan and Australasia, have been slow to reach the USA. This is because pen cartridges can be up to four times more expensive than insulin sold in a vial, a cost that is not covered by US healthcare insurers. Since patients have to pay for use of a pen out of their own pockets, the great majority still use syringes and vials.

The shape of things to come, 2005–2010

Current trends suggest that growth of the market in oral agents is set to accelerate. The first key driver could be the wider adoption of glitazones, which GlaxoSmithKline and Lilly/Takeda hope to achieve by switching patients to fixed combinations with metformin (Avandamet and Actoplus Met) or sulfonylureas (e.g. Avandaryl). This will be backed by marketing the results of outcome studies such as the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) [3] together with the results of the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial and a Diabetes Outcome Progression Trial (ADOPT), which are expected next year. It is still too early to assess the impact of PROactive, in which the reduced number of disease endpoints attributed to the use of pioglitazone was more than matched by the increased number of episodes of heart failure [2]. It remains to be seen how far a somewhat mixed reception by the medical community can be overcome by effective marketing. Heart failure also remains a concern with the newer dual-action glitazones, which target both α and γ receptors. The first of these, muraglitazar (Pargluva), seemed poised to enter the market, until an independent analysis by outside experts of data posted on the FDA website 1 day prior to an advisory committee meeting reviewing safety and efficacy data for Pargluva indicated that the composite endpoint of death, major cardiovascular events and heart failure was increased, with a relative risk of 2.23 (95% CI 1.07–4.66, p=0.03) [4, 5]. There are preliminary indications that newer glitazones at earlier stages of development, particularly the peroxisome proliferator-activated receptor (PPAR)-δ agonists and the PPAR pan-agonists, might not suffer from the major drawbacks of the class (weight gain and oedema), although such agents are unlikely to reach the market during this decade.

A further threat to the PPAR agonists comes from the dipeptidyl peptidase (DPP)-IV inhibitors, which currently look very promising, and appear to have a favourable safety profile. If early promises are fulfilled [6], these might well come to replace the glitazones as the preferred partner for metformin in combination therapy. In either event, the market potential of the wider adoption of combination therapy with the glitazones and/or DPP-IV inhibitors would be considerable. For example, if all patients currently treated with metformin in the USA were also to receive either a glitazone or a DPP-IV inhibitor (assuming similar pricing), we compute a sales potential of US$7 billion using 2005 patient numbers, rising to US$9 billion by 2010. The worldwide potential could be more than twice those figures.

Insulin and other injectable agents

Recent dollar growth in the insulin market has been driven by conversion to analogues, now estimated to be 40–45% complete in Europe and the USA. Manufacturers are pushing aggressively for further conversion, as shown by the recent withdrawal of human Actrapid penfills from the UK, and this should drive further market growth until saturation is

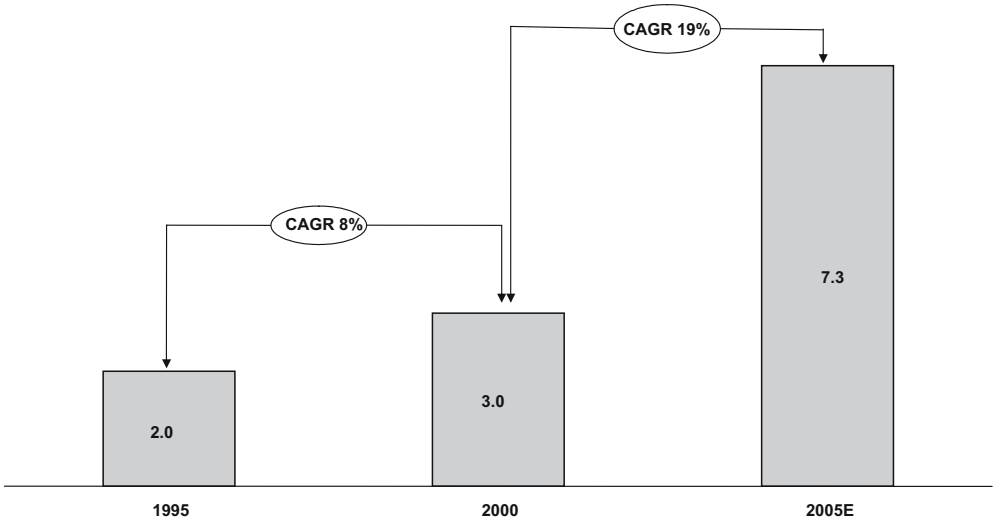

Fig. 3 The global diabetes market (US$ in billions) for insulins in 1995, 2000 and 2005. The figure for 2005 represents an estimate. *CAGR* Compound annual growth rate. Sources: IMS, company data, Bear Stearns estimates

reached, approximately by 2010, when market growth should fall back to previous levels of 5–6% per year (Fig. 4).

Devices remain a major market opportunity, particularly in the USA, where pen use is likely to increase from a very low base. Paradoxically, this may be driven in part by an increased focus on means of administration, as triggered by the introduction of inhaled insulins. Inhaled insulins are an unknown; since their key point of differentiation from injected insulins is patient preference, we expect this to drive the market. In Europe, inhalers will need to compete with pens in terms of convenience, which may well prove a challenge for Exubera, the most advanced inhaled insulin system. Inhaled insulin gains in convenience when compared with syringe injection, which is still the mainstay of administration in the USA. Since the uptake of pens has been hindered by lack of reimbursement, this constraint may also apply to inhaled insulin.

The injectable glucagon-like peptide-1 (GLP-1) analogues present an alternative treatment option for type 2 diabetes. Amylin, partnered with Lilly, launched exenatide (Byetta) in the USA in June 2005 for use as an adjunctive therapy in patients with type 2 diabetes in whom metformin and/or sulfonylureas are insufficient (a submission for a monotherapy indication received an approvable letter). Exenatide provides moderate glycaemic control, requires twice-daily injection, and will initially be positioned as combination therapy for patients poorly controlled on oral agents. In this role it partners or competes with insulins, in particular the long-acting insulin analogues, as a potential therapy option. It has the advantages of a low risk of hypoglycaemia, and of promoting weight loss; however, disadvantages include a relatively high incidence of nausea. Initial uptake is likely to be slow, given the novelty of the product and lack of clinical experience, and there is little visibility on European launch timelines. Other GLP-1 inhibitors are in development, including Novo Nordisk's liraglutide, now in Phase II trials [7].

The developing world represents a huge opportunity—China and India are the largest diabetes markets in terms of patient numbers, and are set to grow further as populations age and adopt Western diets and lifestyles—although it is not clear to what extent Western pharmaceutical companies will benefit from this new market.

Treating the metabolic syndrome

The role of therapies for the metabolic syndrome remains uncertain. The FDA does not currently recognise this as a disease entity, which means that no therapy can be approved as treatment for it. Nonetheless, the market implications of an indication that would include up to one-third of adults in the Western world are immense. The International Diabetes Federation (IDF) has recently proposed new diagnostic guidelines [8] in parallel with the American Heart Association (AHA) and the National Heart, Lung and Blood Institute [9]; the guidelines are similar, except that the IDF requires evidence of abdominal obesity to make the diagnosis whereas the AHA does not [10]. A further difference is that the diagnostic waist circumference for Americans of European extraction by AHA criteria is 8 cm greater than that recommended by the IDF criteria for Europids living elsewhere in the world. The IDF guidelines

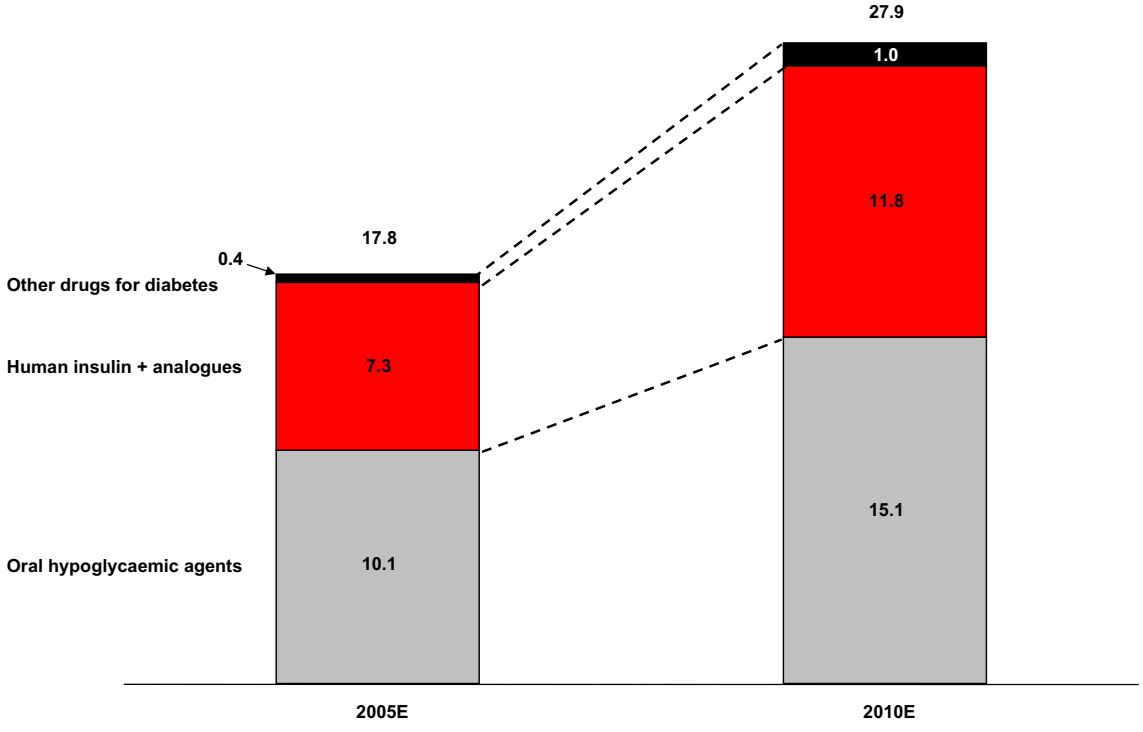

Fig. 4 Projected growth in world diabetes market (US$ in billions), 2005–2010. Source: Bear Stearns estimates

have been questioned in a joint paper from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [11], and it remains unclear whether regulatory approval will be given for this indication in the near future. Should such approval be granted, however, the metabolic syndrome would be an attractive indication for agents influencing risk variables such as obesity, inflammatory markers or endothelial damage, especially agents that combine more than one property —even when such agents are outperformed by other drugs for each of these properties in isolation. Examples include the effect of pioglitazone upon lipid levels and vascular risk, and the actions of rimonabant (Acomplia), an agent in development, which interacts with cannabinoid receptors in the brain and shows promise in the treatment of obesity [12], although central side-effects such as depression and anxiety remain a concern. The wider economic consequences of an approval for the metabolic syndrome would be very substantial.

Conclusion

Recent rapid growth in the diabetes market has been driven by the increasing prevalence of the condition, the implementation of more stringent guidelines for glycaemic control, and the introduction of more expensive therapies. We expect the prevalence of diabetes to continue to grow in the coming decades, and guidelines for diabetes management are likely to be tightened further, as happened with guidelines for hypertension and hyperlipidaemia. Each time the threshold for intervention was reduced in these areas, there followed a large increase in the population indicated for treatment. Earlier intervention for diabetes could be immensely beneficial if it took the form of lifestyle modification, which was shown to outperform metformin in the Diabetes Prevention Program (DPP) trial [13]. It is, however, much cheaper and easier for primary care physicians to reach for the prescription pad, and increased drug sales are therefore a more likely outcome.

The costs and benefits of newer therapies for diabetes are likely to be scrutinised more closely by healthcare payers over coming years. Many patients still fail to achieve desired standards of control, fuelling the desire for newer and better therapies. Not all problems can be solved by improved pharmaceuticals, however; suboptimal control may be associated with psychosocial difficulties, excessive food intake or lack of exercise. Non-adherence to medication is equally common, and is not solved by the issue of new prescriptions. The more fundamental concern is that the advantages of newer medications seem marginal at best when compared with the traditional triad of sulfonylureas, metformin and conventional insulin. This situation could very well be transformed by the introduction of GLP-1-based therapies, which remain by far the most promising agents on the therapeutic horizon, but must first meet the tests of patient acceptability, safety and improved outcome measures.

Meanwhile, and selected populations apart, there is little evidence that diabetes therapies introduced over the past decade have influenced the overall standard of control in patients with established diabetes. Despite a decade of innovation, metformin remains the agent of choice for type 2 diabetes, yet one in five health dollars for diabetes treatment (22%) is spent on a glitazone. The real gains that have been made are in cardiovascular outcomes relating to improved blood pressure and lipid management (using blood pressure-lowering agents and statins), rather than to control of blood glucose.

Newer therapies for diabetes do, however, have other benefits that need to be taken into consideration: in particular, they have helped to improve patient convenience and choice, and have made it easier to tailor therapy to meet individual requirements. As with all other tools, much depends upon the use made of them, and new agents are an aid to skilled management rather than a substitute for it. Mounting costs will inevitably lead to more careful scrutiny of claims relating to newer medications, not all of which are likely to meet the test. The major limitation is the lack of effective head-to-head comparisons with competing therapies, which means that evidence-based medicine cannot be practised. This evidence-free zone is witnessed by the lack of consensus as to how to treat people with type 2 diabetes, and the wide differences in uptake of some pharmaceutical agents in different parts of the world. Provision of evidence-based, cost-effective therapy for diabetes remains a major challenge for healthcare purchasers, for healthcare providers, and for the industry itself.

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