

Insulin Inspires Diabetes Treatment

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With India emerging as the diabetes capital of the world, pharmaceutical companies are racing ahead to grab a piece of the pie with new anti-diabetic drugs

Insulin therapy has evolved in the last century from purified bovine or porcine insulin to biosynthetic human insulin to recombinant human insulin and eventually to recombinant insulin analogs as the third generation of human insulin. Indian companies are also putting in efforts to capture the market amid stiff competition from the established multinational companies such as Novo Nordisk, Eli Lilly and Aventis Pasteur. Wockhardt was the first Indian company to launch the country's indigenously developed recombinant human insulin under the brand Wosulin. A year later Bangalore-based Biocon Ltd announced the launch of Insugen, the new generation bio-insulin in November 2004. Shreya Life Sciences, the Indian arm of Moscow-based Shreya Corporation too launched human insulin under the brand name Recosulin in December 2004, exactly a month after the launch of Insugen.

Besides Indian companies, Eli Lilly entered the Indian insulin market a decade ago in 1995 with the brand Huminsulin. Before that Novo Nordisk launched its human insulin product and went on to introduce insulin analogs under the brand NovoMix 30, a premixed insulin analogue and NovoRapid, a rapid acting insulin analogue, for the first time in India. In August 2005, Eli Lilly and Company (India) too launched its insulin analogs under the brand Humalog Mix 25, 50. In 2007, Eli Lilly launched Byetta (exenatide), a drug derived from the saliva of the Gila monster, for the treatment of type 2 diabetes mellitus. Byetta is the first in a new category of medicines known as incretin mimetics, which is approved as adjunctive therapy to improve blood sugar level in patients with type 2 diabetes.

The year 2008 saw the launch of a Januvia (sitagliptin) by MSD Pharmaceuticals, the first and only prescription medication in a new class of drugs known as dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors), which enhance the body's own ability to lower blood sugar when it is elevated. Very recently Wockhardt has launched a new insulin, Glaritus, a generic version of

Sanofi-Aventis' Lantus, which is a recombinant long-acting human insulin analogue. Glaritus is available as reusable and disposable pen delivery device, which is one of the most preferred modes of insulin injection across the globe today. In a major breakthrough, Mumbai-based Shreya Life Sciences, in collaboration with the US-based Generex Biotechnology Corporation, has announced the launch of world's first buccal insulin spray under the brand name of Oral-Recosulin in India for the treatment of type-1 and type-2 diabetes. Last year has seen two new classes of drugs entering the market, both of which work on the incretin system, injectable glucagon-like peptide-1 (GLP-1) agonists and oral dipeptidyl peptidase-4 (DPP-4) inhibitors. GLP-1 agonists, also known as incretin mimetics, stimulate insulin secretions from beta cells in the pancreas in response to food intake, in a glucose dependent manner. DPP-4 inhibitors inhibit the DPP-4 enzyme, which results in an increase in circulation of the incretin hormone, GLP-1.

Future

The worldwide market of the major human insulin products in 2007 was \$10 billion. Insulin analogs posted double digit sales growth worldwide due to successive replacement of second generation human insulin. As per ORG IMS, the current market for analogues in India is Rs 120 crore with a growth rate of 37 percent per annum. The Indian diabetic market is estimated to be around \$355 million with a growth rate of 20.6 percent as per the ORG IMS. Human insulin market is \$107 million with a growth rate of 23.9 percent while the oral antidiabetic market is \$248 million and is growing at the rate of 19.2 percent. There are various devices used for delivering insulin, including syringes, pens, pumps, needle-free injectors and inhalers.

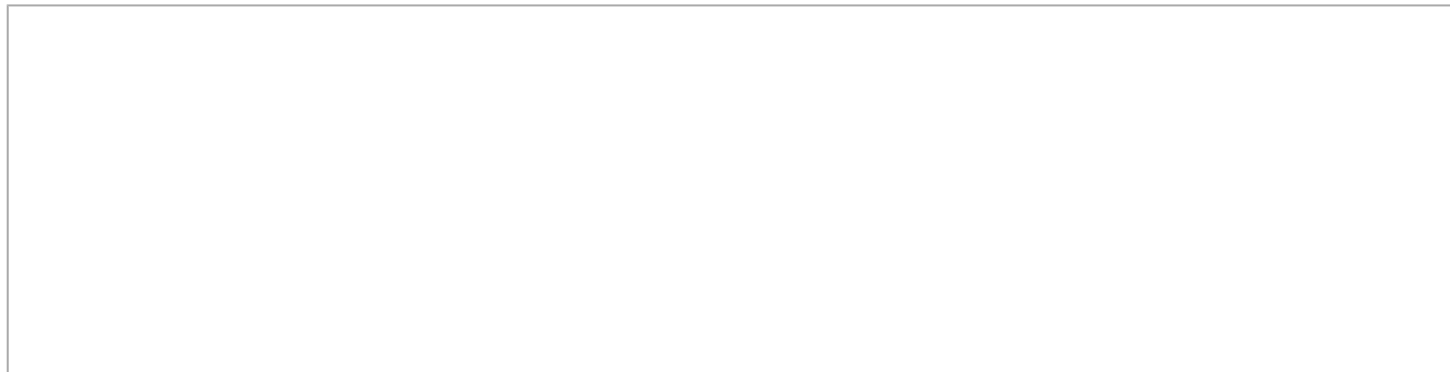
According to estimates by 2025, nearly one-third of total diabetes patients will be from India and China, both of which have fledgling. The next generations of insulin will be 'tailored' insulin, oral insulin and other long-acting insulins for injection with drug delivery solutions, that aims at optimized pharmacokinetic profiles in order to avoid hypo- and hyper-glycemic episodes. After the failure of Pfizer's inhaled insulin Exubera, most of the R&D efforts are now made on oral insulin products. Mannkind's Afresa, an inhaled insulin product that has recently completed phase-III trials, and Generex Oral-lyn from Generex Biotechnology, a buccal spray formulation in phase-III in the US has recently been approved for marketing in Ecuador, India and Lebanon.

Novo Nordisk plans to launch its anti-diabetes drug Liraglutide in India by 2010, which will treat diabetes faster than insulin. The drug has completed phase-III clinical trials successfully in India. Liraglutide is an analog which has revealed better control of blood sugar compared with insulin therapy in diabetes patients. It reduces hypoglycaemia, the sudden lowering of blood sugar levels, by increasing insulin secretion and delaying gastric emptying. Biocon is developing IN-105, a conjugated insulin molecule that is orally delivered and targeted towards the treatment of diabetes.

Biocon's R&D group has successfully developed a tablet for oral delivery of IN-105, its formulation carefully selected to give consistent absorption and glucodynamic effect. In the clinic, this molecule has completed phase-I trials. The results of the dose range finding of phase-II trials were presented at European Association for the Study of Diabetes (EASD), Rome in September 2008, and the product is expected to hit the market in 2010. Its other product, Nasulin, an intra-nasal insulin spray, is being co-developed with Bentley Pharmaceuticals Inc. and shall also hit the markets the same year.

In the future, insulin may be delivered by implanted or transferral systems. Insulin pumps are already popular in the US, where the small mobile phone-size devices which send a continuous flow of insulin into the body through a hypodermic tip. Implantable insulin pumps are currently under development in Europe and the US. Another future option for insulin administration may be the intranasal route that offers ease of delivery and fast absorption time. In addition, gene therapy and the potential for implanting insulin-producing pancreatic cells are also being researched.

With diabetes now the fifth leading cause of death across developed markets and figures from PricewaterhouseCoopers (PwC) suggesting the disease is forecast to grow by 7.1 percent across the globe by 2013, the market for once-a-day drug delivery and non-invasive drug delivery systems continues to offer significant potential for expansion. India is predicted to lead the way with 73.5 million people expected to have the disease by 2025. As such, companies like US-based Eli Lilly by announcing a joint venture with Indian company Jubilant Organisms in October 2008, are looking to secure their place in the market. The next few years promise dramatic change in the treatment of diabetes, much of which will be driven by rapidly developing technology. Every company is striving for two common goals, patient convenience and better control of the disease.



History

In 1921 Canadian research team led by Dr. Fredrick G Banting discovered insulin extracted from the islets of animal pancreas. Later, bovine insulin was given to humans by injection in 1922. In 1936, protamine, a low-weight protein is used to develop a slow-release insulin. In 1950 yet another approach led to the development of presently available Isophane NPH (Neutral Protamine Hagedorn) insulin, which is also bound to protamine. It was only in 1978, scientists from the biotechnology corporation Genentech in San Francisco, California, used a genetically manipulated plasmid of E. coli bacteria to produce insulin with the same amino sequence as seen in humans. The race to mass produce 'human' insulin using gene technology was won by Eli Lilly in 1982 when the Food and Drug Administration (FDA) approved Humulin-R (rapid) and Humulin-N (NPH) for the US market. This was followed by Novo's semisynthetic insulins, Actrapid HM and Monotard HM. Since 1996, different insulin analogues have been introduced worldwide such as Humalog from Eli Lilly, Lantus and Apidra from Aventis, Levemir and NovoRapid from Novo Nordisk to name a few.

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