Human growth hormones: Product differentiation to play a vital role in Europe

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The European human growth hormones (hGH) market was estimated to be $ 0.99 billion in 2012 and is expected to reach $ 1.22 billion in 2019 witnessing a compound annual growth rate (CAGR) of 3.0% from 2012 to 2019. The stable growth of the European hGH market is mainly attributed to a decrease in the price/value and an increase in the overall volume of hGH drugs used. With no new indications for hGH therapy likely to be approved by the European Medicines Agency (EMEA) over the next three to five years coupled with a stable patient population, the European hGH market is saturated and does not provide attractive opportunities for new entrants.

Poor patient compliance to treatment, due to the need for injecting the drug into the blood stream on a daily basis, has traditionally remained one of the key challenges for the hGH market participants The alarming increase in the illegal distribution and use of hGH for unapproved indications such as anti-aging treatment, performance enhancement, and body building over the past five years has not only forced the governments to restrict reimbursement of purchase costs of bigger packs but has also raised doubts regarding product authenticity in the minds of patients and physicians.

Moreover, currently there are only few new product candidates being evaluated in clinical trials and none are likely to reach the market within the next five years. Therefore, technology innovation and product differentiation are likely to play a vital role in the growth of existing industry participants and race for market shares.

CHALLENGES CONFRONTING EXISTING INDUSTRY PARTICIPANTS AND DETERRING NEW ENTRANTS

High Costs Incurred by Manufacturers Due to Complex Manufacturing Process

Recombinant human growth hormones are produced synthetically by isolating the human growth hormone normal (hGH-N) gene, expressed in the pituitary gland, and injecting it into the *E. coli* plasmid vector for expression and replication of desired protein.

Rigorous downstream processing methods are employed for the isolation and purification of bacterial strains with the hGH-N gene. Additionally, the manufacturing process employs the use of live cells and biochemical nutrients, thereby increasing the risk of contamination. Sterile manufacturing conditions and highly-quality reagents are required besides constant monitoring of production processes to ensure the purity of the final product.

Thus, high capital costs are involved in the manufacturing of recombinant hGH owing to the stringent quality control methods, and have in turn translated into high therapy costs for patients. Hence, it is crucial that optimal production processes are used to reduce the associated costs.

Reduced Therapeutic Efficacy Due to Poor Patient Adherence

Till date, there are only six EMEA approved indications for hGH therapy, which include Growth Hormone Deficiency (GHD), Turner Syndrome (TS), Prader-Willi Syndrome (PWS), Chronic Renal Insufficiency (CRI) and Short for Gestational Age (SGA) in children and Growth Hormone Deficiency in adults.

With more than 80% of the target population for hGH being children below the age of 15 years, taking injections on a daily basis proves to be a key challenge and leads to poor therapy-adherence. hGH being a large protein molecule (20,000 daltons), a large amount of it tends to be lost when delivered non-invasively. The pain and discomfort caused by invasive delivery methods, lead to discontinuation of treatment, particularly among children, and could significantly reduce the potential patient population for treatment. Evidences suggest that nearly 70% of children experience discomfort with injections and nearly 30% of them are forced to discontinue the therapy eventually. Therefore, companies have started increasingly focusing on developing such non-invasive delivery methods to improve patient compliance and reduce treatment withdrawal rates.

Decreased R&D Interest Owing to Stable Patient Population

A majority of the EMEA approved indications for hGH treatment are congenital disorders, having a constant rate of incidence. Hence, the target patient population remains almost stable in terms of newly-diagnosed cases. Only the approval of new indications for hGH treatment is expected to increase the market scope for hGH drug manufacturers. Besides, the advancements in medical imaging and genetic and prenatal testing have enabled the determination of congenital malformations in the foetus itself.

It is now possible to detect genetic disorders in the first trimester of pregnancy and safely abort it if required as in the case of Turner syndrome. Other congenital disorders such as Down's syndrome, Prader-Willi syndrome, and achondroplasia can also be identified by prenatal genetic testing in the foetal stage. Thus, the relatively stable target population for treatment coupled with high manufacturing costs makes hGH a less attractive segment for R&D focus and investments.

Reimbursement Issues for Patients Due to High Therapy Costs

Two somatotropin preparations, namely Nutropin Aq (Roche) and Omnitrope (Sandoz), are centrally authorised by EMEA in Europe, while the others have been authorised through the national procedures by the respective governments. Purchase costs of certain hGH drugs are not reimbursed by quite a few national governments across Europe. For example, reimbursement restrictions are imposed on Zomacton 6 mg and 1.3 mg packs in Belgium and Humatrope's 12 mg and 24 mg packs in Italy.

The primary reason for imposing such restrictions on reimbursing purchase costs of higher doses is to check the illegal distribution of hGH drugs for unapproved indications such as body building, anti-ageing, and so on. Additionally, high therapy costs also deter the inclusion of hGH drugs in the reimbursement list. Currently, government reimburse nearly 70% of legal hGH treatment costs in their respective countries. However, budgetary constraints and high therapy costs restrict hGH reimbursement to severely affected children and adults. Europe being a fragmented market, this restraint is expected to have a high impact in the short and medium terms until cost-effective manufacturing methods, which can lower the drug prices, are put into practice.

TECHNOLOGY INNOVATION AND PRODUCT DIFFERENTIATION – GAME-CHANGING STRATEGIES

Product differentiation based on innovative technologies is one of the important tools which companies are increasingly leveraging to increase their market shares in a market as highly concentrated as the European human growth hormones market. Currently, product differentiation in the human growth hormones market is aimed at three different levels, namely drug delivery mechanism, long-acting preparations and improved formulations, and combination therapy.

Drug Delivery Mechanism

Product differentiation with respect to drug delivery has been one of the fastest means to capitalize on market growth opportunities and outsmart competition. It is interesting to note that companies such as Merck Serono S.A and Ferring Pharmaceuticals have paved the way for non-invasive drug delivery systems in the human growth hormones market, while companies such as Novo Nordisk have introduced automatic needle insertion and soft-push technologies in their products to reduce pain of injection. Merck Serono's range of delivery devices for its recombinant hGH, Saizen®, have been exclusively developed to address the long unmet needs of patients on human growth hormones. These include easypod®, the first and only electronic, automated delivery device and cool.click®2, the next-generation, needle-free growth hormone delivery device.

Features	Norditropin Nordiflex	Norditropin FlexPro	Norditropin NordiLet	Humatrope Pen	Genotropin Pen	Genotropin MiniQuick	Genotropin GoQuick
Non-invasive							
No refrigeration after first use	√	√	√				
No reconstitution and mixing	√	√	√			Used only once	
Automatic needle insertion	√	√	√				
Soft-push technology	√						
Battery-free	√	√	√			√	√
Personalized colours and designs	√	√			√	√	√

Features	Saizen easypod	Saizen cool. click	Nutropin AQ Pen	Nutropin AQ NuSpin	Omnitrope Pen	Zomajet Vision
Non-invasive		√				√
No refrigeration after first use						
No reconstitution and mixing	√	√	√	√	√	√
Automatic needle insertion	√					
Soft-push technology	√					
Battery-free		√		√	√	√
Personalized colours and designs						

Table I – Human growth hormones market: Product end-user benefit analysis, Europe, 2012

Likewise, Ferring Pharmaceuticals is one of the very few companies that have focused on the needle-free delivery mechanisms of growth hormones by means of its Zomajet® 2 Vision. Novo Nordisk has developed a wide range of novel, sophisticated, delivery devices for its recombinant somatotropin, Norditropin, which include Norditropin® FlexPro® Pen and Norditropin® NordiFlex® Pen.

Easypod®
Saizen easypod®, an automated, electromechanical delivery device designed for the administration of Saizen 8.8 mg, is the first-of-its-kind for the delivery of growth hormones. The needle gets inserted automatically and a preset dose of Saizen is administered when the device is positioned against the patient's skin. click.easy® cartridge, a disposable, self-contained, reconstitution device developed by Merck Serono, facilitates the mixing of Saizen before use. Incorporated with the soft-push technology, easypod® facilitates easy and effective insertion of the needle with a single touch. No mixing and loading of Saizen® is required, as the solution is readily available in the cartridge.

Cool.click®2
This is one of the recent non-invasive drug delivery devices designed for administration of Saizen 5 mg and 8.8 mg. It operates on a spring mechanism which disperses the medicine through tiny holes in the skin. An advanced version of cool.click™, cool.click®2 has an ergonomic design with an improved nozzle and digital display for dose reading and adjustment. Dosing flexibility (mg or ml) and reverse dose dialling facilitate accurate dosing and thereby ensure better therapeutic efficacy. Besides, the pain-free mode of administration and adjustable injection pressure significantly improve patient compliance and eliminate risk of accidental needle pricks.

Zomajet® 2 Vision
Ferring's Zomajet® 2 Vision is a needle-free mode of hGH administration device. The solution for injection is available at two concentrations, which include 3.3 mg/ml for Zomajet® 2 Vision as well as syringes and 1.3 mg/ml for syringes only. The multidose vials are meant for single patient use only, as the strength and dosing schedule are specific to each individual. The pain-free mode of administration coupled with easy handling of the device has not only improved patient adherence to therapy but has also enhanced the confidence of physicians to recommend growth hormone therapy.

Norditropin® FlexPro® Pen
It is a multi-dose, single-use, pre-filled pen, consisting of a permanently-sealed cartridge, used with NovoFine or NovoTwist disposable needles of length up to 8 mm. The pen consists of an automatic needle insertion accessory, Flexpro® PenMate®, that facilitates easy and effective insertion of the needle with a single touch. No mixing and loading is required as the solution is provided in the pen. Refrigeration too is not required after first use. The easy-push dose button and dose display window enables accurate dose setting and injection. Maximum of 2, 4, or 8 mg can be administered per dose with fine increments of 0.025, 0.05, and 0.1 mg per click respectively. Furthermore, the FlexPro® pens can be personalized with different colours and designs as per patient preferences.

Norditropin® NordiFlex® Pen
Norditropin® NordiFlex® is a next-generation, pre-filled growth hormone pen designed with the soft-push technology, which makes injection 40% easier and reduces pain perception. It is the only growth hormone device that remains stable at room temperature and requires no refrigeration for three weeks after the first use. However, this applies only to the 5mg/1.5 ml and 10 mg/1.5 ml pens. Being already filled with the liquid, the device facilitates easy and quick injection, eliminating the need for mixing. NordiFlex PenMate®, the automatic needle inserter, facilitates easy and accurate needle insertion with a single touch.

Despite the sluggish growth of the overall hGH market, companies such as Merck Serono S.A and Novo Nordisk witnessed steady growth in 2011, mainly driven by these novel drug delivery mechanisms, strong marketing strategies and patient support programs.

Long-Acting Preparations and Improved Formulations

Additionally, there a few biotechnology companies such as Prolor Biotech Inc. that are striving to develop long-acting hGH preparations, which could potentially be administered once a week or twice per month in contrast to the existing preparations, which are injected on a daily basis. Prolor's hGH compound is currently undergoing Phase III clinical evaluation. Versatis Inc. is another such company that has partnered with SynCo BioPartners for the manufacturing of its hGH compound, VRS-317, a monthly once form of hGH indicated for the treatment of GHD in children and adults. Furthermore, companies such as Novartis have collaborated with drug delivery companies such as Emisphere Technologies for the development of oral form of hGH.

Combination Therapy

Currently, all marketed drugs for growth hormone deficiency have only one active ingredient such as recombinant hGH, growth hormone releasing hormone (GHRH), or insulin-like growth factor (IGF-1). On-going clinical development activities aim to study the synergistic effects of combination therapy, wherein two active ingredients are included. For example, combination of growth hormone and IGF-1 (Nutropin AQ + Increlex) is currently being evaluated by Roche (Ipsen) for the treatment of adults with GHD. This new combination product is expected to produce therapeutic effects in the treatment of endocrine disorders such as Type II diabetes and obesity besides other potential indications.

CONCLUSION

Therefore, fostering strategic alliances with technology providers and drug delivery companies are likely to be the sought-after trends in the hGH market in the future. Companies that strive to differentiate themselves from their competitors by developing innovative products and technologies, which contribute to improved patient compliance and therapeutic efficacy, are expected to grow steadily and stay ahead of competition in such a mature market. Emerging companies with enabling technologies in the hGH space, such as Prolor Biotech and Versartis Inc., are likely to leverage the support of tier 1 participants and big pharma companies to take their products through the clinical pipeline and commercialise them. Fostering strategic alliances with technology providers and drug delivery companies are likely to be the sought-after trends in the hGH market in the future.