Applied Medical Informatics
Research Letter Vol. 26, No. 1/2010, pp: 42-50

The Antidiabetics Market: Tendencies and Research Directions

Claudiu MOROGVAN[1,*], Smaranda COSMA[2], Steliana GHIBU[3], Mădălina A. VĂLEANU[4]

[1] Department of Pharmaceutical Marketing and Legislation, Faculty of Medicine, Pharmacy and Dentistry, „Vasile Goldiş" Western University of Arad, 1 Feleacului Street, 310396, Arad, Romania
[2] Department of Business, Faculty of Business, Babeş-Bolyai University, 7 Horea Street, 400174 Cluj-Napoca, Romania, Cluj-Napoca, Romania.
[3] Department of Pharmacology, Faculty of Pharmacy, „Iuliu Haţieganu" Medicine and Pharmacy University Cluj-Napoca, 13 Emil Isac Street, 400023 Cluj-Napoca, Romania.
[4] Department of Medical Informatics and Biostatistics, Faculty of Medicine, „Iuliu Haţieganu" Medicine and Pharmacy University Cluj-Napoca, 13 Emil Isac Street, 400023 Cluj-Napoca, Romania.
E-mail(s): claudiumorgovan@yahoo.com.

* Department of Pharmaceutical Marketing and Legislation, Faculty of Medicine, Pharmacy and Dentistry, „Vasile Goldiş" Western University of Arad, 1 Feleacului Street, 310396, Arad, Romania
Tel.: +40-(257)-212.204; Fax: +40-(257)-212.204.

Received: 12 March 2010 /Accepted: 29 March 2010 / Published online: 30 March 2010

Abstract

Diabetes mellitus is a pathology with multiple and severe implications. Its prevalence has been continuously increasing during the last years, as well as the number of drugs introduced in its therapy. The value of the antidiabetics global market was evaluated at over 18 billion USD in 2005. The following five international producers hold the biggest share: NovoNordisk, Takeda, Sanofi-Aventis, GlaxoSmithkline and Eli Lilly. The two bestselling drugs in the USA in 2008 were **Actos** and **Lantus**, two products of latest generation, which, however, seems to be a global tendency. As far as the OAD (Oral Antidiabetic Drug) category is concerned, the products to be prescribed in the following years will be those of latest generation, such as *thiazolidinedione*, *GLP-1 analogues*, *DPP-4 inhibitors*, as well as their fixed combinations with metformine. Rapid or slow acting Insulin analogues and their combinations with isophane insulins replace the classic insulins which seem to be outdated.

Keywords: Diabetes mellitus; Prescriptions; Tendencies; Brand.

Introduction

The evolution of the marketing environment and the global prevalence of diabetes mellitus will significantly accelerate business on this segment and the tendencies that will appear [1].

The future market of diabetes mellitus will be surely influenced by the cost of treatment; the products with the most attractive index therapeutical efficiency/cost will be likely to penetrate the market.

The market interest evolution of the main antidiabetics brands will be mainly influenced by their going off-patent and, implicitly, by the introduction of generics on the market (Figure 1).

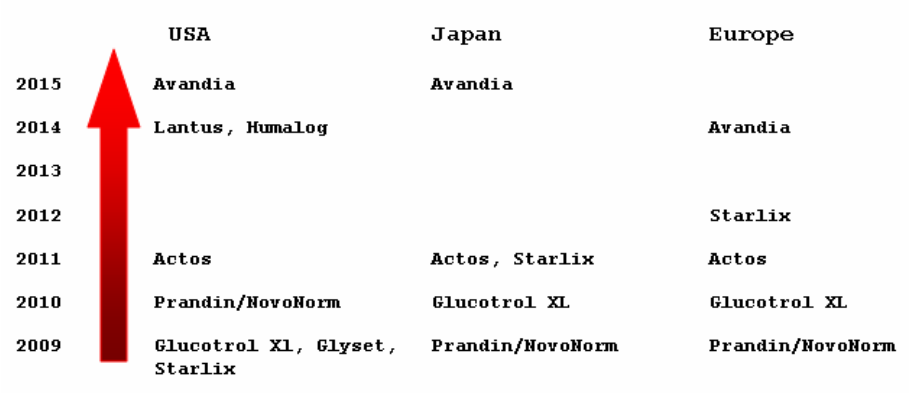

Figure 1. The going off-patent for the main antidiabetics brands between 2009-2015 [2]

In 2005, when the value of the market was estimated at over 18 billion USD, 50% of it belonged to the USA, followed, with 15%, by the region of the Pacific (China, Hong Kong, Korea, Philippines, Malaysia, Singapore, Taiwan, Thailand, and Japan). The next in line are the European countries: Germany (7%), Great Britain (4%), France (3%), Spain (3%), Italy (1%), Poland (1%), and Russia (1%) [3]. Because China and India are the countries with the smallest number of patients suffering form diabetes, they are the newest and most attractive market for drug producers [4].

The global antidiabetics market is estimated to reach in 2010 the value of 27.9 billion USD, out of which 54.2% OAD, 42.3% insulins and analogues and 3.6% other antidiabetics [4].

Material and Method

As far as the antidiabetic therapy is concerned, the global trend is given by the evolution of the American market, which represents >50% of the global one. Thus, the present study analyzed various selling reports and the evolution of antidiabetics sales in the USA form the point of view of: *number of prescriptions/ international common name, number of prescriptions/ brand, the sales value/ brand.*

The methods of study used were the following: The method of exploratory and descriptive research, the comparative method, the logical method, the causal and predictive method as well as some statistical methods. The exploratory method and the descriptive one are useful for accurately identifying and describing, respectively, the characteristics of the market and the factors that interfere in its mechanism of function. The causal method, as well as the logical and the predictive one, respectively, help the researcher in obtaining a lot of information on the phenomena that influence the market and the tendencies that take place in a certain period [5, 6]. These methods also contribute to efficiently predicting the phenomena and the market dimensions of a certain product.

The sales analysis was carried out on the 2004-2008 interval. Then, the index method was used to calculate the average indices of modification (AIM) for each individual series [7].

Results and Discussion

The evolution of the number of medical prescriptions for antidiabetics between 2004-2008 is presented in Table 1 [8-12]. In "Top 200 – Generics (medical prescriptions)" there are 7 OAD and 1 insulin.

Table 1. Prescriptions for generic antidiabetics in the USA between 2004-2008 (million units)

INN						
	2004	**2005**	**2006**	**2007**	**2008**	**AIM**
Metformin	24437	29202	34815	36786	40055	**1.12**
Glyburide (Glibenclamid)	8720	8733	8808	8387	8260	**0.99**
Glipizide ER	8261	7716	7242	6167	5354	**0.90**
Glimepiride	NA	NA	6946	7725	8567	**1.11**
Metformin HCl ER	5982	6616	6551	6956	7624	**1.06**
Glipizide	4900	5398	6376	6672	< 1662	**< 0.83**
Glyburide (glibenclamid)+Metformin	2939	5086	5232	4948	4626	**1.05**
Insuline aspartat (NovoLog/NovoRapid)	1394	1989	2522	3007	3599	**1.23**

NA – not available
INN = International Non-proprietary Name ;
AIM = Average Indices of Modification

As far as the most prescribed brands in the USA are concerned („Top 200 branded drugs by total prescriptions"), according to the data presented in Table 2, these were: **Actos**, Takeda & Eli Lilly (>12.5 million prescriptions AIM = 1.09) and **Lantus**, Sanofi-Aventis (> 10.25 million prescriptions, AIM = 1.09). Starting with 2008 **Lantus SoloStar**, Sanofi Aventis (>1.59 million prescriptions), also enters the top 200, showing an impressive increase, as compared to 2007 (AIM = 8.58) [13-17]. This, actually, represents another conditioning form for insulin glulisine **(Lantus)**, in the form of **SoloStar** prefilled pens.

Table 2. Prescriptions for antidiabetics brands between 2004-2008 in the USA (thousand units)

Brand	2004	2005	2006	2007	2008	AIM
Actos (Takeda & Eli Lilly)	8682	9737	11329	12298	12518	**1.09**
Avandia (GSK)	8130	10385	11331	7127	3103	**0.86**
Lantus (Sanofi-Aventis)	6625	8133	9519	10395	10259	**1.09**
Amaryl (Sanofi-Aventis)	6592	5787	NA	NA	NA	**0.50**
Metformin HCl ER (Caraco)	5948	NA	NA	NA	NA	**-**
Humulin N (Eli Lilly)	3795	3190	2850	2440	2132	**0.86**
Humalog (Eli Lilly)	3719	3612	3538	3587	3722	**1.00**
Glucovance (Merck, Germania)	3131	NA	NA	NA	NA	**-**
Humulin 30/70 (M3) (Eli Lilly)	2760	2338	2189	1908	1767	**0.89**
Avandamet (GSK)	2508	1895	917	1718	1126	**0.73**
Glucotrol XL (Pfizer)	1904	1523	1953	2465	2762	**1.10**
Glucophage XR (Merck)	1604	NA	NA	NA	NA	**-**
Humulin R (Eli Lilly)	1448	NA	NA	NA	NA	**-**
Humalog Mix 75/25 Pen (Eli Lilly)	1367	NA	NA	NA	NA	**-**
Novolin 70/30 (Mixtard) (NovoNordisk)	1221	1352	1457	1373	1207	**0.99**
NovoLog Mix 70/30 (NovoMix) (NovoNordisk)	NA	NA	1319	1415	1506	**1.07**
Januvia (MSD)	NA	NA	NA	2730	4868	**1.78**
Byetta (Eli Lilly)	NA	NA	1869	2530	2550	**1.13**
Actoplus Met (Takeda&Eli Lilly)	NA	NA	783	1332	1567	**1.70**
Lantus SoloStar (Sanofi-Aventis)	NA	NA	NA	186	1596	**8.58**
Levemir (NovoNordisk)	NA	NA	NA	761	1387	**1.82**
Janumet (MSD)	NA	NA	NA	306	1365	**4.46**

NA = not available
AIM = average indices of modification

Tendencies on the USA Market

The most prescribed OAD is *meformine* and its trend seems to be upwards. It is present in the top, both in its simple form (AIM=1.12) and as long lasting troche (RE) (AIM=1.06). Its combination with *glibenclamide (glyburide)* has also been increasing (AIM=1.05). On the other hand, prescriptions for *glibenclamide* have been decreasing starting with 2005 (AIM=0.99). In the analyzed

interval, *glimepiride* manifested an upward trend (AIM=1.11) as well as *aspartate analogue* **(NovoLog/NovoRapid)** (AIM = 1.23). The prescriptions for *glipizide* (AIM < 0.83) and *glipizide RE* (retard release) (AIM = 0.90), respectively, have also shown an upward trend [8-12].

In 2006, **Avandia** (GSK) becomes the most prescribed antidiabetic in the USA, outrunning **Actos.** Starting with 2007, due to the cardiac problems caused by rosiglitazone, their number of prescriptions for **Avandia** *(rosiglitazone)* significantly decreases (AIM=0.86). The same thing happens for the fixed combination of rosiglitazone with *metformine*, **Avandamet** (AIM = 0.73)

The other brands with an upward trend, present in „Top 200 branded drugs by total prescriptions" between 2004-2008 were: **Glucotrol XL**, Pfizer (AIM = 1.1), **NovoLog Mix 70/30 (NovoMix)**, NovoNordisk (AIM = 1.07), **Byetta**, Eli Lilly (AIM = 1.13) – the first antidiabetic type 2, injectable - and ***ActosplusMet***, Eli Lilly (AIM = 1.70), **Januvia,** MSD (*sitagliptine,* AIM = 1.78). Starting with 2008, **Levemir**, NovoNordisk (1387000 prescriptions) and **Janumet**, MSD (1365000 prescriptions) –fixed combination of *sitagliptine* + *metformine* also enter the top.

In the analyzed period, 22 brands were present in the top, out of which 16 were still there at the end of 2008 (8 OAD and 8 insulins). The prescriptions for slow-acting insulin analogues **Lantus, Lantus SoloStar** and **Levemir** are increasing. The prescriptions for **Humalog**, the *lyspro analogue*, have remained constant (AIM = 1.00).As far as the combinations of rapid acting analogues with isophane insulin are concerned, it has been noted that **Novolog Mix 70/30**, NovoNordisk shows an upward trend (AIM = 1.07), whereas **HumalogMix 75/25**, Eli Lilly was present in the top just in 2004.

Analyzing the bestselling antidiabetics brands "Top 200 branded drugs by retail dollars", it can be noted that if in 2004 there were 9 products (6 OAD and 3 insulins), in 2008 their number reaches 15 (7 OAD and 8 insulins) and their value goes from 6.03 billion USD to 8.83 billion USD (AIM = 1.11).

Actos, Takeda-Eli Lilly (2.45 billion USD, AIM = 1.09) was the most prescribed antidiabetic from the point of view of the value, too. Starting with 2006, **Lantus**, Sanofi-Aventis (1.48 billion USD, AIM=1.20) has been a blockbuster (a product that registers sales higher than 1 billion USD), occupying the second place from 2007 on. For **Avandia**, a blockbuster between 2004-2007, the sales registered a spectacular decline in 2008, decreasing with over 54% compared to 2007 (AIM = 0.83), reaching 0.51 billion USD. The sales for the fixed combinations **Avandamet** (AIM = 0.73) and **Humulin N**, Eli Lilly (AIM = 0.96) have also been declining.

The following are excluded from the top: original products for which generics were registered **(Amaryl**). Sanofi-Aventis; **Metformine HCl**, Caraco and Andrx. Corp., respectively) and ***Novolog***, NovoNordisk, which was replaced with the other rapid-acting analogue present in the top, **Humalog**, Eli Lilly (AIM = 1.07) or with premixed combinations of analogues and isophane insulin **(Novolog Mix 70/30 or Humalog Mix 75/25)**. The sales increased for the *lyspro analogue premixed with isophane insulin* **Humalog Mix 75/25,** too, reaching 0.23 billion USD (AIM = 1.07). In spite of this, the sales of the rival product, **Novolog Mix 70/30**, NovoNordisk, are, in 2008, still 50% higher (0.35 billion USD, AIM = 1.21). As far as the fixed combinations of rapid insulin with isophane insulin are concerned **Humulin M30/70**, Eli Lilly, their sales have remained constant (AIM = 1.02).

Levemir and **Lantus SoloStar,** long-acting analogues, which entered the top in 2008**,** have registered an impressive increase, reaching sales of 0.125 and 0.29 billion USD, respectively.

A similar rapid increase was manifested by the latest OAD introduced on the market: **Januvia** (0.91 billion USD, AIM=1.94) and Byetta (0.59 billion USD, AIM = 1.22), as well as by the fixed combinations **ActosplusMet** (AIM=1.30) and **Janumet** (AIM=4.80).

These global tendencies have appeared on the Romanian market too, but at a slower pace. In 2007, **Actos, Avandamet, Avandia,** expensive OAD went up, covering 22.5% of the OAD market, but were still placed on the 5th, 7th and 9th position, respectively among the bestselling OAD. The most prescribed molecules in Romania, in 2007 were *metformine, glimepiride and gliclazide*, the situation of the first two being similar to the USA top [23]. *Gliclazide,* however, does not even appear in „Top 200 generic drugs by total prescriptions" on the American market.

Tendencies on the Market of Oral Antidiabetics

The Kusnik-Joinville study carried out in France between 2000-2005 shows the following tendencies [24]:

- A decrease in oral monotherpay from 54.4±2.5% to 51.5±2.1%;
- A decrease in the treatment with sulfonylurea (from 66.1±2.1% to 54.6±1.9%) and α-glucosidase (from 18.3±1.7% to 11.9±1.2%);
- An increase in oral therapy combined with two OAD (from 34.9±2.3% to 36.0±2.1%) and three OAD, respectively (from 10.7±1.5% to 12.4±1.4%);
- An increase in oral therapy associated with insulin from 8±1.2% to 10.4±1.1%;
- An increase in the number of patients treated with *biguanide, glinide* and *thiazolidinedione*

The same study shows a tendency towards a higher percentage of patients treated with antihypertensive drugs (especially sartani and IEC), hypolipemic (especially statins) and platelet antiaggregant (especially acetylsalicylic acid) [24].

These upward trends can be explained, on the one hand, as a result of a higher prevalence of diabetes and implicitly, of its complications, as well as a consequence of an increased attention paid to their prevention [25, 26].

The new class of incretin mimetics (DPP-4 inhibitors and GLP-1 analogues) will assure a long term decreasing of the second risks of the disease [24] which will encourage their prescription and the establishing of an important market share. The compounds of these two structural classes promise to be, in a couple of years, blockbusters, namely products with a turn off > 1 billion USD [27] **Byetta**, the first non-insulin, injectable antidiabetic, GLP-1 analogue, reached sales of over 0.59 billion USD on the American market in 2008. Among the new class of GLP-1 analogues, Novo Nordisk has *liraglutide* in the process of being clinically studied (phase III) and Roche, Sanofi-Aventis and Ipsen (which sold the license of the product to Roche in July 2006) have a product in phase II. Servier Institute of Research is pre-clinically studying several molecules from the same class. Glaxo has 3 DPP-4 inhibitors in phase I and II, respectively, BMS has one in phase II whereas Sanofi-Aventis has one in phase I [27].

Beth Herskovits, manager of Pharmaceutical Executive, considers that the market of DPP-4 inhibitors *(sitagliptine* and vildagliptine) might reach 6 billion USD in a couple of years. Herskovits, 2007) **Januvia** sales are estimated to increase up to 1.7 billion USD till 2012 [28]. All the data in table 3 show, however, that **Januvia** registered in 2008 in the USA sales of 0.91 billion USD, placing itself the third among the most prescribed antidiabetics.

Novartis, a „freshman" on the segment of OAD, authorized immediately after entering this segment *vildagliptine* (DPP-4 inhibitor), developing the product by obtaining fixed combinations with metformine (**Eucreas 50 mg/1000 mg** and **Eucreas 50 mg/850 mg**) [29].

The classes of glinide and α-glucosidase inhibitors are under research in order to be extended. *Repaglinida* (Novo Nordisk) *nateglinida* (Novartis) are currently authorized within the class of glinide.

Just three representatives are authorized within the class of α-glucosidase inhibitors: *acarbose* (**Glucobay,** Bayer)*, miglitol* (**Glyset,** produced by Bayer and distributed by Pharmacia & Upjohn – Pfizer division) and *voglibose* (**Basen,** Takeda).The last two are not authorized in Romania, even though *voglibose* is among the ten bestselling antidiabetics. **Glucobay** is produced by Bayer, which is better known on the segment of diabetes for the glucometres it produces. Before synthesizing *pioglitazone,* Takeda became a company which was well-known within this segment for its product **Basen** *(voglibose).*Attractive sales determined Ranbaxy to start producing generics for this α-glucosidase inhibitor **(Volix)** [30].

The Guardian announces that the sales of GlaxoSmithKline registered a decrease with 2% in 2007, due to the lower sales of **Avandia**, and this decrease might get higher in 2008 [31]. Taking into account the fact that the sales of **Avandia** decreased with over 54% and those of **Avandamet** with approximately 30% (totally, with 0.69 billion USD) only on the American market (Table 3), the turnover of GSK must have registered a comedown.

Table 3. Top 200 – Value sales in the USA between 2004-2008 (in billion USD) [18-22]

Brand	2004	2005	2006	2007	2008	AIM
Actos (Takeda – Eli Lilly)	1.8	1.61	1.93	2.23	2.45	**1.09**
Avandia (Glaxo)	1.5	1.38	1.66	1.11	0.51	**0.83**
Lantus (Sanofi-Aventis)	0.66	0.77	1.06	1.3	1.48	**1.20**
Amaryl (Sanofi-Aventis)	0.31	0.26	NA	NA	NA	**-**
Metformin HCl (Caraco)	0.34	NA	NA	NA	NA	**-**
Humulin N (Eli Lilly)	NA	0.17	0.16	0.15	0.15	**0.96**
Humalog (Eli Lilly)	0.55	0.48	0.53	0.59	0.7	**1.07**
Humulin M30/70 (Eli Lilly)	NA	0.14	0.15	0.14	0.15	**1.02**
Avandamet (Glaxo)	0.38	0.26	0.14	0.28	0.19	**0.73**
Metformin HCl (Andrx Corp.)	0.25	NA	NA	NA	NA	**-**
Humalog Mix 75/25 Pen (Eli Lilly)	NA	0.19	0.2	0.2	0.23	**1.07**
NovoLog (NovoRapid) (Novo Nordisk)	0.24	0.16	NA	NA	NA	**-**
NovoLog Mix (NovoMix) (Novo Nordisk)	NA	NA	0.24	0.29	0.35	**1.21**
Januvia (MSD)	NA	NA	NA	0.47	0.91	**1.94**
Byetta (Eli Lilly)	NA	NA	0.36	0.54	0.59	**1.22**
Actoplus Met (Takeda – Eli Lilly)	NA	NA	NA	0.23	0.3	**1.30**
Lantus SoloStar (Sanofi-Aventis)	NA	NA	NA	0.03	0.32	**10.67**
Levemir (Novo Nordisk)	NA	NA	NA	0.125	0.26	**2.08**
Janumet (MSD)	NA	NA	NA	0.05	0.24	**4.80**
Total value of the antidiabetics drugs present in Top 200	**6.03**	**5**	**6.43**	**7.39**	**8.83**	**1.11**
No of antidiabetics drugs present in top 200	**9**	**10**	**10**	**11**	**15**	**1.16**
No of OADs present in top 200	**6**	**4**	**4**	**6**	**7**	**1.02**
No of insulins present in top 200	**3**	**6**	**6**	**5**	**8**	**1.17**

NA – not available
AIM = Average Indices of Modification

In the *thiazolidinedione* class, *pioglitazone* manifests an upward trend on a global level whereas *rosiglitazone* a downward one [1], as their combinations with *glimepiride* and *metformine* started to be introduced into therapy. **ActosplusMet** replaces **Avandamet** reaching sales of over 0.3 billion USD at the end of 2008.

In order to obtain new hypoglycemic substances belonging to the class of PPAR receptors activators (thiazolidinedione etc), GLP-1 analogues and DPP-4 inhibitors, the pharmaceutical companies started a real competition. For example, Roche has a product (R-483) in its phase II of the clinical study, Amgen has a γ agonist also in its phase II while GSK has a γ agonist in its phase I and another one in its phase II. The double activators of α and γ receptors are believed to improve the treatment of patients suffering from diabetes and to significantly decrease the cardiovascular risk. Merck and BMS collaborated to obtain **Muraglitazar** (phase III), Sanofi-Aventis for another compound (AVE0847) in its phase II. Takeda also has a compound in its phase II of clinical study while Roche has one in its phase I (R1439) [27].

New directions in the therapy for diabetes have been opened by Amgen and Biovitrum, which are studying the possibility of using inhibitors of the 11b-HSD1 enzyme (responsible for the interconversion of the active and inactive forms of the glucocorticoids involved in the activation of diabetes) as well as by Dia-B Tecor (Australia) which is trying to obtain a short peptide, formed of 4 amino acids, a peptide which would be capable of synthesizing glycogen [27].

Tendencies on the Insulin Market

The Kusnik-Joinville study showed an upward trend for insulin therapy with 13±1.5% - 13.5±1. 3% [24]. Up to 1986 the insulins of animal origin were the most widely used in diabetes practice. Once human insulins were introduced, the animal ones were downgraded. Starting with 1996, short

acting insulin analogues were introduced on the market [31]. Their percentage (50.8%) in the global volume of insulin exceeded the percentage of human insulins (49.2%) in 2005, their upward trend being maintained in the years to follow. The number of prescriptions for rapid acting analogues increased, on a global level, in December 2004 as compared to December 1999, from 850 to 135000, for *aspartate analogue* and from 37000 to 63000 for *lyspro analogue,* respectively. However, the number of prescriptions for long acting insulins decreased form 35000 prescriptions/month to 9000 prescriptions/ month in favor of analogue glargine. The development of new types of insulins will lead to the giving up of outdated types. Present studies of insulin producers focus on long or short acting analogues as well as on their premixed combinations with normal isophane insulin.[32] On the other hand, **Exubera** inhalator insulin was obtained and researches continue for designing insulin with nasal administration (spray), and oral or rectal one [33]. Although **Exubera** sales were estimated at 0.6 – 1.5 billion USD in 2008, the producer decided to draw it back from the market for financial reasons.

Presently, there are 3 other inhalator insulins in the phase of clinical study [2, 27]:

- Dry dust (AIR insulin) – **Alkermes/Lilly;**
- Technosphere insulin – **Mannkind;**
- Liquid formulation (AERx) – **Novo Nordisk/Aradigm.**

As far as the number of prescriptions in the USA is concerned, **Lantus** manifests a strong upward trend, together with aspartate and lyspro analogues as well as the latest on the market**, Levemir** and **Apidra.** The upward trend of *glargine analogue* is expected to be diminished by *detemir analogue*, **Levemir,** introduced on the market only in 2006. Premixed insulins and NPH ones seem to downgrade in prescribers' preferences, a decrease which is due to the introduction in therapy of insulin analogues. There is a growing tendency to associate oral therapy with insulin therapy as well as OAD with *glargine insulin*, the latter being preferred to the association between OAD and the rest of insulins. Sanofi-Aventis show that **Lantus** insulin, conditioned in SoloStar prefilled pens, is preferred to OptiSet cartridges as well as to rival Novo Nordisk insulins, conditioned under the form of **FlexPen (NovoRapid** and **Levemir)** [1].

The insulin which manifest an upward trend on a global level are the ones from the analogue class , especially **Lantus** and **NovoRapid**, and, at a smaller pace, **Humalog**, products that will replace normal NHP and premixed insulins. The insulin analogues held 65% of the French market in 2005, compared to human insulins which were estimated to only 35% [27].

As far as the drug form is concerned, producers replaced 1.5 ml cartridges with 3 ml ones and gave up conditioned substances issued in 40 UI/ml ampoules. 100 UI/ml ampoules also manifest a downward trend due to the fact that they have to be administered with syringes, devices of a smaller precision and with a more uncomfortable handling than pens. Modern devices of insulin administration are preferred (Humapen Ergo, NovoPen, OptiClick). More and more insulins are conditioned in the form of prefilled pens (NovoLet, FlexPen, OptiSet, SoloStar, KwickPen), in spite of their higher cost.

Coremed and two other Chinese companies, Fosun and Wanbang are in phase II in their research to obtain non-injectable insulin **(Alveair)** [27].

Establishing the insulin molecule against its degradation at the level of the digestive tract and its blood absorption at the level of the intestine are problems which were solved by several companies in order to obtain substances with oral administration. Emisphere Technologies (USA), Nobex (USA), Diabetology (Great Britain) have a product in phase II of its clinical study whereas Novo Nordisk and Bristol Meyers Squibb have one in phase I. Biosante Pharmaceuticals has two products in their preclinical phase, products that contain insulin with polyethylenglycole in order to improve the efficacy of insulin administration **(BioOral, BioNasal)**. Products in the form of patches with daily application are in phase I of study (Tuckner, Georgia) [27, 33].

Oramed is a pharmaceutical company which has as objective the development of pharmaceutical forms with oral administration, among its tasks being the formulation of insulin under the following forms [34]:

a) capsules for oral administration, a product in phase I B of its clinical study, already successfully tested on animals
b) suppositories, a product in phase I of study.

The specialists' predictions are that the global market of non-injectable insulins will reach the value of approximately 5 billion USD in 2010, which will determine a real, battle' on this market.

Conclusions

The USA holds 50% of the global market of diabetes significantly influencing this market on a global level. Innovative molecules, whose sales are expanding on the American market **(Actos, Lantus, Januvia, Byetta** etc.) will replace the already existing ones. The diabetes market will be marked by the going off patent of some molecules with representative turnovers as well as by the introduction of new molecules, especially from the class of GLP-1 analogues or DPP-4 inhibitors or of new insulins with non-parentheral administration for which several researches are currently on the roll.

References

1. Sanofi-Aventis, Information meeting, Paris, 12.02.2008 [cited 2008 April 2008]. Available from: URL http://en.sanofi-aventis.com/Images/080212_presentation_results2007_en_tcm24-20285.pdf
2. Owens DR, Grimley J, Kirkpatrick P. Inhalated human insulin. Nature Reviews Drug Discovery 2006;5:371-372.
3. Business Insights, The diabetes market outlook to 2011 [cited 2008 March]. Available from: URL http://www.globalbusinessinsights.com/ content/rbhc0159m.pdf,
4. Hauber A, Gale EAM. The market in diabetes. Diabeologia 2006;49(2):247-252.
5. Williams C. Research Method. Journal of Business & Economic Research 2007;5(3):65-72.
6. Rycroft RS. Microcomputer software of interest to forecasters in comparative review: updated again. International Journal of Forecasting 1999;15:93-120.
7. Văleanu M, Cosma S, Cosma D, Moldovan G, Vasilescu D. Optimization for Date Redistributed System with Applications. International Journal of Computers, Communications and Control 2009;4(2):178-184.
8. Drug Topics, Top 200 generic drugs by units in 2004. [cited 2008 February]. Available from: URL: http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard//drugtopics/102005/150069/article.pdf.
9. Drug Topics, Top 200 generic drugs by units in 2005. [cited at 2008 February]. Available from: URL: http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard//drugtopics/102006/311293/article.pdf,
10. Drug Topics, Top 200 generic drugs by units in 2006. [cited 2008 February]. Available from: URL: http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard//drugtopics/092007/407652/article.pdf.
11. Drug Topics, Top 200 generic drugs by units in 2007. [cited 2008 February]. Available from: URL: http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard//drugtopics/072008/491181/article.pdf.
12. Drug Topics, 2008 Top 200 generic drugs by total prescriptions. [cited 2010 January]. Available from: URL: http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard//drugtopics/222009/599844/article.pdf.
13. Drug Topics, Top 200 Brand Drugs by units in 2004 [cited 2008 February]. Available from: URL: http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard//drugtopics/102005/150068/article.pdf.
14. Drug Topics, Top 200 Brand Drugs by units in 2005. [cited 2008 February]. Available from: URL: http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard//drugtopics/102006/311294/article.pdf.
15. Drug Topics, Top 200 Brand Drugs by units in 2006. [cited 2008 February]. Available from: URL: http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard//drugtopics/092007/407649/article.pdf.

16. Drug Topics, Top 200 Brand Drugs by units in 2007. [cited 2008 February]. Available from: URL: http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard//drugtopics/072008/491207/article.pdf.
17. Drug Topics, 2008 Top 200 branded drugs by total prescriptions. [cited 2008 January]. Available from: URL: http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard//drugtopics/222009/599845/article.pdf.
18. Drug Topics, Top 200 Drugs for 2004, by US Sales. [cited 2008 February]. Available from: URL: http://www.drugs.com/top200 _2004.html.
19. Drug Topics, Top 200 Drugs for 2005, by US Sales. [cited 2008 February]. Available from: URL: http://www.drugs.com/top200 _2005.html.
20. Drug Topics, Top 200 Drugs for 2006, by US Sales. [cited 2008 February]. Available from: URL: http://www.drugs.com/top200_2006.html.
21. Drug Topics, Top 200 Drugs for 2007, by US Sales [cited 2008 February]. Available from: URL: http://www.drugs.com/top200.html.
22. Drug Topics, 2008 Top 200 branded drugs by retail dollar. [cited 2008 January]. Available from: URL: http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard//drugtopics/192009/597083/article.pdf.
23. Morgovan C, Cosma S, Chifu C, Ghibu S, Burta C, Polinicencu C. Evaluation of the oral anti-diabetic drugs market in Romania during 2004-2007. Studia Universitatis Babeş Bolyai Negotia 2009;1:21-36.
24. Kusnik-Joinville O, Weill A, Salanave B, Ricordeau P, Allemand H. Diabète traité: quelles évolutions entre 2000 et 2005? Pratiques et Organisation des Soins 2007;38(1):1-11.
25. Datamonitor, Stakeholder Insight: Diabetes, Diabetes market: A rising patient population, 2004, [cited 2008 April]. Available from: URL: http://www.pharmaceutical-business review.com/article_researchwire.asp?guid=FD090735-5C99-45D5-874D-314622930F56.
26. Herskovits B. Oral diabetes race comes down to marketing, 2007. [cited 2007 January]. Available from: URL: http://www.pharmexec.com/pharmexec/content/printContent Popup.jps?id=381499.
27. Chambre de Commerce et d'Industrie de Paris et Mairie de Paris. Dossier d'Actualités Diabète Paris 2006;12:1-35.
28. Smith A. Surge expected for diabetes drug market. Diabetes drug spending to jump 70 percent through 2009: Medco report, CNNMoney.com 2007. [cited 2009 May]. Available from: URL: http://money.cnn.com/2007/05/17/news/companies /diabetes/index.htm.
29. Vîlceanu N, ANM informează depsre medicamente noi cu autorizaţie de punere pe piaţă validă în România, Farmacist.ro 2008;115:10.
30. Medical News Today. Ranbaxy launches Volis (voglibose) for treatment of diabetes, first time in India, 2006. [cited 2008 August]. Available from: URL: http://www.medicalnewstoday.com /articles/36827.php.
31. Gough S, Smith M. Insulins – past, present and future, Practical Diabetes International Supplement, 2005:1-5.
32. Vioreanu V. Profitul Glaxo în scădere, Capital.ro, 2008. [cited 2008 February]. Available from: URL: http://www.capital.ro/index.php?section= articole&screen=index&id=107073.
33. Leucuţa S. Sisteme de admnistrare a insulinei (în vol. sub redacţia Zaharia V, Rolul farmacistului în asistenţa bolnavului diabetic). Ed. Medicală Universitară „Iuliu Haţieganu", Cluj-Napoca 2005, p. 78-97.
34. Oramed. Information for investors, 2007. [cited 2008 April]. Available from: URL: http://www.oramed.com/investors/ index.html.