

COMPARATIVE STUDY REGARDING COMMERCIAL POLICIES FOR THE ROMANIAN ANTIDIABETICS' MARKET

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Abstract

The success of the marketing activity is based on the right positioning of a product on the market and implicitly on its differentiation from competing products. As diabetes mellitus is a pathology with controversial economic, psychological, social and medical consequences on the population and with continuously growing prevalence, providing a proper drug based treatment becomes an important aspect for improving life quality and life expectancy of diabetic patients. At present, several classes of oral antidiabetic drugs (OADs) and insulins are approved for the Romanian market, several molecules and numerous original or generic preparations are used in the therapy of this disease. For the specific purpose of this paper, oral medication was divided into three classes in relation with their action mechanism, while insulins were included in only one category. In our paper, we allotted a score for each brand, depending on product price and attractivity. Following the survey and analysis of results, we found that no antidiabetic drug was perceived as having a higher cost than attractivity. On the Romanian market some important products from the commercial point of view among oral antidiabetic drugs are registered, their price and attractivity being high: **NovoNorm**[®] (*repaglinide*), **Glucobay**[®] (*acarbose*), **Actos**[®] (*pioglitazone*), **Avandia**[®] (*rosiglitazone*), **Lantus**[®] (*insulin glargine*) etc.). Products with low price and attractivity – **Humalog**[®] (*insulin lispro*), **NovoRapid**[®] (*insulin aspartate*) - and those with high attractivity, low price – **Siofor**[®] (*metformin*), **Amaryl**[®] (*glimepiride*), **Diaprel**[®] (*gliclazide*), **NovoMix**[®] (*insulin aspartate + isophane insulin*)- include most of the antidiabetic drugs.

Rezumat

Reușita activității de marketing are la bază corecta poziționare a oricărui produs pe piață și implicit diferențierea acestuia față de cele concurente. Deoarece diabetul zaharat este o patologie cu implicații economice, psiho-sociale și medicale controversate asupra populației, dar și cu o prevalență în continuă creștere, asigurarea unui tratament medicamentos adecvat tratării acestei boli este deosebit de importantă pentru creșterea calității vieții pacientului diabetic și a speranței de viață a acestuia. Pe piața românească sunt autorizate în prezent mai multe clase de antidiabetice orale sau insuline, mai multe

molecule și numeroase preparate originale sau generice necesare tratării diferitelor tipuri de diabet. În lucrarea de față, medicamentele antidiabetice orale au fost împărțite în trei clase, în funcție de mecanismul lor de acțiune, iar preparatele cu insulină au fost cuprinse într-o singură categorie. S-a alocat un scor pentru fiecare *brand* în funcție de prețul și de atractivitatea produsului. În urma analizării rezultatelor obținute am putut constata că niciun produs antidiabetic nu este perceput cu un cost mai mare decât atractivitatea sa. Sunt înregistrate pe piața românească o serie de antidiabetice importante din punct de vedere comercial al căror preț și atractivitate este ridicată (*NovoNorm*[®] (*repaglinida*), *Glucobay*[®] (*acarboza*), *Actos*[®] (*pioglitazona*), *Avandia*[®] (*rosiglitazona*), *Lantus*[®] (*insulina glargin*) etc.). Produsele cu preț și atractivitate redusă – *Humalog*[®] (*insulina lispro*), *NovoRapid*[®] (*insulina aspartat*) – și respectiv cele cu atractivitate mare și preț redus – *Siofor*[®] (*metformin*), *Amaryl*[®] (*glimepirid*), *Diapret*[®] (*gliclazie*), *NovoMix*[®] (*insulina aspartat* + *NPH*) - sunt cele mai numeroase.

Keywords: positioning, differentiation, antidiabetic drugs, diabetes mellitus

Introduction

Positioning does not refer to the fabrication of a product, but rather to the development in the consumer's mind, of an image referring to the product in question [14]. In other words to position means to group types of similar products on the conceptual map of the consumer [3].

The newly launched drug should be well-placed on the market so that it can live together with or correctly replace similar drugs in a field. Regarding the positioning of the antidiabetic drugs, the aim of the operation consists in identifying a well defined place, where both the *diabetologist* and the *diabetic patient* can find a higher value than the one of already existing products.

Statistics show that the first brand put on the market usually benefits from double market share, unlike the second product introduced on the market, while the third product enjoys a four times less market share [14]. As the drugs market is in full swing and original drugs are patent-based protected for a certain time interval, when they exit the patent protection, their market share diminishes dramatically in favour of generic products. An example could be *Amaryl*[®] (*glimepiride*) which lost its market share after 2005 in the USA, when it was no more protected by the patent. *Avandia*[®] (*rosiglitazone*) became a second place market leader due to its secondary cardio-vascular effects (stroke risks), detected after its introduction in therapy. As a consequence, *Actos*[®] (*pioglitazone*) became the antidiabetic drug with the largest market share.

In "The market and diabetes" study, Hauber and Gale considered that *Byetta*[®] (*exenatide*), put on the market in 2005 by Amylin-Eli Lilly

partnership, was indicated in type II diabetes patients, where *metformin and/or sulfonylureas* did not suffice. [8] **Byetta**[®] was recommended in mono or poly therapy combined with *metformin, sulfonylureas or thiazolidinediones*. Both in *sulfonylureas or metformin* monotherapy patients, and in combined medication patients (*sulfonylurea and metformin*), the association of *exenatide* had, 30 weeks later, statistically significantly decreased glycated haemoglobin - HbA1c - (down to $\leq 8.00\%$), as well as the patient body weight by 1.6- 2.8 kg, as compared to no *exenatide* initial therapy patient groups [5].

Research performed by Bunck et al. indicated that 52-weeks' *exenatide* administration in type II diabetes patients, compared to *insulin glargine* administration, led to significant improvement of pancreatic beta-cell function and implicitly of glycemic control, as well as to a decrease of body weight, respectively of hypoglycemic incidents within the **Byetta**[®] treated patient group [4].

Clinical studies showed that, therapeutically, **Diaprel**[®] (*gliclazide*) was a highly successful sulfonylurea. **Diaprel**[®] reduced the risk of hypoglycemia, if compared to *glibenclamide* ($p < 0.05$). Moreover, the administration of *gliclazide* had positive effects, helping restore HbA1c values. It is tolerated very well, when compared to *glibenclamide, chlorpropamid, glipizide* or *gliquidone* [7].

At the time of its launch on the market, **Amaryl**[®] (*glimepiride*) was positioned by Sanofi-Aventis as a new-generation *sulfonylurea*, of superior action but similar price to **Diaprel MR**[®] [11].

The long-acting insulin *detemir* (**Levemir**[®], **NovoNordisk**[®]) was introduced in therapy in 2004, as direct competitor of the first long-acting analogue **Lantus**[®], *glargine* (**Sanofi Aventis**). Unlike **Lantus**[®], which is administered in one dose and ensures constant glycemic levels for 24 hours [1], the *detemir* analogue has been authorized to twice-a-day administration [2]. This suggests that one dose of *detemir* does not ensure the adequate glycemic level for 24 hours. There are studies such as Waugh et al. that show the differences between the two analogues as being statistically insignificant. They can be summed up to a decrease in body weight under 1 kg and the increase of the daily dose by a couple of units. [16] Another study confirms this fact, but it further shows that in order to have the same therapeutical efficacy, as the HbA1c level has been decreased by the *glargine* analogue intake, a *detemir* analogue dose increase is required, from 38.8 UI/day to 51.5 UI/day [6]. Concerning the two long-acting insulin analogues, *glargine* and *detemir*, another study shows that differentiation between the two is also achieved by treatment costs. Thus, the annual cost

of a patient treated with *glargine analogue* (849 EUR) is 36% (486 EUR) lower than the necessary annual cost of a patient treated with *detemir analogue* (1,334 EUR), which causes considerable thrift in treating diabetic patients. [13] This might be one of the reasons for the difference in these medicine sales on the Romanian market. Following the comparative analysis in their first three years since the market launch of each product, it can be noticed that the registered Romanian sales for **Lantus**[®] were higher than **Levemir**[®]'s. (3,550,979 EUR vs. 537,677 EUR, namely 73,062 units vs. 9,822 units) [15].

Insofar as the situation of Romanian sales is concerned, until October 2006 the only antidiabetic drugs to be prescribed by the doctors and implicitly used by the patients could be those that were accepted according to the national tender in June 2003. An important role in the positioning of a drug on a market, mainly on the Romanian market in this case, depends on the treatment cost and funds available for the doctors. Thus, in Romania, the most expensive medicines, though prescribed at international level, are strictly limited and cannot increase as those on the world market.

The present study presents the position on the market of the antidiabetic drugs, considering the market shares of these products as well as some aspects regarding their clinical efficacy. Lately, means of differentiating among drugs on the Romanian market have also been considered.

Materials and Methods

When launching a new product on the market, companies rank it in comparison with competing products. The positioning map shows the place desired by the company on the market; it does not represent the customer point of view, which represents the perception map. The study proposes a positioning map of the oral antidiabetic drugs (OADs) sold in Romania at the beginning of 2008 taking into account two dimensions: their price and their attractiveness.

As for price, a score between 0.05 and 13 points was assigned to indicate the function of the price/therapeutic unit: < 0.05 RON – 0.5 points; 0.051-0.10 RON – 1 point; 0.11-0.15 RON – 1.5 points;; 0.851-0.90 RON – 8.5 points; 1.00- 2.00 RON – 10 points; 2.01 – 2.30 RON – 11 points; > 3.00 RON – 13 points (the average currency in 2009 was 1 RON = 4.2373 EUR – National Bank of Romania). In order to establish market attractiveness, further factors have been marked and scored (0.5-1 points/factor): potency, action and indications, average number of daily

doses, presence of other drugs with new concentrations, preparations with clinical packaging, special pharmaceutical formulations, covering of the active substance with products having the entire range of concentrations, national or import product, promoted or well-known product by prescribers. The brands exhibiting severe adverse reactions (such as hypoglycemia, increase of body weight, lactic acidosis) have also been underscored (1 point/adverse reaction).

Only the drugs whose prices are approved by the Ministry of Health were positioned and grouped in three categories:

- I. substances stimulating the insulin secretion (*sulfonylureas* and ***glinides***);
- II. substances acting by means of other mechanisms (increasing sensitiveness to insuline: *biguanides*, *thiazolidinediones* and gastrointestinal glucose absorption inhibitors: *alpha-glucosidase inhibitors*);
- III. **fixed combinations of two OADs** (*metformin* + *glibenclamide*; *metformin* + *rosiglitazone*).

For insulin positioning, product attractiveness has been determined considering the number of preparations, conditioning (vials, pens, prefilled pens) of each brand, product release time. The function of the price/therapeutic unit (TU), namely the score given to each brand, was proportionally calculated (20 RON = 1 point).

Results and Discussion

Figure 1A reveals that the most attractive brands considering the concerned features (pharmacological properties, technological properties etc.) are ***Glucotrol***[®] (*glipizide*), ***Diaprel***[®] (*gliclazide*), ***Amaryl***[®] (*glimepiride*). A set of products containing *glimepiride* were placed in the proximity of the original product ***Amaryl***[®], presenting a strong threat to this brand. Insofar as the study performed by Morgovan et al. (2009) showed, price decrease and aggressive promotion may trigger the seizure of an important part from the original product's market share, if the producers use these strategies.[12] The threat is also valid for ***Maninil***[®], if Romanian generics (***Glibenclamid LPH*** and ***Glibenclamid Arena***) will be placed in its proximity. This phenomenon is likely to further manifest since the Romanian product price equals the foreign product's. ***Diabrezide***[®] is the only medicine containing *gliclazide* 80 mg that could be subsidized by The National House of Health Insurance, through the national diabetes programme that was centralized between 2003 and 2006. Still, despite this and its low price, ***Diaprel***[®] had in 2007 a market share smaller than ***Esquet***[®] [12].

Then, it can be seen that **NovoNorm**[®] possesses attractiveness and a higher price. In spite of its many properties, **Glucotrol XL**[®] is not so attractive considering the price.

Siofor[®], the Romanian market leader of the *biguanides*, and OADs, is threatened by the presence of other generics containing *metformin* and having similar prices (**Metfogamma**[®], **Metformin Al**[®], **Metformin Arena**[®], similar levels of attractiveness as well as by other Romanian generics (**Diguan**[®], **Meguan**[®], **Diaformin**[®], **Metformin LPH**[®]), whose costs are lower though less attractive. Despite it is very attractive qualitatively and pricewise, **Glucophage**[®] has a minor market share (0.23% quantitatively and 0.33% as price). [12] This can be explained by a poor product promotion, since the producer probably does not consider the marketing of this product to be a priority. Increased sales in case of **Glucobay**[®] are determined by the qualities of the product, though its price remains the highest in the OADs present group (Figure 1B).

Both Eli Lilly and Glaxo SmithKline Beecham have placed on the market last generation products that exhibit special properties: **Actos**[®] (*pioglitazone*), **Avandia**[®] (*rosiglitazone*), **Avandamet**[®] (*rosiglitazone* + *metformin*). As they are original products, producers maintain a high price. In the group of fixed combinations *metformin* + *glibenclamide*, the original **Glucovance**[®] covers more strengths and presentations. However, its sales are insignificant and the group is clearly dominated in sales by **Glibomet**[®], with which the prescribers were acquainted during the national tender. At an approximately similar level one can find **Gliformin**[®] (Figure 2A).

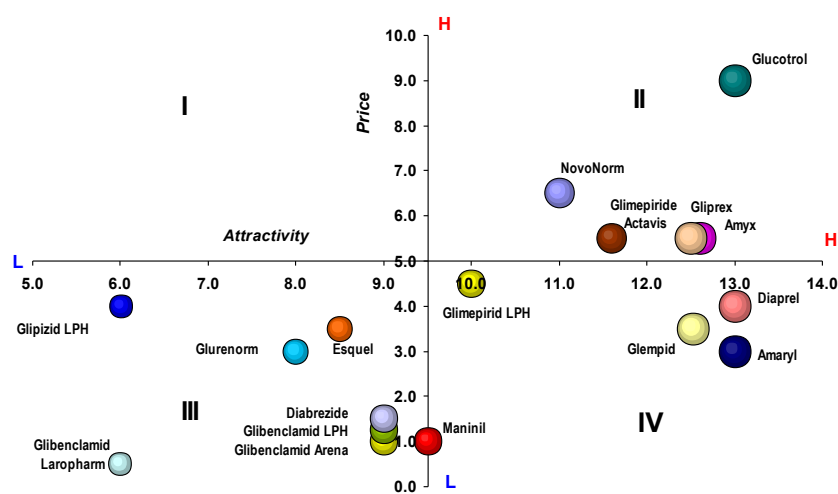


Figure 1A
Position of sulfonylureas and glinides

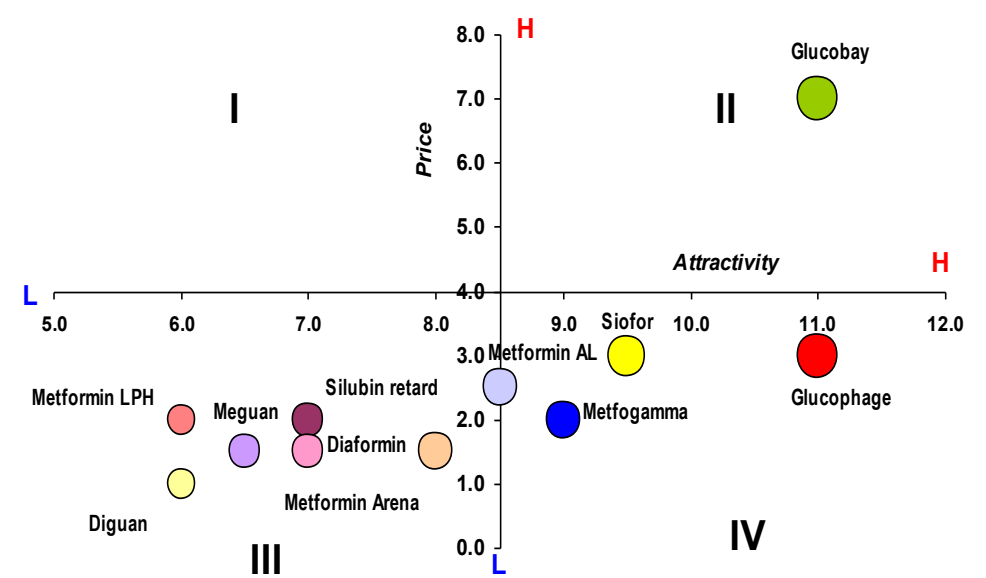


Figure 1B
Position of biguanides and alfa-glucosidase inhibitors

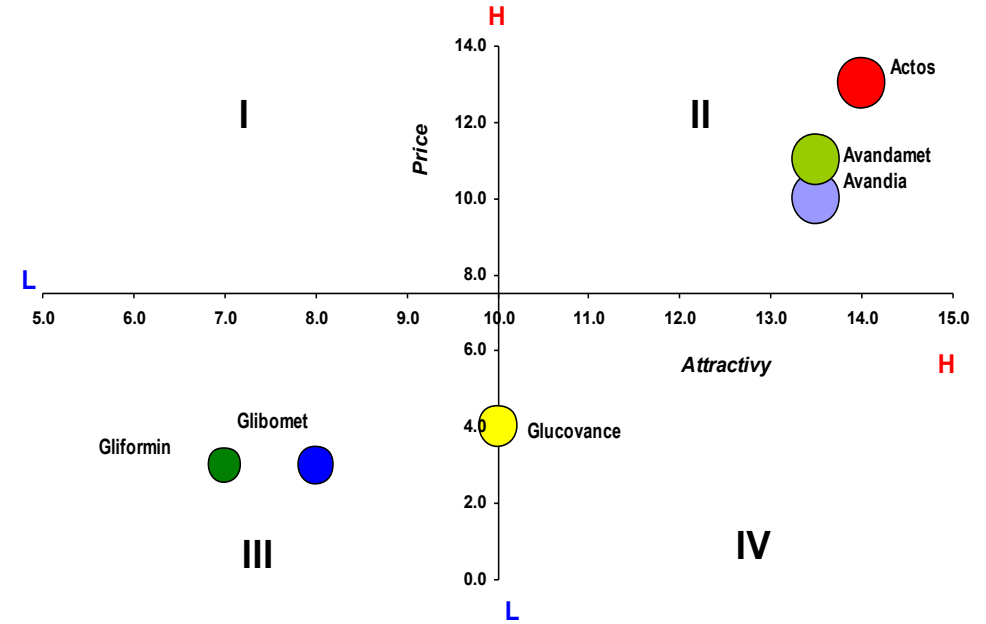


Figure 2A
Position of thiazolidinediones and fixed combinations

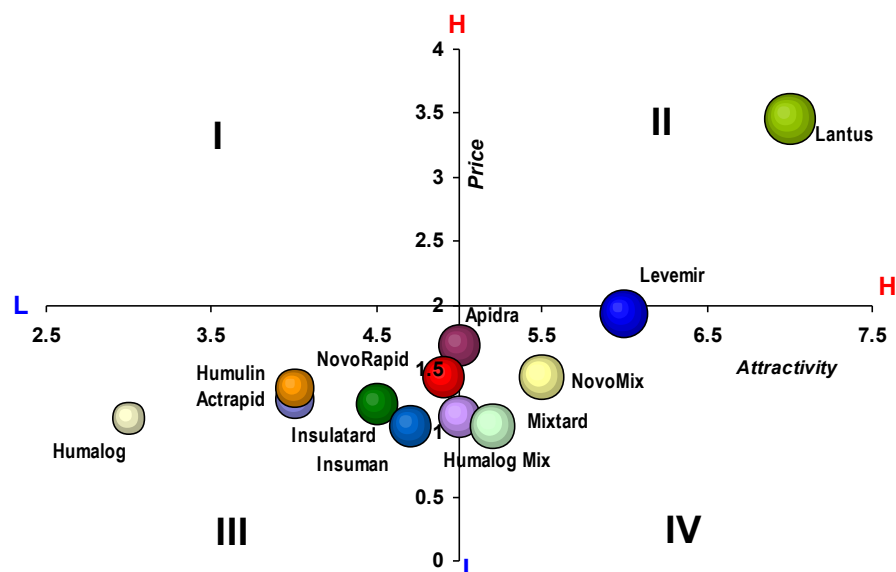


Figure 2B
Position of insulins

Eli Lilly has the lowest prices and more diminished brand attractiveness, if compared to Novo Nordisk and Sanofi-Aventis, when considering analogues and their combinations, as well as human insulins. This is due to the absence of prefilled devices and a smaller number of preparations. The most expensive brand and the most attractive at the same time seem to be *Lantus*[®], followed by *Levemir*[®]. However, Novo Nordisk does not dominate human insulins. Novo Nordisk gave a distinct name to each type produced (*Actrapid*, *Insulatard*, *Mixtard*); and it sells attractive conditioned products under the form of prefilled pens (Fig. 2B).

The graphical representations in Figures 1A, 1 B, 2A, 2 B, illustrate four dials: I - High-Low (low price – low attractiveness); II - High-High (high price – high attractiveness); III - Low-Low (low price – low attractiveness); IV - Low –High (low price – high attractiveness).

Dial I represents the products positioned as being more costly than attractive. It is noticed that none of the antidiabetic drugs is positioned as having a higher cost than the conferred attractiveness. Dial II refers to “star” products which have both high attractiveness and high price. In general, one can find here the drugs most recently introduced in the therapy, with special pharmacological and/or technological properties (e.g.: *NovoNorm*[®], *Glucobay*[®], *Actos*[®], *Avandia*[®], *Avandamet*[®], *Lantus*[®] etc.). In dial III (Low-Low) there are products that are not worth investing as they have low

prices and low attractiveness, too. Generally, the Romanian products and the generic drugs can be met here or products that did not undergo development or improvement or which have few presentations. Though rapid acting insulin analogues, *Humalog*[®] and *NovoRapid*[®] are last generation products and present significant turnover at world level, their low sphere of action and small number of variants on the Romanian market makes them less attractive. In the Low-High group (dial IV) one can encounter, developed products, relatively recently introduced on the market and whose attractiveness is higher than the price one has to pay for it. The most prescribed antidiabetic drugs on the Romanian market are *Amaryl*[®], *Diaprel*[®], *Siofor*[®], *NovoMix*[®], *Mixtard*[®] [12].

The advantages of a product can be distinguished by **differentiation**. Pharmaceutical companies try to differ among their products by conferring them specific properties, such as:

- **unique properties:** *analogue glargine (Lantus*[®]*)* provides unique and constant insulenic profile along 24 hours in one single administered dose; (*rosiglitazone and pioglitazone*) have beneficial effects on the lipidic metabolism (triglycerides level decreases), while *pioglitazone* also determines, an increase in HDL-cholesterol.
- **important properties:** reducing the risk of hypoglycemia by micronised *glibenclamide* – *Maninil*[®] **1.75 mg și 3.5 mg**, or by the *extended release with the help of gastro-intestinal therapeutic system (GITS)* at *Glucotrol XL*[®]; the lack of or a very low hypoglycemia risk for the following substances: *gliclazide*, *glimepiride*, *metformin*, *acarbose*; the risk of getting overweight is of extreme importance for the diabetic and overweight patients; preparations containing *metformin*, *gliclazide*, *repaglinide*, *acarbose* present a very low risk of this type.
- **beneficial properties:** *gliclazide* provides a global metabolic and vascular control; it is well tolerated by the diabetic patients and the micronized form requires a single dose; the fixed combination *glibenclamide + metformin (Glibomet*[®]*)* presents the advantage of increased compliance of patients requiring mixed combinations, as one tablet instead of two will be administered. By administering premixed insulins (*Insuman Comb*[®], *Mixtard*[®], *Humulin M3*[®]), patients can use only one product instead of two insulins; fast-action analogues insulins (*lispro*, *aspartate* and *glulisine*) enable a good glycemic control after meal and can be administered 5 minutes before or 15 minutes after the meal, as compared to the classical insulins.

The **ADOPT study** (A Diabetes Outcome Progression Trial) financed by Glaxo and performed in North America and Europe for five

years on 4,360 patients, aged between 30-75, has proved that *Avandia*[®], administered as an initial treatment is more efficient in type 2 diabetes mellitus than *metformin* and *glibenclamide*. As compared to the two hypoglycemic drugs mentioned earlier, after five years of treatment, *rosiglitazone* decreases the failure risk of monotherapy by 32% (compared to *metformin*) and 63% compared to *glibenclamide*. The control of glycemia (HbA1c < 7) was performed for a longer time interval (60 months), compared to *metformin* (45 months) and *glibenclamide* (33 months). [9]

Lantus[®] (*glargine*) insulin will probably gradually replace isophane insulin, and the analogue *Apidra*[®] (*glulisine*) will conquer the market of the *aspartate* and *lispro* analogue. *Lantus*[®] preparation can also be found as solution, unlike the rest of *NPH* (*isofan*) *insulins* and long acting suspensions, which have to be carefully homogenised by the patients to dissolve the crystals within. Clinical studies have highlighted a significant reduction of nocturnal hypoglycemia, which represents an enormous advantage as compared to the other products. The administration of this kind of insulin, in unique daily dose, does not require pumps.

Moreover, Sanofi-Aventis has introduced on the market the concentrated insulin (400 UI) for the insulin pumps and has developed new prefilled pens: *OptiSet*[®], *SoloStar*[®]. Hoechst in cooperation with Pfizer and Nektar Therapeutics has tried to develop inhaled insulin. The cooperation with Pfizer went on in the co-promotion of the *Lantus*[®] insulin on the American market, both companies having previously registered OADs on the market. Before product launching, in 1999, the Hoechst company manager thought there was only one problem to be overcome, namely the "market's conservatory attitude" that could be explained by the fact that one does not change the medication of a stabilised patient.[10]

The producers of *metformin* generic products have tried to differentiate products by selling them in various forms of preparation: tablets, filmed tablets, tablets for oral solution (*Formiran*[®] – Terapia), retard release tablets (*Glucophage XR*[®], Merck).

Conclusions

The correct positioning of the antidiabetic drugs plays an important role both for the identification of the diabetic patients' needs and the producer company, as it directly affects sales and profit. In the present study, one can see that the most frequently prescribed brands (*Siofor*[®], *Amaryl*[®], etc.) are threatened by the generic therapy equivalent drugs more recently introduced on the market. The original brands lately introduced on

the Romanian market (*Lantus*[®], *Levemir*[®], *Actos*[®], *Avandia*[®], etc.) have the highest prices, but also the highest clinical attractiveness. The differentiation among antidiabetics is performed by means of their pharmacological, therapeutic, clinical, biopharmaceutical properties (*Lantus*[®], *Maninit*[®], *Glucotrol XL*[®]), such as: insulinemic profile, lipidic metabolism, hypoglycemia risk, weight-related risk, metabolic control, patient compliance, preparation type and formula.

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