Questions d'économie de la Santé

n° 187 - May 2013

The Diffusion of New Anti-diabetic drugs: an International Comparison

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Regulation of the diffusion of pharmaceutical innovation represents a key issue in France where the structure of consumption distinguishes itself by the large place given to the most recent drugs that are also often the most expensive. This is the case for anti-diabetic drugs which for the National Health Insurance represent not only a public health issue but also a financial issue. The analysis of consumption data for this class of drugs indicates that France still tends to consume the most recent and most expensive molecules: in 2011, gliptins represented 8.2% of oral anti-diabetic agents consumed in France against 6.2% in Germany, 5.8% in the United Kingdom and only 4% in Australia.

This study, based on the analysis of the regulatory processes accompanying the market entry and diffusion of pharmaceutical innovation, reveals a dividing line between countries that systematically carry out economic evaluations, like Australia and the United Kingdom, and Germany where the practice is more occasional and France where it has only recently been adopted. Economic evaluations can have an impact on drugs reimbursement rules, such as the conditional reimbursement of gliptins in Australia. They also have an influence on prescribing recommendations for health professionals. In Australia and the United Kingdom, and more recently in France, these prescribing recommendations hierarchize diabetes treatments according to their efficiency.

In 2000, France was in one of the top three positions in Europe for seven of the eight most commonly used classes of drugs (antibiotics, anxiolytics, antidepressants, anti-ulcer drugs, lipid-lowering agents, anti-hypertensive drugs, anti-diabetic drugs and anti-asthmatic drugs) In 2011, it was in one of the top three positions for only two of the eight classes (Essec Lir, 2012). If French pharmaceutical consumption falls within the higher European average, it nevertheless continues to distinguish itself by the important place given to new drugs. In several therapeutic classes such as statins, anti-hypertensive drugs, proton-pump inhibitors (PPI), and anti-diabetics, the high treatment cost in France can be explained by the structure of consumption that tends to favour the latest entries on the drug market (Balsan and Chambaretaud, 2002; Sabban and Courtois, 2007).

These new drugs can be a major source of therapeutic advances (anti-retroviral drugs, PPI…) but the majority of new molecules provide little or no added therapeutic benefit. In 2011 for example, 91.6% of drugs assessed on initial introduction or on extension of indication provided no added therapeutic value compared to existing alternatives (HAS, 2012). The introduction of these new drugs often generates an increase in medical expenditures if prescribing health professionals favour these expensive new drugs to the detriment of lower priced, older drugs or generic drugs. If the dissemination of pharmaceutical innovation can be justified for certain targeted therapeutic indications, there is no obligation to systematically replace

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T1

Composition of the anti-diabetic drug class by group

Group	Active substance(s)	Market autorisation (MA)	Daily cost of treatment in France[1] january 2013	Comments
Insulin	Human insulin and analogue - rapid - semi rapid - slow	First therapeutic utilisation of insulin in 1921	Variable price according to speciality	-
Biguanides	Metformin	1959	0.28€	Generics
Sulphonylureas	Glibenclamide, glipizide, glimepiride	1969	De 0.22€ à 0.36€	Generics
Alpha-glucosidase inhibitors or IAG	Acarbose	1994	0.70€	Generics
Glinides, meglitinides	Repaglinide, nateglinide	1998	1.21€	Generics
Glitazones or thiazolinediones PPARγ receptor agonists)	Rosiglitazone and pioglitazone	2000	-	**Withdrawn from the market:** rosiglitazone in France, Germany and the United Kingdom and pioglitazone in France.
Gliptins or DPP-IV inhibitors	Sitagliptin, vildagliptin, saxagliptin	2007	De 1.51€ à 1.62€	-
	Linagliptin	2011	Not marketed in France	-
GLP-1-agonists (injectable)	Exenatide, liraglutide	2006 et 2009	3.67€	-

[1] **Data:** Summary of product characteristics (RCP) Vidal on line. The prices presented are face value prices (public prices including VAT), and do not take pharmaceutical discounts into account.

Sources: National Authority for Health (HAS) and National Drug Safety Agency (ANSM), 2013.

old molecules with new molecules in an existing class of drugs.

The aim of this study is to compare data on the use of anti-diabetic drugs by type of molecule in four countries (France, Germany, the United Kingdom and Australia) in relation to the different processes regulating the diffusion of pharmaceutical innovation. The choice of anti-diabetic drugs was essentially motivated by public health reasons due to the increased prevalence of diabetes in the majority of countries and also because of the high financial stakes they represent. In 2011 in France, reimbursements for anti-diabetic drugs represented close to 1.2 billion euros of which around 650 million euros for oral anti-diabetic drugs. The latest generation of oral anti-diabetic drugs, the gliptins or DPP-IV inhibitors, cost almost 300 million euros.

The anti-diabetic class of drugs is also marked by a sustained pace of innovation with the introduction of eight different generations of products over a period of forty years (table 1).

The gradual introduction over time of the different molecules composing the anti-diabetic class of drugs has resulted in highly differentiated daily treatment costs; low for the older products (from 0.22 € to 0.36 € for sulfonylureas) and higher for the injectable GLP-1-agonists (3.67 €), the latest entrants in the anti-diabetics class. In a class of drugs presenting such variable treatment costs, the dissemination of innovation can be questioned from the point of view of the costs generated.

The choice of countries for this study was motivated by the wish to represent inter-country differences regarding the place given to medico-economic evaluation in the process of introducing innovation on the market, and by the imposed constraint of consumption data availability (Sources insert). Of the four countries selected (France, Germany, the United Kingdom and Australia), medico-economic evaluation has more recently been adopted in the first two whereas it is more profoundly rooted in the latter two.

Comparison of the use of anti-diabetic drugs

More oral anti-diabetic drugs used in France than in the other countries

Among the four countries studied, Germany was the highest consumer of anti-diabetic drugs in 2011 with 74.5 defined daily doses per 1,000 inhabitants per day (DDD/1000 /day) [Sources insert]; the defined daily dose being the assumed average maintenance dose per day for a drug used for its main indication to treat an adult weighing 70 kg (Methods insert). France was in second position with 69.3 DDD/1000/day, ahead of the United Kingdom (60.1) and Australia (46.6) [table 2]. In terms of distribution between oral and injectable anti-diabetic drugs, France has a fairly atypical profile compared to the three other countries. The proportion of oral anti-diabetic drug consumption within the total range of anti-diabetic treatments reached 78.3% in France; much higher than Germany with 59.8%, the United Kingdom with 66.5% and Australia with 62.2%. On the contrary, the use of insulin in France is low: 20% of DDD *versus* 31.7% in the United Kingdom, 39.1% in Germany and 37.4% in Australia.

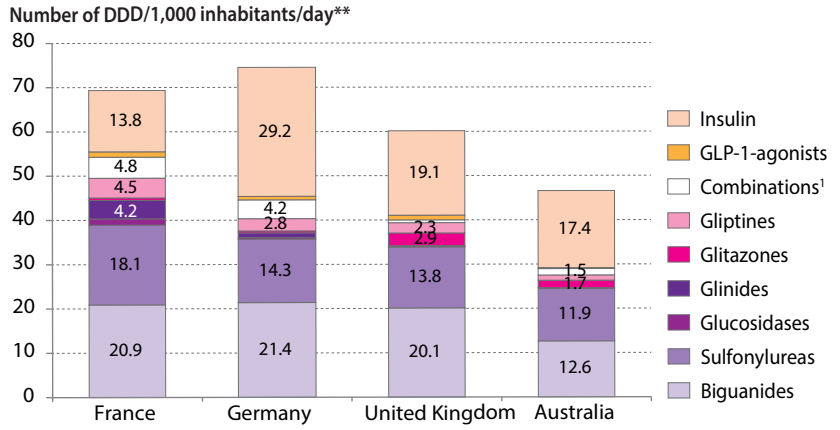
Insulin consumption in France is thus only 13,8 DDD/1.000/day, considerably lower than in Germany (29.2) and to a lesser degree the United Kingdom (19.1) and Australia (17.4) (graph 1). The other injectable anti-diabetic drugs, the new GLP-1 agonists are not yet widely diffused and only have a higher rate than 1 DDD/1000 /day in France and the

CONTEXT

This edition of *Issues in Health Economics* is an extract of a more complete study carried out in 2012 at the request of the National Public Health Insurance (CNAMTS) and aimed at analysing the different modes of entry regulation for pharmaceutical innovation for several classes of drugs (anti-diabetics, anti-TNF alpha and human papillomavirus vaccine) in several countries (France, Germany, the United Kingdom and Australia). This study concerning anti-diabetic drugs was produced in collaboration with the CNAMTS and is ointly published by two bodies: by IRDES in the *Issues of Health Economics* collection and by the CNAMTS in the *Points de repère* collection. It fits within the framework of broader research carried out at IRDES on prescription drug regulation.

G1

Consumption of oral anti-diabetic drugs in *Defined Daily Dose* (DDD) per 1,000 inhabitants per day in 2011



[1] The group 'Combinations' includes combinations of metformin with sulfonylureas, metformin with glitazones and metformin with gliptines.

Data: IMS-Health (Allemagne, France, Royaume-Uni), PBS et RPBS (Australie). Analysis by IRDES.

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United Kingdom. They were not available in Australia prior to 2011.

On the other hand, oral anti-diabetics have an especially high usage rate in France with a total of 54.3 DDD/1000/day compared to Germany with 44.6 DDD/1000/day, 40.0 in the United Kingdom and 29.0 in Australia.

Among the oral anti-diabetics, metformine (biguanide) has the highest consumption rate whatever the country, but the number of defined daily doses is much lower in Australia (12.6 DDD/1000/day) than in the three European countries studied (respectively 20.9 in France, 21.4 in Germany and 20.1 in the United Kingdom). The sulfonylureas are the second most used class of drugs: 18.1 DDD/1000/day in France, 14.3 in Germany, 13.8 in the United Kingdom and 11.9 in Australia.

The three other classes are clearly less utilised. The consumption of glinides at 4.2 DDD/1000/day appears to be a French exception. This class of drugs is very little used in Germany, hardly ever used in the United Kingdom and is not marketed in Australia.

Glitazones are relatively recent molecules, put on the market in the years 2000, but have been subject to market withdrawal or variable safety precautions according to country. In 2011, the United Kingdom was the highest consumer (2.9 DDD/1000/day).

Finally, France distinguishes itself by its high consumption rate of gliptins (4.5 DDD/1000/day against 2.8 in Germany, 2.3 in the United Kingdom and 1.2 in Australia). In France and Germany, to this high DDD rate for monotherapy gliptin treatment can be added a high rate of fixed combination treatments associating a gliptin with metformine.

T2

Anti-diabetic drug sales in Defined Daily Dose (DDD) in France, Germany, the United Kingdom and Australia in 2011

Groupe	France		Germany		United Kingdom		Australia	
	In DDD per 1000 inhabitants / day	% (DDD)	In DDD per 1000 inhabitants / day	% (DDD)	In DDD per 1000 inhabitants / day	% (DDD)	In DDD per 1000 inhabitants / day	% (DDD)
Biguanides	20.88	38.5 %	21.38	48.0 %	20.12	50.3 %	12.63	43.6 %
Sulfonylureas	18.06	33.3 %	14.30	32.1 %	13.80	34.5 %	11.87	41.0 %
IAG (glucosidase)	1.41	2.6 %	0.35	0.8 %	0.07	0.2 %	0.12	0.4 %
Glinides	4.16	7.7 %	1.10	2.5 %	0.19	0.5 %	0.00	0.0 %
Glitazones	0.54	1.0 %	0.43	1.0 %	2.86	7.2 %	1.72	5.9 %
Gliptines	4.46	8.2 %	2.78	6.2 %	2.32	5.8 %	1.17	4.0 %
Combinations[1]	4.77	8.8 %	4.24	9.5 %	0.63	1.6 %	1.45	5.0 %
Oral anti-diabetics	**54.28**	100.0 %	**44.58**	100.0 %	**39.99**	100.0 %	**28.96**	100.0 %
		78.3 %		*59.8 %*		*66.5 %*		*62.2 %*
GLP-1-agonists	1.22	1.8 %	0.78	1.0 %	1.06	1.8 %	0.18	0.4 %
Insulin	13.84	20.0 %	29.15	39.1 %	19.09	31.7 %	17.44	37.4 %
Total	**69.3**	100.0 %	**74.5**	100.0 %	**60.1**	100.0 %	**46.6**	100.0 %

[1] The group 'Combinations' includes metformin combined with suphanomides, metformin with glitazones and metformin with gliptines.

Data: IMS-Health (Germany, France, United Kingdom), PBS and RPBS (Australia). Data analyses by IRDES.

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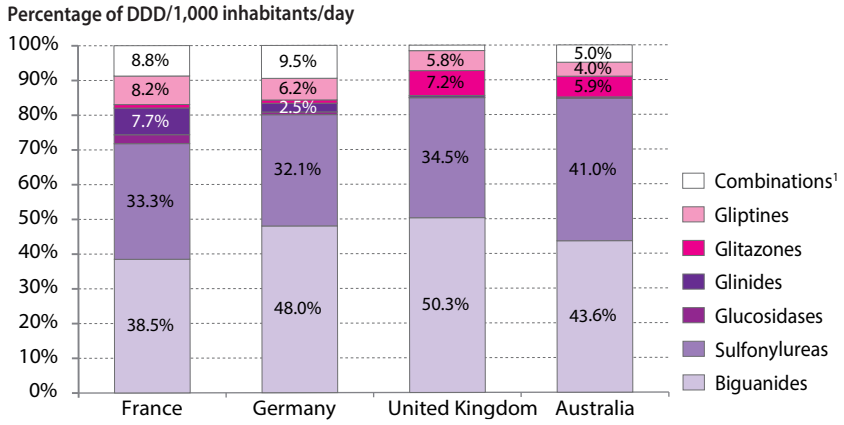
The French structure of consumption leaves more room for more expensive new products

The structure of consumption analysis reveals a tendency in France to use more expensive recent molecules. Thus in 2011, gliptins represented 8.2% of oral anti-diabetic drugs consumed in France against 6.2% in Germany, 5.8% in the United Kingdom and only 4% in Australia (graph 2). If one adds the consumption rate of monotherapy treatments to bitherapy treatments containing gliptins, the new oral anti-diabetic drugs represent 15% of prescriptions in France and Germany and only half as much in the United Kingdom and Australia.

Furthermore, the growth in gliptin consumption has been much higher in France and Germany than in Australia or the United Kingdom. Introduced in Germany and the United Kingdom at the same time in 2007, consumption increased moderately in the United Kingdom to reach 2.6 DDD/1000/day in 2011 whereas it increased more rapidly in Germany reaching 6.8 DDD/1000/day in the same year (graph 3). Introduced in France at a later date, gliptin consumption nevertheless increased more rapidly in France than in Germany as it had reached 8.2 DDD/1000/day in 2011.

G2 Structure of oral anti-diabetic drug consumption in *Defined Daily Dose* (DDD) per 1,000 inhabitants per day in 2011



[1] The group 'Combinations' includes combinations of metformin with sulfonylureas, metformin with glitazones and metformin with gliptines.

Data: IMS-Health (Allemagne, France, Royaume-Uni), PBS et RPBS (Australie). Analysis by IRDES.

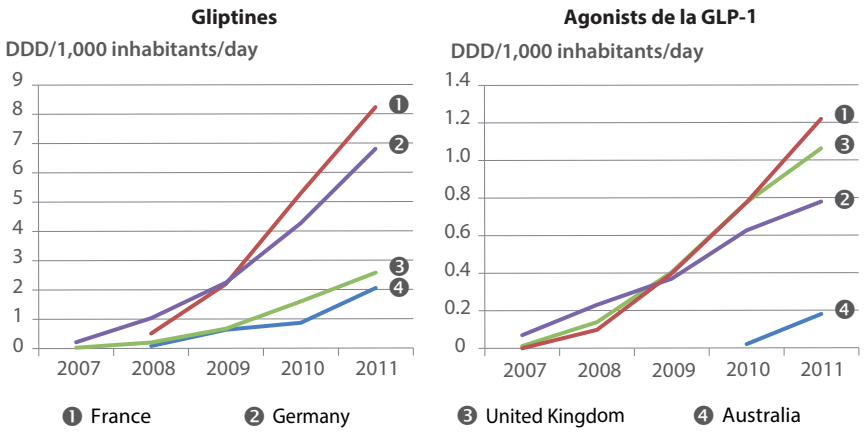
Download the Excel© file from the IRDES web site.

In Australia, the gliptin consumption growth curve follows the trend observed in the United Kingdom.

The same trend has been observed for the new and rapidly adopted injectable anti-diabetic treatments; the consumption rate increased more rapidly in France and the United Kingdom than in Germany. In Australia, the consumption rate is much lower but it was only commercialised in 2010 and only exenatide is currently reimbursed.

This large scale uptake of pharmaceutical innovation has its inevitable impact on costs if one compares the daily treatment cost for biguanides and suphanomides (around 0.30 €) to that of gliptins (from 1.50 € to 1.60 €) or injectable GLP1-agonistes (3.67 €). Graph 4 shows the increase in expenditures in France from 2007 to 2011. Three groups of prescription drugs contribute to breaking the observed trend from 2009: gliptins, and fixed combinations of gliptin and GLP-1 agonists.

G3 Evolutions in the use of gliptines (including fixed combinations) and GLP-1 agonists in *Defined Daily Dose* (DDD) per 1,000 inhabitants per day



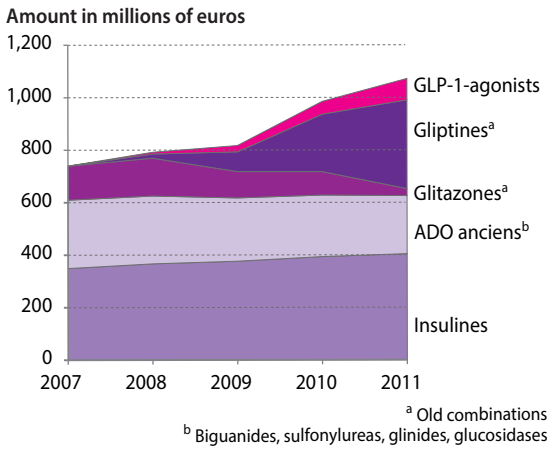
Data: IMS-Health (Allemagne, France, Royaume-Uni), PBS et RPBS (Australie). Analysis by IRDES.

Download the Excel© file from the IRDES web site.

Comparison of the regulatory processes determining the introduction and dissemination of pharmaceutical innovation

Data comparisons regarding the utilisation and dissemination of new oral anti-diabetic drugs reveal an opposition between two groups of countries. France and Germany on the one hand give an important place to the most recent and thus more expensive anti-diabetic drugs whereas the United Kingdom and Australia, on the other hand, favour the more targeted diffusion of new anti-diabetic drugs. These results raise questions regarding the support mechanisms set up to ensure the correct usage and efficient prescription of new drugs entering the market. The comparison of different

G4 Evolution of costs related to the use of anti-diabetic drugs in France from 2007 to 2011



[a] Old combinations
[b] Biguanides, sulfonylureas, glinides, glucosidases

Data: IMS-Health. Analysis by IRDES.
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systems will enable us to identify the differences in practice between countries.

Marketing authorisation (MA) is not a source of divergence between countries

During the first phase of the regulatory process, marketing authorisation (MA) determines the presence of a drug on the national market and defines the therapeutic indication perimeters. More or less stringent restrictions concerning the therapeutic scope can theoretically condition the diffusion of pharmaceutical drugs by determining whether its usage will be restricted or not. In the European countries, margins for variability are nevertheless reduced through the existence of a centralised marketing authorisation procedure. The European MA procedure is not intended to be country-specific, especially regarding indications and dosages that are rigorously evaluated by means of clinical trials. On the other hand, countries may have some leeway concerning the conditions under which drugs are prescribed or issued. In Australia, it is the Therapeutic Goods Administration (TGA) that delivers the MA (AusPAR: Australian Public Assessment Reports for prescription medicines) defining the therapeutic indication perimeters and recommended dosage.

The comparison between European and Australian MAs for the three most recent classes of anti-diabetic drugs does not reveal any differences in terms of indications. The gliptins (sitagliptin, vildagliptin and saxagliptin), have the same indications in all four countries. The glitazones which were marketed before the gliptins, could potentially have been their main competitors, but following an alert on increased vascular risk, the MA for rosiglitazone was withdrawn in all countries excepting Australia. Pioglitazone, the second glitazone on the market, was subjected to an alert concerning an increased risk of bladder cancer. The MA for pioglitazone was suspended in France but was maintained in Australia and the United Kingdom. In Germany, pioglitazone is still on the market even if the Gemeinsamer Bundesausschuss (G-BA) decided to withdraw the drug from the reimbursement list in 2010. The various events concerning glitazones since 2006 are reflected in the radical drop in sales in France and Germany, stagnation in Australia and continued growth in the United Kingdom (graph 5).

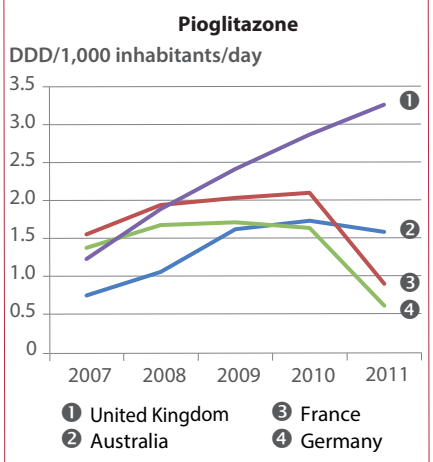
Concerning the indications for GLP-1 agonists, the differences between Europe and Australia are minimal. For exenatide, we note that Australia has added the mention of treatment by diet and physical exercise prior to a double or triple therapy. For liraglutide, Australia does not mention the possibility of combining this molecule with glitazones.

Reimbursement rules are determinant for diffusion

Comparisons between the four countries studied show that reimbursement rules are determinant for the diffusion of a prescription drug. Even if a molecule is authorised on the market by the competent authorities (European Medicines Agency (EMA) for Europe, TGA for Australia) it will not be used if it is not reimbursed.

All the countries studied use economic evaluation, Australia and the United Kingdom quasi systematically contrary to France and Germany. The Australian Pharmaceutical Benefits Advisory Committee (PBAC) thus systematically evaluates a new drug's cost-effectiveness ratio before approving its inclusion on the positive reimbursement list and establishes rules of priority. In the United Kingdom, the National Institute of Health and Clinical Excellence (NICE) has carried out numerous and frequent medico-economic evaluations on anti-diabetic drugs (rosiglitazone in 2004, two studies in 2010 comparing gliptins and glitazones). In Germany, economic evaluations carried out by the Institute for Quality and Efficiency (IQWIG) only intervene in certain cases, for example when price negotiations between the GKV Spitzenverband (German National Health Insurance Union) and the pharmaceutical laboratory have failed for new drugs with added therapeutic value that cannot therefore be integrated in an existing reference group.. None of the gliptins or GLP-1 agonists have been subject to an economic evaluation. In France, economic evaluation, introduced in 2012, had not been applied to anti-diabetic treatments during the period observed in this study but has been integrated in the new recommendations published at the beginning of 2013.

G5 Evolutions in the use of pioglitazone in *Defined Daily Dose* (DDD) per 1,000 inhabitants per day



Data: IMS-Health (Germany, France, United Kingdom), PBS et RPBS (Australia).
Analysis by IRDES.
Download the Excel© file from the IRDES web site.

Australia differentiates itself from the other countries by the way in which it uses economic evaluation to vary reimbursements on anti-diabetic drugs. In this respect, liraglutide is a characteristic example. Commercialised in the United Kingdom and Germany since 2009 and in France since 2010, in Australia it was only included in the positive reimbursement list in March 2013. At the end of 2011, the laboratory had already submitted three requests for approval to the PBAC (Pharmaceutical Benefits Advisory Committee) which had all been refused. The last refusal argued that the drug's superiority in terms of effectiveness had not been proven and uncertainties remained regarding its cost-effectiveness. Contrary to Australia, the economic evaluation carried out in the United Kingdom concluded that the drug was both therapeutically effective and cost-effective (Davies *et al.*, 2012; Shyangdan *et al.*, 2011) as its cost per QALY remained below the threshold generally considered acceptable by the National Institute for Health and Care Excellence (NICE) (£20,000 to £30,000).

In Australia, economic evaluation is also used to establish rules of priority. Concerning anti-diabetic treatments, only metformin, sulfonylureas and glucosidases are automatically reimbursed whereas other drugs can only be prescribed according to a specific procedure. Gliptins, exenatide, pioglitazone and more recently liraglutide are subject to a procedure known as Authority Required Streamlined. A special medical prescription is required for items listed under this procedure, indicating an authority approval number providing information on the type of treatment involved (for example, a bitherapy combining metformin with sulphanomide). Rosiglitazone is the only molecule subject to the more rigorous 'Authority Required' procedure using the same special prescription forms but requiring formal authorisation before delivery by the pharmacist. In addition, a bitherapy combining metformin and sitagliptin will only be reimbursed in Australia if the physician is able to prove by the information provided in the medical file that the patient has a level of glycated haemoglobin (HbA1c) superior to 7% despite previous treatment based on metformin or sulfonylureas.

Contrary to Australia, the economic evaluations carried out in the United Kingdom do not result in rules of priority other than in the recommendations inciting physicians to prescribe low-cost sulphanomides.

In the absence of economic evaluations, a Health Technology Assessment (HTA) process measuring a new drug's added therapeutic value is used in France and Germany. In France, it is used to control prices or drug reimbursement rates. The sitagliptin assessment concluded a minor improvement in added therapeutic value (ASMR IV), and no ASMR for vildagliptin and saxagliptin. The GLP-1 agonists also benefitted from a minor improvement (ASMR IV) partially explaining the price gap with glitazones or glinides and a very dynamic diffusion over the period studied. In Germany HTA of pioglitazone concluded that it provided no added therapeutic value compared to existing anti-diabetic drugs which led the G-BA to pronounce its exclusion from the positive reimbursement list. Linagliptin was also re-assessed and the report concluded that it provided no added therapeutic value.

Only Australia differentiates itself from the other countries by its conditional reimbursement of gliptins, glitazones and exenatide and its long-lasting refusal to reimburse liraglutide. Germany, the United Kingdom and France unconditionally reimburse all anti-diabetic drugs.

Notable differences concerning recommendations aimed at health professionals

In France, the National Authority for Health (HAS) 2006 recommendations concerning the medical treatment of diabetes were withdrawn at the end of 2010 and replaced by new recommendations published at the beginning of 2013. As this study analyses the use of anti-diabetics up to 2011, it is thus based on the 2006 recommendations and the 2007 guidelines concerning long-term illnesses.

The recommendations aimed at health professionals first of all reflect inter-country differences in medical evaluation. This diversity has led to establishing trigger points that act as prescribing guidelines for the different treatments available. In France, monotherapy is recommended from a 6% HBA1C level whereas in Germany it is only triggered at 6.5%. Furthermore, recommendations are based on specific criteria that differ according to country. In France and Germany, they are based on HBA1C thresholds whereas in the United Kingdom, they are based on a patient's level of overweightness or obesity. Metformin is prescribed if the

SOURCES

Information relating to health systems, price regulation and reimbursements, recommendations and information tools and prescription guidelines were obtained via the web sites of the authorities responsible for drug regulation in each of the countries concerned, learned society web sites on diabetes, specialised web sites, grey literature documents and scientific articles (cf. for further details see p. 8).

Anti-diabetic drug consumption data was obtained from two different sources

For France, the United Kingdom and Germany, data was provided by the international IMS-Health database. IMS Health (Intercontinental Marketing Service Inc.) is an American services and consulting company that provides information relating to the pharmaceutical market, prescriptions, and the sale and promotion of pharmaceutical products. The data used here concern pharmaceutical laboratory sales figures and wholesale distributor sales to pharmacies. Sales volumes for pharmaceutical products not distributed via pharmacies, notably hospital deliveries, were not taken into account in this study. The study examined the years 2006 to 2011. Sales volume data concerning the United Kingdom are collected on delivery to pharmacies. For the other two countries, they are collected on pharmacy sales figures.

For Australia, data was taken from statistics provided by the Pharmaceutical Benefits Scheme (PBS) and the Repatriation Pharmaceutical Benefits Scheme (RPBS) that is in charge of funding prescription drugs in Australia. It includes all prescriptions reimbursed by the PBS for the general population and the RPBS for veterans. It excludes drug prescriptions not reimbursed by the PBS (including hospital prescriptions), that is to say 5% of all prescriptions.

patient is overweight or obese, otherwise metformin or sulphanomide.

In the United Kingdom and Australia, clinical guidelines are determined by the medico-economic analyses. The first line of treatment is thus oriented towards the older subclasses of anti-diabetic drugs that contain the less expensive products: metformin only in Australia, and metformin or a sulfonylurea, and in priority a sulfonylurea with a low acquisition cost, in the United Kingdom. In Australia and the United Kingdom, guidelines systematically hierarchize molecules for each treatment phase, contrary to French 2006 recommendations that allowed the choice of any appropriate molecule (AFSSAPS and HAS, 2006; Diabetes Australia, 2012; HAS, 2007; The National Collaborating Centre for Chronic Conditions, 2008). It should be noted that the new French recommendations published in January 2013 now advocate prescribing the least expensive molecules thus limiting choice in the matter (HAS and ANSM, 2013).

More or less widespread dissemination of information tools and prescription guidelines.

In this section, as a retrospective analysis is impossible, comments are based on tools available in 2012 and the beginning of 2013. There is considerable inter-country variation concerning the existence and dissemination of information tools and prescription guidelines. Whatever the country, recommendations are effectively published on the publishing authority's web site, but certain countries have gone even further. Up to 2013, the United Kingdom distinguished itself by its abundant supply of information tools aimed at physicians, whether to encourage efficient prescribing practices (interactive care pathway tool supplied by the NICE[1]) or to provide assistance in the implementation of recommendations (Guidance NICE[2]). In all countries, recommendations are relayed by learned societies (Association of British Clinical Diabetologists[3] , Royal Australian College of General Practitioners, Deutsche Diabetes Gesellschaft (DDG[4]), Société Francophone de Diabétologie [5]), but it can be more or less dynamic as in Australia where a support tool for the implementation of recommendations[6] is provided, or in Germany where the DDG proposes complementary training for diabetologists to obtain the title 'DDG certified diabetologist'. In Australia, the diabetic patients' association, Diabetes Australia[7], even provides information aimed at health professionals. Finally, certain authorities responsible for issuing recommendations have set up tools aimed at the patients: information concerning recommendations[8] or care quality standards[9] provided by the NICE in the United Kingdom, information files provided by the IQWIG[10] in Germany. Since the 1980s in the United Kingdom, a black triangle on the packaging and safety notices alerts users of high-risk drugs under intensive surveillance. This measure has recently been extended to all European countries and on April 25th 2013, the EMA published a first list of prescription drugs under surveillance[11].

In France, between May 2011 and January 2013, the only tool available to physicians on the HAS web site was the long-term illness (ALD[12]) guidelines that had not been updated since 2007. However, the new recommendations published in 2013 are now accompanied by numerous tools aimed at physicians (algorithm, interactive application to apply recommendations to each patient…) or patients (video)[13].

* * *

The management of new entrants on the prescription drug market has become essential in the regulation of health systems. In effect, the overly rapid diffusion of new drugs is a real risk without the necessary support to ensure their correct usage in conformity with recommendations in terms of quality and/or efficiency. International literature echoes these concerns and proposes management models for new market entrants including a three tier system of regulation: 1-prior to market entry including budgetary impact assessments and horizon scanning that consists in identifying molecules about to enter the market, 2-at the time the drug is

Method

Comparative methodology for prescription drug consumption

The four countries studied here represent varying population sizes (in 2011, 22.6 million inhabitants in Australia (Australian Bureau of Statistics, 2012), 63.2 million in the United Kingdom (Office for National Statistics, 2012), 65.1 million in France (Bellamy and Beaumel, 2013) and 81.8 million in Germany (Statistisches Bundesamt, 2012)). The analysis is based on indicators per inhabitant and therefore neutralises these differences. The results are expressed using two indicators: the Defined Daily Dose (DDD) is a unit of comparison proposed and recommended by the World Health Organisation (WHO, 2012). It represents the assumed maintenance dose per day for a drug used for its main indication to treat an adult weighing 70 kg and renders comparable drug consumption levels between countries. Another indicator based on standardised units is also used occasionally in international comparisons of drug consumption levels (Viens et al., 2007). It indicates the number of units used and is defined according to the smallest common dose for a product (for example the tablet, or the teaspoon for syrups…). One of the limitations of this type of indicator is 'that the smallest common dose in one country is not necessarily the same in another country since it depends on the pharmaceutical forms commercialised that can vary from one country to the next' (Viens et al., 2007). The comparison of consumption structures presented in DDD per 1000 inhabitants on the one hand and standard units on the other reveal inter-country differences in prescriptions. In the United Kingdom, for example, we observe a high prescription rate for biguanides in standard units whereas it is much lower in DDD. This paradoxical observation reveals prescribing practices more oriented towards low dosage metformin in the United Kingdom which explains both the low proportion of DDD and the high proportion of standard units.

In this study, data is mainly presented in DDD per 1,000 inhabitants per day.

1 http://pathways.nice.org.uk/pathways/diabetes
2 http://guidance.nice.org.uk/CG66
3 http://www.diabetologists-abcd.org.uk/home.htm
4 http://www.deutsche-diabetes-gesellschaft.de/ueber-uns.html
5 http://www.sfdiabete.org/
6 http://www.racgp.org.au/download/documents/Guidelines/Diabetes/cat1_rapidpdsacycles.pdf
7 http://www.diabetesaustralia.com.au/en/For-Health-Professionals
8 http://www.nice.org.uk/nicemedia/live/12165/44323/44323.pdf
9 http://www.nice.org.uk/nicemedia/live/13827/60174/60174.pdf
10 http://www.gesundheitsinformation.de/hormone
11 http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/04/WC500142466.pdf
12 http://www.has-sante.fr/portail/jcms/c_419389/ald-n8-diabete-de-type-2
13 http://www.has-sante.fr/portail/jcms/c_1022476/fr/strategie-medicamenteuse-du-controle-glycemique-du-diabete-de-type-2

launched, with clinical and economic evaluations and reimbursement procedures and finally, 3-after market entry with post-AMM studies on prescriptions, good practice recommendations and the dissemination of prescription guideline tools (Godman et al., 2012).

The example of new anti-diabetic drugs shows that practices differ considerably according to country and reveals a dividing line between countries that have implemented numerous measures or procedures accompanying new market entrants (United Kingdom and Australia) and countries where these practices are less developed (France and Germany). This has recently been confirmed with the arrival of new oral anticoagulants that have raised a number of questions regarding their safety, diffusion and cost (Malmström et al., 2013). In France, the programmed entry of new and ever more sophisticated, expensive molecules should be the occasion to introduce new regulatory tools. Foreign examples and literature appears to indicate that one can favour access to new technologies whilst at the same time guaranteeing patient safety, and the quality and efficiency of prescriptions. ♦

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Director of the publication: Yann Bourgueil •
Technical senior editor: Anne Evans •
Associate editor: Anna Marek •
Reviewer: Anna Marek •
Translator: Véronique Dandeker •
Layout compositor: Sandrine Béquignon•
ISSN: 1283-4769.

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