

Study on orphan drugs

Phase I

**Overview of the conditions
for marketing orphan drugs
in Europe**

We thank all those persons who were kind enough to give their time to help with this report, in particular François Cornu for his valuable help throughout the project.

Authors: Ariadne de Varax, Marc Letellier and Géraldine Börtlein, ALCIMED

Glossary

AFSSAPS	Agence Française de Sécurité Sanitaire des Produits de Santé
ALA	Acute lymphoblastic anaemia
ALS	Aziende Locali Sanitarie
ASMR	Amélioration du Service Médical Rendu
APL	Acute promyelocyte leukaemia
ARMD	Age related macular disease
ATI	All taxes included
ATU	Authorisation for Temporary Use
ATUc	ATU, cohort
ATUi	ATU, individual
CEPS	Comité Economique des Produits de Santé (Health Products Economic Commission)
CHU	Centre Hospitalier UnIntravenousersitaire (UnIntravenousersity Teaching Hospital)
CIPE	Comitato Interministeriale per la Programmazione Economica
CML	Chronic myeloid leukaemia
CNAM	Caisse Nationale d'Assurance Maladie (National Health Insurance Fund)
COMP	Committee of Orphan Medicinal Products
CPMP	Committee of Proprietary Medicinal Products
CPS	Carbamyl phosphatase synthetase
CTI	Cell Therapeutics
CVZ	College voor Zorgverzekeringen
DGCC	Direccao General do Comercio e da Concorrencia
DHOS	Direction de l'Hospitalisation et de l'Organisation des Soins (Office of Hospitalisation and Organisation of Care)
DSS	Direction de la Sécurité Sociale (Office of Social Security)
EMA	European Medical Evaluation Agency
ESP	Excellence in Specialty Pharmaceuticals
EU 25	European Union of 25
GIST	Gastro-intestinal stromal tumour

GMS	General Medical Service
HHS	Health and Human Services
HSC	Hematopoietic stem cells
INAMI	Institut National d'Assurance Maladie and d'Invalidité (National Institute of Health and Disability Insurance)
INFARMED	Instituto Nacional de Farmacia e do Medicamento
INTRAVENOUS	Intravenous
KELA	Kansaneläkelaitos
MA	Marketing Authorisation
MHLW	Ministry of Health Labour and Welfare
MPBT	Manufacturer's price before taxes
MPS	Mucopolysaccharidosis
NAGS	N-acetyl-glutamate synthetase
ND	Not determined
NHF	National Health Funds
NHS	National Health System
NICE	National Institute for Clinical Excellence
NORD	National Organization for Rare Disorders
OD(s)	Orphan Drug(s)
OODD	Office of Orphan Drug Development
PBB	Pharmaceutical Benefits Board
PCT	Primary Care Trust
PHT	Pulmonary Hypertension
PMDA	Pharmaceuticals and Medical Devices Agency
POM	Prescription Only Medicines
PPIT	Public price including taxes
PPRS	Pharmaceutical Price Regulation Scheme
QALY	Quality Adjusted Life Years
RFV	Riksförsäkringsverket
SSN	Servizio Sanitario Nazionale
T2A	Activity price determination
VAT	Value added tax

Table of contents

Glossary	3
Context and objective.....	6
Introduction.....	7
I/ Inventory of prices practised in the Europe of 25.....	12
II.1 Methodology	12
II.2 Distribution circuit and site of delivery	13
II.3 Manufacturer's prices before taxes	14
II.4 Public prices ATI and annual cost per patient	17
II.5 Pricing by the industry.....	19
II/ Inventory of accessibility levels in the Europe of 25	20
III.1 Methodology	20
III.2 Accessibility before the MA	21
III.3 Presence of the OD in the country concerned	22
III.4 Reimbursement	24
III.5 Interval between the date of the MA and that of commercialisation and/or listing for reimbursement	28
III.6 National policy in favour of ODS.....	29
III/ Inventory of price setting and reimbursement systems in the Europe of 25	30
IV.1 Criteria for evaluating price level and reimbursement.....	30
IV.2 Prices.....	31
IV.3 Reimbursement	32
IV/ Price comparators	33
V.1 Methodology	33
V.2 Comparison of the price of European ODs for their orphan and non-orphan indications	34
V.3 Comparison of the MPBT of American and European ODs	34
V.4 Cost analysis of European orphan drugs	35
V.5 Analysis of potential revenues from European orphan drugs.....	38
Summary	39

Context and objective

The conditions for marketing orphan drugs with European status in the EU 25 are poorly understood and are a source of concern for market players, whether they be Member States, patient associations or industry executives. Among the problems raised are differences in prices between countries, the « black box » of pricing and reimbursement systems, and the fairness of prices practiced. Moreover, homogeneity of accessibility to ODs in European countries is of major concern today.

The above issues motivated the European Commission to seek a precise overview of the conditions for marketing these products as well as to launch discussion over whether or not these costs are reasonable.

This will initially involve « mapping » prices and accessibility to these medicines in Europe by identifying distribution circuits, the mechanisms for pricing and reimbursement, and the reimbursement rates for these medicines in each country.

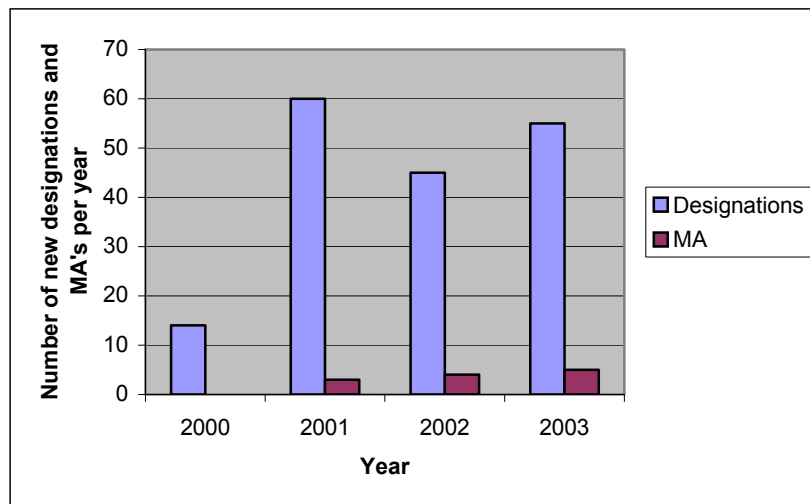
Secondly, in order to assess the costs of these treatments, they will be compared to various types of data (pricing practices for other non-orphan indications, suitable economic references to qualify pricing levels practices, drug company revenues from orphan drugs).

Introduction

The results after the first four years of application of European regulation EC141/2000 on orphan drugs are very encouraging.

At the present time, 198 orphan designations have been recorded by the COMP and 15 marketing authorisations for orphan drugs by the CPMP¹. These numbers are higher than those of the first four years of the American Orphan Drug Act (1983-1986), that included 93 designations and 17 marketing authorisations².

In addition, the dynamics of these first four years are positive, with a constant number of new designations every year and new MA's increasing by 25 to 30% per year (Figure 1).



Source: EMEA

Figure 1: Trends in the number of designations and Marketing Authorizations of orphan drugs since 2000

¹ EMEA, revised July 26, 2004

² « The US Orphan Drug Program, 1983-1995 », Shulman SR and Manocchia M, Pharmacoeconomics 1997 Sep; 12(3): 312-326

It should also be noted that this regulation has favoured the formation of a start-up incubator (since about 80% of the sponsors are small and medium size companies³) and European research has also been stimulated (since about 80% of the products were designed initially in Europe based on European research³).

Even so, it is premature to speak of a genuine success.

The 15 MA's have not all borne their expected fruits. Several problems remain to be resolved, including the time between obtaining the MA and commercialisation of these orphan drugs in Member States, the reimbursement of these products by each Member State and prescribing physicians' lack of experience concerning the real medical benefits of these medicines. This is why, in addition to their recent launch, most of these products have not yet reached their full market potential.

Finally precaution is the watchword concerning the conclusions of the present study of the conditions for marketing these first European orphan drugs, partly because the regulation is only 4 years old.


- As we have seen above, most of these orphan drugs have not yet proved themselves.
- In addition, among the 15 MA's, only 11 will be examined in this report, i.e. 10 orphan drugs of which one has two indications, since the most recent four are not yet effectively commercialised in Europe.
- Furthermore, these medicines account for a small part of all current and future treatments of rare diseases:
 - o medicines without an MA: off-label or compassionate use, as original or hospital preparations,
 - o medicines with an MA:

³ « Value of Innovation », EPPOSI Workshop, June 28, 2004

- medicines imported from the United States (about 100 accessible in the first 15 EU Member States and about 100 others accessible in at least one of the 15 States³),
 - orphan drugs with a national or European MA registered before the regulation,
 - finally, a pipeline of 177 designations that could become medicines commercialised within the coming years.
- Remember also that the new members of the European Union have arrived only recently.
 - Finally, the 10 orphan drugs studied here are highly diverse and cannot be considered in the same light (Appendix 1 and Table 1):
 - The origin of the active ingredients differs from one orphan medicine to another, requiring different levels of investment: an innovative active ingredient obtained chemically or via biotechnology, purification of a starting chemical product, reformulation of an active ingredient, extension of indications (for 2 of the 4 new medicines).
 - The potential market volume may also be very different:
 - prevalence from 0.03/10,000 to 0.95/10,000 depending on the pathology and the number of orphan indications per product,
 - place in the different therapeutic strategies (chronic treatment or not, first intent or not, highly specific indication for a given patient category,...),
 - presence of direct competitors (exceptional case of competition between similar medicines with the same indication) or indirect competitors (between non-similar medicines with the same indication),
 - product marketed outside Europe or not,

- different extent of understanding the pathology and thus different diagnostic levels.
- Finally the size, core business and strategies of MA holders are very different. There are three types of companies on the market: « big pharma » with global revenues in excess of € 20 billion, medium size companies with global revenues between € 0.2 and 2 billion and small companies with revenues less than € 50 million. This explains why the strategic role of these products differs from one sponsor to another: products whose revenues are used for corporate development, products enabling a company to position itself on a new market, anchor products for the company as a result of extensions of potential indications, products enabling a company to communicate on orphan drugs,...

Name of medicine	International Non-proprietary Name	MA holder	Indication	Date of EMEA Marketing Authorisation
Fabrazyme	Alpha-galactosidase A	Genzyme	Fabry's disease	03/08/2001
Replagal	Alpha-galactosidase A	TKT 5S	Fabry's disease	03/08/2001
Glivec	Imatinib mesylate	Novartis	Chronic myeloid leukaemia	07/11/2001
			CML (extension*)	19/12/2002
			Gastrointestinal stromal tumours (GIST)	24/05/2002
Trisenox	Arsenic trioxide	Cell Therapeutics	Acute promyelocyte leukaemia	05/03/2002
Tracleer	Bosentan	Actelion	Pulmonary hypertension, functional class III	15/05/2002
Somavert	Pegvisomant	Pfizer	Acromegaly	13/11/2002
Zavesca	Miglustat	Actelion	Gaucher's disease, type I	20/11/2002
Carbaglu	Carglumic acid	Orphan Europe	Hyperammonaemia secondary to an NAGS deficit	24/01/2003
Aldurazyme	Laronidase	Genzyme	Mucopolysaccharidosis type I (MPS I) (Hurler's syndrome)	10/06/2003
Busilvex	Busulfan	Pierre Fabre	Conditioning treatment prior to an HSC graft	09/07/2003
Ventavis	Iloprost	Schering AG	PHT, functional class III	16/09/2003
Onsenal	Celecoxib	Pfizer	Familial adenomatous polyps	17/10/2003
Photobarr	Porfimer Sodium	Axcan Pharma	High grade dysplasia with Barrett's oesophagus	25/03/2004
Litak	Cladribine	Lipomed	Indolent non-Hodgkin's lymphoma	14/04/2004

 Orphan drugs studied in this report

* Extension to children and newly diagnosed cases of CML

Table 1: The first 14 European orphan drugs

I/ Inventory of prices practised in the Europe of 25

II.1 Methodology

When we speak of « price », there are two distinct realities for a medicine.

First there is the manufacturer's price before taxes (MPBT) that is the pharma company's price to its clients (distributors, wholesalers, pharmacies, hospitals). This is the price to consider when we speak in terms of margin (or profit for the manufacturer).

Then we have the public price including taxes (PPIT) that, in addition to the MPBT, includes middleman mark-ups, taxes such as VAT or tax on advertising, etc. The latter is the price to consider when we speak in terms of health care expenditures or patient access to orphan drugs.

In order to validate the data gathered and be as thorough as possible, different sources of information have been used: data from the pharmaceutical industry, health authorities, retail or hospital pharmacies and national databases. Only one pharmaceutical form per product was used in order to simplify the analysis.

It should also be noted that in most cases the prices collected from the different sources are the same, although there are some divergences:

- PPIT can vary with the point of delivery: they are usually higher in retail pharmacies than in hospital pharmacies because of the respective profit margins and price/volume agreements that are possible for hospitals.
- In some cases (as in Italy) the public price can be as much as twice that of the hospital price. As a result, this public price is « virtual » for uniquely hospital-dispensed medicines and will not be considered in the analysis.

- When there is a difference in the sources of MPBT and PPIT, the values chosen in priority will be those of the industry or health authorities, followed arbitrarily by the lowest values (correction for any discrepancy due to a MPBT that is a wholesaler price in the case where this middleman exists, correction for a possible discrepancy resulting from a retail price or a negotiated public price that is not the same as the hospital price, which is generally lower).

II.2 Distribution circuit and site of delivery

(These raw data are found in Appendix 3)

There are two types of distribution for ODs:

- direct distribution by the MA holder in most countries, with several countries having exceptional recourse to an outside distributor, e.g. Genzyme medicines,
- distribution totally assured by an outside company for all the countries, e.g. the CTI product).

Concerning the site of delivery, ODs are often dispensed by a hospital pharmacy.

In most cases, orphan drugs are prescribed in a hospital. The few experts in charge of the management of these rare diseases are often hospital physicians who have been involved in clinical trials. Moreover, some orphan drugs are administered only in hospitals (Trisenox and Busilvex). In addition, networks of referral centres are being organized in some countries, e.g. France, to ensure an overall and consistent management of rare diseases. Finally, in some countries and for some products, the initial prescription or even all prescriptions are reserved for a few specialists. For example, in France the prescription of Tracleer is reserved for specialists in pneumology, cardiology and internal medicine, and that of Glivec to haematologists, oncologists, internal medicine specialists or gastroenterologists. In Spain a specialist must make the initial prescription of

Somavert, and in Holland all ODs must be prescribed by hospital specialists (Appendix 3).

Prescription in a hospital does not automatically mean that the medicine is delivered in the hospital. In some countries (Austria, or Sweden), practically all ODs are available in retail pharmacies. These countries employ either a mixed retail/hospital delivery system or uniquely retail. In addition, some ODs (Glivec and Somavert) are available in retail pharmacies in practically all countries. In France, there is also a special procedure called « hospital retrocession » that authorises hospital pharmacies to deliver certain medicines to outpatients (Fabrazyme, Replagal, Tracleer, Zavesca and Carbaglu).

II.3 Manufacturer's prices before taxes

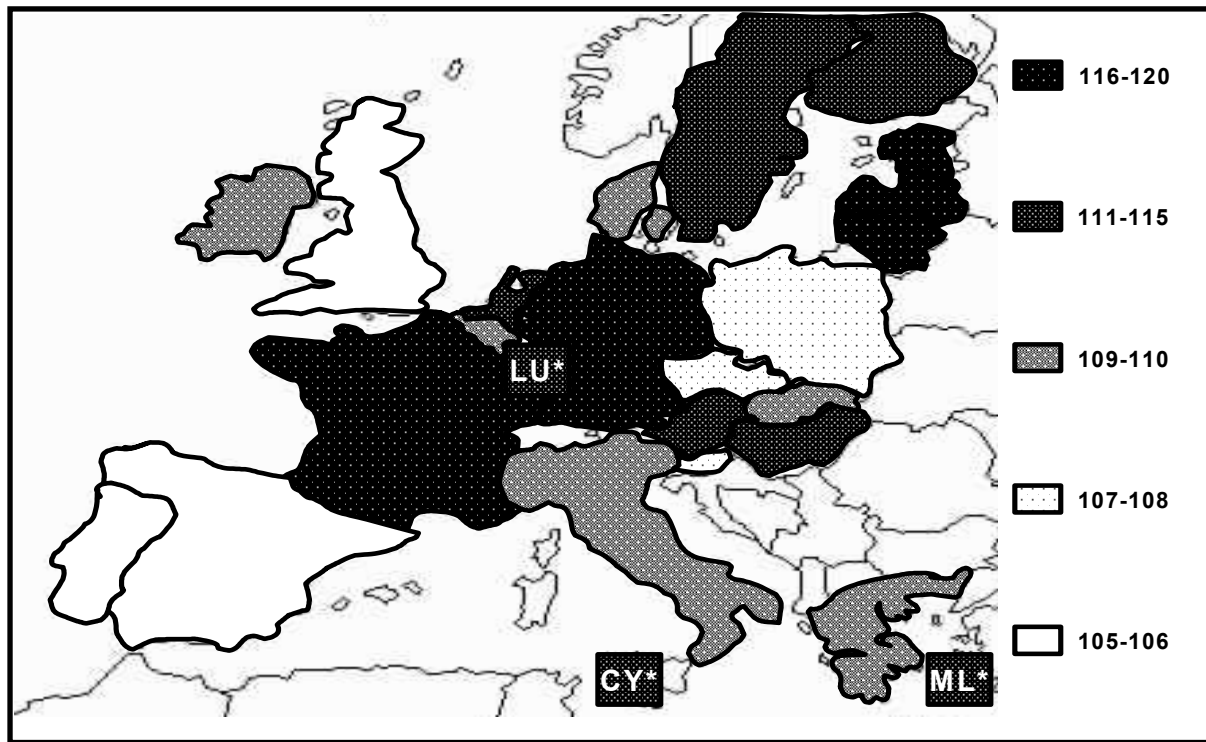
The analysis of the variability of MPBT among countries for the products in question reveals the existence of several phenomena.

First of all, it is quite clear that the pharmaceutical industry is trying to harmonise its prices so as to limit parallel imports. The maximal variations of MPBT between countries are in fact not very different, being on average 122% of the lowest price, and with the two the two extremes being 105% and 173% (Appendix 3).

Next, MPBT differences between countries do not obey a classical pharmaceutical industry scenario. Among the countries of the former EU of 15, the MPBT's of Germany and France are the highest, followed by Austria, Finland and Luxembourg, Holland, Sweden, then Belgium, Denmark, Greece, Ireland and Italy. The three countries with the lowest MPBT are Spain, Portugal and the United Kingdom. Furthermore, the new members are not at the same price level: MPBT's are higher in the smaller of new members, such as the three Baltic countries or Malta, than in the larger nations such as Poland or the Czech Republic (Map 1).

There are several reasons that explain these differences:

- In France, the Authorisations for Temporary Use system enables the drug company to freely set a price that will be 100% reimbursed. This is an incentive for setting high prices, since even once the Marketing Authorisation is obtained, the price practiced for an ATU remains unchained. It should also be noted that ODs are practically all hospital medicines in France and thus prices are set without restriction.
- In Germany, prices are freely set, which generally increases prices in comparison to the lowest figures.
- In the United Kingdom, in spite of an unrestricted launch price for a new product and a price level generally higher in the classical pharmaceutical industry, the PPRS and the pharmaco-economic guidelines of the NICE exert considerable pressure on the price of ODs.
- In the new countries of the EU 25, as well as in Greece and Ireland, the price level of ODs which are not among the lowest in Europe, as is traditionally found in the pharmaceutical industry, could be explained by the small market size that these countries represent.
- Spain and Portugal have kept their classical position of European countries where medicine prices are the lowest.



Source: Appendix 3
LU: Luxembourg, CY: Cyprus, ML: Malta

Map 1: MPBT (in mean percentage of the lowest price) in the EU 25

II.4 Public prices ATI and annual cost per patient

The PPIT was used to estimate the average annual cost per patient for each product and an average per country was calculated (map 2).

In this case, the ranking of countries is very different from the MPBT seen above. The four new categories of countries are: Austria with the highest annual cost per patient, followed by Germany and Denmark; then Finland, France and Ireland and finally Spain, Portugal, the United Kingdom and Sweden.

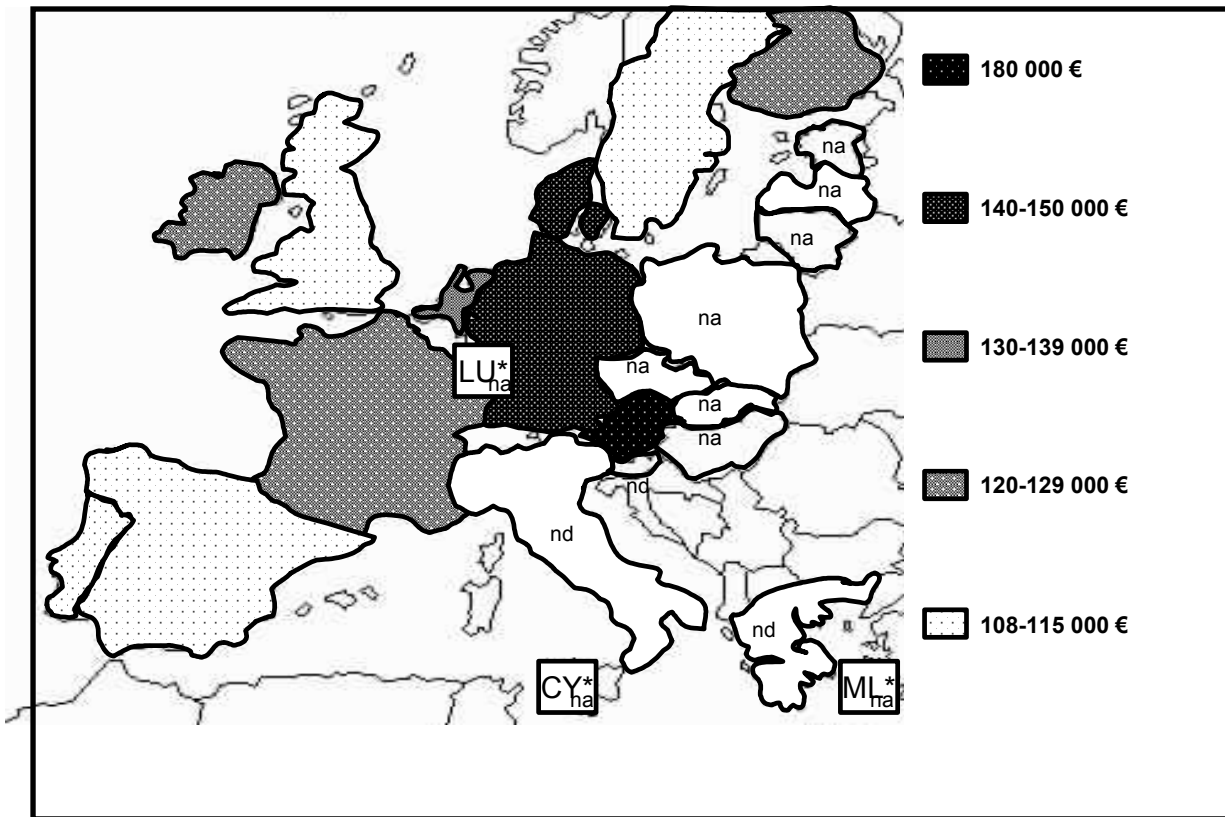
The price difference between countries (calculated on the basis of the PPIT) is much greater (ratio of about 1.7) than the difference in the MPBT (ratio of 1.2). Once again, this points out the fact that price differences between countries do not arise from the desire of sponsors, who try to harmonise their prices.

The PPIT/MPBT ratio can in fact vary from 1.00 to 1.60 depending on the country and the distribution site inside the country (Appendix 3).

The ratio can approach 1 in countries that do not require taxes on these medicines and that do not permit commercial transactions between hospital pharmacies and patients. This is the case for Luxembourg, Holland and Sweden. This ratio of 1.00 can also be encountered in some countries that allow mixed hospital/retail delivery.

In other countries this ratio can be in the range of 1.40 to 1.60. These are countries in which ODs are often distributed in retail pharmacies, or where taxes on medicines are high (Austria and Denmark).

It should also be noted that in some countries such as France, even if medicines are available only in hospitals and are exonerated from taxes on medicines, the PPIT/MPBT ratio is not 1, since hospital pharmacies can realise profit margins (15% in France) for medicines sold to outpatients in the context of « hospital retrocession ».



Source: Appendix 5
 LU: Luxembourg, CY: Cyprus, ML: Malta
 na: data not available

Map 2: Average annual cost per patient for ODs in the EU 25

II.5 Pricing by the industry

Beyond the mapping of orphan drug prices in Europe, it is interesting to observe that the prevalent pricing mechanisms employed by the Orphan Drugs Industry are similar to what is observed in the pharmaceutical industry in general.

The classical scenario is that the parent company sets an acceptable price level from the point of view of overall company profitability and return on investment for the product.

This price level is then compared to the reality of the target market: the objective then becomes to be as consistent as possible, in terms of the product's added value compared to current solutions, and with the available budgetary resources of company clients to acquire this product. This market reality may vary from one country to another and can explain price variations between countries. This price level thus corresponds to a one that can be defended during commercial and product promotion negotiations.

Finally, the price level is adapted to the regulatory restrictions of each country, in terms of both usual price administration criteria and reimbursement criteria. This is why the analysis of price and reimbursement levels accepted by health authorities for comparable products is extensively considered in defining the price requested by the company.

II/ Inventory of accessibility levels in the Europe of 25

III.1 Methodology

The best indicator of accessibility to a medicine is the proportion of patients who are effectively treated and reimbursed. At the European level, it is clear that very little data on ODs are available on this subject. No thorough study has in fact been conducted and only the industry has data on the volumes of medicines sold, that are not yet public, and that do not always include reimbursement rates.

This is why three other indicators were used: the number of medicines effectively marketed in the country, the number of medicines on a national reimbursement list and the interval between obtaining the MA and the dates the product is placed on the market and/or is reimbursed.

These three indicators correspond to the three distinct realities of the notion of accessibility, that determine the ease with which a patient can consume an orphan medicine: the possibility of obtaining a medicine in the patient's home country, the reimbursement of costs associated with administration of the product and the interval between obtaining the MA and the dates the product is placed on the market and is reimbursed.

This data was collected from two complementary sources: the pharmaceutical industry and health authorities (Appendices 3 and 7).

III.2 Accessibility before the MA

Before addressing the question of accessibility to ODs having obtained an MA, namely the 10 ODs studied here, it should be remembered that a first level of accessibility exists for ODs that are not yet authorised.

There are three types of non-MA possible accessibility: compassionate use, clinical trials and prescription of medicines authorised for another indication (« off-label » prescription).

The majority of the 10 ODs studied have been prescribed for compassionate use in some countries. France is in the lead for the compassionate use of these medicines, followed by Portugal (Appendix 3).

This mode of access to treatments has been authorised in Europe since May 1989 (Directive 89/341/EEC). Member States have the right to deliver non-authorised medicines domestically under certain conditions (specific need, recommendation of a medical expert, individual basis), and if the product is registered in a country, to make it available to other Member States.

Several regulations have thus been implemented at the national level, with two types of programmes: cohort or individual compassionate use. The principal differences between the countries involve⁴:

- whether or not these two programmes are cumulated,
- the demand for an authorisation from the competent national authority or simple delivery after notification of the pharmacist,
- assuming responsibility by the physician or the drug company,
- authorisation only if the medicine is or is not already registered in certain countries,

⁴ « Compassionate Use and Early Access to the Market in the USA and EU », Bourg E and de Crémiers F, The Regulatory Affairs Journal, 2000, Vol 11 (9), 640--645

- and the origin of the budget (patient, industry, hospital or national health insurance system)

Accessibility nevertheless remains limited by the origin of the budget. Only the French and Portuguese systems systematically reimburse these prescriptions, either via the hospital budget or national health insurance systems⁴. It should not be forgotten that price negotiations between the industry and health authorities are particularly difficult since the medicines are still investigational new drugs.

In addition, within the framework of clinical trials, these 10 ODs were already accessible to recruited patients before the MA was granted. In this case, the sponsor assumes the entire treatment, but accessibility nevertheless remains limited only to included patients.

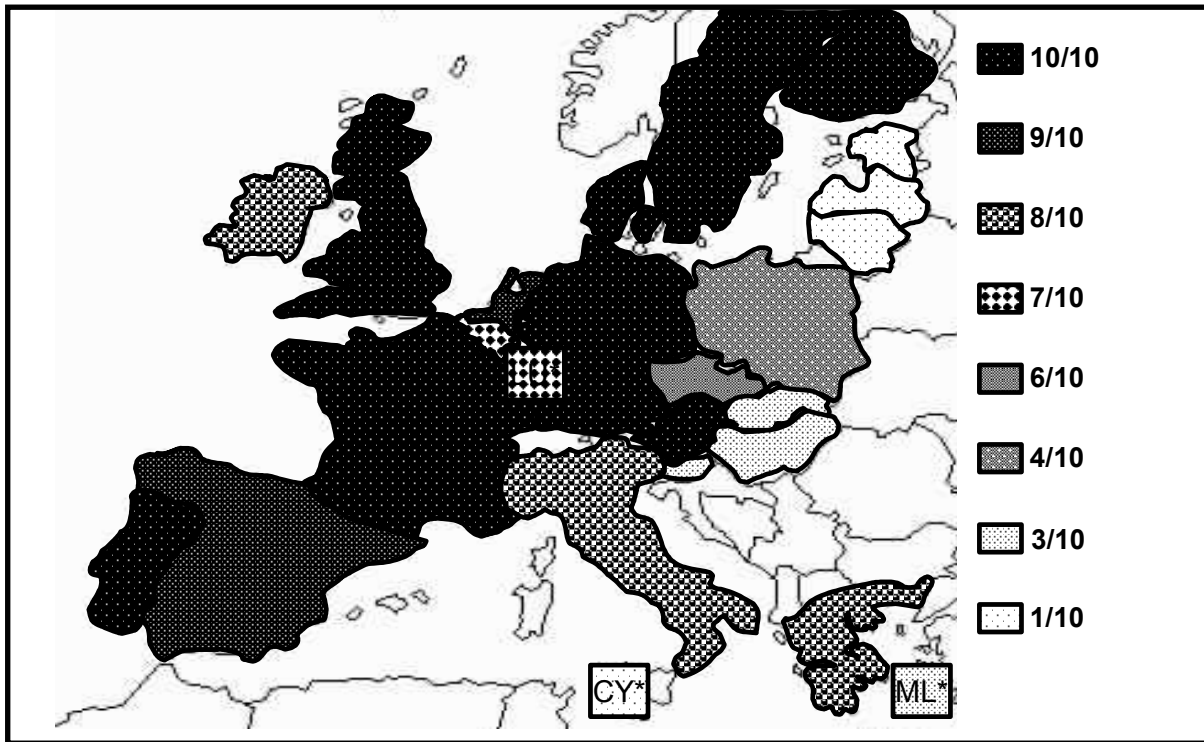
Finally, in the case of ODs that have already received an MA for another indication, e.g. Glivec, Onsenal or Photobarr, practitioners can prescribe these products for the new, as yet unauthorised indication. This is not the most ideal form of accessibility due to its associated health risks (absence of control that, on the contrary is present in cases of compassionate use and clinical trials).

III.3 Presence of the OD in the country concerned

The truest indication of the accessibility of an OD with an MA is the presence of the medicine in the country in question. This is not a very limiting factor in accessibility to orphan treatments. In fact, there are two existing possibilities:

- The product is distributed by a country's own network and is rapidly available in case of need in pharmacies authorised to deliver it. This is the case for more than half the ODs in the Europe of 15 and is starting to become the case in the largest new members, such as Poland and the Czech Republic (map 3).

- The product is not subjected to specific distribution but can be ordered from the company, which then organises its importation on a case-by-case basis. For example, in the three Baltic nations, some ODs can be obtained in this way (Appendix 3). In all cases, it is possible to obtain any of the 10 medicines right throughout the Union and all the companies concerned propose this service, particularly when there is no local distribution structure (case of small pharmaceutical companies).



Source: Appendix 3 and 7

*LU: Luxembourg, CY: Cyprus, ML: Malta

Map 3: Number of ODs marketed in the EU 25

III.4 Reimbursement

The second factor conditioning access to health care is the reimbursement of these treatments by national health insurance systems. The annual cost of these treatments (€ 6,000 to 300,000) is beyond the possibilities of average households. Maximal accessibility to a treatment thus involves total reimbursement of the treatment by insurance. This requires total coverage of a given patient and reimbursement of all the patients in a country.

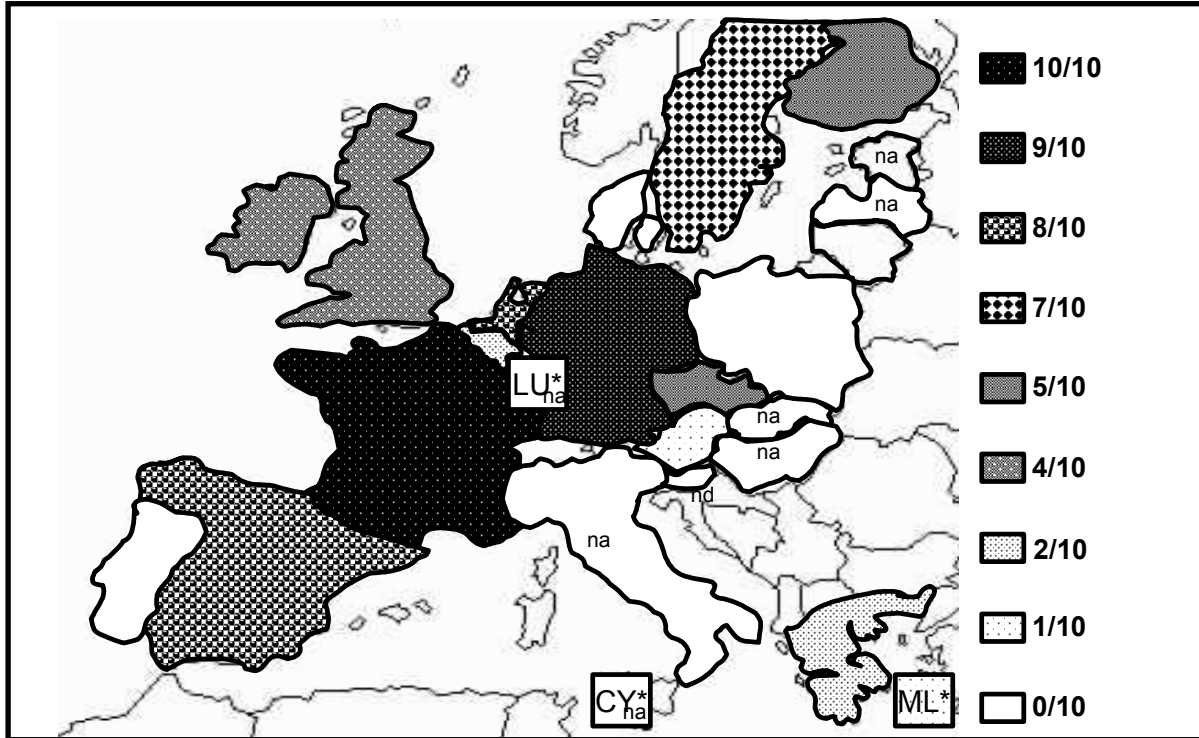
There are two situations in Europe:

- The OD is included in the national reimbursement list,
- It is not.

It should also be borne in mind that most of these ODs have received a conditional MA that requires conducting post-MA clinical trials for which a certain number of patients benefit from the treatment free of charge, outside the context of classical commercialisation.

III.4.1 ODs on a national reimbursement list

In most cases, ODs on a national reimbursement list are automatically reimbursed. Some countries such as Germany, Spain, France, Holland and Sweden have adopted this policy (map 4).



Source: Appendix 3 and 7

LU: Luxembourg, CY: Cyprus, ML: Malta

na: data not available

Comment: Exclusively hospital medicines are not on a reimbursement list in Denmark and Portugal

Map 4: Number of ODs on a national reimbursement list in the EU 25

This would seem to be the most sure way of guaranteeing access to patients, but two considerations influence the quality of this reimbursement: the reimbursement rate accorded and the origin of the budget. These two criteria often depend on the type of list chosen for ODs.

Since reimbursement for ODs is often close to 100%, this is not a limiting factor to their access:

- the medicine is dispensed in a hospital and is totally paid for,

- the medicine is on a special list of innovative and/or costly and/or vital medicines that includes 100% reimbursement, e.g. Category A medicines in Belgium, the special Austrian list, the Irish « High Tech Scheme », the list of essential French medicines,
- the medicine is part of a classical list of partially reimbursed medicines but with a « payable » limit for the patient, that is systematically exceeded by the cost of ODs (Finland, Spain or Germany),
- the OD cannot be included in the price reference system (set in some countries such as Germany) in the absence of a therapeutic alternative and is thus entirely reimbursed.

There are special considerations to be given to the new Member States. Faced with budget difficulties (for the same population, health care budgets can be as much as 10 times lower than in the 15 countries of the "old" EU (Appendix 7)), reimbursement levels can differ. In the Czech Republic for example, a maximum reimbursed price is set at the national level, which can be included between 70% and 99% of the PPIT.

The nature of the budgets, hospital or not, local or national, dedicated or not, will also affect access to treatments, enabling a more or less rapid delivery of the budget and introducing varying degrees of disparity between regions and hospitals.

As a result of their hospital nature, many ODs are reimbursed in several countries by the overall hospital budgets (case of France up to the present, Greece, Spain, Portugal, Sweden,...). This mode of reimbursement leads to disparities of access between hospitals that do not all have the capacity to assume this cost at the level of the establishment.

In addition, while health insurance systems are nationally funded in some countries, such as in France or Belgium, funding comes from premiums of local contributors in countries such as Germany, Spain or Finland, giving rise to accessibility differences between

regions. It should be noted that hospital budgets are also funded either locally or nationally.

Finally, ODs are on a list of specific medicines in some countries and may be granted a dedicated budget, whether or not they are hospital drugs. This is the case of the Irish « High Tech Scheme », the soon to be French list « of costly and/or innovative medicines » or ODs on the list of medicines benefiting from a government subsidy in Holland. It should also be noted that public health programmes specific to a given disease with dedicated budgets have been implemented, for example Gaucher's disease in Portugal.

Finally, even after an OD is on a list and its reimbursement is more systematic, it is still particularly controlled: specific lists to which ODs often belong, e.g. the Austrian Special List, may provide for an examination of patient files individually.

III.4.2 ODs not included in a national reimbursement list

ODs not on an official reimbursement list are reimbursed on a patient by patient basis, generally with the submission of a patient file by the prescribing physician to the health insurance organization. This reimbursement can occur either after examination of a file by a central authority or without any systematic procedure. This situation complicates reimbursement and reduces the level of accessibility. The origin of this situation involves several scenarios:

- a national policy of not placing hospital medicines on a reimbursement list (Denmark or Portugal); in this case, ODs in these countries are essentially hospital-dispensed drugs and are not on an official list,
- the delay before the end of the procedure for listing on the national reimbursement list, especially for certain medicines in Belgium or Austria,

- the absence of a demand for inclusion on a national reimbursement list, as is the case for most ODs available in Austria and the United Kingdom,
- the impossibility of placing the OD on a national reimbursement list (the case of most new Member States).

There may be several budget origins in this case:

- public budget (non-dedicated via the hospital or national health insurance funds, or dedicated in the framework of special public health programmes such as in Poland for certain rare pathologies, in Belgium for the payment of treatments before inclusion on the reimbursement list),
- budget accorded by the sponsor (in a humanitarian context such as the example of Genzyme),
- private budget from private insurance or the patient himself (to finance all or part of the treatment).

III.5 Interval between the date of the MA and that of commercialisation and/or listing for reimbursement

Another factor correlated with accessibility to orphan drugs and closely linked to the « reimbursement » factor is the time taken to analyse « price and reimbursement » applications in the different countries of the Union. A possible tool for measuring this parameter is to monitor the intervals between the date of the European MA and the date the medicine is reimbursed. Several difficulties have been encountered when carrying out this measurement:

- Initially, the date reimbursement is granted is not always the date on which the product is placed on the market. Orphan drugs may in fact be available before the end of application analyses by competent authorities and even without having submitted an application with the competent authority.

- The results of the survey of Member States on the time taken to analyse application dossiers are not sufficiently complete (Appendix 7),
- In addition, the observed differences in these intervals are just as great between several ODs in the same country as for the same product between different countries (Appendix 6).
- Finally, during the period « MA date – date launched on the market», it is not always easy to distinguish between the interval related to the drug company's submission of the file, and that pertaining to examination of the application. It is in fact quite clear that for a number of countries (« small countries» and new Member States in particular), the company prefers not to submit the application at the national level. For new members, companies have decided to wait for admission and the extension of the European MA to these countries before submitting a dossier.

III.6 National policy in favour of ODs

Faced with the diversity of these situations (schematically, each medicine in each country is a specific case), it would seem that the one real factor of accessibility is a strong desire (politically motivated by the professionals managing these pathologies or by patient associations) to favour orphan drugs and have them handled specifically in well-established procedures.

The examples of France and Holland illustrate this. These two countries are among the « best students » in patient access to ODs and they are also the only countries to have instituted a specific commission for ODs in their respective Ministries.

III/ Inventory of price setting and reimbursement systems in the Europe of 25

Orphan drugs follow the classical system of pricing and reimbursement in the Europe of 25. Nevertheless, these medicines are often reserved for hospitals and thus subjected to specific procedures. They are often cases of exception in negotiations and granting reimbursement due to public health issues.

The data used for this analysis can be found in Appendices 3 and 7.

IV.1 Criteria for evaluating price level and reimbursement

Most countries have either one competent national authority, e.g. the NICE in the United Kingdom or the Transparency Commission in France, or several decentralised authorities (as is Germany up to the present) that publish reference guidelines for pricing and reimbursement negotiations for medicines.

The following criteria may be used: the prices practised in other European countries, the extent of investment by the company and the level of innovation, the medical benefit, the costs of comparators or more generally the level of « cost effectiveness ». For orphan drugs, however, price setting remains highly arbitrary since by definition these medicines do not have an alternative and their level of medical benefit is often still the subject of investigation. Faced with this situation, health authorities have limited negotiating power and often accept the price announced by the company, all the more so since they are influenced by the media and patient associations. In order to determine the true value of orphan drugs, however, some Member States, in particular the United Kingdom but also Finland and Holland, refer to « cost effectiveness » (gain provided by the medicine over total expenses for managing the pathology) and to QALY (Quality Adjusted Life Years, or the improvement level of the patient's quality of life).

IV.2 Prices

Even if ODs are most often hospital drugs, they may also be available in retail pharmacies. This is why the two systems for pricing hospital and outpatient medicines should be examined.

IV.1.1 Retail pharmacies

In most EU countries, with the exception of Germany and the United Kingdom and perhaps several new members where prices are unrestricted, the price of medicines delivered to outpatients is regulated by a competent authority.

Nevertheless, in the United Kingdom a control of overall company profit is conducted (the PPRS), which can lead to a revision of the initially unrestricted price. In addition, in Germany the freely set price must be published in order to guarantee its uniform application.

IV.1.2 Hospital medicines

For most ODs delivered in a hospital, on the other hand, prices are most often unrestricted. Individual or groups of hospitals negotiate the price with the company on the basis of price/volume agreements, which also explains the possible price differences between hospitals.

Even so, some countries such as Belgium, Spain, Greece and Italy exert price control. In Spain, a maximum price is accepted at the national level. In Italy, a « virtual » public price in the case of uniquely hospital medicines is decided on the national level: the real price of the medicine delivered by a hospital pharmacy must not exceed 67% of this price,

although there are several exceptional cases such as biological medicines and certain orphan products, where this discount is not obligatory.

Finally, the French exception of « hospital retrocession » that allows hospital pharmacies to deliver medicines to outpatients who in turn are reimbursed by the national health insurance system, is currently being reformed: prices that were once unregulated will be controlled at the national level.

IV.3 Reimbursement

The same competent authority can carry out the stages of both pricing and reimbursement (as in Ireland, Lithuania, France or Scandinavian countries), or this can be done by two different commissions (as in Belgium, Malta or Spain). Even though the data gathered on the intervals are neither comprehensive nor objective, it would seem that the separate evaluation of these two steps increases the total duration of the procedure (Appendix 7).

The reimbursement rates accorded and the origin of budgets have been discussed in part III.

IV/ Price comparators

V.1 Methodology

First of all, this analysis should be considered with precaution since it is based on only 10 products. Furthermore, apart from geographic comparisons between the United States and Europe, where an average European price will be estimated, the prices practised in France will be used as reference since this is the country from which the largest quantity of data could be obtained.

Four types of comparisons were made:

- Comparison of the price of European ODs for their orphan and non-orphan indications
- Comparison of the average European MPBT with the American MPBT for ODs marketed in Europe and the United States. It is not possible to compare the annual cost per patient because in the United States it is extremely difficult to determine the average public price, since hospital margins are not controlled.
- Cost analysis of European orphan drugs:
 - o Individual cost per patient: this analysis involves determining what types of indicators can be compared to the individual price of each European OD and is based on the annual cost per patient of ODs in France that it compares to four indicators: the medical benefit, the origin of the active ingredient, prevalence and annual cost per patient of treatments with the same therapeutic target.
 - o Average cost per patient: this positions the average cost of these ODs per patient with respect to two indicators: cost per patient in the EU of ODs without European status and that of non-orphan medicines but that are

considered as expensive and innovative and/or that treat severe diseases.

These comparisons that are independent of the countries use French data.

- Average cost per country: this estimates the average cost per orphan medicine per country, and the proportion of total medicinal product budgets devoted to European ODs, both today and after 10 years of existence of the regulation. This analysis was conducted in France and Holland, where a maximum of data is available.
- Analysis of potential revenues from orphan drugs, revenues that will be estimated on the basis of currently available data.

V.2 Comparison of the price of European ODs for their orphan and non-orphan indications

The only two European ODs that received an MA for an orphan indication whereas they had already been on the market for non-orphan indications are Onsenal and Photobarr (Appendix 1). Glivec also has two indications but both are orphan and the price of this medicine is the same regardless of the indication.

It has not been possible to conduct this comparison for Onsenal and Photobarr since these medicines have been authorised only very recently and have not yet been priced by Member States. The data gathered indicates only that even though the brand name and pharmaceutical form of Onsenal have changed, there is no change in the formulation compared to Celebrex, and that this medicine is marketed in the United States for non-orphan and orphan indications under the same brand name, the same pharmaceutical form and the same price.

V.3 Comparison of the MPBT of American and European ODs

The MPBT of the 8 ODs marketed in Europe and America is approximately the same (Appendix 9). It is difficult to conclude on differences in the annual cost per patient

between Europe and the United States because American data is unknown and also because there are diverging opinions on the question.

V.4 Cost analysis of European orphan drugs

V.4.1 Analysis of individual cost per patient of European orphan drugs

V.4.1.1 Medical benefit, origin of the active ingredient and prevalence

There is apparently only a correlation between the cost per patient of ODs and the prevalence of the indicated diseases or conditions.

Concerning the medical benefit (Appendix 2), the two 2 ODs most appreciated in France (level I ASMR) are not the most costly. It is in fact very difficult to estimate the medical benefit of orphan drugs. Experts do not have sufficient experience for determining the real impact of these medicines on life expectancy and patients' quality of life. The absence of ASMR in France for some of these ODs is proof of this (Appendix 1).

In addition, it was not possible to conclude on a correlation between cost per patient of ODs and the origin of the active ingredient (Appendix 2) since the most expensive product is in one of the two categories of least innovative active ingredients and that one of the least expensive is in that of the most innovative.

On the other hand, figure 1 shows that the rarer the target disease, the more expensive treatment is per patient.

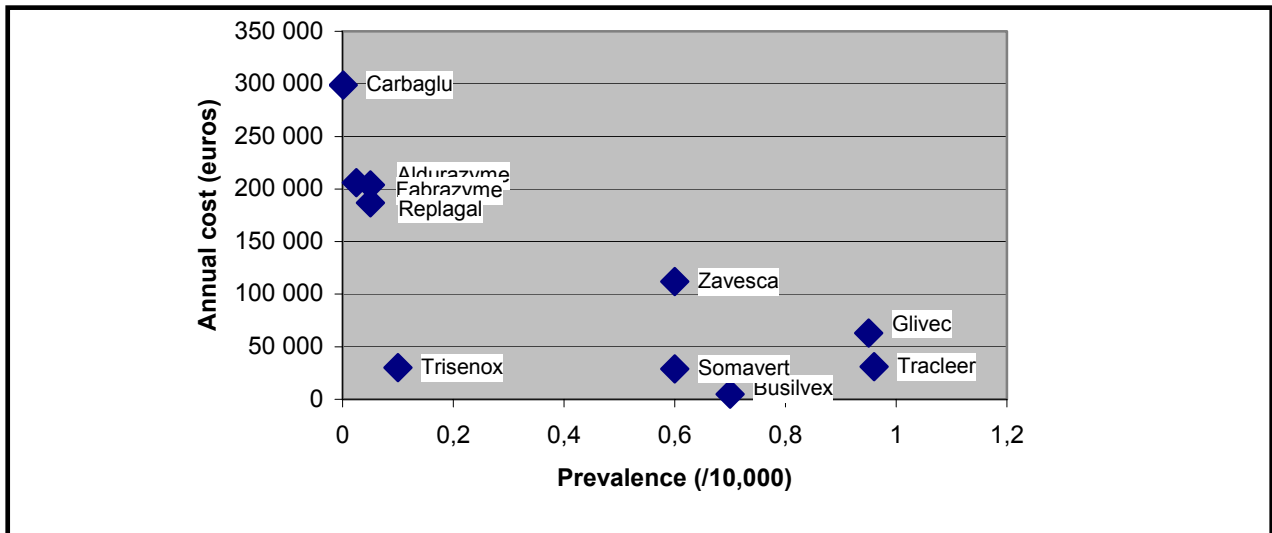


Figure 1: Correlation between annual cost per patient and prevalence

V.4.1.2 Annual cost per patient of treatments with the same therapeutic target

The cost per patient of the 10 ODs studied can be compared to that of treatments with the same therapeutic target. It should nevertheless be mentioned that these treatments (not counting the exceptional cases of Fabrazyme with Replagal, and Tracleer with Flolan and Ventavis) are not alternatives but are used at other levels in the therapeutic strategy.

The analysis revealed three types of situations (Appendix 10):

- surgical treatments (bone marrow transplant, lung transplant, blood clot resorbition,...) are in most cases 2 to 3 times more expensive than the ODs studied,
- orphan drugs without European status, e.g. Cerezyme or Flolan, or non-orphan drugs (classical chemotherapy) are 1.5 to 3 times more expensive than the ODs studied,
- finally, orphan drugs without European status, e.g. Ammonaps or Myleran are 10 to 20 times less expensive than the ODs studied. In this case, the higher cost of

the ODs studied is explained by a superior medical benefit (better specificity, better absorption, better patient compliance,...).

V.4.2 Analysis of average cost per patient of European orphan drugs

The average cost per patient of the 10 ODs studied in France is about 3 times higher than that of ODs without European status (ODs imported from the United States and/or marketed before the regulation, such as Cystagon, Cerezyme, Tobi or Flolan,...) (Appendix 11). It is also about 10 times higher than that of non-orphan medicines but which are still considered expensive since they are innovative and/or treat severe diseases (tritherapy, chemotherapy, Remicade, Actilyse or Aranesp,...) (Appendix 12). These two observations should be considered with precaution, however, since again the analysis is based on a small number of products (the cost scale of the 10 ODs studied ranges between € 6,000 euros and € 300,000, while within the four most recently authorised ODs, the annual cost per patient of Onsenal, if it does not differ from that of Celecoxib would be € 2000⁵ and would thus be outside this scale).

V.4.3 Analysis of average cost per country of European orphan drugs

Even if, as seen above, the annual cost per patient of these orphan drugs is higher than that of other treatments already considered expensive, their cost expressed on the basis of the total population of a country would be lower than these medicines. The prevalence of the rare diseases studied is in fact on average 100 times lower than that of the pathologies indicated for comparative medicines, for example rheumatoid arthritis, HIV or ARMD (Appendix 13).

⁵ DHOS, Dutch Steering Committee Orphan Drugs

In addition, ODs currently account for only a small part of national health budgets.

Based on analyses conducted in France and Holland (Appendices 14 and 14'), the total cost of European ODs per country in 2004 was estimated at between 0.7 and 1% of national budgets earmarked for medicines.

This part may, however, become non-negligible after 10 years of the regulation. The French and Dutch analyses predict that it will reach 6 to 8% of total budgets by 2010.

V.5 Analysis of potential revenues from European orphan drugs

The potential revenues from some of the 10 ODs studied were estimated using current sales figures, the potential market in terms of patient numbers (obtained from epidemiological data modified with respect to the place of the medicine in the therapeutic strategy and the presence of indirect competitor treatments) and of current market penetration (French data on the number of patients treated in Appendix 15). It should not be forgotten that this estimation is based on epidemiological data that are not totally reliable and that can change in either direction, and on the hypothesis of non-competition, while in spite of market exclusivity non-similar competing medicines could be marketed. Finally, in order to avoid introducing a misleading bias with the non-representative case of the European OD status of the two direct competing medicines Fabrazyme and Replagal, the total potential market of these two ODs was taken into account.

The analysis concluded that estimated potential annual turnover is included between € 100 million and 1.5 billion, depending on the medicine (2002-2003 figures, Appendix 16). Thus, even if some ODs could become « blockbusters », the maximal sales of these medicines would remain below real sales of the top ten medicines, that are included between € 2 and 7 billion (2002 figures, Appendix 16).

Summary

- Differences in annual costs per patient between the countries of the EU 25 for a given OD may reach 70%. These differences arise more from different distribution and taxation policies between countries than from differences in original manufacturer's prices, which is more uniform between countries and which reflects the desires of pharma companies to harmonise their prices (prices also equivalent to those in the United States).
- It is difficult to determine accessibility to ODs in Europe, partly because the delivery of these medicines, often in hospitals, is not monitored. But the analysis did reveal two facts: more than half of these ODs are marketed in the first 15 EU countries, and that the several « good students », i.e. countries in which a maximum of ODs are on a reimbursement list and thus benefit from systematic reimbursement, are France, Germany, Spain, Holland and Sweden.
- National systems of drug pricing and reimbursement of ODs are linked to accessibility and are the same as those applied to classical medicines. Nevertheless, their cost is most often non-regulated and their reimbursement total because in some countries they are on a list of specific products and are often delivered in hospitals. In addition, Member States have little negotiating leverage since these medicines have no therapeutic alternative and are often still investigational new drugs. Finally, ODs are less totally reimbursed in the new EU members whose health budgets may be 10 times lower than those of other Member States.
- Finally, concerning the fairness of OD prices, even though the average cost per patient of an OD is higher than that of other medicines considered expensive in Europe, given the narrowness of the markets considered here, on the one hand this cost is no higher than that of treatments with the same therapeutic target, and on the other hand the total cost of ODs currently accounts for only a small part of total budgets earmarked for medicinal products.