ISPOR Educational Symposia

ORPHAN DRUGS IN EUROPE: FUNDING CHALLENGES FOR PAYERS AND DEVELOPERS

ISPOR 13th European Congress, Prague, November 6th, 2010

Overview

- The development of new orphan drugs (OD) appears to give patients with rare diseases opportunities for newer and better treatments; however, the challenges for health authorities, sickness funds, or insurers to pay for these new treatments are becoming more acute.
- Unless new ways of funding and allowing patients access to these new drugs can be found, the lack of commercial incentives may discourage future development.
- This symposium will explore various challenges and issues associated with funding for and patient access to orphan drugs.
- An emphasis will be placed on recent developments and expected changes to the market access environment which could lead to easier and broader market access for orphan technologies and hence better incentives for developers to invest in such technologies.
- Our panellists will present different stakeholder perspectives regarding some of the key issues to set out how the environment is changing, followed by a panel discussion to answer delegates’ questions.

Agenda

- Introduction to the key issues and challenges
  Adam Barak, UBC
- Patient access for ODs: towards a new consensus
  - Recent EU and Member State initiatives e.g. EUROPLAN/CAVOD/EURORDIS initiatives; Societal vs economic challenges.
    Wills Hughes-Wilson, Genzyme
- OD access in Germany: an IQWiG perspective
  - Decision-making for ODs; if and what concessions should be made; impact of high prices, possible AMNOG OD exemptions.
    Dr Stefan Lange, IQWiG
- In-market challenges for ODs
  - OD HTA; new UK AGNSS process; potential solutions moving forward incl. optimising cost-effectiveness analysis, evidence generation methods and patient registries/PROs; broadening evaluative scope.
    Francis Pang, Shire Human Genetic Therapies
- Audience Q&A

Definition

- “Orphan Drugs: Medicinal products intended for diagnosis, prevention or treatment of life-threatening or debilitating rare diseases. They are ‘orphans’ because the pharmaceutical industry has little interest under normal market conditions in developing and marketing drugs intended for only a small number of patients suffering from very rare condition” Source: EURORDIS (www.eurordis.org)

- Orphan Disease criteria varies:
  - EU = <5 per 10,000
  - USA = <200,000 or prevalence <7.5 per 10,000
  - Japan = 2.5 cases per 10,000
  - WHO = 6.5-10 per 10,000

- Why Orphan Drugs are Different – The Challenge
  - Very low patient numbers
    - Misdiagnosis / under-reporting
    - Few specialist treatment centres
    - But lots of ODs (30m Europeans, 25m North Americans)
    - 5000-8000 rare diseases affect 3-6% of the total EU population
  - Extreme unmet need
    - No effective therapies ever, desperation
    - Death or serious morbidity without treatment
    - Often children and babies affected
  - Potential to “cure” or significantly
    - Extend life
    - Improve quality of life
  - Potential good sales revenue but high R&D risk
    - Clinical trials difficult (itraconazole severe fungal infection study: 10y to recruit 39pts)
    - Significant investment vs uncertain outcomes
  - Difficult to recoup R&D costs without “disproportionate price”
    - Especially for smaller companies

- Funding Orphan Drugs
  - Pricing (can be) very contentious
  - Payers have to “fairly” distribute scarce resources to needy cases
    - Who is to say which group should be funded and which miss out?
  - Cost justification arguments different to ‘regular pharma’
    - QALY > $150,000 / £100,000 not atypical
    - Chronic, expensive therapy for decades
    - Cost offsets not straightforward
    - ‘Equity-weighted QALYs’
      - age, baseline health status,
  - Payers devolving funding decisions can create inequities:
    - Aldurazyme (MPS I) funded by some regional UK payers but not others
    - Soliris (PNH) funded by some Spanish Autonomous Regions, not others

*Weinstein, Torrance & McGuire. Value in Health Vol 12, supl 1, 2007

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HTAs for Orphan Drugs

- NICE (UK) discussing since 2004
  - 2006 Proposal to Department of Health separated out
    - Orphan <5 per 10,000
    - Ultra Orphan 1 in 50,000 (or less than 1,000 in UK)
- Appreciation that special case makes assessment hard but ODs can be reviewed normally, but for UODs additional factors should be considered (Genzyme's Ceredase for Gaucher’s Disease was used as a case study)
- Examples:

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Brand</th>
<th>Company</th>
<th>Condition</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imiglucerase</td>
<td>Cerezyme®</td>
<td>Genzyme</td>
<td>Gaucher’s Disease</td>
<td>Possible for multiple agents to be granted Orphan status</td>
</tr>
<tr>
<td>Velaglucerase alfa</td>
<td>Vpvr®</td>
<td>Shire</td>
<td>Gaucher’s Disease</td>
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<tr>
<td>Miglustat</td>
<td>Zavesca®</td>
<td>Actelion</td>
<td>Gaucher’s Disease</td>
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<tr>
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<td>Soliris®</td>
<td>Alexion</td>
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Some examples

Molecule | Brand | Company | Condition | Comments |
----------|-------|---------|-----------|----------|
Imiglucerase | Cerezyme® | Genzyme | Gaucher’s Disease | Possible for multiple agents to be granted Orphan status |
Velaglucerase alfa | Vpvr® | Shire | Gaucher’s Disease | |
Miglustat | Zavesca® | Actelion | Gaucher’s Disease | |
Eculizumab | Soliris® | Alexion | Paroxysmal nocturnal haemoglobinuria | Cost ~€300,000/yr |
Zinc acetate | Wilzin® | Orphan Europe | Wilson’s disease | $4.50/day |

Regulatory Enthusiasm to Address the Issue

- Financial and other incentives to encourage R&D and investment in ODs
  - Extended market exclusivity (7-10 years)
  - Tax and fee reductions (clinical trials, inspections, MAs)
  - Protocol assistance, free advice
  - Research grants
  - Central European filing / expedited regulatory review

Regulatory Enthusiasm to Encourage Rare Disease Treatment

- Governments, payers, regulators and patients keen to improve patient access to orphan medicines – number of dedicated bodies already in place:
  - USA 1983 (Orphan Drug Act, Office of Orphan Products Development), 2115 products designated, 344 (16%) FDA approved
  - First OD to be approved: diaziquone (1983) for treatment of primary brain malignancy
  - Japan 1993
  - Australia 1998
  - Europe 2000 (EU Orphan Drug Regulation, COMP), 725 ODs (around ⅓ in oncology and ⅓ enzymes / metabolic)

- Governmental Initiatives
  - MS (Spanish Govt. grant €16m 2008) into R&D where little commercial interest
  - EC
  - Also various NGOs
    - EURORDIS (alliance of Eur. Patient organisations)
    - NORD (National Organization for Rare Diseases) runs >30 OD programmes
  - CLIMB (UK), GIG (USA), EPPOSI (Ita), FEDER (Esp) etc.

Steady stream of OD applications – ‘no avalanche’

ORPHAN DRUGS APPROVED AND REIMBURSED BY THE NHS IN SPAIN DURING LAST 5 YEARS

Expected that 10 new ODs will be approved for marketing every year in the EU over the next 5 to 10 years [Tejada, 2010]
In lieu of financial support for our speakers today, a charitable donation has been made to UNICEF on their behalf.

**Agenda**

- Introduction to the key issues and challenges
  - Adam Barak, UBC

- Patient access for ODs: towards a new consensus
  - Wills Hughes-Wilson, Genzyme

- OD access in Germany: an IQWiG perspective
  - Dr. Stefan Lange, IQWiG

- In-market challenges for ODs
  - OD HTA; new UK AGNSS process; potential solutions moving forward incl. optimising cost-effectiveness analysis, evidence generation methods and patient registries/PROs; broadening evaluative scope.

- Audience Q&A

**Introduction to the key issues and challenges**

Adam Barak, Head International Pricing & Reimbursement
United BioSource Corporation

Adam has over 14 years of international pricing and reimbursement practice in the health care industry with extensive experience in establishing global pricing, reimbursement and market access strategies for pharmaceutical, biotech and medical device and diagnostics companies.

After an early career involving sales, marketing and pricing in the automotive industry with General Motors Europe, Adam joined GlaxoSmithKline’s International Pricing & Reimbursement division in 1999, since when he has also worked at Oxford Glycosciences as International Pricing & Reimbursement Manager, developing the global pricing, reimbursement and market access strategy for orphenoxim, miglustat/Zavesca, treatment for the rare, inherited disorder Gaucher’s Disease, the company’s only pharmaceutical launch.

In 2002 Adam established ARPPC Ltd to provide the healthcare industry with specialised support in developing pricing, funding and market access strategies, out of ARPPC grew the international network PPI, covering 25 countries and providing global coverage supporting commercialisation, planning and implementation for drugs, diagnostics and medical devices.

In 2009 Adam moved to UBC to build on the synergy of working with health economic specialists and health outcomes research experts to support the growing need for a broader approach to creating and demonstrating value for developing comprehensive and successful market access and commercialisation strategies.

Adam, a Chartered Marketer, has experience with many therapeutic areas and has authored a number of health care market access publications. He has directed many orphan drug strategic assessments in such as mucopolysaccharidosis, Gaucher’s Disease, vaso-occlusive disease, soft tissue atheroma, nutritional deficiency and intrauterine analysis.

**Patient access for ODs: towards a new consensus**

Wills Hughes-Wilson
Senior Director Health Policy Europe, Genzyme

In this function, Wills is responsible for public policy and public affairs, including activities related to market access and reimbursed patient access in Europe for Genzyme.

She leads and coordinates European and EU-based activities, working with a network across the company, including chairing Genzyme’s European Market Access Committee – a cross-functional leadership group reporting to the President of Europe.

Wills, who has been with Genzyme since September 2005, has been active on a range of issues of importance to the company and its patients, in particular advanced therapies and orphan medicinal products, including market access issues and the future of the EU frameworks relating to these fields. She is a member of the European Commission’s newly established EU Committee of Experts on Rare Diseases (EUCERD) and Chair-elect of the joint EBDD and European Biotechnology Sector Forum on Orphan Drugs & Rare Diseases.

Prior to joining Genzyme, she led the Emerging Biopharmaceutical Enterprises (EBE), a specialised group of the European Federation of Pharmaceutical Industries & Associations (EFPIA). EBE represents the interests of biotechnology companies in Europe. She has also worked in the animal health / veterinary medicines industry and for several years at Ernst & Young Consulting. Wills is a graduate in Law.

**OD access in Germany: an IQWiG perspective**

Dr. Stefan Lange
IQWiG

Stefan Lange completed his medical studies at the Heinrich-Heine-University in Düsseldorf in 1989 and received his MD in 1994.

In 1993 he joined the department of medical computer sciences, biometrics and epidemiology at the Ruhr-University in Bochum and was appointed to the position of intern/resident physician.

In 1999 he joined the department of medical computer sciences, biometrics and epidemiology at the Ruhr-University in Bochum and was appointed to the position of research assistant in 1999. He was awarded the certificate of Biometrics in Medicine with the title of “Qualified Statistician” by the German Association for Medical Computer Sciences, Biometry and Epidemiology (GMDS) in 1999.

In 2002 he received his PhD (second thesis, the Habilitationsschrift) at the Ruhr University and received his venia legendi (right to teach) in Medical Biometry and Clinical Epidemiology.

He joined the Institute for Quality and Efficiency in Health Care in 2004, and has held the position of Deputy Director of the institute since 2005. He headed the department of Non-Medical Interventions until 2007.

**In-market challenges for ODs**

- OD HTA; new UK AGNSS process; potential solutions moving forward incl. optimising cost-effectiveness analysis, evidence generation methods and patient registries/PROs; broadening evaluative scope.

**Audience Q&A**
Francis Pang  
Senior Director, Market Access and Public Affairs,  
Shire Human Genetic Therapies

Francis is a health economist with over 15 years experience in both academic and commercial settings. He started his health economics career at the Centre for Health Economics at the University of York where he was the first Research Fellow specialising in Pharmacoeconomics under the direction of Professor Michael Drummond. This was followed by a period as Monbusho Scholar in Health Economics at the Department of Economics, Kyoto University, Japan.  

Francis moved into the pharmaceutical industry, where he established health economics as a key support function at Abbott UK as Head of Health Economics and at Takeda Pharmaceuticals as Director of Health Economics, Outcomes Research & Pharmacoepidemiology.  

Francis has presented and published widely including a contribution to the textbook ‘Economic Evaluation: Merging Theory with Practice’ (Oxford University Press) and is known in the field for his methodological research on the generalisability and transferability of health economic data across countries.  

At Shire HGT, Francis leads a department responsible for pricing, health economics, government affairs and patient advocacy – the first of its kind in the industry with all four disciplines grouped under a single umbrella. Francis retains an interest in the application of methodological techniques for the demonstration of value in the emerging area of orphan drugs. Francis graduated in Health Economics from the University of York, UK.

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An agreement that…

- “Patients suffering from rare conditions should be entitled to the same quality of treatment as other patients”

- “It is therefore necessary to stimulate the research, development and bringing to the market of appropriate medications by the pharmaceutical industry”

REGULATION (EC) No 141/2000 on orphan medicinal products

Modelled on the US OD Act, BUT…

Intended for diagnosis, prevention or treatment of a life-threatening or chronic debilitating condition (= rarity is not enough)

AND

Prevalence less than 5 in 10,000

OR

Financial – unlikely to generate sufficient return to justify investment

AND

No other method authorised in EC for this condition or if it is available the new product has “significant benefit” for patients

The legislation is working: cumulative number of orphan medicines with EU Positive Opinion
Orphan Drug Development in Europe – Three Phases

I. Increasing Criticism:
- Low number of authorized orphan drugs
- High costs of (several) orphan drugs

II. Increasing Awareness
- Increasing number of orphan designations
- High costs of (several) orphan drugs

III. Treatment approved: Unique or significant benefit

A potential country perspective?

Available OMPs by country: the current situation

The problem

Governments:
- We need to know that what we are asked to pay for is something that works before we reimburse it.

Sponsor:
- We need to develop the data but how to do it with no market access?

EMA / European Commission:
- Single EU Marketing Authorisation but 27+ different in-use follow up plans?

Patients:
- Why can we not get access to an approved treatment?

EU High Level Pharmaceutical Forum – October 2008

1) Establish early dialogue between companies & P&R authorities;
2) Exchange of knowledge amongst Member States & European authorities on the scientific assessment of the clinical added value;
3) Promotion of the initial uptake of orphan medicines through conditional pricing & reimbursement decisions; and
4) Building EU-level awareness and expertise on orphan diseases.

November 2008

EU Commission Communication on Rare Diseases: Europe’s Challenges

Council Recommendation on a European Action in the Field of Rare Diseases

Develop European Cooperation & Improve Access to High-Quality Healthcare for Rare Diseases

Gathering expertise at European level

EU High Level Pharmaceutical Forum – June 2009

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With thanks & acknowledgement to Harald Heemstra, Pharmerit, Netherlands; Adapted from Leufkens, EPPOSI 2007

Something needs to be done about orphan drugs

We will set up a working party with Member States

We will work together
Proposal: Clinical Added Value of Orphan Drugs (CAVOD)

1. Acknowledge the EU Regulation’s concept of "unique" treatment / one that provides "significant benefit":
   - Needs to be proven in development
   - Is specific to Orphan Drugs
2. Working Group at EMEA to prepare report for Member States on clinical value & role of the treatment at time of Marketing Authorisation
3. Member States to grant access
4. In-use data-gathering to build up real-life experience of product’s clinical value

CAVOD & the new proposals: A solution?

- Task 1: Clinical Added Value Report prepared by Committee @ EMEA
  - Composition = orphan experts
- Task 2: Annex / "Roadmap" – minimum data set required to continue reimbursement
  - Stakeholders:
    - What do Member States want / need to see?
    - What is realistic for sponsor to develop
    - Role & involvement of patients
    - Treating physicians
    - Methodology
    - Timelines
  - Composition = reflect questions

The problem – solved?

- Treatment approved:
  - unique or significant benefit
  - Acknowledging just small number of patients in Clinical Trial
  - maybe not enough data yet to make definitive reimbursement decision... but we have a plan*

- Governments:
  - Get to know that what they are asked to pay for is something that works

- Sponsor:
  - Get realistic timeline, methodology to develop in-use data with wider patient access

- Patients:
  - Get immediate access to an approved treatment

CAVOD is not “all alone” in the EU landscape!

-- Methodologies --

- Parallel Scientific Advice: MEDEV +/- HTA bodies
- EUNetHTA I + II
- Swedish EU Presidency project

-- Mechanisms --

EUPAR project

- European Commission’s study
- DG Enterprise - Corporate Social Responsibility in Pharmaceuticals
  - (Belgium) National Plan(s) for Rare Diseases – ETR proposals
  - Hungarian Presidency – potential workshop?
  - European – Centres of Expertise

Conclusions

- Political will to create mechanisms to speed reimbursed access to orphan drugs
- Shared challenges – Multi-stakeholder engagement
- POLICY → MECHANISM(S) → METHODOLOGIES
  - In development
  - To be discussed
  - Key framework developments over next 12-24 months
  - Pilots = concrete experience
  - Not limited to orphans…
  - Not limited to Europe…

Thank you!

wills.hughes-wilson@genzyme.com
Resources (1)

- European Commission call for tender to conduct study on the added value for orphan medicines: http://ec.europa.eu/eahc/health/tenders_H05_2010.html

Resources (2)

- Eurodis: http://www.eurodis.org/content/eurodis-advocating-improve-patient-access-orphan-drugs-europe
- EUNetHTA: http://www.eunethta.net
- Europalan: http://www.euronetproject.eu

ISPOR 2010

Orphan drugs in Europe: funding challenges for payers and developers
OD access in Germany: an IQWiG perspective

Stefan Lange, MD, PhD
Deputy Director
Institute for Quality and Efficiency in Health Care (IQWiG)

IQWiG and G-BA

The IQWiG is solely commissioned by the Federal Joint Committee (G-BA) and the Federal Ministry of Health (BMG), but can also cover topics on its own initiative under a general commission:

IQWiG
Assessment of benefits and harms

G-BA
Decision making body of the social insurance

IQWiG and G-BA were founded in the course of a health care reform in 2004
The legal foundation of IQWiG and G-BA is the social code book V (SGB V)

prohibitory right

… and at a price, which is in fact determined by the pharmaceutical manufacturer
- free pricing system

1 Insured persons have the right to be provided with pharmacy-only medicines, insofar as they are not excluded according to § 34* or by directives according to § 92 section 1, sentence 2, no. 6*. …

* Drugs for minor health problems
* Drugs which have no proven benefit, are not necessary or not cost-effective (i.e. cost-minimization approach in the past

AMNOG*: principles

Early benefit assessment at the time of market access
- Status: draft of the cabinet, July 2010
- Free pricing within the first year of approval
- Assessment of a (n) (additional) benefit of all drugs with new active agents
  - New active agents which are marketed for the first time
  - Approval for an additional area of application
- Burden of proof lies with the pharmaceutical manufacturer (provision of a dossier which will be assessed)
- Assessment within 3 months
- Resolution within further 3 months

* Arzneimittelmarktneuordnungsgesetz (Drug market re-organization act)
Critiques

Analysis of the dossiers for 44 approved orphan medicinal products (up to 2007) according to regulation (EC) No 141/2000

"Moreover, clinical and public health needs are poorly met by inadequately documented orphan drugs’ efficacy and safety profiles. Limitations include frequent lack of dose-finding studies, often inappropriate clinical design or lack of active comparator where available, insufficient exposure to the treatment, surrogate end-points or weak proof of clinical benefit. The lack of reliable methods for evaluating the effect of drugs on small numbers of patients is also a factor in the general poor quality of the dossiers."

Hierarchy of evidence

- Systematic Reviews (of RCTs)
- Randomised, Controlled Trials
- Controlled Trials (non-RCTs)
- Uncontrolled studies
- Case series / case reports
- Opinions

Uncertainty

Problem

- Quantifiable (precision)
- not quantifiable (bias)
- uncertainty

Are other criteria a possibility?

"…regarding small samples and as recommended for other problematic constellations [121], it can be reasonable to accept p-values larger than 5% (10% for example) as a proof of statistical significance, thus increasing the quantitative uncertainty."

IQWiG – General methods, version 3.0

Summary

- Free access to orphan drugs in Germany
- AMNOG: Moving away from free pricing
- Exception: "low volume (orphan) drugs" (< 50 Mio. € sales volume within 12 months)?
- Evidence for (additional) benefit of orphan drugs often weak
- Orphan medicinal products should be subject to the normal evaluation process (regulation [EC] No 141/2000)
- It may be wise to increase the quantitative uncertainty rather than the qualitative uncertainty for the benefit assessment of drugs for treatment of genuinely rare diseases

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Thank you very much!