Supporting the Value of Transformative Medicines: Netherlands Outlook

April 2016
Suggested structure

• Introductory facts, focused on OD and CF
• OD and CF
• Future pressures on budget
• Key take away/exec summary
• GE healthcare case
Executive Summary: financial facts and figures associated with the Netherlands market

<table>
<thead>
<tr>
<th>Metric</th>
<th>Figures 2015 (unless specified)</th>
<th>CAGR 2011-15 (unless specified)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDP</td>
<td>€655bn (2014)</td>
<td>1% (2009-14)</td>
</tr>
<tr>
<td>GDP per capita</td>
<td>€38,876 (2014)</td>
<td>1% (2009-14)</td>
</tr>
<tr>
<td>Healthcare spend</td>
<td>€72bn (2014)</td>
<td>3% (2009-14)</td>
</tr>
<tr>
<td>Healthcare spend as a % GDP</td>
<td>11.1% (2014)</td>
<td>n/a</td>
</tr>
<tr>
<td>Rx drug spend</td>
<td>€3.9bn</td>
<td>1%</td>
</tr>
<tr>
<td>Rx drug spend as a % healthcare spend</td>
<td>5% (2014)</td>
<td>n/a</td>
</tr>
<tr>
<td>OD drug spend</td>
<td>€54mn</td>
<td>38%</td>
</tr>
<tr>
<td>OD spend as a % Rx drug spend</td>
<td>1.4%</td>
<td>n/a</td>
</tr>
<tr>
<td>CF drug spend</td>
<td>€22mn</td>
<td>14%</td>
</tr>
<tr>
<td>CF spend as a % Rx drug spend</td>
<td>0.6%</td>
<td>n/a</td>
</tr>
<tr>
<td>CF budget impact</td>
<td>€40mn*</td>
<td>n/a</td>
</tr>
</tbody>
</table>

*Excludes Kalydeco
Orphan and CF drug sales have been growing above market average over the course of 2011-15

Total drug spend, 2011-15, €Bn

- **Total drug spend has increased at an average rate of 1% per annum** over 2011-15, driven by the hospital channel.
- **However, OD and CF spend has increased significantly**, driven by both new launches (e.g. Kalydeco) and existing product growth (e.g. ODs Tasigna and Revlimid) over the period.

Note: Rx segment only

Source: IMS MIDAS, IMSCG analysis

Please note that MIDAS data for the Netherlands does not represent the whole market and should only be used to assess trends. For example, major discrepancies within the hospital channel for Revlimid and Tasigna, some discrepancies for Enbrel and Remicade, minor discrepancies for Herceptin.
Orphan drugs serve a small population of patients with high unmet need

**ODs represent a specialist category with high unmet need**
- Between 5,000 and 8,000 distinct rare diseases exist globally
- Over 30 million people living in the EU suffer from a rare disease
- Only 5% of rare diseases have approved drug treatment

**Environment at EU level has become favourable for ODs**
- Orphan designation is a status assigned to a medicine intended for use against a rare condition
- Benefits include protocol assistance, access to the centralised authorisation procedure, ten years of market exclusivity, additional incentives for SME’s, regulatory activity fee reductions and research grant funding

**At individual member state level differences may exist in speed and ease of access**
- Due to differences in legislation among EU members, ease and speed of access may vary
- Dutch and Belgian ministers already have joint price and reimbursement negotiations, however, are also looking to exchange information, share registries and harmonise evaluation methods in the near future

**Given market dynamics high prices are achievable, although challenges exist**
- Owing to low patient numbers and high unmet need it is possible to achieve high prices for ODs (e.g. Netherlands is pushing back on Sanofi to reduce the cost of its Pompe disease OD Myozyme, which can cost about 700,000 euros / year / patient)

Orphan definition from the EMA and information from ec.europa.eu/ Public Health 2015 - Source: IMS Health Thought Leadership 2015 - The new challenges of Orphan drugs in Europe
There has been an increasing number of ODs authorised for use within the EU, most of which are within oncology.

Number of ODs in Europe with European market authorisation (MA) and orphan designation

- Oncology represents the largest category, including blockbusters such as Revlimid (MA achieved 2008) and many other high earning products such as Tasigna, Sprycel and Nexavar.

- Cystic Fibrosis treatments account for ~5% of all approved ODs (Cayston, TOBI Podhaler, Bronchitol, Kalydeco).

Vigorous patient advocacy, medical breakthroughs, legislative incentives, venture capital investment and industry collaboration, are dramatically changing the landscape of rare disease research.

Source: European Medicines Agency
The majority of OD sales are within oncology, representing a third of revenue as of 2015

- The majority of OD sales (~35%) are for oncologic conditions (2015)
- Top oncologic drugs in 2015 include: Tasigna, Revlimid, Sprycel, Imnovid.
- PAH* is accounted for by three products: Adempas, Opsumit and Volibris
- Cystic fibrosis OD sales from 2011 onwards following launch of Cayston (first sales Q3 2011), followed by Tobi Podhaler (Q3 2011) and Kalydeco (Q4 2014)

Note: Oncology excludes drugs for Cushing’s disease/syndrome and certain products associated with disease but not directly involved in treating the condition e.g. Defitelio
*PAH Pulmonary arterial hypertension
Source: IMS MIDAS, IMS Knowledge Link
There are some key OD pipeline assets expected to launch in the near future

<table>
<thead>
<tr>
<th>Preferred Name</th>
<th>Company</th>
<th>Pipeline Status</th>
<th>2020 global forecast sales (Mn$)</th>
<th>Indication</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obeticholic acid</td>
<td>Intercept</td>
<td>Pre-reg</td>
<td>1800*</td>
<td>Cirrhosis, diarrhea, liver disease, non-alcoholic steatohepatitis</td>
<td>Novel therapeutic to treat chronic underserved liver diseases</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>Abbvie; Roche</td>
<td>Phase III</td>
<td>1463</td>
<td>Relapsed / refractory Chronic Lymphocytic Leukaemia (CLL)</td>
<td>First potential BCL-2 inhibitor for CLL</td>
</tr>
<tr>
<td>Selexipag</td>
<td>Actelion</td>
<td>Registration</td>
<td>1265</td>
<td>Pulmonary Arterial Hypertension</td>
<td>Delays disease progression and reduces risk of hospitalization for PAH; approved in US Jan 2016</td>
</tr>
<tr>
<td>Nusinersen</td>
<td>Biogen; Ionis</td>
<td>Phase III</td>
<td>714</td>
<td>Spinal Muscular Atrophy</td>
<td>No approved treatments on market</td>
</tr>
<tr>
<td>SD-809</td>
<td>Teva</td>
<td>Reg, Phase III</td>
<td>600</td>
<td>Huntington’s Disease (HD); Tardive Dyskinesia</td>
<td>Analogue of an already established HD treatment, no treatments for Tardive Dyskinesia</td>
</tr>
<tr>
<td>Tremelimumab</td>
<td>AstraZeneca</td>
<td>Phase III</td>
<td>593</td>
<td>Malignant mesothelioma</td>
<td>Limited alternatives on the market</td>
</tr>
<tr>
<td>Duvelisib</td>
<td>Abbvie; Infinity</td>
<td>Phase III</td>
<td>300</td>
<td>Chronic Lymphocytic Leukaemia</td>
<td>Competition in the pipeline with other products targeting PI3 kinase</td>
</tr>
<tr>
<td>Pegvaliase</td>
<td>BioMarin</td>
<td>Phase III</td>
<td>252</td>
<td>Phenylketonuria</td>
<td>BioMarin acquired rights to Phenylketonuria franchise from Merck Serono Oct 2015</td>
</tr>
<tr>
<td>Dacomitinib</td>
<td>Pfizer</td>
<td>Phase III</td>
<td>232</td>
<td>1st Line EGFR mutant Non-Small Cell Lung Cancer (NSCLC)</td>
<td>For NSCLC patients with EGFR, HER2, HER4, or DDR2 mutations</td>
</tr>
<tr>
<td>Selumetinib</td>
<td>AstraZeneca</td>
<td>Phase III</td>
<td>228</td>
<td>Uveal melanoma</td>
<td>Could potentially become the first effective treatment for these patients</td>
</tr>
</tbody>
</table>

Source: IMS R&D Focus Feb 2016; Forecasts: IMS Health AnalyticsLink, Consensus Analyst forecasts; DrugAnalyst Consensus Database, Feb 2016; Global forecasts may include sales forecast for other non-orphan indications; some products may not be under investigation by EMA; *2020 forecast sales from EP Vantage -2016 Preview; **2016 forecast from DrugAnalyst Consensus Database.
New treatments for cystic fibrosis have resulted in improvement in lifespan

As development of CF therapeutics continues to progress, there has been a proportional increase to the median age at death

Note: Launch defined as point at which first sales recorded in IMS MIDAS database.
Source: IMS MIDAS, IMSCG analysis
Spend per CF patient is greatest in 12-17 year olds, where split between outpatient and inpatients costs is roughly equal.

### Total average costs of CF care per patient in the Netherlands, according to age (2013), €

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Outpatient</th>
<th>Inpatient</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>16,275</td>
<td>13,117</td>
<td>29,392</td>
</tr>
<tr>
<td>18-53 years</td>
<td>16,684</td>
<td>14,828</td>
<td>31,512</td>
</tr>
<tr>
<td>12-17 years</td>
<td>15,521</td>
<td>16,764</td>
<td>32,285</td>
</tr>
<tr>
<td>6-11 years</td>
<td>19,137</td>
<td>6,856</td>
<td>25,993</td>
</tr>
<tr>
<td>0-5 years</td>
<td>12,514</td>
<td>5,266</td>
<td>17,780</td>
</tr>
</tbody>
</table>

### Estimated annual budget impact for CF population, £Mn

- SoC excl. Kalydeco (2013): 40
- Kalydeco spend 2015: 6

Average direct costs per patient: €29,392

Note: SoC budget impact based on cost per patient of €29,392 and diagnosed patient pool of 1,353.

Payers have historically accommodated new high cost drugs which offer a step change in innovation

Average cost per patient per day, €

- Xarelto 5x more expensive per DoT vs. Warfarin
- Xarelto within new class of drugs (NOACs); advantages include a lower incidence of major bleeding, convenience of use, minor drug and food interactions, a wide therapeutic window, and no need for laboratory monitoring
- Total sales for Xarelto are €16mn in 2015

- Significant price increase when treating patients with Sovaldi
- Sovaldi represents step-change treatment with the ability to cure patients (cure rates range from 82% to 95% for a treatment duration of 12 or 16 weeks of Sovaldi + ribavirin)
- Total sales for Sovaldi are €74mn in 2015

1) Price of Xarelto based on a 10 mg / 10 pill pack at €27.28, where recommended dose is 10mg daily; 2) Warfarin induction dose of 10mg daily, 5 mg / ml, AMP 2ml, quantity 11.25 at a price of €6.54; 3) Price of Sovaldi based on a 400mg tablet at €517.39; 4) Interferon pack price €137.97 15 million IU/ml, where recommended dose for CHC is 3 million IU three times a week for adult patients

Note: Retail prices
Source: medicijnkosten.nl, IMS MIDAS, IMSCG analysis
Moving forward several ‘blockbusters’ are expected to launch in 2016, with potential major impact on drug spend

<table>
<thead>
<tr>
<th>Product</th>
<th>Mnf</th>
<th>Indication(s)</th>
<th>WW peak sales estimate 2020 (bn)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir alafenamide</td>
<td>Gilead</td>
<td>HIV infection and chronic hepatitis B</td>
<td>$3.7 (€3.4)</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>Roche</td>
<td>Melanoma, breast cancer, non-small-cell lung carcinoma, bladder cancer, renal cell carcinoma</td>
<td>$2.6 (€2.4)</td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td>Roche</td>
<td>Multiple sclerosis</td>
<td>$2.4 (€2.2)</td>
</tr>
<tr>
<td>Grazoprevir/elbasvir</td>
<td>Merck &amp; Co</td>
<td>Hepatitis C</td>
<td>$2.1 (€1.9)</td>
</tr>
<tr>
<td>Obeticholic acid</td>
<td>Intercept</td>
<td>Cirrhosis, diarrhea, liver disease, non-alcoholic steatohepatitis</td>
<td>$1.8 (€1.6)</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>Sanofi</td>
<td>Asthma, dermatitis, eosinophilic esophagitis, nasal polyp</td>
<td>$1.7 (€1.5)</td>
</tr>
<tr>
<td>Disc repair project</td>
<td>Mesoblast</td>
<td>Damaged spinal discs</td>
<td>$1.4 (€1.3)</td>
</tr>
<tr>
<td>Ventoclax</td>
<td>AbbVie</td>
<td>Relapsed/refractory chronic lymphocytic leukaemia</td>
<td>$1.2 (€1.1)</td>
</tr>
<tr>
<td>Uptravi</td>
<td>Actelion</td>
<td>Cardiovascular disease, pulmonary hypertension</td>
<td>$1.1 (€1.0)</td>
</tr>
<tr>
<td>Elagolix</td>
<td>Abbvie</td>
<td>Endometriosis, fibroids</td>
<td>$0.9 (€0.8)</td>
</tr>
</tbody>
</table>

*Figures based on analyst consensus estimates (source EP Vantage)

Source: IMS Knowledge Link, EP Vantage 2016 Preview, Exchange rate: $1 = €0.70
For future high cost drug therapies, innovative funding arrangements could cover reimbursement costs

Example innovative financing models that payers could deploy to cover high cost therapies

**National funding schemes**
- To ensure regional burden of treatment is spread, schemes can promote the development of a national level budgets across regions
- Alternatively, in areas where multiple payers in the same region, reimbursement funds can be pooled in order to spread costs
- This model will ease local budgetary impact of high one-offs, but large populations may still be problematic

**The annuity model**
- Payments broken down into annual instalments to allow payers to reimburse manufacturers over time of therapeutic benefit. This model allows for sharing of the risk of treatment failure with the manufacturer
- If the manufacturer is unwilling to take payments in instalments, it may be possible to bring in financial institutions that, for a fee could take on the risk and provide payment in lump sum to the manufacturer, and get annuity payments from the payer

**Pay for performance**
- This annuity style of reimbursement utilizes Real World Evidence (RWE) to assess efficacy of treatment on a patient-by-patient basis
- Linked to scores of efficacy, or payment could even be given as a proportion of RWE measured savings of treated patients when compared to those which remain untreated
- If the efficacy of treatment for a particular patient decreased overtime, annuity payments for that patient would fall accordingly

Source: IMS Health Thought Leadership White Paper ‘Cell & Gene Therapies: Innovation to commercialisation’
Executive Summary: key takeaways for the Netherlands market

**Orphan Drugs**
- Within the orphan drug (OD) segment, the top 5 products account for nearly 50% of 2015 revenues
- The majority of OD sales are within oncology, which represent 1/3 of revenues as of 2015
- Products launched pre-2010 make up the majority of sales but new drugs (e.g. Kalydeco) are driving most of the growth in 2015

**Cystic Fibrosis**
- Kalydeco launch resulted in a considerable increase in total cystic fibrosis (CF) sales, yet CF still represents a small portion of total drug spend
- Launch of Orkambi and continued growth of the existing therapies is expected to add €79mn to total annual CF spend in 2020

**Future drug pressures**
- Several ‘blockbusters’ are expected to launch in 2016, with potential major impact on drug spend; these products are expected to reach €95Mn sales in 2020
- For future high cost drug therapies, innovative funding arrangements could cover reimbursement costs (i.e. Annuity and ‘Pay for performance’ models)

**Healthcare system waste and potential savings**
- It is estimated that at least €100mn is still spent annually on medicines that go unused
- Despite generic availability, some premium price originator products are still used; switching all patients to generics for specified ‘basket’ of off-patent drugs could have reduced spend €14Mn in ‘15
This leaves a significant question open to manufacturers

Do you ignore the problem and continue with the status quo?

OR

Do you try a new way of engaging hospitals to be part of the solution?
Customer engagement can range from the transactional model to a transformational business model

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Transactional Relationship</th>
<th>Transformational Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Solution</strong></td>
<td>Selling the product – “off the shelf”</td>
<td>Client support is majority of value – “bespoke solutions”</td>
</tr>
</tbody>
</table>
| **Continued transactional procurement model:** | • Limited effort beyond selling a product with no customization or implementation  
• No relationships beyond provision of the end product  
• Manufacturer seen as mere “supplier” | **True step change in partnership relation:**  
• Selling customized, capability-building services built around products  
• Services are driven by customer implementation needs and not necessarily related to a particular product |
These solutions can take on a range of forms, addressing several unmet needs.

The management consulting arm of GE Healthcare, helps leading healthcare organizations manage the interdependencies between cost, quality and access.

Project objectives:
1. Improve capacity management
2. Better manage length of stay
3. Enhance staff satisfaction

Results: Improvements in capacity utilization
- Increased OR capacity by 750 cases per year,
- Increased use of the OR Block Schedule by 22%
- Reduced bed request-assignment time by 42%

Unmet needs addressed
- Developed with long term sustainability of services and relationship in mind
- Recognised needs outside of the hospital pharmacy
- Manages demand in a resource constrained environment
- Delivers year-on-year efficiencies
- Utilises external competitive advantage

OR, operating room