To examine pricing, reimbursement and market access of orphan drugs approved by Spain:

Germany is consistently above EU5 average whereas UK and Spain are All 13 drugs available and reimbursed in Germany

Orphan drugs are perceived as offering significant incremental value only in selected France:

3 drugs launched pre-AMNOG and one exempt from AMNOG assessment Reimbursement and HTA 9 were orphan designated but received EMA approval either before 2009 or

In theory 12 of the 13 orphan drugs available in the UK

8 orphan drugs reimbursed; no agreement reached with the manufacturer on

Time to access is significantly longer in the EU than in the US possibly related to

Germany:

In the UK, although in theory launch time is short, it took on average 71 weeks

In the EU, prevalence must be fewer than 5 per 10,000 of the population, i.e.

Time to market

Only the 13 remaining drugs (12.7%) were orphan designated in both the US

49 were not designated as orphan drugs in the EU including 12 approved

Price differential between EU5 and US widens due to price inflation in the US as

Italy:

Although no official definition of ‘ultra-orphan disorders’ has been adopted globally,this

Intra EU price differences reported using EU5 average ex-factory price as the base

31 were not available in the EU including specific actions of 4 having marketing

9 evaluations, only 2 oncology orphans (Imnovid, Jakavi) and 1 ultra

Time to regulatory approval longer in the EU vs. the US (66 weeks compared to 45

Orphan Drug Approvals: US vs. EU

Comparison of EU5 Average vs. US Launch and US Current WAC/Ex-Factory Prices

Reimbursement & HTA

France:

8 orphan drugs reimbursed; no agreement reached with the manufacturer on

Germany:

8 orphan drugs reimbursed; no agreement reached with the manufacturer on

Italy:

8 orphan drugs reimbursed; 6 of which classified as hospital only (Class H)

Spain:

Only 5 of the 13 orphan drugs completed P&R negotiations

All 5 drugs fully reimbursed for hospital use only with hospital only restriction

UK:

In theory 12 of the 13 orphan drugs available in the UK

However, only 3 recommended for reimbursement by the SMC, 2 of which were recommended

Conclusions

Significant differences exist between the number of orphan drug approvals in the US and EU (only 12.7% are common in the study period)

The differences can be explained in part by the different definitions of orphan drugs as per US and EU legislations

Furthermore, innovative cases of soliciting molecules are not always rewarded in the EU as reflected by fewer launches in the EU compared to the US

Time to regulatory approval longer in the EU vs. the US (96 weeks compared to 45 weeks)

Time to access is significantly longer in the EU than in the US possibly related to country processes and varying financial constraints

Orphan drugs are perceived as offering significant incremental value only in selected cases by HTA agencies

Variation across EU countries in HTA assessment process frequently means the same molecule with the same clinical package is likely to receive different benefit evaluations

For pricing, the US is not always the highest price country although the gap widens due to post-launch price increases in the US

Within the EU5, Germany tends to have higher prices than the EUS average

Table 1: Comparison of EU5 average vs. US launch/current WAC price and intra EU ex-factory price variance

<table>
<thead>
<tr>
<th>Country</th>
<th>EU5 Avg. WAC</th>
<th>US Launch WAC</th>
<th>EU5 Current WAC</th>
<th>US Current WAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>54,000</td>
<td>65,000</td>
<td>58,000</td>
<td>68,000</td>
</tr>
<tr>
<td>Germany</td>
<td>50,000</td>
<td>60,000</td>
<td>55,000</td>
<td>65,000</td>
</tr>
<tr>
<td>Italy</td>
<td>45,000</td>
<td>55,000</td>
<td>50,000</td>
<td>60,000</td>
</tr>
<tr>
<td>Spain</td>
<td>50,000</td>
<td>60,000</td>
<td>55,000</td>
<td>65,000</td>
</tr>
</tbody>
</table>

Note: Product not available in the country or price not available available.