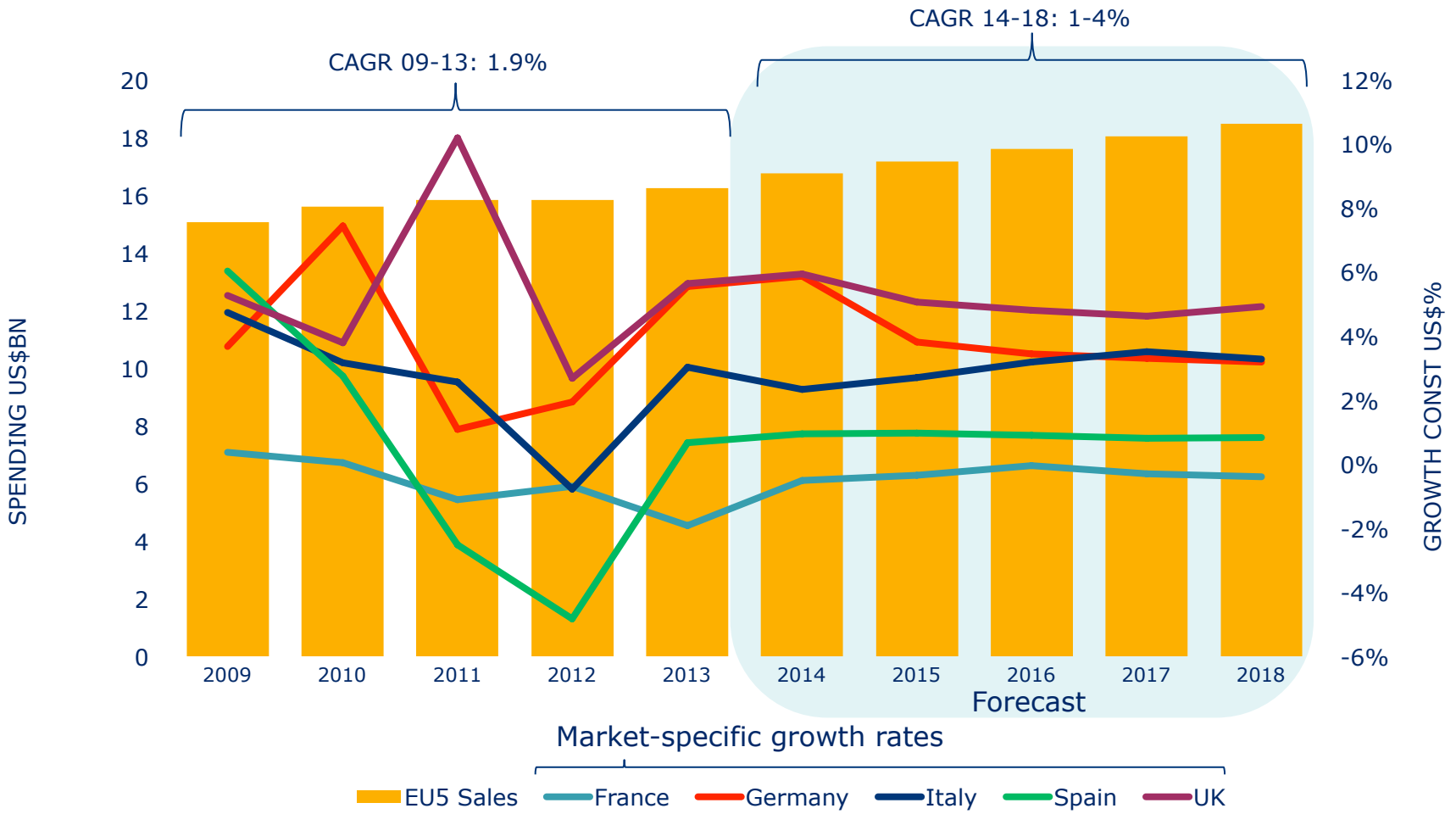
# Situational Analyses on Health Technology Assessment

January 2015

# Contents

# EU5 spending projected to grow, at varied rates

## Top 5 Europe spending and growth[1], 2009-2018




[1] Forecasts using ex-mnf price before rebates and discounts for consistency between markets; UK does not include impact of PPRS
Source: IMS Health Market Prognosis, September 2014



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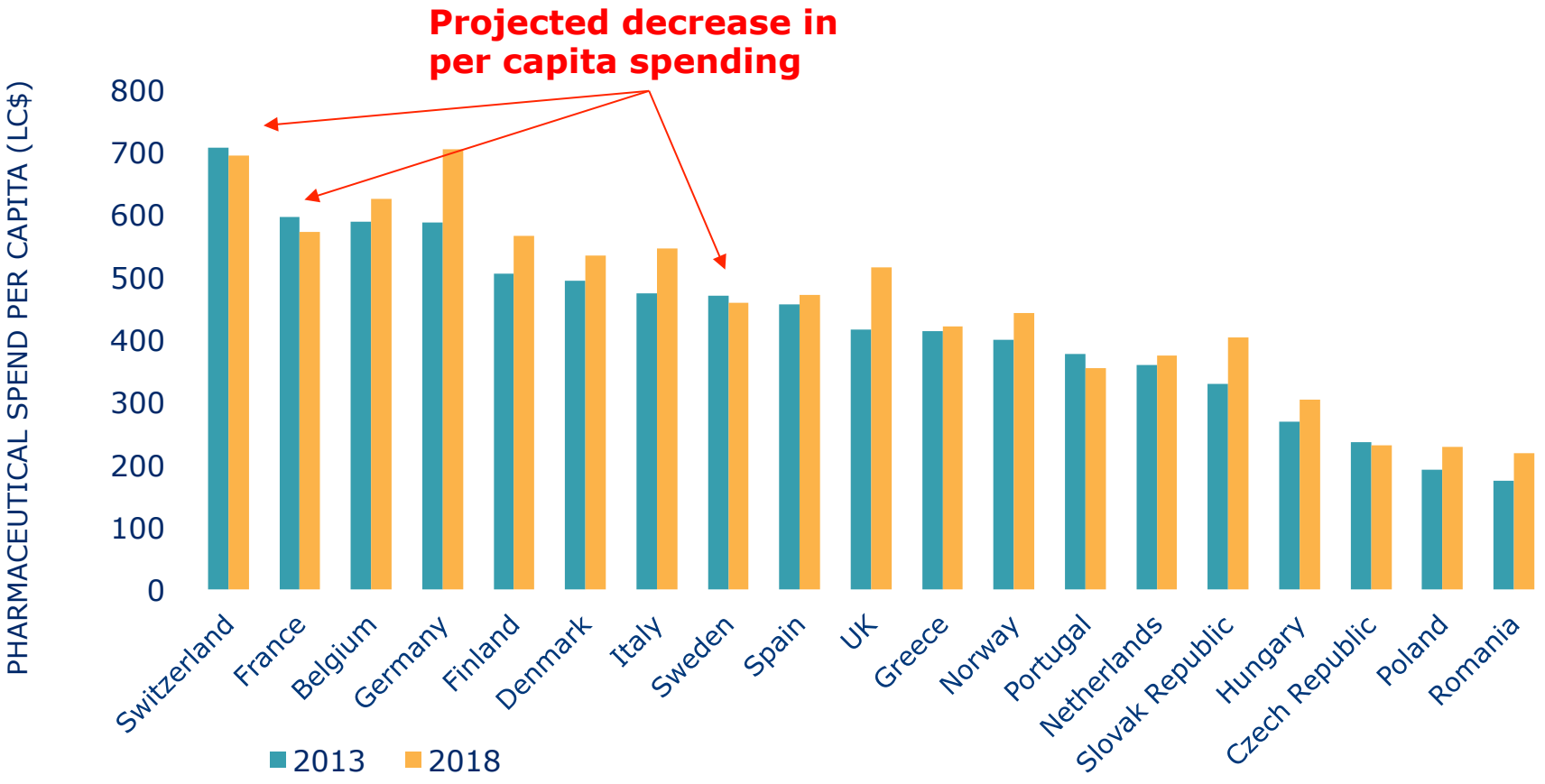
# Growth across markets, with a few exceptions

## Per capita spending, 2013 versus 2018 (projected)




Note: only includes countries covered by IMS Health Market Prognosis
Source: Economic Intelligence Unit 2014; IMS Health Market Prognosis, September 2014.



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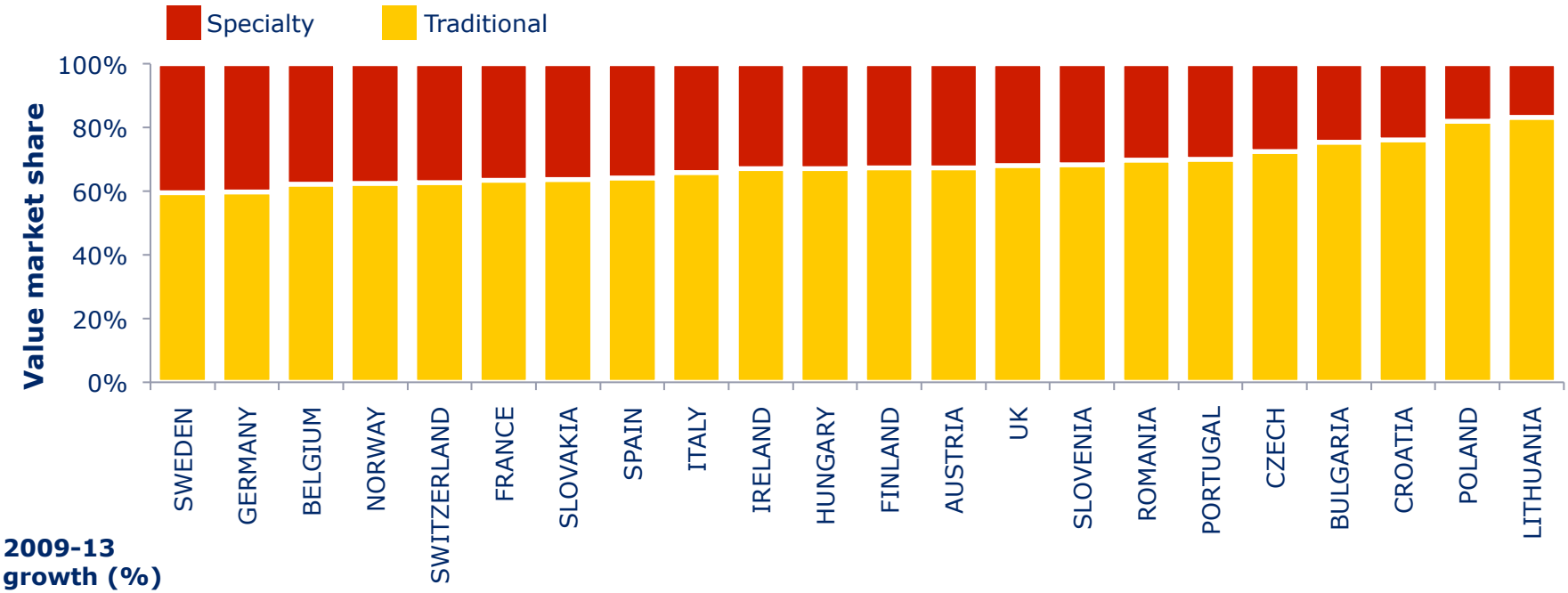
# Specialty market has grown faster than traditional

## Specialty versus traditional medicine market value dynamics (2013 value market share)




| 2009-13 growth (%) | SWEDEN | GERMANY | BELGIUM | NORWAY | SWITZERLAND | FRANCE | SLOVAKIA | SPAIN | ITALY | IRELAND | HUNGARY | FINLAND | AUSTRIA | UK | SLOVENIA | ROMANIA | PORTUGAL | CZECH | BULGARIA | CROATIA | POLAND | LITHUANIA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Specialty | 5 | 13 | 7 | 8 | 10 | 3 | 11 | 4 | 6 | 9 | 7 | 7 | 6 | 11 | 7 | 13 | N/A[1] | 2 | 23 | 7 | 12 | 14 |
| Traditional | -1 | 0 | -3 | -1 | -3 | -3 | -2 | -3 | 0 | -4 | -1 | -1 | 0 | 1 | -3 | 9 | N/A[1] | -2 | 9 | -1 | 0 | 2 |

**In Europe, specialty products are a major growth driver, and are expected to contribute ~94% of Europe's growth from 2013-2018**

[1] IMS did not audit Portugal hospital prior to 2010 so five year growth rate is not available
Note: IMS defines specialty therapies as medicines that treat specific, complex chronic diseases with 4 + of the following attributes: initiated by a specialist; generally not oral; require special handling; unique distribution; high expense; warrants intensive patient counseling; requires reimbursement assistance
Source: IMS Institute for Healthcare Informatics



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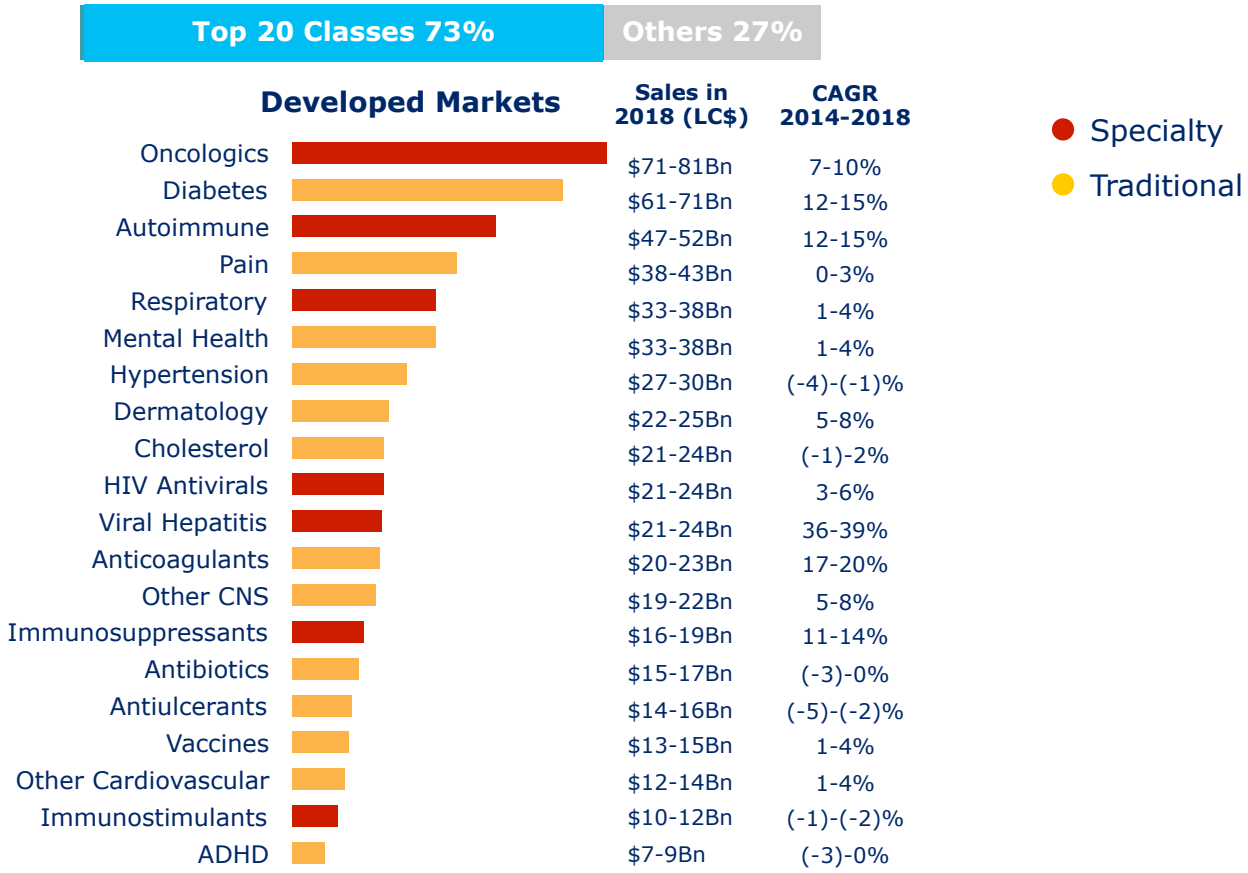
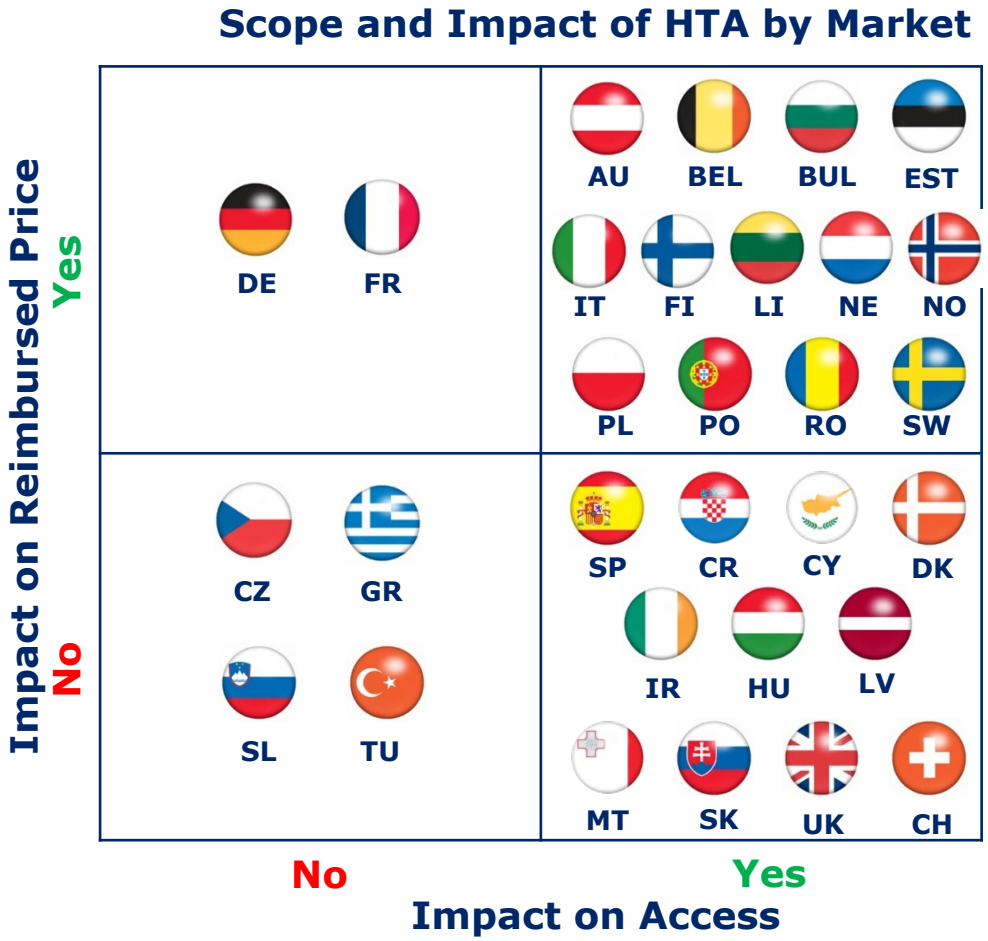
# Top projected therapeutic classes in 2018




Note: IMS defines specialty therapies as medicines that treat specific, complex chronic diseases with 4 + of the following attributes: initiated by a specialist; generally not oral; require special handling; unique distribution; high expense; warrants intensive patient counseling; requires reimbursement assistance
Source: IMS Institute for Healthcare Informatics, October 2014; IMS Therapy Prognosis, October 2014

# Current state of HTA[1] in EU markets

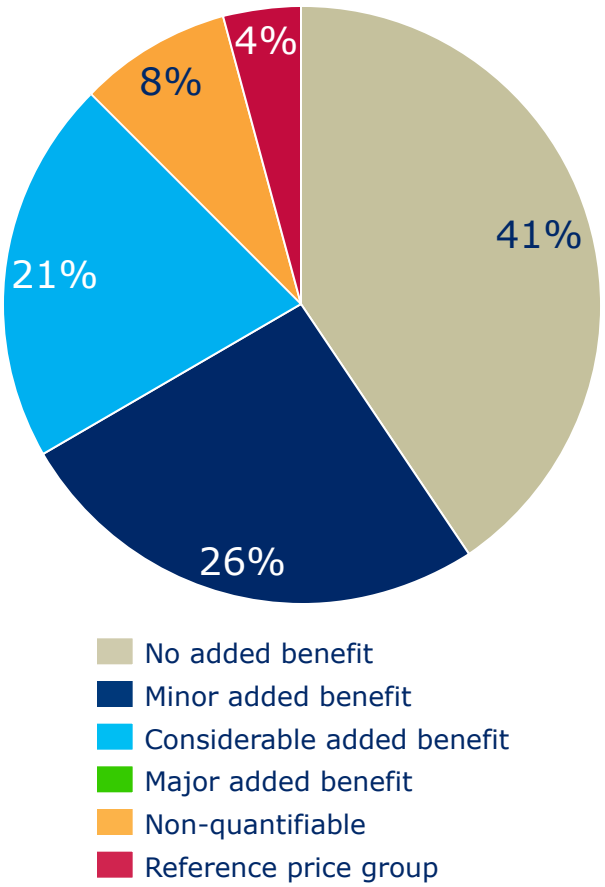



- Factors driving HTA assessments vary
  - Clinical effectiveness used by all
  - Use of cost effectiveness and budget impact varies
  - Societal factors (e.g. unmet need, quality of life) are often secondary
- Application of HTA can vary by market for retail vs. hospital settings
- HTA reforms are planned in several markets (e.g. Poland), with proposals to model after other agencies (e.g. France, Germany)
- New HTA models are being piloted
  - Denmark (KRIS) conducting mini-HTAs to support hospital decisions
- Informal referencing is increasingly common, typically including neighbor markets, or similar value systems
  - A positive NICE outcome has correlated to a positive outcome in other HTAs; no correlation for negative NICE evaluations

[1] HTA definition (EUnetHTA): a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value

# Impact of AMNOG in Germany

**Highest Additional Benefit Category per Assessment**




- Since AMNOG enacted and new IQWiG and G-BA assessments put in place
  - 96 assessments (as of December 2014)
  - 55% resulted in additional benefit
  - In oncology, 43 % achieved a "considerable" additional benefit level
  - In many cases an additional benefit was reached only for a subpopulation, not for the whole indication
- Since AMNOG was enacted, there have only been 10 opt-outs or market exits
- The G-BA has highlighted the following areas for further internal evaluation
  - Oncology endpoints, looking at QoL in addition to overall survival
  - Evaluation of new drugs for curing chronic diseases, since long-term data is not available at launch
  - High prices within first year, before the reimbursed price negotiation

Source: IMS Consulting Group analysis, January 2015



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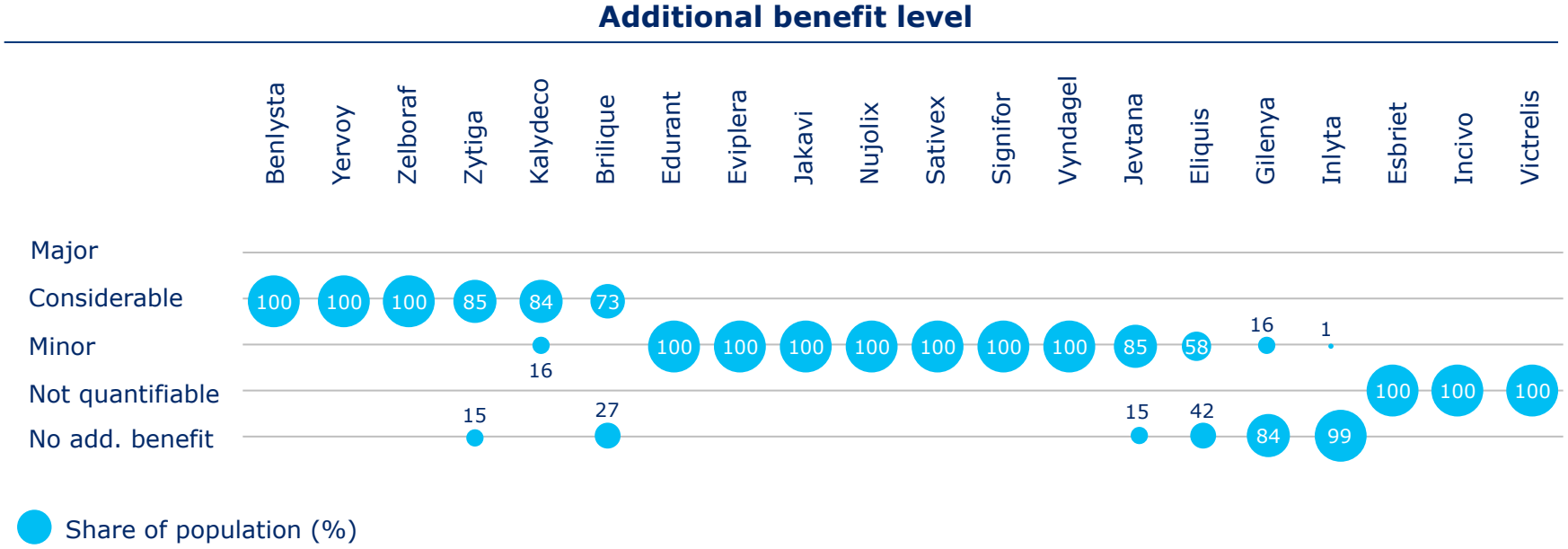
# Benefit ratings achieved in Germany

## Selected drugs evaluated over first three years post-AMNOG




- Comparator choice and direct evidence have been key; not using one of the appropriate comparators set by G-BA leads to "no additional benefit" result
- Hard endpoints (morbidity, mortality, safety, QoL) and well-justified surrogate endpoints help maximize extent of additional benefit
- Patient sub-populations have been used to interpret lower level of additional benefit; all sub-populations should have robust and statistically significant clinical endpoints

Source: IMS Consulting Group analysis, evaluated IQWIG assessments and G-BA decisions through October 2013



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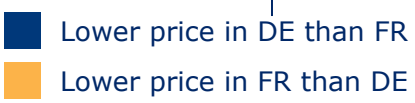
# Comparison: recent German vs. French evaluations

## Comparison of Product Evaluations and Reimbursement Price Achieved (launches from 2011-2013)

| | G-BA Rating[1] | HAS ASMR Rating | Negotiated reimbursed price |
|---|---|---|---|
| Zelboraf | Considerable | Moderate | -53 |
| Gilenya | Minor | Minor | -31 |
| Esbriet | Not Quantifiable | Minor | -27 |
| Victrelis | Not Quantifiable | Moderate | -21 |
| Brilique | Considerable | Minor | -11 |
| Halaven | Minor | Minor | -8 |
| Incivo | Not Quantifiable | Moderate | -8 |
| Yervoy | Considerable | Minor | -7 |
| Zytiga | Considerable | Moderate | -4 |
| Edurant | Minor | No add. benefit | 25 |
| Eviplera | Minor | No add. benefit | 27 |




- Scores suggest G-BA ratings are more positive than ASMRs
- Factors include benefit in sub-populations & comparator choice
- Recent German assessments resulted in lower prices than lower ASMRs in France, even when German rating was higher than French ASMR
- Only in extreme cases, where the French evaluation finds no additional benefit and GBA is positive, German reimbursed prices exceeded those in France

[1] Rating is the final G-BA rating given after initial IQWiG assessment
Source: IMS Consulting Group analysis, GBA, ASNM



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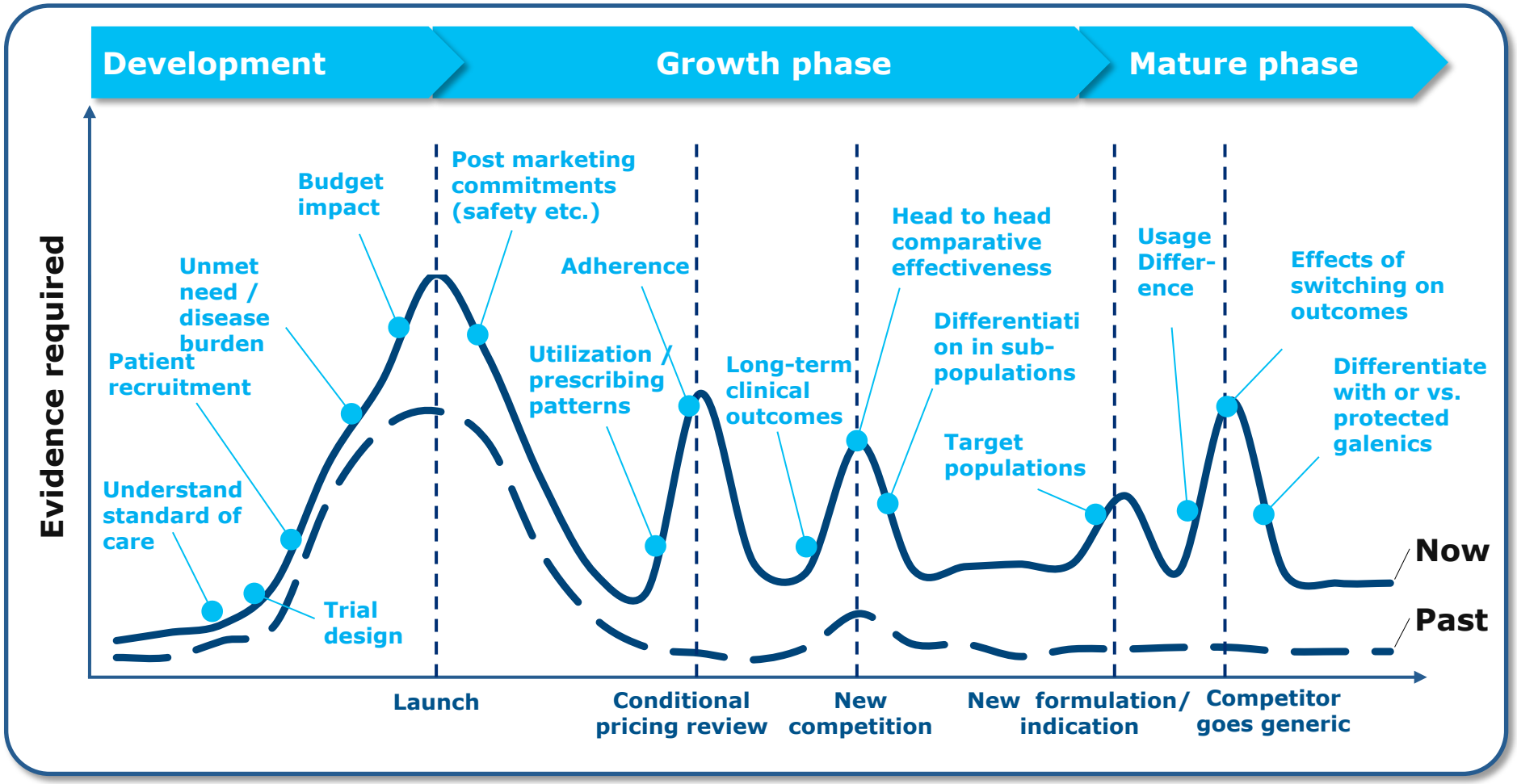
# RWE can support access throughout the lifecycle

## Real World Evidence (RWE) Use Cases



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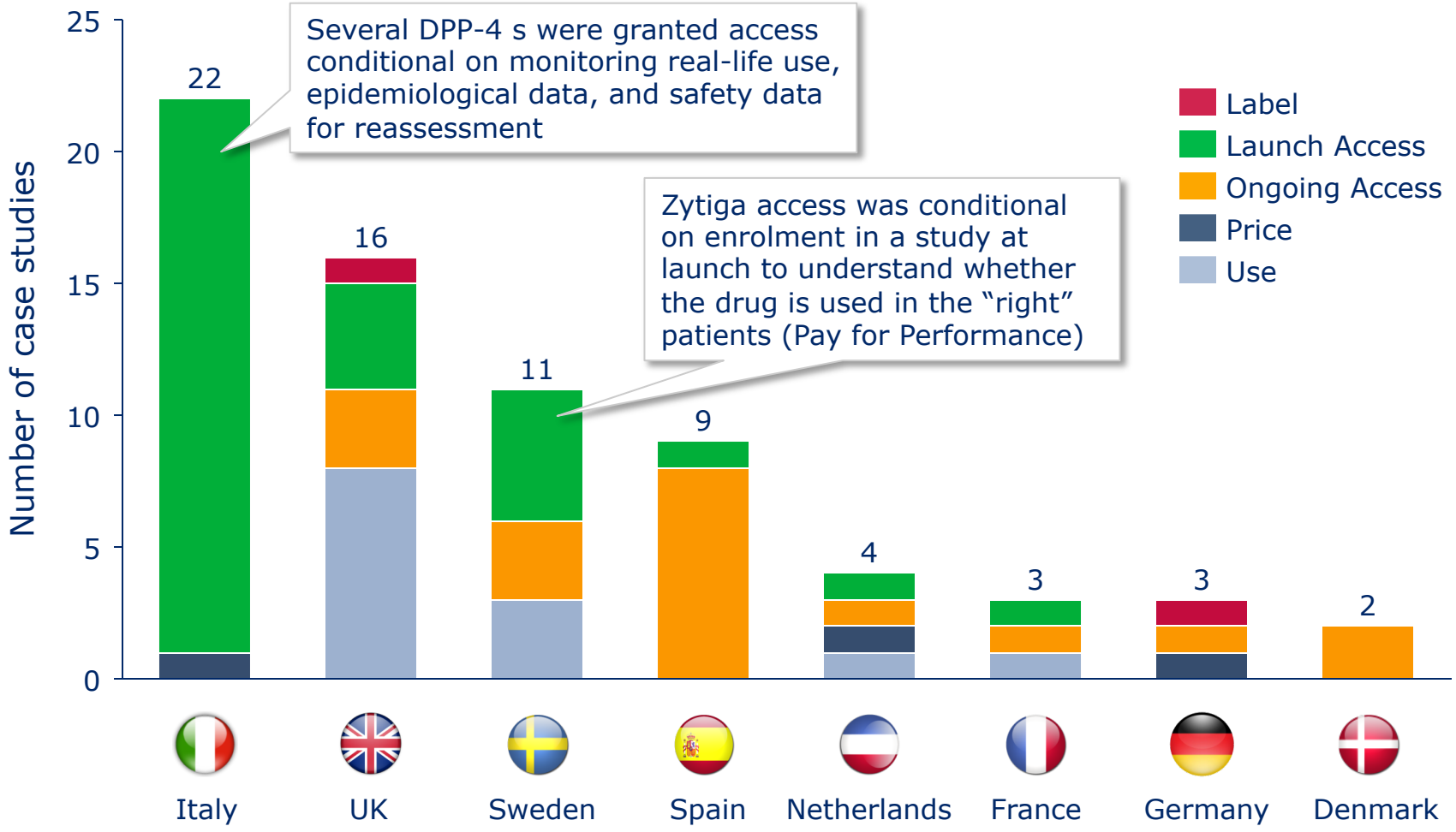
# RWE has had an impact both at- and post-launch

## Case examples of RWE use




Source: IMS Health, "RWE Market Impact on Medicines: A Lens for Pharma," 2013



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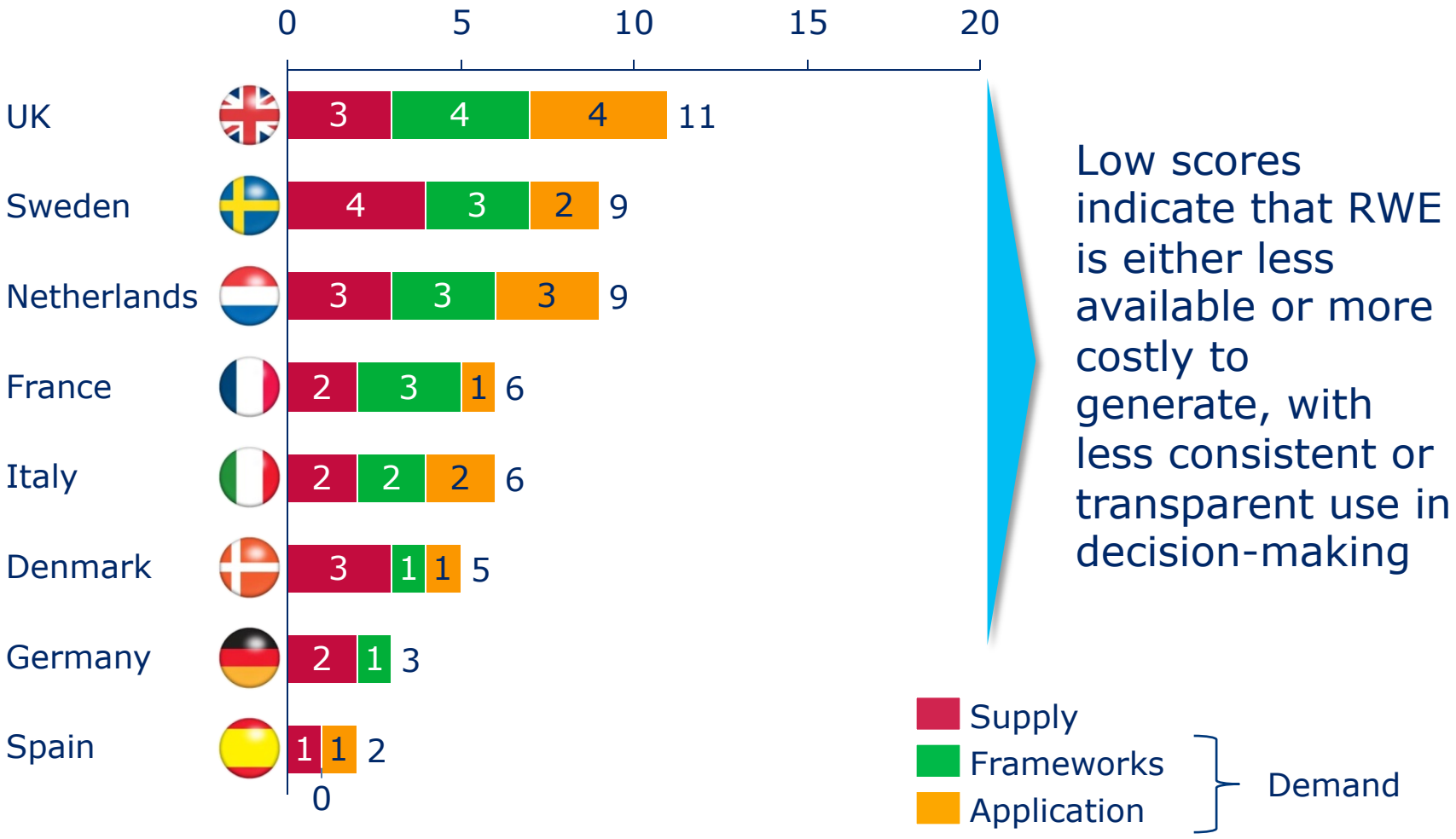
# RWE supply and demand are key drivers of impact




Source: IMS Health, "RWE Market Impact on Medicines: A Lens for Pharma," 2013



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# Anticipated future changes in EU P&MA

**Increased Alignment of HTA**

- Convergence through EUnetHTA, which may help drive more similar consideration of evidence base
- Efforts to align regulatory and HTA (medical / scientific), reducing the risk that comparators or endpoints are rejected during HTA
- Formal and informal referencing, heightening the importance of alignment with key agencies

**Growth of Post-Market Evaluations**

- Increase in reassessments based on RWE (e.g. France lowered the therapeutic (SMR) value of Pradaxa (dabigatran) and raised Eliquis (apixaban) given evidence and level of value perceived vs. warfarin)
- Leverage of secondary data to more efficiently conduct Ph IV studies, and facilitate conditional agreements

**Evolution of Pricing Models & Payment Infrastructure**

- Continued growth in P&MA tactics (e.g. managed entry agreements) to support launch access, increasing the need for evidence planning pre-launch, and mechanisms to collect RWE for conditional reimbursement
- Use of healthcare system data to enable new mutually beneficial payment models through payment by use infrastructure, which will help manage the cost and risk around high-cost therapies & combinations

**Scrutiny on Patient Privacy**

- Proposed changes to EU General Data Protection Regulation potentially substantially reduce life sciences companies' ability to generate & apply RWE to quantify burden of disease, evaluate post-launch comparative benefit-risk, measure drug utilization, and administer innovative contracting

# Contents

# Criteria for selecting case study TAs and products

## TA-Specific Prioritization Criteria

**1** **Select TAs, which on a standalone basis meet the following criteria for relevance and importance…**

- ✓ **Minimum of 2 product launches since 2010** analysis to allow for comparison
- ✓ **At least one product launch before 2013** to assess HTA reviews and impact on uptake through several quarters of sales data
- ✓ **High priority disease for pharma (Top 20 TA by spend, >$20Bn globally in 2018)** in the next 5 years based on new launches and R&D investments

**2** **…and together comprise a representative set of TAs along dimensions that influence HTA and market access variability**

- ✓ **Traditional vs. specialty care**, influencing budgets, reimbursement, and management
- ✓ **High vs. low budget impact**, influencing level of scrutiny and different management approaches
- ✓ **High vs. low perceived unmet need**, due to urgency and perceived societal need
- ✓ **Predominately innovative vs. genericized**, driving comparators, therapeutic choice, treatment paradigms, and payer management

# TAs prioritized for analysis

| | | Type | Budget Impact | Unmet Need | Level of Generics |
|---|---|---|---|---|---|
| **Type 2 Diabetes (SGLT2s)** | • Forxiga (dapagliflozin)<br>• Invokana (canagliflozin)<br>• Jardiance (empagliflozin) | Traditional | High | Low | High |
| **Multiple Sclerosis** | • Aubagio (teriflunomide)<br>• Gilenya (fingolimod)<br>• Lemtrada (alemtuzumab)<br>• Tecfidera (dimethyl fumarate) | Specialty | Low | Low | Low |
| **Prostate Cancer** | • Jevtana (cabazitaxel)<br>• Xofigo (radium 223 dichloride)<br>• Xtandi (enzalutamide)<br>• Zytiga (abiraterone) | Specialty | Moderate | Moderate | Low |
| **Hepatitis C** | • Sovaldi (sofosbuvir) | Specialty | High | Moderate | Low |

40+ products across 16 TAs were evaluated and prioritized according to selected criteria
*The following TAs were deprioritized: Atrial Fibrillation, CML, CLL, COPD, Epilepsy, HIV, Melanoma, Multiple Myeloma, NSCLC , Neutropenia, Renal Cell Carcinoma, Rheumatoid Arthritis*

Source: IMS Institute for Medical Informatics, "Global Outlook for Medicines through 2018"; IMSCG analysis



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# Type 2 Diabetes: Key takeaways

**Heterogeneity in HTA Assessments**

- Significant differences were observed in HTA outcomes among countries, for a given product
- Differences seem to be driven by "relevance" of the data (e.g. comparator in DE), and perceived clinical effectiveness (e.g. importance of superiority data in FR)

**Consistency within Markets**

- Products within the SGLT2 class were evaluated similarly within a market; differences were driven by Ph III study therapy regimens and the existing treatment paradigm
- Active comparator data without clear demonstration of superiority did not drive more positive assessments

**Impact on Market Access & Uptake**

- The SGLT2 class has relatively few access restrictions, despite HTA scrutiny of the clinical evidence
- Little correlation between HTA assessment and uptake was observed; Forxiga shows a strong first mover advantage
- In a crowded TA, HTA evaluations of a class with perceived limited incremental benefit and similar evidence packages influenced price more than access or uptake

# Type 2 Diabetes: Evidence base

| Type of evidence | | Forxiga (dapagliflozin) | Invokana (canagliflozin) | Jardiance (empagliflozin) |
|---|---|---|---|---|
| Endpoints | HbA1c | ✓ (1º) | ✓ (1º) | ✓ (1º) |
| | Change in body weight | ✓ (2º) | ✓ (2º) | ✓ (2º) |
| | Change in BP | ✓ (2º) | ✓ (2º) | ✓ (2º) |
| | Hypoglycemia | ✓ (2º) | ✓ (2º) | *Included in AEs* |
| Comparators & Clinical Effectiveness | H2H / active comparators | ✓ **Non-inferior** vs. SU, +met | ✓ **Superior** vs. SU, +met<br>✓ **Superior** vs. sitagliptin, +met+SU<br>✓ **Non-inferior** vs. sitagliptin, +met | ✓ **Non-inferior** vs. SU, +met |
| | Placebo-controlled | ✓ **Superior** vs. placebo +met<br>✓ **Superior** vs. placebo, add-on to insulin | ✓ **Superior** vs. placebo +met, +met+SU, and +met+pioglitazone<br>✓ **Superior** vs. placebo, add-on to insulin | ✓ **Superior** vs. placebo +met, +met+SU, +met +pioglitazone<br>✓ **Superior** vs. placebo, add-on to insulin |
| Safety & tolerability | | Higher rates of genital and urinary tract infections; bladder, prostate, and breast cancer | Higher rates of genital infections | Higher rates of genital infections |
| Cost effectiveness | | UK (NICE): range of ICER £2671- £4358 / QALY | UK (NICE): range of ICER £607-£27,419 / QALY | UK (SMC)[1]: range of ICER £806-£12,798 |

Note: synthesis based on interpretation of clinical and economic information provided in manufacturer HTA submissions and published guidance
[1] SMC referenced for empagliflozin as NICE review is ongoing
Abbreviations: SU, sulfonylurea; met, metformin; 1º, primary endpoint; 2º, secondary endpoint
Source: Manufacturer submissions

# Type 2 Diabetes: HTA evaluation

Positive | Positive with limitations | Negative

| Country | Forxiga (dapagliflozin) | Invokana (canagliflozin) | Jardiance (empagliflozin) |
|---|---|---|---|
| FRANCE | **ASMR V:** modest glycemic control; safety; unknown place within Tx paradigm | **ASMR V:** non-inferiority; lack of superiority vs. Januvia; lack of LT safety | **ASMR V:** modest glycemic control (non-inferiority); superiority study vs. SU |
| GERMANY | **No added benefit:** no relevant data | **No added benefit:** differences in Tx arms and lack of relevant data | **No added benefit:** no relevant data and starting dose too high |
| SWEDEN | • Clinical: glycemic control, ↓ weight<br>• Cost effective | Not reviewed | Not reviewed |
| UK (NICE) | • Comparable glycemic control, ↓ in weight<br>• Insufficient evidence for triple therapy (+met+SU)<br>• Cost effective: similar vs. DPP4s | • Comparable glycemic control, ↓ in BP, ↓ weight<br>• Cost effective | Under review |
| UK (SMC) | • Non-inferior to SU, ↓ in weight, hypos<br>• Insufficient economic evidence in combo with insulin | • Non-inferior to SU and DPP4, ↓ in BP, ↓ weight<br>• Cost effective | • Non-inferior to SU<br>• Cost effective |

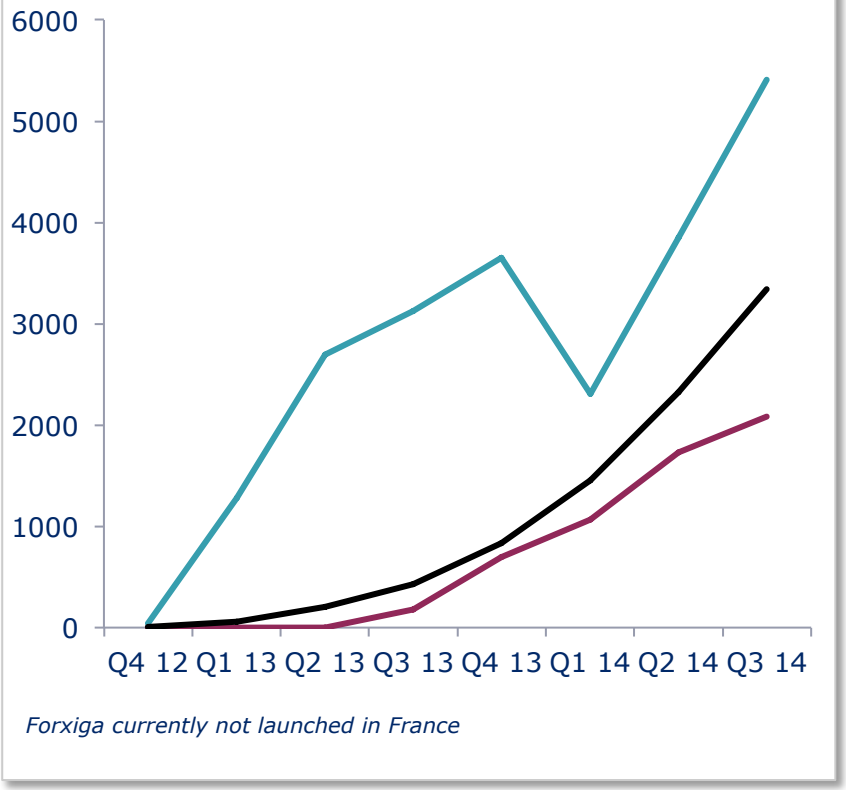
Note: synthesis based on interpretation of clinical and economic information provided in manufacturer HTA submissions and published guidance
Abbreviations: SU, sulfonylurea; met, metformin, BP, blood pressure
Source: HTA published guidance, assessments, and reimbursement decisions

# Type 2 Diabetes (SGLT2): Impact on uptake[1]

## Product Uptake (DDD/100,000 people)

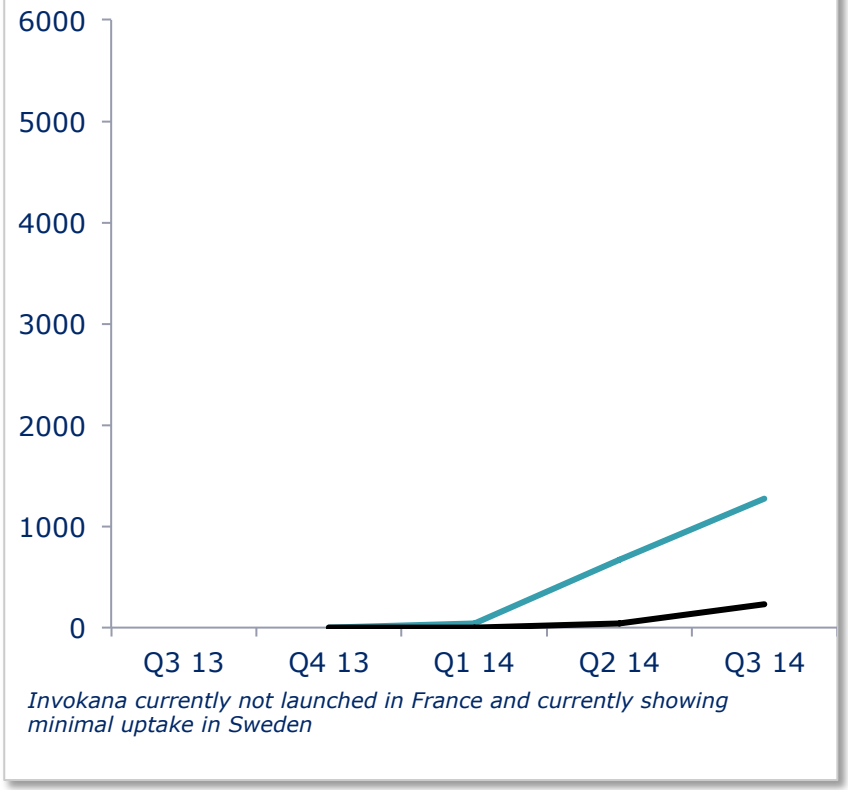
FRANCE GERMANY SWEDEN UK

### Forxiga (dapagliflozin)




*Forxiga currently not launched in France*

### Invokana (canagliflozin)




*Invokana currently not launched in France and currently showing minimal uptake in Sweden*

[1] Jardiance (empagliflozin) first launched in Q3 2014 in Germany, Finland, Ireland and UK; there is not adequate sales to track product uptake
Source: IMS Health MIDAS Q3-2014. Population from Eurostat. Countries where IMS does not audit the hospital market have been excluded (Estonia, Greece, Latvia, Netherlands and Luxembourg). In some countries uptake may be impacted by parallel trade which cannot be adjusted for. Note: sales include both private and public reimbursed market, in countries where reimbursement status has not been granted data represents uptake into the private market only



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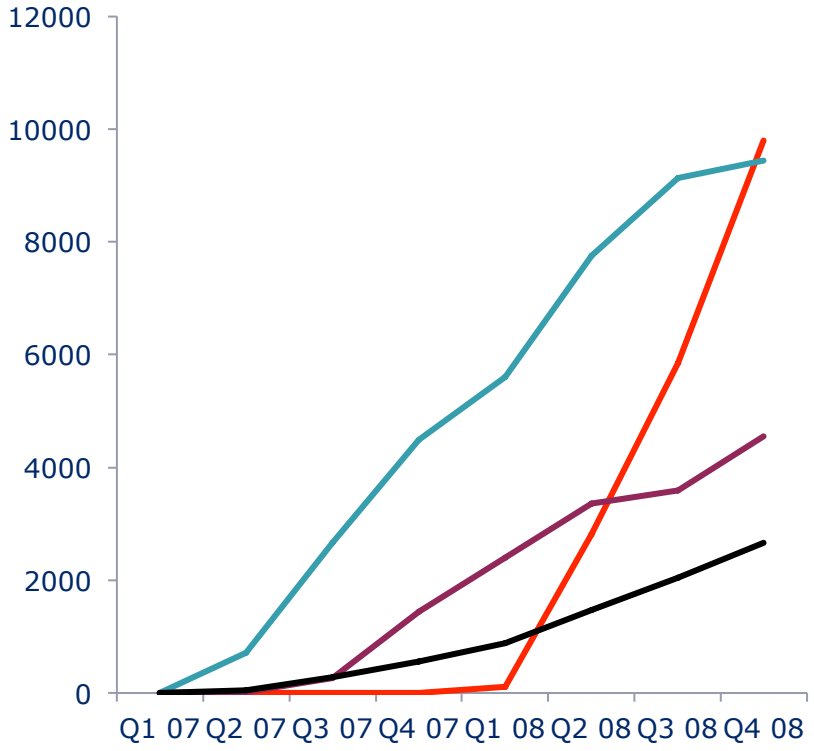
# Type 2 Diabetes: DPP4 & SGLT2 launch comparison

## Product Uptake (DDD/100,000 people)

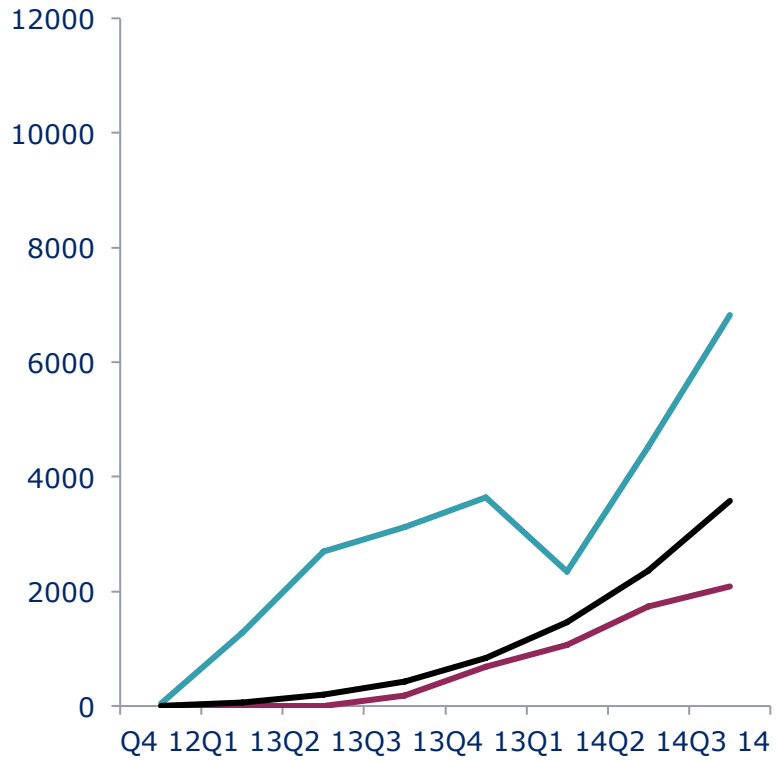
FRANCE GERMANY SWEDEN UK

### DPP-4 (GALVUS, JANUVIA, NESINA, ONGLYZA, TRADJENTA)




Initial 8 quarters post-launch shown for comparability

### SGLT2: (FORXIGA, INVOKANA, JARDIANCE)




*SGLT2's currently not launched in France*

Source: IMS Health MIDAS Q3-2014. Population from Eurostat. Countries where IMS does not audit the hospital market have been excluded (Estonia, Greece, Latvia, Netherlands and Luxembourg). In some countries uptake may be impacted by parallel trade which cannot be adjusted for. Note: sales include both private and public reimbursed market, in countries where reimbursement status has not been granted data represents uptake into the private market only



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# Multiple Sclerosis: Key takeaways

**Heterogeneity in HTA Assessments**

- Assessments varied by market for a product, with no consistent pattern between countries
- While relapse rate was weighed similarly, influence of "soft" outcomes, e.g. tolerability and QoL varied by market
- France and Germany tended to agree in cases of "no added benefit," although Germany was more positive for Gilenya

**Consistency within Markets**

- UK (NICE, SMC) & Sweden were relatively consistent, primarily focusing on relapse rate and cost effectiveness; Sweden also considered QoL
- Patient Access Schemes (England, Scotland) were key to achieving cost effectiveness
- France consistently rewarded active comparator data
- Germany showed least consistency between products

**Impact on Market Access & Uptake**

- In Sweden, positive assessments (Gilenya, Tecfidera) correlate with stronger uptake
- The UK has had limited uptake of new MS launches, despite positive evaluations and few access restrictions
- In Germany, HTA assessments of MS launches showed little correlation with uptake; Tecfidera consumption is highest, despite having a negative IQWiG assessment

# Multiple Sclerosis: Evidence Base

| Type of evidence | | Aubagio (teriflunomide) | Gilenya (fingolimod) | Lemtrada[1] (alemtuzumab) | Tecfidera (dimethyl fumarate) |
|---|---|---|---|---|---|
| Indication | | RRMS | Highly active RRMS (post IFN-β) | RRMS with active disease | RRMS |
| Endpoints | Annualized relapse rate | ✓ (1°) | ✓ (1°) | ✓ (1°) | ✓ (1°), at 2 years |
| | Time to onset of disability | | | ✓ (1°) | |
| | % with relapse at 2 years | | | | ✓ (1°) |
| Comparators & Clinical Effectiveness | Active | | ✓ **Stat sig ↓** in ann. relapse vs. Avonex | ✓ **Stat sig ↓** in annualized relapse vs. Rebif | ✓ Not powered vs. glatiramer acetate |
| | Placebo | ✓ **Stat sig ↓** in ann. Relapse | ✓ **Stat sig ↓** in ann. Relapse | | ✓ **Stat sig ↓** in ann. relapse<br>✓ **Stat sig ↓,** % w/ relapse 2 yrs |
| Safety & tolerability | | Similar to placebo | Similar to placebo, ↓ vs. Avonex | Similar to Rebif; ↑ thyroid-related AEs | Similar to placebo |
| Cost effectiveness | | UK (NICE): <£20k/ QALY vs. glatiramer acetate | UK (NICE): ICER £25-35K /QALY | UK (NICE): ICER £13.6 -24.5K/QALY (vs. glatiramer acetate) | UK (NICE): ICER £15.9K - £19.7K/ QALY |

Note: synthesis based on interpretation of clinical and economic information provided in manufacturer HTA submissions and published guidance
[1] Previously marketed as MabCampath in Europe for B-CLL; withdrawn in August 2012
Abbreviations: RRMS, Relapsing-remitting multiple sclerosis; ; PAS, patient access scheme; IFN-β, beta-interferon; 1°, primary endpoint; 2°, secondary endpoint
Source: Manufacturer HTA submissions

# Multiple Sclerosis: HTA evaluation

Positive | Positive with limitations | Negative

| Country | Aubagio (teriflunomide) | Gilenya (fingolimod) | Lemtrada (alemtuzumab) | Tecfidera (dimethyl fumarate) |
|---|---|---|---|---|
| FRANCE | **ASMR V:** No conclusive H2H study; oral benefit | **ASMR IV:** Relapse rate, reassessment for LT tolerance | Not reviewed | **ASMR V:** no superiority study vs. active Tx; oral benefit |
| GERMANY | **No added benefit:** lack of clarity on side effects, conclusions on mortality | **Minor :** fewer flu-like symptoms | Not reviewed | **No added benefit:** No suitable data; inappropriate comparator |
| SWEDEN | Fewer side effects<br>Not cost effective vs. Extavia (initial)<br>Cost effective vs. Copaxone (appeal) | ↓ Relapse rate<br>Cost effective | ↓ relapse rate<br>Small gain in QoL vs. Tysabri, at a lower cost | ↓ Relapse rate<br>Cost effective; economic assessment Dec 2016 with RWE |
| UK (NICE) | Contingent on PAS<br>↓ relapse rate<br>Cost effective | Contingent on PAS<br>↓ relapse rate<br>Cost effective | More effective (disability / relapse rates)<br>Cost effective | Contingent on PAS<br>↓ proportion patients with a relapse at 2 yrs<br>Cost effective |
| UK (SMC) | Contingent upon PAS<br>↓ rate of relapse | Contingent on PAS<br>↓ Relapse rate<br>Cost savings over 5 years vs. Tysabri | ↓ rate of relapse<br>Cost effective | Contingent on PAS<br>↓ proportion patients with a relapse at 2 yrs |

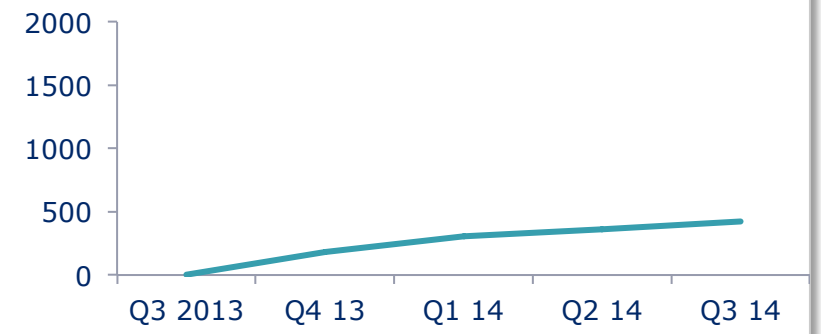
Note: synthesis based on interpretation of clinical and economic information provided in manufacturer HTA submissions and published guidance
Abbreviations: RRMS, Relapsing-remitting multiple sclerosis; PAS, patient access scheme; IFN-β, beta-interferon
Source: HTA published guidance, assessments, and reimbursement decisions

# Multiple Sclerosis: Impact on Uptake

## Product Uptake (DDD/100,000 people)

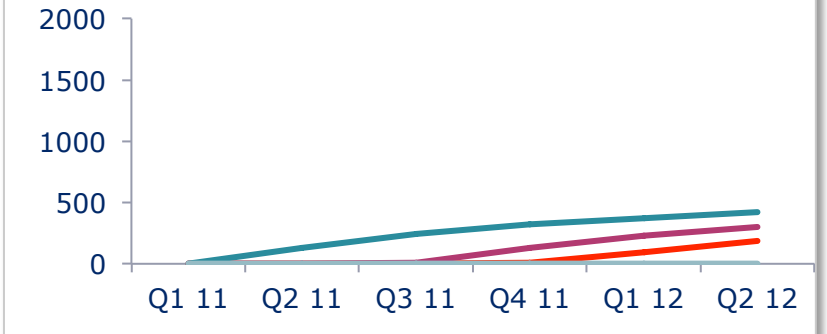
FRANCE GERMANY SWEDEN UK

### Aubagio (teriflunomide)



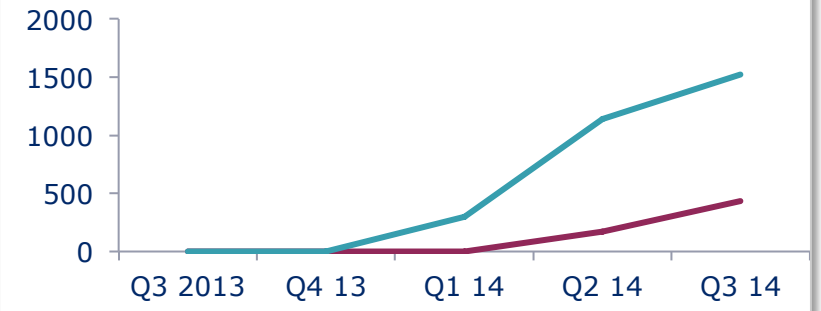

*Not launched in FR and currently showing minimal uptake in SE & UK*

### Gilenya (fingolimod)




*Currently showing minimal uptake in UK*

### Tecfidera (dimethyl fumarate)




*Not launched in FR and currently showing minimal uptake in UK*

*For Gilenya, initial 6 quarters post-launch are shown here for comparability; full consumption data since launch is available in the appendix*

Note: Lemtrada consumption is not shown, as MS uptake cannot be disassociated from spillover from Campath sales after withdrawal from market
Source: IMS Health MIDAS Q3-2014. Population from Eurostat. Countries where IMS does not audit the hospital market have been excluded (Estonia, Greece, Latvia, Netherlands and Luxembourg). In some countries uptake may be impacted by parallel trade which cannot be adjusted for. Note: sales include both private and public reimbursed market, in countries where reimbursement status has not been granted data represents uptake into the private market only



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# Prostate Cancer: Key takeaways

**Heterogeneity in HTA Assessments**

- Overall HTA decisions were similar for a product, but rationale differed; for example, for Jevtana, all countries recognized OS, but found different critiques (importance of QoL, focus on subgroup efficacy, subjectivity of PFS components, cost effectiveness)
- HTA decision limitations varied significantly, driven by these critiques

**Consistency within Markets**

- Within a country, evaluations were consistent, with similar benchmarks for efficacy, and value placed on pain and QoL
- Reassessments reinforce consistency, e.g. Sweden acceptance of manufacturer agreements Xtandi and Zytiga appear to have been agreed within the same time frame
- PAS were key for cost effectiveness in UK and Sweden

**Impact on Market Access & Uptake**

- Despite similar HTA assessments, Zytiga has had stronger uptake; success has been driven by its label expansion to 1L, even though HTAs were less positive on this indication
- In the case of a "neutral" HTA, with similar access across products, uptake seems to be primarily driven by physician preference and perceived value for the patient

# Prostate Cancer: Evidence Base

| Type of evidence | | Jevtana (cabazitaxel) | Xofigo (radium 223 dichloride) | Xtandi (enzalutamide) | Zytiga (abiraterone) |
|---|---|---|---|---|---|
| Indication | | 2L+ mCRPC (post docetaxel) | 2L+ mCRPC (post docetaxel), bone mets | 2L+ mCRPC (post docetaxel) | 1L and 2L+ mCRPC |
| Endpoints | Overall survival | ✓ (1°) | ✓ (1°) | ✓ (1°) | ✓ (1°) |
| | PSA progression | ✓ (2°) | ✓ (2°) | ✓ (2°) | ✓ (2°) |
| | Pain response | ✓ (2°) | ✓ (2°) | ✓ (2°) | |
| | SSE / SRE | | ✓ (2°) | ✓ (2°) | |
| Comparators & Clinical Effectiveness | | Vs. mitoxantrone<br>✓ **↑ OS**<br>✓ **↑ PFS**<br>✓ **↑ time to PSA progression**<br>✓ **No stat. sig difference in pain response** | Vs. Placebo + BSC<br>✓ **↑ OS**<br>✓ **↓ SSE**<br>✓ Positive effect on **bone pain**<br>✓ **QoL** did not reach minimally important difference | Vs. Placebo + BSC<br>✓ **↑ OS**<br>✓ **↑ PFS**<br>✓ **↑ time to PSA progression**<br>✓ **↑ time 1st SRE**<br>✓ **↓ rate of pain**<br>✓ **↑ QOL** | Vs. Placebo<br>✓ **↑ OS**<br>✓ **↑ PFS**<br>✓ **↑ PSA progression**<br>✓ **↑ QoL** |
| Safety & tolerability | | ↑ neutropenia, febrile neutropenia | Diarrhea, nausea, vomiting, thrombocytopenia | Similar rate of Aes | |
| Cost effectiveness | | UK (NICE): plausible ICER £75K /QALY | Not yet available | UK (NICE): ICER £15K/QALY vs abiraterone | UK (NICE): ICER £53K/QALY vs prednisone alone |

Note: synthesis based on interpretation of clinical and economic information provided in manufacturer HTA submissions and published guidance
Abbreviations: mCRPC, metastatic castration-resistant prostate cancer; PFS, progression free survival; SSE, symptomatic skeletal events; SRE, skeletal related event; PSA, prostate specific antigen; QoL, quality of life; 1°, primary endpoint; 2°, secondary endpoint
Source: manufacturer HTA submissions

# Prostate Cancer: HTA evaluation

Positive | Positive with limitations | Negative

| Country | Jevtana (cabazitaxel) | Xofigo (radium 223 dichloride) | Xtandi (enzalutamide) | Zytiga (abiraterone) |
|---|---|---|---|---|
| FRANCE | **ASMR III** (reassessment)<br>↑OS; no diff. in pain; no QoL data<br>Reassess: RWE on safety | **ASMR IV:** place in sequence lacking data | **ASMR III :** ↑OS, favorable secondary endpoint results | **ASMR III (2L+):** improved efficacy and safety; QOL<br>**ASMR IV (1L):** efficacy |
| GERMANY | **Considerable:** patients >65 yrs, due to better survival prospects<br>**Minor:** patients <65 yrs<br>No QoL data | **Major:** <65 yrs, or >65 yrs w/ bisphosphonate Tx; survival, bone symptoms<br>**Minor:** >65 yrs w/o bisphosphonate Tx | **Major:** w/o visceral mets; OS, pain<br>**Considerable:** patients w/ visceral mets, pain | **Considerable (2L+):** morbidity, time to severe pain<br>**Minor (1L):** ↑ OS |
| SWEDEN | Cost effective in patients progressing on docetaxel within 3 months | ↑ OS<br>Cost effective vs. Jevtana and Zytiga | ↑ OS<br>Cost effective, contingent on ↓ price | Contingent on pay for performance<br>↑ OS, ↓ pain |
| UK (NICE) | ↑ OS<br>No QoL data, subjective outcomes in PFS (pain)<br>Not cost effective | Contingent on PAS<br>**Initial negative:** No data vs docetaxel or abiraterone; no QoL data<br>**Reassessment:** cost effective (PAS) | Contingent on PAS<br>Few options for patients after docetaxel<br>Cost effective | Contingent on PAS<br>↑ OS , oral<br>Cost effective |
| UK (SMC) | ↑ OS<br>No QoL data, subjective outcomes in PFS (pain)<br>Not cost effective | Not reviewed | Contingent on PAS<br>↑OS<br>Cost effective | Contingent on PAS<br>Not approved 1L |

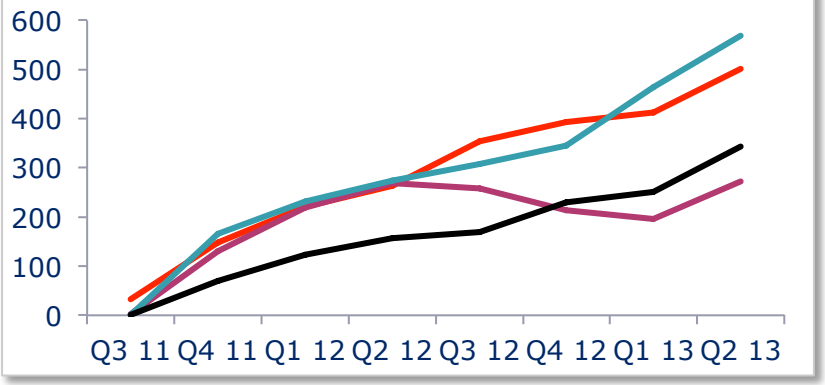
Note: synthesis based on interpretation of clinical and economic information provided in manufacturer HTA submissions and published guidance
Abbreviations: PAS, patient access scheme
Source: HTA published guidance, assessments, and reimbursement decisions

# Prostate Cancer: Impact on Uptake

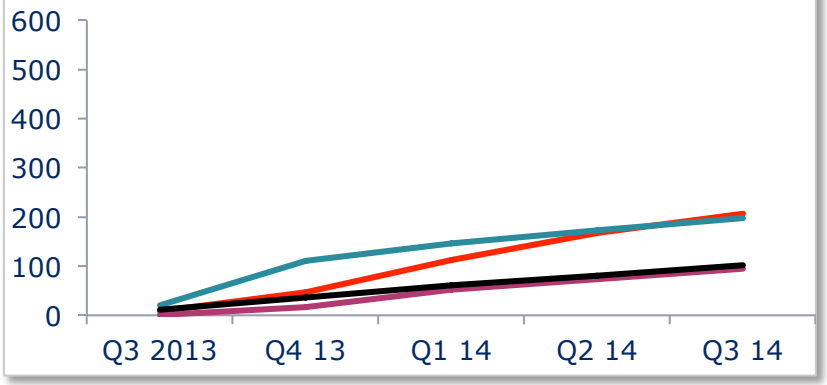
## Product Uptake*

FRANCE GERMANY SWEDEN UK

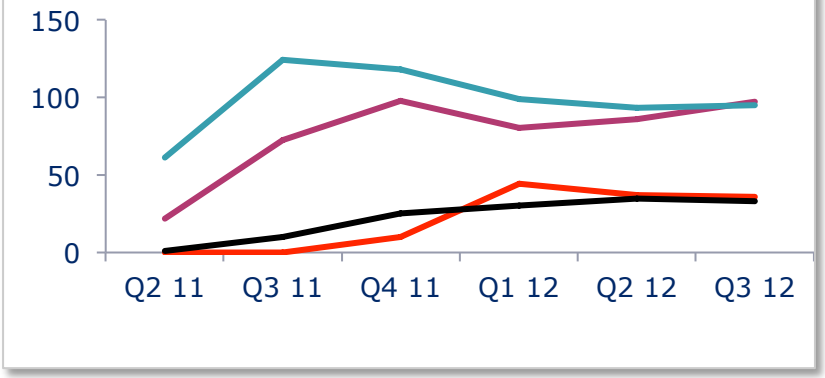
**Zytiga (abiraterone):** DDD/100,000 people



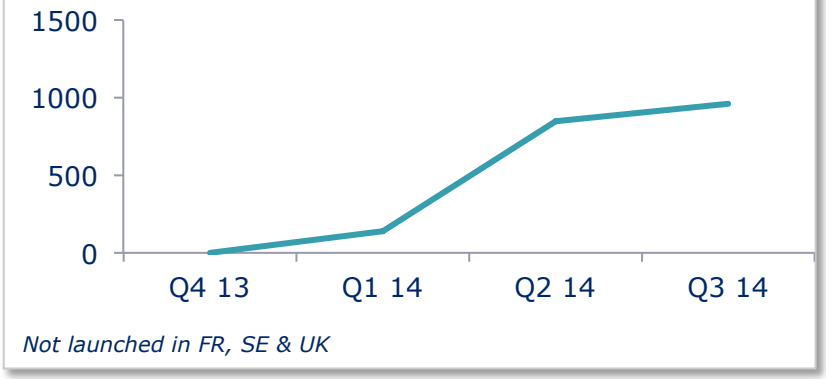

**Xtandi (enzalutamide):** DDD/100,000 people




**Jevtana (cabazitaxel):** MG/100,000 people




**Xofigo (radium RA-223):** Treatment cycles




*Not launched in FR, SE & UK*

Source: IMS Health MIDAS Q3-2014. Population from Eurostat. Countries where IMS does not audit the hospital market have been excluded (Estonia, Greece, Latvia, Netherlands and Luxembourg). In some countries uptake may be impacted by parallel trade which cannot be adjusted for. Note: sales include both private and public reimbursed market, in countries where reimbursement status has not been granted data represents uptake into the private market only

*Initial 8 quarters post-launch shown for comparability; full consumption data since launch is available in the appendix
Jevtana & Xofigo: "No DDDs have been established because of highly individualised use and wide dosage ranges. The doses used vary substantially because of various types and severity of neoplastic diseases, and also because of the extensive use of combination therapy. Consumption has been measured in MG for Jevtana and treatment cycles for Xofigo, with the latter based on number of mls used to treatment a 75kg male

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# Hepatitis C: Key takeaways

**Heterogeneity in HTA Assessments**

- All HTA agencies considered recognized Sovaldi benefit in at least a subset of the populations (genotypes) studied
- Specific genotypes with recognized benefit largely varied by country
- Genotype prevalence, while noted in HTA assessments, seems to primarily influence budget impact assessment, rather than efficacy evaluation or cost effectiveness
- The main issue for HTA evaluations and access has been high budget impact due to price and eligible population

**Impact on Market Access & Uptake**

- Despite some limitations in reimbursed treatment populations (genotype or disease severity), initial uptake has been strong across all markets
- For an innovative product with high clinical benefit and physician demand, uptake has been strong across most markets; access restrictions driven by cost effectiveness appear to have slowed uptake only in the UK
- Given potentially high budget impact, many payers have negotiated discounts (national or local); payers are expected to continue to monitor use and budget impact, and reassess evaluations based on RWE

# Hepatitis C: Evidence Base

| Type of evidence | | Sovaldi (sofosbuvir) |
|---|---|---|
| Indication | | In combination with other medicinal products for the treatment of chronic hepatitis C |
| Endpoints | Sustained virological response (12 weeks post therapy) | ✓ (1°) |
| | QoL | ✓ (2°) |
| | Mortality | ✓ (2°) |
| Comparators & Clinical Effectiveness | Active | ✓ **High SVR across subgroups**<br>✓ ↑ **SVR** vs. placebo<br>✓ **Non-inferior**, in combination with ribavirin vs. peginterferon + ribavirin<br>✓ **Lowest SVR in genotype 3** patients with shorter (12 week) Tx duration |
| Safety & tolerability | | Generally well tolerated |
| Cost effectiveness | | Not yet available |

Note: synthesis based on interpretation of clinical and economic information provided in manufacturer HTA submissions and published guidance
Abbreviations: 1°, primary endpoint; 2°, secondary endpoint
Source: Manufacturer HTA submissions

# Hepatitis C: HTA evaluation

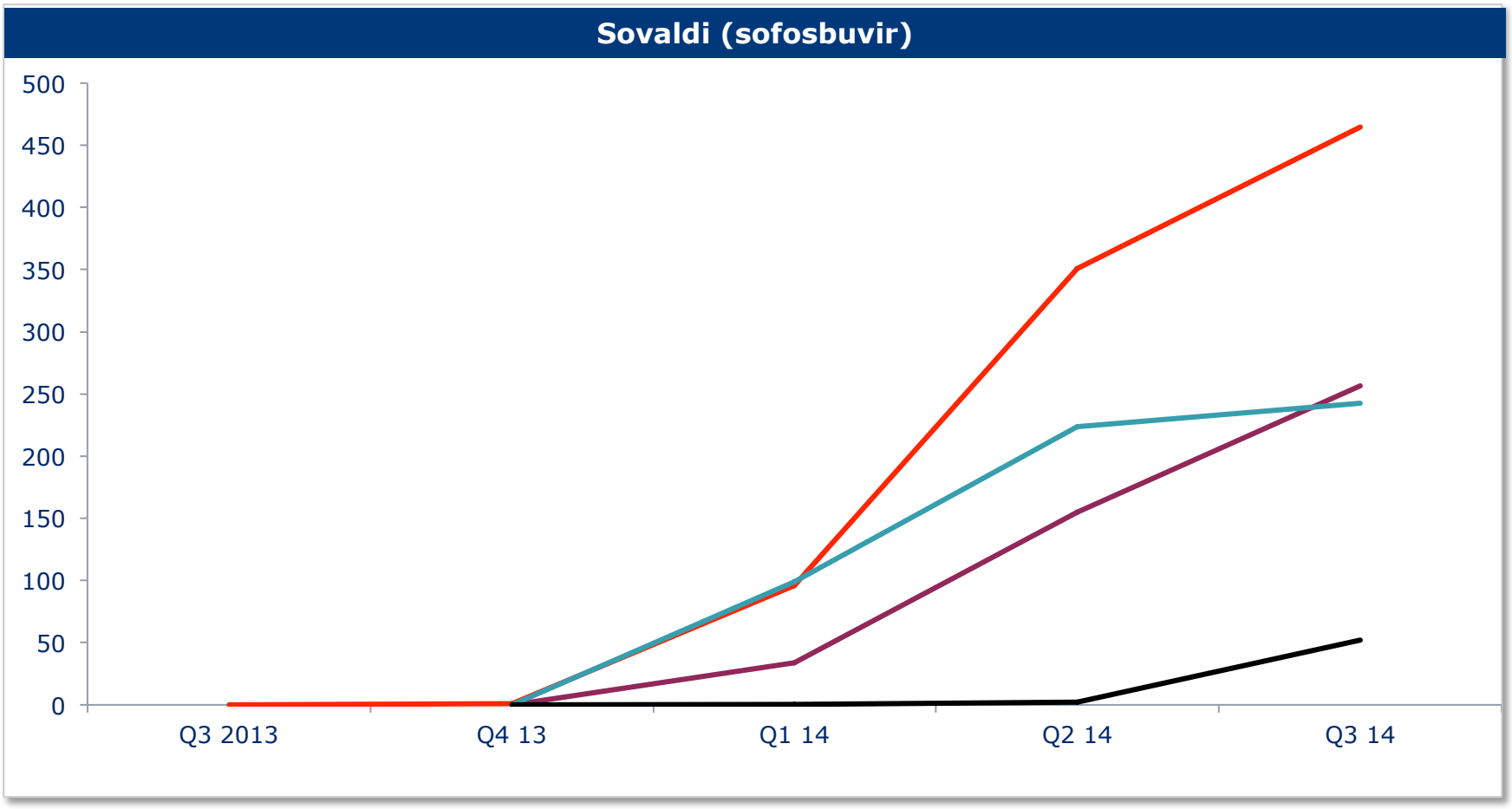
Positive | Positive with limitations | Negative

| Country | Sovaldi (sofosbuvir) |
|---|---|
| FRANCE | **ASMR II:** genotypes except treatment naive genotype 3<br>**ASMR III:** genotype 3 (treatment naive)<br>Virological efficacy |
| GERMANY | **"Non-quantifiable" added benefit:** genotype 2 (treatment naive); sustained virologic response recognized as acceptable surrogate<br>**No added benefit:** for genotypes 1,3,4-6, or patients infected with HIV; no suitable data |
| SWEDEN | Budget impact exceeds capacity to treat full potential patient population |
| UK (NICE) | Draft guidance:<br>• Recommended for genotype 1,2 & 3<br>• Not recommended for genotype 4-6 (not cost-effective) |
| UK (SMC) | • Accepted for use in patients with genotypes 1-6<br>  • Use in treatment-naive genotype 2-3 is restricted to those ineligible for / unable to tolerate peginterferon alfa (due to cost effectiveness)<br>• Clinical: sustained virological suppression in all genotypes<br>• Cost effective |

Note: synthesis based on interpretation of clinical and economic information provided in manufacturer HTA submissions and published guidance
Source: HTA published guidance, assessments, and reimbursement decisions

# Hepatitis C: Impact on Uptake

## Product Uptake (DDD/100,000 people)




Source: IMS Health MIDAS Q3-2014. Population from Eurostat. Countries where IMS does not audit the hospital market have been excluded (Estonia, Greece, Latvia, Netherlands and Luxembourg). In some countries uptake may be impacted by parallel trade which cannot be adjusted for. Note: sales include both private and public reimbursed market, in countries where reimbursement status has not been granted data represents uptake into the private market only



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