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Reimbursement of Active Immunotherapeutics: An Analysis Based On a Study of Current Reimbursement Approaches

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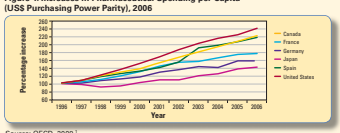
BACKGROUND

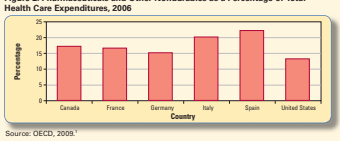
- Health care expenditures continue to increase in all countries, and pharmaceutical expenditures are the fastest growing part (Figure 1).
- Although the majority of health care costs are attributed to staffing and facilities rather than pharmaceuticals, reducing staffing, decreasing salaries, or closing facilities would be extremely unpopular and politically difficult to implement (Figures 2 and 3).
- In contrast, reducing the cost of pharmaceuticals is an attractive method to save costs in the short term; therefore, cost containment measures are being implemented with increasing frequency in all countries.

Figure 1. Increases In Pharmaceutical Spending per Capita (US$ Purchasing Power Parity), 2006



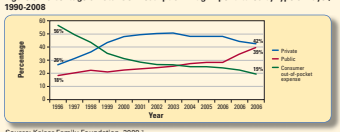
Source: OECD, 2009.[1]

Figure 2. Pharmaceuticals and Other Nondurables as a Percentage of Total Health Care Expenditures, 2006



Source: OECD, 2009.[1]

Figure 3. Percentage of Total US Prescription Drug Expenditures by Type of Payer, 1990-2008



Source: Kaiser Family Foundation, 2009.[2]

Cost Containment Measures In Different Markets

- Despite implementation of radical cost-control measures, pharmaceutical expenditures are expected to continue to increase due to highly innovative, expensive drugs, including immunotherapeutics.
- The reimbursement approval processes in most markets (e.g., Canada and most European countries) have some form of price regulation, negotiation, or approval process (Tables 1 and 2).
- The United States (US), United Kingdom (UK), and Germany have free pricing systems, so it could be expected that drug prices would be consistently higher in those countries compared with the others. However, there are several rules and hurdles in place in these markets that ensure that drug prices are at price levels very similar to those in more regulated markets

Table 1. Market Access Hurdles

Hurdle	Requirement	Output
1. Safety	Required for market authorization	Market authorization
2. Efficacy		
3. Quality		
4. Value	Effectiveness, cost-effectiveness	Listing recommendation
5. Price	Internal and external price referencing	Maximum nonexcessive price
6. Affordability	Budget impact, risk sharing	Reimbursement decision
7. Local/regional	Financing/funding	Local guidelines, funding decision

Table 2. Pricing and Reimbursement Cost Containment

Country	External Referencing	Internal Referencing	Budget Impact	Health Economics
Canada	✓	✓	✓	✓
France	✓	✓	✓	✗
Germany	✗	✓	✗(✓)	✗(✓)
Italy	✓	✓	✓	✓
Spain	✓	✓	✓	✗(✓)
UK	✗	✗	✗(✓)	✓
US	✗	✗	✗(✓)	✗(✓)

✗(✓) = not a national requirement but important at regional or local level.

Formal Pricing Procedures

- Internal price referencing:
  - Price of new drug is established with reference to prices of similar drugs in the national market.
- External price referencing:
  - Price of new drug is established with reference to prices of the same drug in other markets. In a direct or indirect way, all countries are subject to some sort of external price referencing as a regulated formal procedure, on an informal basis, as a consequence of parallel trade, or for political reasons.

Payer Instruments to Control Expenditures

- Listing and risk sharing agreements:
  - Very often payers are not involved in the pricing process; in order to control and afford costs, they are forced to restrict access or to establish agreements with suppliers, particularly if uncertainty of results and high costs are associated with the therapy.
  - Types of agreements include financial (rebates and discounts), risk-sharing, expenditure and utilization caps, pay for performance/ therapeutic guarantees, and trial periods.
  - These agreements are increasingly common in certain markets (e.g., Canada, Italy, UK, US), and they are often not transparent.
- Health Technology Assessments (HTAs):
  - Conducted in all countries by different bodies and with growing implications in the actual use of the drugs in their markets.
  - Although all countries have their own assessment bodies, some agencies have become references for other countries (e.g., National Institute for Health and Clinical Excellence [NICE], Scottish Medicines Consortium [SMC], Amélioration du Service Médical Rendu [ASMR], Institute for Quality and Efficiency in Health Care [IQWiG]).
- Cost-effectiveness thresholds:
  - While the UK is the only country with an established threshold for reimbursable therapies, the concept was not acceptable in other countries.
  - Recently, more countries are implementing "efficient frontiers" (e.g., Germany) and informal thresholds (e.g., Sweden, Belgium, Canada).
- Restriction rules:
  - Other countries are establishing restriction boards for certain therapies that are authorized (reimbursed) in a case-by-case basis.

Table 3. ASMR Clinical Improvement as a Basis of Price Negotiation

ASMR	Clinical Improvement	Price Implications
I	Major	Innovative product of significant therapeutic benefit	Premium possible
II	Important	Product of therapeutic benefit, in terms of efficacy and/or reduction in side-effect profile	Premium possible
III	Moderate	Moderate improvement in terms of efficacy and/ or reduction in side-effect profile	Premium possible
IV	Minor	Minor improvement in terms of efficacy and/or utility	Price no higher than comparators
V	None	No improvement	Price must be lower than comparators
VI	Not reimbursable		

Table 4. Canada Patented Medicine Prices Review Board

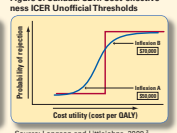
Clinical Improvement	Price Test	All Patented Medicines
Breakthrough	International median price	Prices of patented medicines can never exceed the international maximum price
Substantial improvement	Higher TCC and international median	
Moderate improvement	Midpoint TCC and international median (but not lower than TCC)	
No, little improvement	TCC or reasonable relationship test	

TCC = therapeutic class comparison.

Figure 4. UK/NICE Cost-effectiveness Thresholds

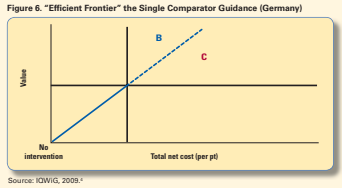
Source: Longson and Littlejohns, 2009.[3]

Figure 5. Canada/CDR: Cost-effectiveness ICER Unofficial Thresholds



Source: Longson and Littlejohns, 2009.[3]

Figure 6. "Efficient Frontier" the Single Comparator Guidance (Germany)



Source: IQWiG, 2009.[4]

OBJECTIVE

- To understand how different markets are responding to cost containment pressures by comparing reimbursement decisions for three recently approved treatments for metastatic renal cell carcinoma (mRCC)

METHODS

- We examined commonalities and differences of three drugs for mRCC, assessing drug costs, HTAs, and reimbursement decisions across seven countries with similar pharmaceutical funding schemes (Canada, France, Germany, Italy, Spain, Sweden, and the UK).
- Primary reimbursement criteria for these drugs were identified, local HTAs were reviewed, and specific qualitative research with local payers and experts was conducted.
- For country comparisons, drug treatment costs were calculated from a payer perspective (6 weeks therapy) (Tables 5 and 6).

Table 5. Oral Angiogenesis Inhibitors in mRCC in France, Germany, Italy, Spain, and the UK

Brand Name	Strength/ Form	Unit	Dose in mRCC	mRCC Indication
Avastin[5]	25 mg/ml concentrate for solution for infusion	Each vial contains 100 mg bevacizumab in 4 ml and 400 mg in 16 ml, respectively	10 mg/kg of body weight given once every 2 weeks as an intravenous infusion; initial dose should be administered over 90 minutes; if well-tolerated, second dose may be administered over 60 minutes; if well-tolerated, subsequent doses may be administered over 30 minutes	In combination with IFN-α-2a, first-line treatment of patients with advanced and/or mRCC
Nexavar[6]	200 mg film-coated tablets	Bottle of 112 tablets	400 mg (2 tablets of 200 mg) twice daily (equivalent to a total daily dose of 800 mg	Treatment of patients with advanced renal cell carcinoma for whom prior IFN-α or IL-2 based therapy has failed or cannot be used
Sutent[7]	12.5 mg, 25 mg, 50 mg hard capsules	Bottle of 30 capsules[a, b, c]	One 50 mg dose orally, taken daily for 4 consecutive weeks, followed by a 2-week rest period (schedule 4/2) to comprise a complete cycle of 6 weeks	Advanced and/or mRCC

EMEA = European Medicines Agency; IFN = interferon alfa; IL-2 = interleukin 2.
[a]Units were not listed by the EMEA for Nexavar and Sutent, so we turned to the Rote Liste[8] as an alternative source for this information.
[b] Sutent may also be supplied in blisters.[9]

Table 6. Pricing and Reimbursement/Funding Status of Oral Angiogenesis Inhibitors

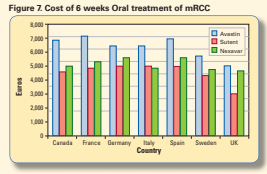
Drug	France[10,11]		Germany[9]		Italy[12,13]		Spain[14,15]		UK[9,16,17,18]	
	Price	Reimbursement Funding Status[a]	Price	Reimbursement Funding Status[b]	Price	Reimbursement Funding Status[c]	Price	Reimbursement Funding Status[d]	Price	Reimbursement Funding Status[e]
Avastin	**4 ml:** P: €351.50 W: €342.78 **16 ml:** P: €1,406.00 W: €1,371.10	Reimbursed ASMR: Level IV	**4 ml:** P: €338.38 W: €319.35 **16 ml:** P: €1,353.52 W: €1,277.39	Reimbursed	**4 ml:** P: €336.47 W: €305.94 **16 ml:** P: €1,345.88 W: €1,223.78	Reimbursed Class H: hospital use only	**4 ml:** P: €337.69 W: €332.49 **16 ml:** P: €1,350.78 W: €1,329.98	Hospital drug	**4 ml:** P: £236.88 W: £210.56 **16 ml:** P: £947.52 W: £842.24	• NICE: not recommended March 2009 • SMC: recommended against use, citing the lack of manufacturer submission (as of November 6, 2008) • AWMSG: no review available
Nexavar (price per tab)	P: €32.01 W: €31.36	Reimbursed ASMR: Level II	P: €32.59 W: €31.95	Reimbursed	P: €31.57 W: €28.70	Reimbursed Class H: hospital use only	P: €31.81 W: €31.73	Hospital drug	P: £22.36 W: £19.88	• NICE: negative March 2009 • SMC: not recommended for mRCC • AWMSG: not recommended for mRCC (June 5, 2007)
Sutent (price per capsule)	**12.5 mg:** P: €44.00 W: €43.04 **25 mg:** P: €87.50 W: €85.68 **50 mg:** P: €174.50 W: €170.98	Reimbursed ASMR: Level III	**12.5 mg:** P: €46.40 W: €44.00 **25 mg:** P: €90.40 W: €88.00 **50 mg:** P: €178.40 W: €176.00	Reimbursed	**12.5 mg:** P: €48.39 W: €44.00 **25 mg:** P: €96.78 W: €88.00 **50 mg:** P: €193.57 W: €176.00	Reimbursed Class H: hospital use only	**12.5 mg:** P: €42.91 W: €42.64 **25 mg:** P: €85.41 W: €85.14 **50 mg:** P: €170.41 W: €170.14	Hospital drug	**12.5 mg:** P: £28.03 W: £24.91 **25 mg:** P: £56.05 W: £49.82 **50 mg:** P: £112.10 W: £99.64	• NICE: acceptable at a QALY ~£55,000 • SMC: not recommended (June 2008) • AWMSG: not recommended for mRCC (August 2007)

AWMSG = All Wales Medicines Strategy Group; P = ex-factory price to pharmacy; W = ex-factory price to wholesaler; QALY = quality-adjusted life-year.

RESULTS

- Treatment cost differences in the seven countries were minimal and mostly related to exchange rates, indicating that for innovative drugs, price convergence has been achieved. Only the SMC assessment recommended against the use of the t studied drugs (Figure 7).
- Most countries apply or are studying some type of risk-sharing scheme or access/restriction program for forthcoming drugs.

Figure 7. Cost of 6 weeks Oral treatment of mRCC



CONCLUSIONS

- Most payers accept high-priced drugs; however, they restrict patient access or set up different types of agreements with suppliers to maintain budget control.
- Current reimbursement schemes in the countries studied are evolving according to similar parameters in order to give access to highly complex therapies such as active immunotherapeutics. In the past, many countries established special funds for highly innovative drugs to ensure patient access to innovations without unbalancing hospital budgets. However, the high budget increase that this is generating is necessitating restrictive measures such as prior authorization boards systems, enforcing treatment guidelines like those in the UK, establishing patient access agreements, and increasing bureaucracy.
- In each country, the feasibility of implementing processes to track drug use, cost, and outcomes will determine how these reimbursement schemes develop.

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