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Do reassessments reduce the uncertainty of decision making? Reviewing reimbursement reports and economic evaluations of three expensive drugs over time

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ABSTRACT

Objective: To investigate the desirability and feasibility of a cyclic reimbursement process to address uncertainty accompanying initial decision making.
Methods: We performed desk research for three expensive outpatient drugs: imatinib, pegfilgrastim, and adalimumab. We analysed the evidence base at the time of decision making ($T=0$) and May 2011 ($T=1$). For $T=0$, public reports of the Dutch reimbursement agency were investigated regarding available clinical and economic evidence, and a systematic review was performed to retrieve additional economic evidence. For $T=1$, the systematic review was extended till May 2011.
Results: The evidence base at $T=0$ lacked information on clinically relevant outcomes such as mortality, morbidity, and quality of life (5/8 reports), (long-term) adverse events (2/8 reports) and experience in use (1/8 reports). One budget impact analysis and one economic evaluation were available but no pharmacoeconomic dossiers. The systematic review identified 39 cost-utility studies (of 52 economic evaluations) for $T=1$, characterised by methodological heterogeneity.
Conclusions: Given the considerable uncertainty accompanying initial decision-making, a more cyclic reimbursement process seems feasible to reduce uncertainty regarding the therapeutical and economical value of expensive drugs. A mandatory evidence development requirement seems desirable to sufficiently meet decision makers' needs.

1. Introduction

Reimbursement decisions regarding new drugs are characterised by uncertainty at the time of decision making. Striking an optimal balance between ensuring early access to new innovative drugs and having sufficient evidence regarding long-term effectiveness, cost-effectiveness and budget impact remains a challenge in many countries.

Governments have introduced several types of policies that attempt to reduce on-going uncertainty, such as patient access schemes [1], managed entry agreements [2], price-volume agreements [3], performance-based risk-sharing schemes [4], coverage/access with evidence development [5], and systematic revisions [6].

All approaches address the limitations of single, fixed decisions. Uncertainty is especially problematic if accompanied by a high budget impact, adding the question of whether societies obtain sufficient value for money. A cyclic approach may ensure a more reasonable management of the benefit package.

In the Netherlands, only new and expensive *inpatient* drugs were subject to revision until 2012 even though 18

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outpatient drugs were responsible for 22% of the total outpatient pharmaceutical expenditure in 2010 [7]. From 2013 onwards, coverage with evidence development policy will be extended to (expensive) outpatient drugs [8].

This article investigates the desirability and feasibility of a more cyclic approach in drug reimbursement to ensure long term value for money. Using three case studies, we aim to answer the following questions: (i) What was the evidence base at the time of the reimbursement decision? (ii) How did the economic evidence evolve over time? (iii) Would a cyclic decision-making process have been desirable? (iv) Is a cyclic decision-making process feasible?

2. Methods

We performed desk research to analyse the evidence base of three drugs at the time of decision making ($T=0$) and May 2011 ($T=1$). The Dutch reimbursement agency (CVZ) determines whether a drug is included in List 1A (mutually interchangeable) or List 1B (no similar alternative, drugs qualify for premium price). If restrictions apply, drugs can also be on List 2 (describing reimbursement conditions). Applications for List 1A require evidence only on therapeutic value; applications for List 1B also require an estimate of budget impact and, since 2005, evidence on cost-effectiveness. Applications for extensions of indication require new evidence only for drugs on List 2. Reimbursement reports are published online; for details of the Dutch reimbursement system see Polain et al. [6] and Schaefer et al. [9].

The three cases were selected based on the Dutch definition of expensive inpatient drugs: daily drug costs that are at least ten times higher than average and more than 0.5% of the total budget [10]. We applied this definition to outpatient drugs in the absence of an official one [11], yielding 25 expensive outpatient drugs for the period 1989–2010 [7]. In 2010, 18 drugs fell within the definition and cost about €770 million or 22% of the total Dutch pharmaceutical expenditure (see Table S1 at: online-appendix). Antineoplastic and immunomodulating agents (ATC-code 'L') were most prevalent (9/18) and accounted for €516 million or two-thirds of the reimbursed costs. Therefore, we selected our three cases from the ATC-code 'L' group, including a drug with an orphan status, a drug with no special distinctions, and all with a high budget impact (i.e. imatinib: €36 million; pegfilgrastim: €41 million; adalimumab: €170 million). These three drugs were included in the Dutch formulary in 2002, 2003, and 2004, and classifiable as expensive since 2004, 2005, and 2004 [7], respectively.

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.healthpol.2013.03.006.

2.1. Evidence base at reimbursement decision ($T=0$)

We investigated all relevant Dutch reimbursement reports regarding the seven criteria used by the reimbursement agency for assessing therapeutic value: efficacy (in terms of intermediate outcomes), effectiveness (in terms of clinically relevant outcomes like mortality and morbidity), quality of life, adverse events, applicability, ease of use, and experience in use [12]. Next to the clinical part of the dossiers we investigated available and applicable economic evidence. Last, we systematically reviewed published economic evaluations available at $T=0$. Regarding the reimbursement criteria, CVZ's application of efficacy and effectiveness was not consistent with international epidemiological literature until 2010, and we thus adopted CVZ's framework a priori. We also use CVZ's terminology throughout.

2.2. Evidence base at 2011 ($T=1$)

We performed a systematic review of all available economic evaluations using the MEDLINE database via PubMed from inception to May 2011. Results were cross-checked with the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, and the Cost-Effectiveness Analysis Register at Tufts Medical Center.

Keywords included 'cost effectiveness', 'cost utility', 'cost benefit', 'cost minimization', 'economic evaluation', 'pharmacoeconomics', and 'health economics' in combination with the generic drug names. Inclusion criteria included peer-reviewed full economic evaluations written in English, Dutch, or German.

We then performed a title and abstract search to identify relevant articles. Reference lists were investigated for additional material. Full-text articles were carefully examined, extracting general information (i.e., author(s), title, journal, year of publication, country setting), study design, perspective, modelling techniques, time horizon, utility elicitation, incremental cost-effectiveness ratios, and sensitivity analysis.

Retrieved incremental cost-effectiveness ratios (ICERs) are presented per quality-adjusted life years (QALYs). The costs reference year is 2010 unless otherwise stated. To enhance comparability, results were converted and inflated to 2010 euros using the currency exchange rate derived from the Dutch Central Bank and the Harmonised Indices of Consumer Prices from the European Central Bank for The Netherlands (2010 exchange rate: €1 = £0.86 = US$1.33). Absent a specific price year, we used the year of publication.

3. Results

Table 1 provides an overview of the results for the three cases.

4. Case i: imatinib

Imatinib is an immunomodulating agent indicated for six different malignancies with orphan designations, of which chronic myeloid leukaemia (CML) was EMA-registered as main indication in 2001. Other indications are gastrointestinal stromal tumours (unresectable GIST in 2002 and after surgical intervention in 2009), acute lymphoblastic leukaemia (ALL 2006), dermatofibrosarcoma protuberans (DFSP 2006), advanced hypereosinophilic syndrome or chronic eosinophilic leukaemia (HES&CEL