VALUE IN HEALTH 15 (2012) 381–388

Available online at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/jval

Health Policy Analysis

Antihypertensive Drugs: A Perspective on Pharmaceutical Price Erosion and Its Impact on Cost-Effectiveness

Rodrigo Refoios Camejo, PharmD, MSc[1,2,], Clare McGrath, BSc (Hons)[1], Ron Herings, PhD[2,3], Willem-Jan Meerding, PhD[4], Frans Rutten, PhD[2]*

[1]*HTA Policy - International Affairs, Pfizer Inc., Surrey, United Kingdom;* [2]*Department of Health Policy & Management, Erasmus University, Rotterdam, The Netherlands;* [3]*PHARMO Institute for Drug Outcomes Studies, Utrecht, The Netherlands;* [4]*Interhealth, Dordrecht, The Netherlands*

ABSTRACT

Objective: When comparators' prices decrease due to market competition and loss of exclusivity, the incremental clinical effectiveness required for a new technology to be cost-effective is expected to increase; and/or the minimum price at which it will be funded will tend to decrease. This may be, however, either unattainable physiologically or financially unviable for drug development. The objective of this study is to provide an empirical basis for this discussion by estimating the potential for price decreases to impact on the cost-effectiveness of new therapies in hypertension. **Methods:** Cost-effectiveness at launch was estimated for all antihypertensive drugs launched between 1998 and 2008 in the United Kingdom using hypothetical degrees of incremental clinical effectiveness within the methodologic framework applied by the UK National Institute for Health and Clinical Excellence. Incremental cost-effectiveness ratios were computed and compared with funding thresholds. In addition, the levels of incremental clinical effectiveness required to achieve specific cost-effectiveness thresholds at given prices were estimated. **Results:** Significant price decreases were observed for existing drugs. This was shown to markedly affect cost-effectiveness of technologies entering the market. The required incremental clinical effectiveness was in many cases greater than physiologically possible so, as a consequence, a number of products might not be available today if current methods of economic appraisal had been applied. **Conclusions:** We conclude that the definition of cost-effectiveness thresholds is fundamental in promoting efficient innovation. Our findings demonstrate that comparator price attrition has the potential to put pressure in the pharmaceutical research model and presents a challenge to new therapies being accepted for funding.

Keywords: cost-effectiveness, health technology assessment, pharmaceutical innovation, pharmaceutical price erosion, pharmaceutical research and development.

Introduction

Policy context

Cost-effectiveness (CE) analysis is used to support funding decisions for new drugs by estimating their clinical and economic value. The purpose of CE thresholds is to achieve efficiency in drug spending by requiring an acceptable or affordable cost per unit of incremental effect compared to existing therapies. In some disease areas, the prices of existing therapies fall over time [1] due to market competition, entrance of generic drugs, or negotiated price cuts. The implications of this price erosion for new drugs entering the market are that they either need to demonstrate greater incremental clinical effectiveness (IE) or be developed for a lower price.

The factors underlying this are often external to the development process and difficult to resolve. Development costs depend greatly on the level of biologic uncertainty and the costs of meeting regulatory requirements. At the same time, within a disease area, there is a physiologic limit to the incremental effect that a new medicine can have [2]. This limit is composed of the efficacy of the drug on its target mechanism and the number of mechanisms involved in the disease process. Because the pharmaceutical industry assesses this at various stages of the research and development (R&D) process, molecules that cannot meet these limits of price or clinical effect will not be taken forward and investment will be stopped.

Research-based industries like the pharmaceutical industry follow a dynamic process [3]. At a time where the average development cost per viable drug is reported to have significantly increased [4], continued innovation depends on achieving sufficient return on investment to develop new compounds. Because the benefits of innovative products accrue not only to the current generation but to all future generations [5,6], there is a trade-off between increasing the welfare of current patients by adopting only the most cost-effective technologies and increasing the welfare of future patients by providing incentives for future innovation through current pricing [7] and acceptance

* *Address correspondence to:* R. Refoios Camejo, IPC 4-1-06, HTA Policy - International Affairs, Walton Oaks, Dorking Road, Walton on the Hill, Tadworth, Surrey, KT20 7NS, United Kingdom.

E-mail: rodrigo.refoioscamejo@pfizer.com

1098-3015/$36.00 – see front matter

doi:10.1016/j.jval.2011.08.1736

levels. This is now being recognized in newly proposed pricing systems [8] and alternative frameworks that attempt to balance the effects of price erosion and equity concerns across generations [9].

Theoretical framework

This study follows the framework proposed by Refoios Camejo et al. [2] to discuss the dynamic effects of fixed CE constraints on drug development. They suggest the existence of a physiologically defined clinical effectiveness ceiling for each disease area (E_D max). The maximum IE a new drug could attain over the existing standard care (E_c) if R&D resources were not finite is then defined by

$$IE_d \max = E_D \max - E_c \quad \text{(Eq. 1)}$$

where subscript $_d$ refers to the new drug entering the market, $_c$ to the comparator technology being used in the cost-effectiveness assessment, and $_D$ to the disease area in question.

The drugs' cost effectiveness can be represented by the incremental cost effectiveness ratio (ICER), which is a ratio of the incremental differences (on costs and benefits) between the new drug and any existent comparator; that is, $ICER = (P_d - P_c)/(E_d - E_c)$. If a fixed CE threshold (L) is in place, a drug will be considered cost-effective if the given ratio is lower than L. In this way, the maximum price premium allowed for a drug reaching E_D max can be computed taking in consideration the price of the comparator (P_c). Whilst this price margin tends to diminish with time, the minimum possible launch price (P_d min) for a product to be considered a viable investment tends to increase with inflation [2].

If P_d min is assumed to be exogenous, a minimum IE required for approval (IE_d min) can be calculated using L, E_c and P_c. When $P_d \min > (E_D \max - E_c) * L + P_c$ or $E_D \max < E_c + \frac{(P_d \min - P_c)}{L}$, i.e., $E_D \max < E_c + IE_d \min$, funding by the health system will most likely be rejected. These considerations are increasingly part of the portfolio selection criteria in the drug development process. Therefore if this is the case, unless the R&D cost structure changes significantly, no more R&D will be conducted for a particular disease area once it meets the above conditions.

The case of hypertension

We have selected hypertension to populate empirically the framework proposed by Refoios Camejo et al. [2] because arguably IE_d max can be defined. Hypertension (classified as systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg) is a risk factor for cardiovascular and renal conditions. For individuals aged 40 to 70 years, an increment of 20 mm Hg in systolic blood pressure doubles the risk of cardiovascular disease across the entire blood pressure range [10]. The goal of antihypertensive therapy is the reduction of cardiovascular and renal morbidity and mortality. This may include both adoption of healthy lifestyles and the use of pharmacologic treatment for the prevention and reduction of high blood pressure. Since the first drug was approved for the treatment of hypertension in 1946, several other pharmacologic treatments have proven clinical and economic outcomes with an overall estimated benefit-to-cost ratio of at least six to one [11]. Nevertheless, the economic burden of hypertension remains substantial and cardiovascular disease is still one of the main causes of death worldwide.

The study

Hoyle has found the reduction in the real price of drugs for hypertension and coronary disease in the United Kingdom to be on average of 2.5% per year [1]. In this study we examined nominal pharmaceutical prices of antihypertensive drugs in the United Kingdom market during the past 10 years to detect if significant price erosion, shown as a decrease in comparator drug prices, took place. We simulated the IE of new entrants and estimated the likelihood of funding approval if current CE decision rules had been applied at time of launch. We also assessed the influence of such price erosion on cost-effectiveness by calculating the size of incremental decrease in systolic blood pressure that a new entrant would need to demonstrate to be cost-effective according to current criteria. In this article we propose an empirical basis for the trade-offs between reimbursement rules, price erosion, and the likelihood that new drug candidates will be developed based on their ability to meet requirements for incremental effectiveness, development costs, and price at launch.

Methods

We calculated the ICER at launch for new entrants to the hypertension market between June 1998 and June 2008. Market and pricing data on all antihypertensive drugs available in the United Kingdom were used to identify comparators and drug prices. Because no historical head-to-head clinical trial data were available for every drug at time of launch, different hypothetical values of IE expressed as reduction in systolic blood pressure were assumed. Using those, we estimated the likelihood of new entrants meeting the £20,000 per quality-adjusted life year (QALY) cost-effectiveness threshold as applied by the UK National Institute for Health and Clinical Excellence [12]. We then estimated the IE required to achieve acceptable CE standards at launch prices and compared it with the physiological effectiveness limit set for hypertension.

Economic model

A cost-utility model was adapted to calculate the ICER in cost per QALY gained for each new entrant to the hypertension market. Reduction in systolic blood pressure was converted in the model into cardiovascular events averted via a Framingham study-based risk equation [13]. It has been suggested that Framingham-based risk scores overestimate the patients risk of a cardiovascular event [14] and that their use to predict clinical outcomes of drug interventions have not been validated [15]. Framingham-based risk equations, however, have been widely applied in the technology assessments this analysis intends to mimic. To simplify the analysis no adverse events or drug side effects were considered and compliance was assumed to be 100% for all treatments administered. The model followed the base case advocated by the UK National Institute for Health and Clinical Excellence in their guide to the methods of technology appraisal [12]. A brief description of the economic model used can be found in Appendix 1 in Supplemental Materials at: doi:10.1016/j.jval.2011.08.1736.

Data sources

Pharmaceuticals included in the study comprised all antihypertensive drugs (i.e., main indication and primary use is hypertension) with reported sales in the UK market between June 1998 and June 2008 as identified from the Intercontinental Medical Statistics health database. The analysis was restricted to the same plan of clinical management to guarantee comparability amongst all drugs. Hence, retail pricing (price per pack) and market data (market share in units sold) were retrieved for the drugs currently recommended for first, second, and third line treatment of hypertension in the United Kingdom [16]. Products were classified into seven different therapeutic subclasses using the European Pharmaceutical Market Research Association anatomical classification system [17]: diuretics (C3), calcium antagonists plain (C8), angiotensin-converting enzyme inhibitors plain (C9A), angiotensin-converting enzyme inhibitors combination (C9B), angiotensin II antagonists plain (C9C), angiotensin II antagonists combination (C9D), and other renin-angiotensin agents (C9X).