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ORIGINAL RESEARCH ARTICLE

Reimbursement Decisions for Pharmaceuticals in Sweden: The Impact of Disease Severity and Cost Effectiveness

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Abstract

Objective The Swedish Dental and Pharmaceutical Benefits Agency (TLV) is the government body responsible for deciding whether outpatient drugs are to be included in the pharmaceutical benefits scheme. This paper analyzes the impact of cost effectiveness and severity of disease on reimbursement decisions for new pharmaceuticals.

Methods Data has been extracted from all decisions made by the TLV between 2005 and 2011. Cost effectiveness is measured as the cost per quality-adjusted life-year (QALY) gained, whereas disease severity is a binary variable (severe–not severe). In total, the dataset consists of 102 decisions, with 86 approved and 16 declined reimbursements.

Results The lowest cost per QALY of declined reimbursements is Swedish kronor (SEK) 700,000 (€79,100), while the highest cost per QALY of approved reimbursements is SEK1,220,000 (€135,600). At a cost per QALY of SEK702,000 Swedish kronor (non-severe diseases) and SEK988,000 (severe diseases), the likelihood of approval is estimated to be 50/50 (€79,400 and €111,700).

Conclusions The TLV places substantial weight on both the cost effectiveness and the severity of disease in reimbursement decisions, and the implied willingness to pay for a QALY is higher than the often cited 'rule of thumb' in Swedish policy debates.

Key Points for Decision Makers

Using data on reimbursement decisions on new pharmaceuticals made by the responsible Swedish government authority, we show that cost effectiveness and severity of disease substantially affects the likelihood of reimbursement.

We show that the implied willingness of the government authority to pay for a quality-adjusted life-year is between €80,000 and €135,000.

Holding the cost effectiveness constant, pharmaceuticals targeting a severe disease are up to 29 percentage points more likely to be reimbursed.

1 Introduction

The use of health economic evaluations to influence governmental decisions on reimbursement, coverage and subsidies of medical technologies has increased over time and is part of the standard decision making in countries such as the UK, Australia, Canada, New Zealand and Sweden [1–5]. In Sweden, the Pharmaceutical Benefits Board was the public authority set up in 2002 to function as the authority legally responsible for deciding, by means of a value-based pricing approach, whether outpatient drugs are to be included in the pharmaceutical benefits scheme. In 2008, the authority changed its name to the Dental and Pharmaceutical Benefits Agency (TLV) when its mission was expanded to include dental procedures (in Swedish: Tandvårds- och läkemedelsförmånsverket, http://www.tlv.se).

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According to Swedish healthcare legislation, the TLV is mandated to base reimbursement decisions on three principles: (1) human dignity/value, which states that no one is to be discriminated against; (2) need and solidarity, which states that those with high need should receive a larger share of the resources; and (3) cost effectiveness, which states that the cost of using a medicinal product should be reasonable from a medical, humanitarian and socioeconomic perspective. The human dignity principle is difficult to explicitly operationalize in the decision-making process, and the TLV does not consider any specific operationalization of this principle. The need and solidarity principle is operationalized by the TLV in terms of disease severity, i.e. more severe conditions should be given a higher priority, while the cost-effectiveness principle is operationalized in terms of cost per quality-adjusted life-year (QALY) gained [6, p. 28]. The TLV also explicitly states that, jointly, these criteria imply that the accepted cost per QALY should be allowed to vary depending on the severity of the disease. For pharmaceuticals, the TLV has direct decision-making power over prescription drugs, whereas the 21 regional county councils are independently responsible for reimbursement decisions for hospital/in-patient drugs [7].

The aim of this paper was to analyze how cost effectiveness and severity of disease affect the decisions made by the TLV. Specifically, this aim is addressed via the two following research questions:

1. Does the cost effectiveness of a new drug, in terms of the cost per QALY, significantly affect the probability of reimbursement?
2. Does the need and solidarity principle, operationalized as the severity of the condition, significantly affect the probability of reimbursement?

Several previous studies have conducted quantitative analyses of Health Technology Assessment (HTA) authorities' decision making. One of the first studies analyzed the decision making of the Australian Pharmaceutical Benefits Agency (PBAC) between 1991 and 1996. The authors showed that decisions were to some degree in accordance with criteria for economic efficiency and that drugs with a cost per life-year gained exceeding Australian dollars ($A) 76,000, year 1998/1999 values (€49,500) were unlikely to be recommended for listing [8]. A more recent study analyzing PBAC decisions between 1994 and 2004 revealed that clinical significance, cost effectiveness, costs to government and severity of disease were significant influences on decisions to recommend (or not) drugs for coverage under the Pharmaceutical Benefits Scheme [9]. Studies have also analyzed decisions made by the UK National Institute for Health and Care Excellence (NICE), and an analysis of recommendations on 39 technologies in 2002 showed that cost effectiveness, uncertainty and burden of disease explained the recommendations by NICE fairly well [10]. Based on the modeling results, the authors conclude that NICE appeared to accept a cost per QALY gained slightly above the often-mentioned thresholds of £20,000–30,000 (€24,000–36,000). Several papers on NICE decision making have been published in the last couple of years, and findings tend to show that higher cost-effectiveness ratios increased the probability of technologies being rejected and that pharmaceuticals (compared with non-drug interventions) and technologies with more systematic reviews were also more likely to be recommended for use [11, 12]. Most recently, a study covering NICE decisions up to 2011 confirmed many of the previous findings and showed that cost effectiveness was the most significant predictor of NICE acceptance of new technologies and that technologies costing more than £40,000 have a 50 % likelihood of being rejected [13]. An exception to these findings is a study on factors influencing recommendations of the All Wales Medicines Strategy Group, which did not find that cost effectiveness was statistically significantly related to recommendations [14]. Regarding reimbursement in Sweden, the only previous analysis available is a poster abstract which descriptively examined early decisions by TLV and found that reimbursed drugs may be allowed a higher cost per QALY if targeting a severe disease (but without quantifying the relationship) [15].

To address the aim in this paper, we analyze all the decisions made by the TLV between 2005 and 2011 where cost per QALY of the product was reported. We estimate whether or not the cost per QALY and severity of the disease are significantly related to the reimbursement decisions made by the TLV. Further, we analyze in more detail how the cost per QALY affects the likelihood of approved reimbursement by modelling the predicted probability of approval at different levels of the cost per QALY, i.e. what is the willingness to pay (WTP) per QALY as revealed by government decisions, or the implicit 'QALY threshold'. Our contribution to the literature includes the fact that we analyze data from a new international context, with a decision-making context that uses a societal perspective (i.e. costs/effects beyond the healthcare sector should be accounted for), and also analyze decision making from an HTA authority that explicitly follows a value-based pricing (VBP) system, which is a direction towards which other HTA authorities, e.g. NICE, appear to be moving [16].

2 Methods

2.1 Data

Data for this study were extracted from all decisions made by the TLV between 2005 and 2011 ($n = 354$). Decisions are

either based on a simple cost-minimization analysis (CMA) or a cost-utility analysis (CUA) [17]. CMA (price comparison) is used when a drug is judged to be clinically equivalent to the comparator ($n = 252$), whereas a CUA is needed if a pharmaceutical company claims an added therapeutic value and a price premium over its comparators ($n = 102$). We excluded two decisions beforehand since they were based on cost savings and QALY losses, and according to the TLV were treated as separate and unique cases.

We retrieved the cost-per-QALY estimates and disease severity statements from the decisions based on a CUA. The cost per QALY estimate is supplied by the producer applying for reimbursement and then checked and evaluated by civil servants at the TLV, whereas the severity statement is made by the TLV board. In most cases, this information could be found in the official published decision ($n = 70$, comprising 45 severe diseases and 25 non-severe), but, if not, we retrieved this information from the assessment reports produced by the Reimbursement Application Unit at TLV ($n = 32$, comprising 11 severe diseases and 21 non-severe). The data extraction was performed independently by two individuals and then cross-checked. When discrepancies were found, the data were checked jointly and all discrepancies were resolved. Only data from the published decision can be regarded as the board's official statement; the data from the assessment report are a product of the civil servants at the agency. As such, the latter is a weaker source of evidence. The board sometimes refrains from including cost-per-QALY and severity of disease data in the public decision without stating the reason for it (although one reason may be that the data are judged to be uncertain). It should also be noted that a number of companies withdrew their applications sometime during the TLV process but before the board decision (the number of withdrawn applications varied from 3 to 12 during the years studied).

In sum, the dataset used for analysis contains 102 observations when using all information and shrinks to 70 observations when only relying on the data from the public decision by the board.

Table 1 summarizes the outcome and explanatory variables used in this paper. The outcome variable 'Approved reimbursement' is a binary variable that equals one if the technology was approved for reimbursement, and zero otherwise. The board can decline reimbursement or grant either (1) full reimbursement, (2) restricted reimbursement (e.g. to particular patient characteristics or indications), or (3) reimbursement conditional on evidence gathering. We categorize all three positive reimbursement decisions described in the introduction as referring to an approved reimbursement (full reimbursement, restricted reimbursement, conditional reimbursement). The dichotomization simplifies the interpretation of the analyses and is supported by analyses where we have examined whether or not the type of reimbursement affects our results. Specifically, we validated the dichotomization of the reimbursement decision by conducting regression analyses, including interactions between the reimbursement type (full, restricted or conditional) and our main explanatory variables of interest. We find no significant differences between the explanatory variables of interest and the type of approved reimbursement (see the Electronic Supplementary Material [ESM]). Further, a very large majority of approved reimbursements are full reimbursements, implying a power problem if restricted and conditional reimbursements are separately analyzed.

The explanatory variables of interest are 'Cost per QALY' and 'High severity'. The variable 'Cost per QALY' is simply the reported incremental cost per gained QALY for the drug. As seen in Table 1, the mean cost per QALY summed to Swedish kronor (SEK) 572,770 (€65,000). 'High severity' is a binary dummy variable equal to one if the drug targets a high-severity disease/condition as judged by the TLV (not the producer). Slightly more than half (53 %) of all decisions in our dataset are judged to concern a high-severity condition. The TLV has not clearly stated the criteria for when a disease is to be classified as being highly severe [18]. However, statements made by the agency indicate that diseases that lead to substantially shortened life expectancy with current treatments, or that are severely mutilating, are likely to be classified as severe [19]. Hence, in health economic terms, this could be stated such that "high severity" indicates a low preference-based health-related

Table 1 Variable description

	Description	Mean (SD)
Outcome variable		
Approved reimbursement	=1 if application for reimbursement is approved, 0 otherwise	0.84 (0.37)
Explanatory variables used in the model		
Cost per QALY	The cost per QALY per application in SEK1000	572.77 (1066.28)
High severity	=1 if disease of high or very high severity, 0 otherwise	0.53 (0.50)

Numbers of observations = 102

QALY quality-adjusted life-year, *SD* standard deviation, *SEK* Swedish kronor

quality of life given a certain disease (and the prevalence of the disease is not considered a relevant factor for the severity judgement).

2.2 Statistical Analysis

We start the analysis with a conceptual model where we consider the reimbursement decision (R) to be a function of the cost per QALY, i.e. R = f(cost per QALY). We then move on to consider an extended model, where we consider that the TLV are also mandated to consider the principle of need and solidarity, operationalized through whether or not the technology targets a high-severity population; R = f(cost per QALY, high severity), which is in essence the decision-making model the TLV should use according to the interpretation of the legislation. This decision-making model of the TLV may be described as a simple 'production function' approach, whereby the authority combines the input data for each drug on cost effectiveness and severity of the disease, evaluates the quality of the input data, and the output is the 'yes or no' decision on reimbursement [13]. Based on the legislative text, the hypotheses are that the likelihood of an approved reimbursement decreases in the 'cost per QALY' and increases in 'high severity'.

Additionally, we also examine interaction models that combine the cost per QALY with high severity and the year of decision (to examine whether the decision-making model has changed over time), i.e. R = f(cost per QALY, high severity, cost per QALY × high severity) and R = f(cost per QALY, high severity, cost per QALY × high severity, decision year). We conducted the analysis using both the larger dataset ($n = 102$)—i.e. information from both the public decision and (if lacking in the published decision) the assessment report—and the smaller set ($n = 70$), i.e. data from the published decision only. This was conducted to examine whether the source of the information (board statement or assessment report) has an impact on the model results.

Considering that the outcome variable is a binary variable, we estimate the models using a logit regression and present the results in terms of the marginal effects on reimbursement of a change in the explanatory variables. All estimations are conducted using Stata with additional commands from the SPost program [20].

3 Results

As seen in Table 2, out of 354 total decisions, 102 contained health economic data on cost per QALY and disease severity, of which 86 were approved reimbursement (84 %) and 16 were declined reimbursement. The share of approved decisions varies somewhat across the years, but this is not statistically significant, which is expected given the relatively low number of decisions taken each year.

Table 3 tabulates all the decisions containing cost per QALY and severity data (approved/declined reimbursement), with the mean, median, minimum and maximum cost per QALY. The results reported in Table 3 include all cost-per-QALY information, irrespective of whether the data were retrieved from the public board decision or from the TLV assessment report. For all approved reimbursements, the mean and median cost per QALY are SEK353,640 (€40,000) and SEK350,000 (€39,500), respectively. We also see that the range of approved reimbursements goes from technologies being cost saving (cost per QALY <0) to technologies with a cost per QALY of SEK1,220,000 (€137,900).

If cost effectiveness is considered, all else being equal we would expect mean and median costs per QALY to be higher among declined reimbursements, i.e. as we see in Table 3. The mean and median costs per QALY among declined reimbursements are SEK1,750,625 (€197,800) and SEK1,000,000 (€113,000), respectively. The mean is higher than the median in large part due to a single declined reimbursement with a reported cost per QALY of SEK10,000,000 (€1,130,000). Among declined technologies, the lowest cost per QALY is SEK700,000 (€79,100). When considering high-severity and non-high-severity diseases separately, we see that the mean and median incremental cost-effectiveness ratios (ICERs) are higher,

Table 2 Number of reimbursement decisions per year in dataset

	2005	2006	2007	2008	2009	2010	2011	Total
Total number of decisions CMA only	56	59	52	49	41	49	48	354
Decisions with cost per QALY and severity data	12	16	21	14	7	16	16	102
…of which were approved reimbursement	10	16	17	13	4	13	13	86
…of which were declined reimbursement	2	0	4	1	3	3	3	16
% approved of decisions with cost per QALY and severity data	83.3	100	81.0	92.9	57.1	81.3	81.3	84.3

CMA cost minimization analysis, *QALY* quality-adjusted life-year

Table 3 Cost per quality-adjusted life-year and reimbursement decision (in Swedish kronor, SEK1 = €0.11)

	Decisions: all diseases ($n = 102$)		Decisions: high-severe diseases ($n = 56$)		Decisions: non-severe diseases ($n = 46$)	
	Approved reimbursement ($n = 86$)	Declined reimbursement ($n = 16$)	Approved reimbursement ($n = 49$)	Declined reimbursement ($n = 7$)	Approved reimbursement ($n = 37$)	Declined reimbursement ($n = 9$)
Mean cost per QALY	353,634	1,750,625	374,184	2,861,429	326,432	886,667
(SD)	(275,100)	(2,339,135)	(261,408)	(3,331,738)	(293,669)	(127,377)
Median cost per QALY	350,000	1,000,000	363,000	1,300,000	300,000	900,000
Min cost per QALY	<0	700,000	<0	730,000	<0	700,000
Max cost per QALY	1,220,000	10,000,000	1,220,000	10,000,000	1,220,000	1,000,000

QALY quality-adjusted life-year, *SD* standard deviation

Table 4 Regression results: explaining reimbursement decisions

	Model 1: all decisions		Model 2: all decisions		Model 3: only decisions with cost per QALY data in the public decision	
	Coeff. (SE)	Marginal effect	Coeff. (SE)	Marginal effect	Coeff. (SE)	Marginal effect
Cost per QALY	−0.007*** (0.002)	−0.0005	−0.007*** (0.002)	−0.0004	−0.011*** (0.004)	–0.0006
High severity	–	–	1.568* (0.913)	0.11	3.07** (1.56)	0.29
Constant	6.375*** (1.348)	–	5.852*** (1.355)	–	7.49*** (2.44)	–
Observations	102		102		70	
Pseudo-R^2	0.54		0.58		0.69	

QALY quality-adjusted life-year, *SE* standard error

*** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$

marginally so for approved technologies but rather substantially so for declined technologies. This may give an indication that the board has a higher value per QALY for severe diseases than for non-severe diseases.

In sum, based on raw data, we can see that the lowest cost per QALY declined for reimbursement is SEK700,000, and the highest sum for a drug-approved reimbursement is SEK1,220,000 (€79,100 and €135,600, respectively).

Table 4 shows the results from the logistic regressions, providing both regression coefficients and marginal effects. We did not find any significant interaction effects or changes over time in the decision-making process, and the results from the models that show the interaction effects are consequently not included in the paper (see the ESM). Model 1 shows that the cost per QALY of a technology is statistically significantly related to the decision with a negative coefficient, i.e. the higher the cost per QALY, the lower the likelihood that the technology is approved. For interpretation, we turn to the marginal effect, which shows that for each SEK1000 higher cost per QALY, the probability of an approved subsidy decreases by 0.05 percentage points. Model 2 also includes high severity, and the results show that the cost per QALY is still significant and the coefficient is not affected. Further, the results show that the severity of the disease is significant at $p < 0.10$. Based on the marginal effect, the interpretation is that if the drug is judged to concern a high-severity disease, the likelihood of approval is 11 percentage points higher. Model 3 differs in that it only includes data where the cost per QALY was reported in the public (board) decision, reducing the number of observations from 102 to 70. The marginal effect shows that for each SEK1000 higher cost per QALY, the probability of an approved subsidy decreases by 0.06 percentage points, whereas the likelihood of approval increases by 29 percentage points if the disease is judged to be of high severity.

In Fig. 1 we show the relationship between the predicted probability for approval and the cost per QALY for severe and non-severe diseases. We see that up to a cost per QALY of SEK500,000 (€56,500), which is an often-stated 'rule-of-thumb' for the threshold value in the Swedish

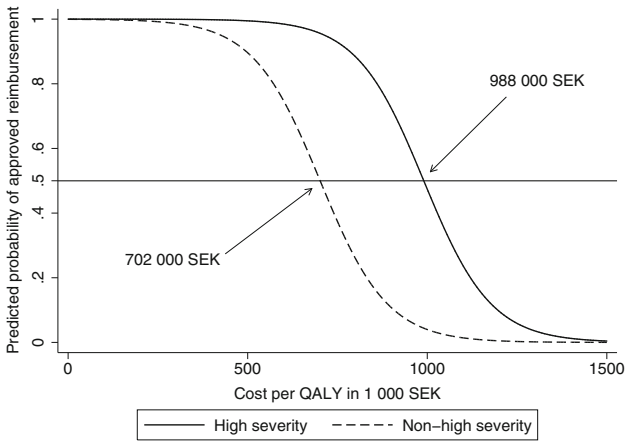

Fig. 1 Predicted probability of approved reimbursement at different costs per quality-adjusted life-year. *QALY* quality-adjusted life-year, *SEK* Swedish kronor

policy debate [21], the likelihood of approval is 91–98 % for non-high- and high-severity diseases, respectively. We also included a horizontal line to show the cost per QALY at which the likelihood of approval is equal to 50 %. For non-high-severity diseases, the likelihood of an approval reaches 50 % at SEK702,000 (€79,400), and, for high-severity diseases, the model predicts that the board exhibits somewhat higher acceptance, and approval is predicted at 50 %, i.e. at SEK988,000 (€111,700). When cost per QALY estimates reach SEK1,000,000 (non-severe) and SEK1,250,000 (severe), the probability of approval is very low (3–4 %).

4 Discussion

The results show that (1) the likelihood of approval is higher the lower the cost per QALY and (2) the likelihood of approval is higher in cases of high-severity disease. Thus, the TLV seems to follow pretty clearly the operationalization of the decision criteria of 'need and solidarity' and 'cost effectiveness'. Based on estimated marginal effects, we reported that for each SEK1000 higher cost per QALY, the probability of an approved subsidy decreases by 0.04 to 0.06 percentage points, whereas the likelihood of approval increases by 11 to 29 percentage points if the disease is judged to be of high severity. The rather large difference in the marginal effect of a severe disease may be explained by the fact that there are very few observations in the non-public data that are non-severe ($n = 11$), which makes the results for severity less robust in the different models. The implied maximum WTP among the decisions taken, all else being equal and as measured by the highest cost per QALY among approved reimbursements, is SEK1,200,000 and concerned a drug targeting a severe disease (€135,600). Based on predictions from our preferred model, we have shown that the likelihood of approval is 50/50 at a cost per QALY of SEK702,000 (€79,400) and SEK988,000 (€111,700) for non-high- and high-severity diseases, respectively.

The TLV does not, at the moment, use a formal definition of what constitutes a severe disease. The judgment is instead made by the board on a case-by-case basis. To retrieve some more information on which types of drug are associated with a higher WTP in the board, we examined the anatomical therapeutic chemical (ATC) code for each reimbursement decision judged to concern a severe disease. The most common drug type classified as targeting a severe condition was cancer medication (35 % of all decisions classified as severe), followed by drugs targeting Parkinson's disease, epilepsy and HIV.

As stated in the introduction, the VBP approach in Sweden is based on a societal perspective, and it has been argued by some that the threshold value therefore should constitute the societal WTP for a QALY [16]. Further, based on a recent model of value-based differential pricing, it has been shown that if countries set prices so the cost per QALY equals societal WTP, this will be roughly consistent with second-best static and dynamic efficiency [22]. It may therefore be of interest to compare the results in this paper with estimates of the societal WTP in Sweden. Such estimates are lacking, but some guidance may be drawn from a recent paper that performed a literature review of Swedish estimates of the value of a statistical life, where the authors also discussed and provided a rough conversion for the value of a QALY [23]. They reported a median WTP for a QALY of SEK1.2 million (€135,600). Hence, based on this evidence, it seems as if the implicit WTP for new drugs as indicated by the decisions of the TLV is reasonably in line with the societal WTP for a QALY.

The results in this paper are in line with other recent studies on decision making by different international HTA bodies (in the UK and Australia) showing that cost effectiveness and severity of the targeted disease significantly affects the likelihood of reimbursement [9, 11, 24]. However, the actual level of acceptable cost per QALY (the 'threshold value') by different HTA bodies differs substantially. Studies analyzing the decision making by NICE suggest that there is a 50 % likelihood of approval at a cost per QALY of £40,000 (€48,000), which is perhaps surprisingly high given NICE's explicit statement that they only accept a cost per QALY above £30,000 if there are many (or strong) additional arguments favoring reimbursement (e.g. severity of the underlying illness, end-of-life treatments, etc.). But it is still well below the results in this paper, which show the Swedish TLV accepting substantially higher costs per QALY for new drugs compared with NICE. An important factor explaining this difference

is probably the contrasting perspectives of the different HTA bodies, i.e. societal (TLV) versus health sector (NICE). The healthcare perspective used by NICE implies that—theoretically at least—the threshold value is based on the value of displaced services, whereas in the societal perspective used by TLV, the threshold value is based, according to some analysts, on the demand-driven WTP for new drugs [16, 25].

A concern in this paper may be that our simple model with few predictors of the reimbursement decision misses some important factors for reimbursement. A recent empirical analysis of NICE decision making showed that, in addition to cost effectiveness, decision making was also affected by the burden of disease (measured as disability-adjusted life years [DALYs]), technologies involving a paediatric condition, and whether or not the input data on effectiveness stem from large randomized controlled trials (RCTs), etc. [13]. If this is also the case in TLV decision making, and if such variables are correlated with our explanatory variables, we will have biased estimates. Unfortunately, the fact that the producers' applications are confidential in our setting strictly limits the opportunities to explore such a concern. However, we believe this to be of less relevance compared with the decision making in—for example—the UK, where NICE should explicitly take other factors into account. In Sweden, the TLV should, according to the interpretation of the law, only consider disease severity and cost effectiveness for reimbursement decisions [6, 18]. Still, future studies could analyse TLV decisions on a case-by-case basis to try and establish whether factors that formally should not affect decision making actually have an impact after controlling for cost effectiveness and disease severity.

Finally, the research reported in this paper also relates to the discussion across HTA bodies concerning whether or not they should operate with explicit threshold values (an acceptable cost per QALY for new drugs). Some authors have argued that the lack of an explicit threshold value reduces consistency and transparency [26]. On the other hand, setting an explicit threshold is politically sensitive and also removes the possibility of more 'ad hoc' considerations that may be attractive to policy makers in a situation where cost effectiveness is only one of several criteria they are mandated to follow [2]. And, depending on the behavioural response of producers, it may be beneficial from a distributional perspective to not state an explicit threshold given that the ICER is endogenous, i.e. the risk is that the welfare gain would be completely captured in the producer surplus [27]. It should also be remembered that, in an actual decision setting, there is usually a range of cost-per-QALY estimates that are more or less likely. That is, even if a best-case estimate can be presented, there is a distribution of estimates that must also be considered. It is obvious from this paper that the TLV adopts this approach, given that certain conditions were declined reimbursement at a cost of SEK700,000 per QALY, while others were approved reimbursement at a cost of SEK1,200,000 per QALY.

5 Conclusion

The results in this paper show that, all else being equal, the Swedish TLV takes both the cost per QALY and the severity of disease into consideration in reimbursement decisions. Based on the modelling, we found that, at a cost per QALY of SEK702,000 (non-severe diseases) and SEK988,000 (severe diseases), the likelihood of approval is estimated to be 50/50 (€79,400 and €111,700).

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