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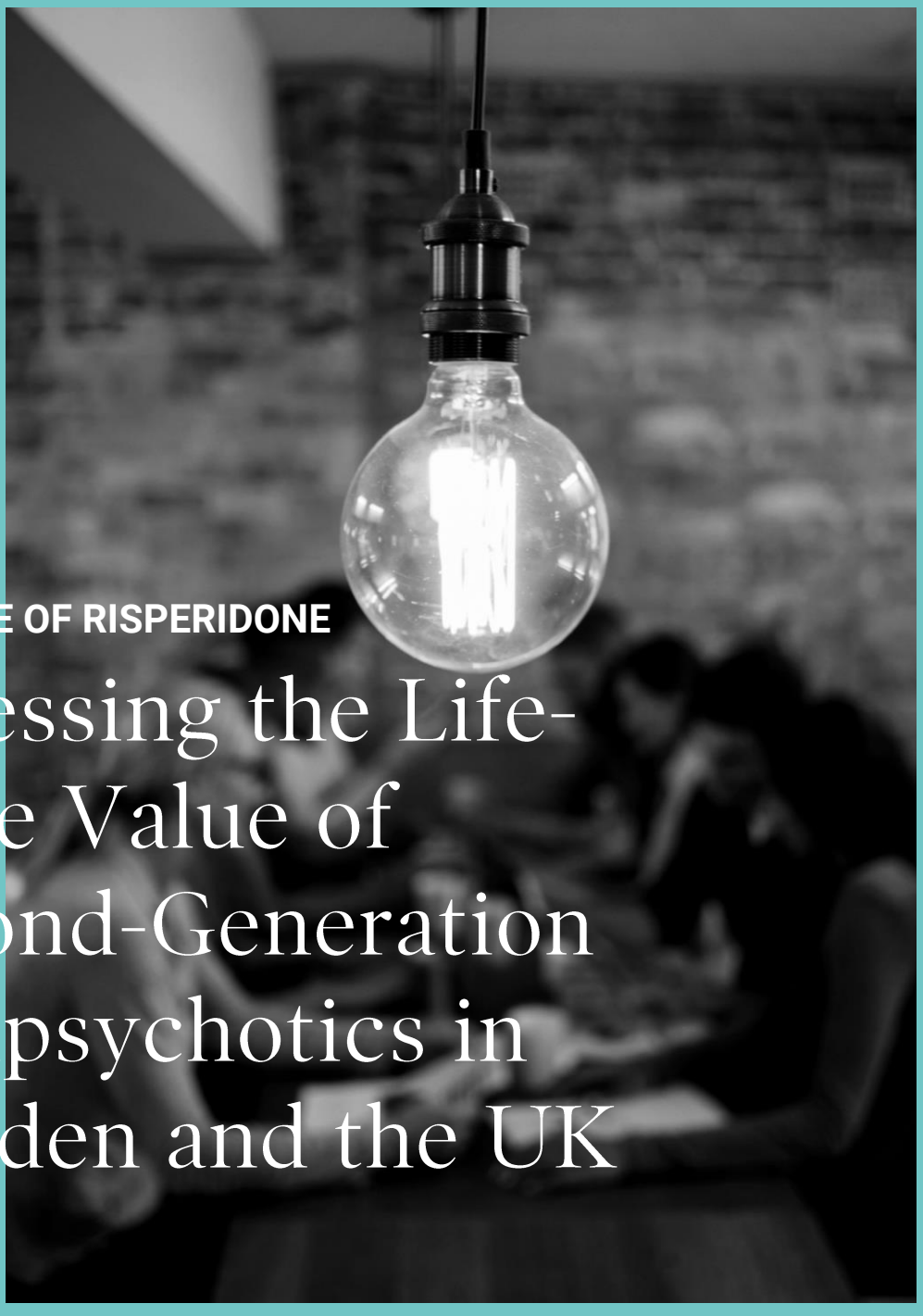

THE CASE OF RISPERIDONE

Assessing the Life-cycle Value of Second-Generation Antipsychotics in Sweden and the UK

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RESEARCH | REPORT
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RESEARCH

Please cite this report as:
Berdud, M., Wallin-Bernhardsson, N., Zamora, B., Lindgren, P., and Towse, A., 2019. Assessing the Life-cycle Value Added of Second-Generation Antipsychotics in Sweden and the UK: The Case of Risperidone. OHE Research Paper, London: Office of Health Economics. Available at: https://www.ohe.org/publications/case-risperidone-assessing-life-cycle-value-second-generation-antipsychotics-sweden-and

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Funding and Acknowledgements

This study was commissioned and funded by Johnson and Johnson Services, Inc.

The authors are grateful to Nicholas Mays for helpful comments and review on an earlier draft. However, authors alone are responsible for the views expressed and any errors remaining.

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Abstract

OBJECTIVES: To estimate the life-cycle value of risperidone – representative of Second-Generation Antipsychotics – relative to First Generation Antipsychotics to balance the view that cost per Quality-Adjusted Life Year (QALY) estimates at launch are enough to guide access decisions. Study results aim to quantify the nature of value added by pharmaceutical innovation over the long-run to support consideration as to how access decisions can be informed by these life cycle effects.

METHODS: We estimated the number of patients with schizophrenia who were treated with risperidone in Sweden and the UK, 1994-2017, based on data of usage and volume sales. We collected data from the literature on the effectiveness (QALYs per patient per year) and direct (health services) and indirect (productivity) costs (per year € 2017) of risperidone and haloperidol – the latter representative of First-Generation Antipsychotics. Using a comparator from the inferior class proxied the incremental value added by the new class of innovative medicines. Next, we modelled the life-cycle uptake of risperidone to estimate the life-cycle incremental cost (i.e., direct, indirect and medicine costs), incremental QALYs and Net monetary Benefit (NMB) of risperidone. We also assessed the life-cycle distribution of the social surplus between the payer (consumer surplus) and the innovator (producer surplus). For the UK, we estimated the consumer surplus (at a £20K/QALY threshold), the producer surplus, the NMB and Incremental Cost-Effectiveness Ratio (ICER) annually and in aggregate terms (1993-2017). For Sweden, we estimated the consumer surplus (at a €70K/QALY threshold) and used the same set of metrics used for the UK.

RESULTS: For the UK, the producer surplus represents around 28% of the total surplus before patent expiration and around 5% after patent expiration. Life-cycle NMB for the health system is estimated at €1,116m. During the life-cycle, the NMB for the health system significantly increased in response to two events: (i) the launch of Risperidone Long-Acting Injectable (RLAI); and (ii) generic entry. The ICER was negative (dominant) for the whole period, and savings generated per unit of incremental health gain significantly increased with both the launch of RLAI and generic entry. For Sweden the producer surplus represents around 6% of the total surplus before patent expiration and around 1% after generic competition. Smaller shares of social surplus captured by the producer in Sweden result primarily from society's higher willingness to pay as reflected in the Swedish cost-effectiveness threshold. The impact of generic entry produces a proportional decrease of the same relative size as in the UK. Life-cycle NMB is estimated at €803m, and both NMB and ICER follow the same pattern as in the UK.

CONCLUSION: Analysis of the life-cycle value of risperidone shows that health systems (consumers) were able to appropriate most of the life-cycle value (surplus) generated. The evolution of surplus distribution, NMB and the ICER show that the value added by risperidone – and, by implication, SGAs as a class in general – significantly increased over time with the launch of Risperdal long-acting injectable and generic competition. This suggests that, considering the entire life-cycle, the value added by SGAs to the system is higher than the expected value estimated using cost-effectiveness analysis at launch. This is because the latter considers neither the impact of generic entry which significantly reduces costs for the same benefits, nor the launch of new and more effective presentations or indications and the incremental value they deliver. Pricing and reimbursement decisions should take into account the dynamic nature of pharmaceutical markets and the value added by innovative medicines over the long-run.

1. Introduction

The value to society of pharmaceutical innovation depends on the long-term health and related benefits, net of additional costs. Substantial gains have been realised to society by medical innovation in the form of higher quality of life and longer life expectancy. Thus, how much society should pay for new medicines, in order to reward and incentivise innovation, has become a crucial question for policy makers. Research to generate accurate estimates of the long-term value that innovative medicines can potentially generate, is important in informing this question (Lakdawalla et al., 2017; Puig-Junoy, 2018).

Countries, governments and/or health authorities often use either Therapeutic Added Value or Cost Effectiveness (CE) Analysis to inform decisions about whether to adopt new medicines at launch. Such analysis is often based on short-term clinical trial outcomes with assumptions about longer term effects. It is usually indication-based and does not reflect the value that the appraised drug may add to society through other possible indications. It also fails to assess the additional gains to the health care system that will accrue from lower prices when the product goes off-patent, or whilst still on-patent, when new competitors of the same class enter the market.

The value of a medicine may change over its life cycle in response to several factors. These factors may impact directly on the total cost of supplying the treatment and/or its true effectiveness (real world outcomes). One important factor affecting the value of new medicines, which is subject to change over time, is the price. Generic competition may reduce the price of a drug still in use, reducing the average lifetime cost per prescription (Berndt and Dubois, 2016; Morton and Kyle, 2012; Lindgren and Jönsson, 2012; Berndt, McGuire and Newhouse, 2011). On-patent competition from products in the same or related therapy classes could also affect the price, reducing the cost of treating patients for payers (Berdud et al., 2018; Wiggins and Maness, 2004; Lu and Comanor, 1998; Reekie, 1998). Price reductions over the life-cycle of a drug increase the lifetime sum of consumer surplus at the expense of the innovators' surplus.

Two immediate questions arise after recognising that the size and distribution of social value may change over the life-cycle of drugs. First, it is possible that decision makers do not recommend reimbursement of some innovations at launch, deemed not cost-effective, that may be viewed as cost-effective if a longer-run perspective is used[1]. Second, without a proper assessment of the entire social value added by medicines during the life-cycle we may end up with an arbitrary and inefficient distribution of that value. That could happen in either direction with problems of patient access arising when too much surplus is appropriated by the developer through the life cycle (static inefficiency) or, alternatively, a lack of incentive to invest in pharmaceutical innovation when too much surplus is appropriated by health systems (dynamic inefficiency (Danzon, Towse and Mestre-Ferrandiz, 2015; Jena and Philipson, 2008). In principle, a longer perspective on the stream of value that medicines deliver to all stakeholders could provide additional information for policy makers to balance the share of reward for the long term benefit of populations. [2]

The types and numbers of patients treated with a given drug may also change over its life cycle. Both can be affected by on- and off-patent competition and by new clinical indications for use (Lindgren and Jönsson, 2012; Grabowski et al., 2012; Garrison Jr and Veenstra, 2009). In the absence of multi-indication pricing, the price of a drug with potentially multiple indications is set only for the initial indication and cost-effectiveness appraised according to this price. New indications with different

[1] One option is to delay reimbursement until the point at which the drug is cost-effective. However, subsequent changes in cost-effectiveness may be path dependent, i.e. without initial use the full life cycle benefits are not realised.
[2] This of course begs the policy question as to what is the appropriate balance which we do not pursue in this applied paper.

effectiveness and numbers of patients may arise over a medicine's lifetime and hence the value delivered by it –and consequently the Incremental Cost-Effectiveness Ratio (ICER) – might increase or decrease, on average. For example, Garrison Jr and Veenstra (2009), estimated that the overall (volume weighted) life-cycle ICER for trastuzumab was less than half the ICER of the initial indication.

Other factors like the long-term response of patients to a new treatment, long-term adherence to new treatments, the development of more effective new formulations with observable additional benefits or cost offsets, or recognition of, and inclusion of, indirect cost savings that new treatments produce would also change the estimates of the value delivered by new medicines.

The present work aims to assess the life-cycle value of innovative medicines based on the example of Second-Generation Antipsychotics (SGA)[3]. Using risperidone as representative of the SGA class and comparing it to haloperidol – its counterpart from the First-Generation Antipsychotics (FGA) – this research estimates the life-cycle cost-effectiveness of the SGA class against FGA class in incremental terms. It also estimates the absolute social value added, measured by the sum of the consumer and producer surpluses.

Countries covered in the analysis are Sweden and UK. Results do not aim to be representative of all of Europe. We use the two countries to illustrate the importance of considering a life-cycle view when assessing the value added by innovative medicines. We select the UK and Sweden because of our knowledge about available data sources.

We focus on the indication of schizophrenia, for which risperidone was originally granted marketing authorisation. Risperidone also has added value in bipolar disorder and dementia, the other indications for which it was granted marketing authorisation during its life-cycle. However, data to do analyses for these two indications are not available. Instead, a qualitative assessment of the value added by these two indications is included in an additional findings section under Results.

By providing evidence about the long-run cost-effectiveness of innovative medicines in Sweden and UK, this research contributes to informing policy decision makers, payers, and HTA bodies about the importance of putting cost per QALY estimates at launch in the context of long-run estimates of the value added by drugs throughout their entire life-cycle. The use of cost-effectiveness thresholds is a form of indirect price control using the concept of willingness to pay for health gain. Thus, if the ICER of an innovative medicine is subject to change by factors explained in preceding paragraphs, while the CE threshold is constant, the distribution of the social surplus between stakeholders will change. This will, in turn, impact on the producers' surplus by changing the incentives for innovation and will potentially also impact on the consumers' surplus by constraining market access for some medicines which might be cost-effective in the long run. Such situations should be predicted, as far as is feasible, at launch, and used to improve decision making and maximise social welfare. However, difficulties arise as the estimation of the long-run value of an innovative medicine at the time of its launch has obvious limitations. The ability to overcome this issue would presumably depend on payers having access to information, for example, on the typical price trajectory over time of similar drugs and a willingness to judge whether these data are predictive of what is likely to happen with the new drug. As we have noted, the question at to how this value should be shared among stakeholders, notably health systems and developers, is beyond the scope of this project.

The paper is organised as follows: section 2 describes the methods and data used for the analysis; section 3 presents the results; section 4 discusses the study results and their implications; section 5 summarizes the main conclusions and recommendations.

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[3] Also know as atypical antipsychotics, SGAs is a class of antipsychotic drugs authorised for the treatment of psychiatric conditions. Some SGAs, including risperidone, olanzapine and aripiprazole have received regulatory approval (e.g. FDA, EMA and/or MHRA) for the treatment of schizophrenia, bipolar disorder and dementia.

2. Methods

We estimated the life-cycle cost-effectiveness, as well as the producer, consumer and social surplus as follows:

1. Estimating the number of patients receiving the drug over time;
2. Estimating the annual cost of risperidone and the comparator over time;
3. Estimating the annual direct and indirect costs of risperidone and the comparator over time;
4. Quantifying and valuing the health gains in terms of QALYs;
5. Calculating the net value added, producer surplus, consumer surplus and total cost over time (discounted to the present value where relevant).

These five steps are followed for Sweden and UK. However, the methods used for the estimation of the number of patients were different for Sweden and UK due to differences in the availability of data. The methods used for each country are explained separately.

2.1. Estimating number of patients in the UK

To estimate the number of patients treated, volume usage data were obtained from IQVIA (formerly IMS)[4] in the form of Counting Units (CU) per month for the period 2003-2017. Volume usage data obtained were broken down by formulation (e.g., oral, long-acting injectable), strength in milligrams (mgs), branded/generic status, and primary care/hospital use.

Prescription Cost Analysis (PCA)[5] data on the volume usage of risperidone were also obtained for the period 1998-2017. PCA data only cover primary care use. In addition, only data for England was available for the full period. PCA usage data for all four nations of the UK – England, Northern Ireland, Scotland and Wales – were only available from 2002. The PCA data were therefore used as a check on IQVIA data quality and to generate assumptions to cover data gaps so we could extrapolate IQVIA volume data based on PCA trends.

For the years 1994- 2002, not covered by IQVIA data, we applied assumptions based on data on risperidone usage for schizophrenia in Sweden. Specifically we took the trend of use in Sweden for the period 1994-2013, normalised it to the UK by reference to usage for the period 2003-2013 from the IQVIA data in the UK, and so were able to extrapolate backwards data for the UK for 1994-2002, using Swedish trends but based on UK data for later periods.

Not all risperidone was prescribed to treat schizophrenia patients. To make an informed assumption on the schizophrenia share, we collected data on indication use from the IQVIA Corporation Prescription database (CPRX)[6] for the years 2004-2014. Data gaps were covered by: (i) assuming the same percentages of schizophrenia use in the UK as in Sweden for the period 1994-2002, (ii) assuming a linear progression for 2003 based on the 2002 number from the backwards

[4] *See: https://www.iqvia.com*
[5] *See: https://www.nhsbsa.nhs.uk/prescription-data/dispensing-data/prescription-cost-analysis-pca-data*
[6] *Prescription data of the UK database is based on an extrapolation from a sample of general practitioners.*

extrapolation and the IQVIA 2004 number, and (iii) assuming moving averages based on the latest two periods, to cover data gaps for the period 2015-2017.

To apportion volumes to the number of schizophrenia patients, we used a staged approach:

1. We converted CUs (e.g., tablets, vials, injections) into mgs using product pack information;

2. We aggregated the total mgs consumed per year, separately for oral and long acting injectable formulations;

3. We calculated the daily use of risperidone by dividing the per year figure by 365;

4. Using the Summary of Product Characteristics (SmPC) of oral and long acting injectable formulations of risperidone for the in-label indications and assuming a Defined Daily Dose (DDD) for off-label indications, we estimated the average DDD for all patients treated, weighted by the percentage use of each indication. Table 1 shows below how the weighted average DDD is calculated using year 2000 as an example

TABLE 1: EXAMPLE OF WEIGHTED AVERAGE OF DDD FOR 2000

INDICATION	DDD	% OF USE	INDICATION WEIGHT
Schizophrenia	5 mg	44%	2.2 mg
Other	1 mg	56%	0.56 mg
AVERAGE DDD WEIGHTED BY INDICATION USE			**2.76 mg**

Note: 'other' includes bipolar disorder, Alzheimer disease andall off-label use. We take the median DDD for each indication from risperidone's SmPC. We assume a daily use of 1 mg for off-label use
Source: electronic medicines compendium at https://www.medicines.org.uk/emc

5. We were then able to convert the total mgs per year into patients treated per year in total for all indications by dividing average daily total mgs used (step 3) by the DDD weighted average;

6. We apportioned the number of patients treated per year for each indication in the UK (result of step 4). For the period 1994-2002 we applyied the percentages of use for each indication from Sweden. For the period 2003-2017, we applied percentages based on the number of prescriptions per indication (IQVIA).

We can summarise stages 1.-6., set out above, to convert the total mgs per year into the total number of patients (schizophrenia) in a formula as follows:

$$Schizophrenia\ patients = \frac{\frac{Total\ mgs}{year} \div \frac{365\ days}{year}}{DDD} \cdot \%\ schizophrenia$$

where the DDD is the volume-weighted average for all indications and '% schizophrenia' is the percentage of the total volume of risperidone used for the treatment of patients with schizophrenia.

2.2. Estimating the number of patients in Sweden

Two data sources were used to estimate the number of treated patients in Sweden. For the period 1994 – 2002, we relied on the Medicine Index Sweden, a survey administered twice yearly to one in

eight physicians in Sweden[7]. The survey estimated both the number of patients treated and the indications for treatment, thus providing an estimate of the proportion of patients treated with risperidone that were diagnosed with schizophrenia each year over the period.

From 2006, data on the number of treated patients were available from statistics maintained by the National Board of Health and Welfare. To bridge the gap between the two sources, the number of patients was imputed based on the moving average. No data on diagnosis were available from this source. We therefore assume that the same proportion of treated patients had schizophrenia as in the UK (described above) for this period.

Neither of the two data sources in Sweden included information on the formulation prescribed. Again, the same proportion as observed in the UK was assumed to apply.

2.3. Literature review to identify costs and QALYs

For steps 2-4 above, data on medicine cost, direct cost to the health system, indirect cost (productivity losses) to society and QALY gains were collected through a semi-systematic literature review performed by two researchers (BZ and MB). Researchers consulted two databases: PubMed; and Database of Abstracts and Reviews of Effects (DARE). Further complementary and targeted searches for relevant papers were carried out in Google Scholar.

The search strategy is described in Table 2, including keywords used, databases searched and the number of hits per search.

[7] *Medical Index Sweden. Läkemedelsstatistik AB, Stockholm.*

TABLE 2: SEARCHES FOR LITERATURE REVIEW

DATABASE	KEYWORD COMBINATION	NUMBER OF HITS
PubMed	(Risperidone[Title/Abstract] AND antipsychotics[Title/Abstract]) AND review[Publication Type] AND ("economics, pharmaceutical"[MeSH Terms] OR ("economics"[All Fields] AND "pharmaceutical"[All Fields]) OR "pharmaceutical economics"[All Fields] OR "pharmacoeconomics"[All Fields])	18
PubMed	((Risperdal[Title/Abstract]) AND atypical[Title/Abstract]) AND review[Publication Type]	14
PubMed	(Risperidone[Title/Abstract]) AND Cost offsets	**1**
PubMed	Risperidone[Title/Abstract] AND cost savings[Title/Abstract]	15
PubMed	Risperidone[Title/Abstract] AND (("health"[MeSH Terms] OR "health"[All Fields]) AND gains[All Fields])	**15**
PubMed	("risperidone"[MeSH Terms] OR "risperidone"[All Fields]) AND ("economics, pharmaceutical"[MeSH Terms] OR ("economics"[All Fields] AND "pharmaceutical"[All Fields]) OR "pharmaceutical economics"[All Fields] OR "pharmacoeconomics"[All Fields])	92
PubMed	((((atypical antipsychotics) AND Risperidone) AND Cost effectiveness)) AND direct costs	26
PubMed	((((review[Publication Type]) AND pharmacoeconomics)) AND Risperidone) AND cost effectiveness	16
PubMed	((atypical antipsychotics) AND Risperidone) AND Cost effectiveness	91
PubMed	(Risperidone[Title/Abstract]) AND Direct costs	56
DARE: Cochrane reviews	(Antipsychotics [All fields] OR reisperidone [All fields)]	456
DARE: HTA	((antipsychotics)c OR (risperidone):TI) and ((Systematic review:ZDT and Bibliographic:ZPS) OR (Systematic review:ZDT and Abstract:ZPS) OR (Cochrane review:ZDT) OR (Cochrane related review record:ZDT) OR (Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT)	38

The first set of searches produced 823 hits. We then applied a set of inclusion criteria to reduce the number of hits to a manageable size. The set of criteria comprised:

- Indications covered in the research: schizophrenia, bipolar disorder and dementia;
- Country of study: United Kingdom, Sweden, European Union Member States, United States of America and Canada;
- Comparators were pharmacological treatments;

- Studies referred in articles, included either cost (e.g., direct, indirect, medicine) and/or effectiveness data, including incremental or absolute estimates.

Reading abstracts and applying the set of inclusion criteria above, we reduced the number of papers to 155. We classified the hits in the reduced list based on the year of publication and on indications covered in the study. Reviewers then read articles and collected the relevant information from them: study year, study country, risperidone and comparator formulations, currency and year for monetary values, methodology used, medicine cost, healthcare direct cost, indirect cost and QALYs gained.

After the review, the number of studies was reduced to 48 distributed as follows: 39 for schizophrenia; 7 for bipolar disorder; and 2 for dementia. We then applied an additional set of inclusion criteria based on research objectives and on other technical reasons. We used haloperidol as the comparator to estimate the incremental cost-effectiveness metrics used in the analysis. Consequently, only studies that included data on either risperidone or haloperidol were included. As methods vary across studies, relevant inputs of risperidone and haloperidol coming from different studies are not comparable. Therefore, a study was only used to estimate incremental metrics (e.g., QALYs gained, healthcare service cost, medicine cost, indirect cost) if it contained data on both risperidone and haloperidol.

As far as possible, we tried to use data from UK studies for the UK analysis, and from Swedish studies for the Swedish analysis. This was not always possible. Hence, we assessed the transferability of data collected from other countries.

There are several guidelines that can be followed to deal with variables potentially affecting the appropriateness of transferring evidence between countries and the subsequent adjustments needed to make evidence relevant. This paper follows two widely used guidelines on transferability: (i) the decision chart described in Welte et al. (2004); and (ii) the guidelines from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) by Drummond et al. (2009).

Table 3 shows the final selection of studies from which we extracted all relevant inputs for the present study.

We split the life-cycle of risperidone into four time periods of similar duration (1994-2000, 2001-2007, 2008-2012 and 2013-2017). The first two belong to the on-patent part of the life-cycle. The last two belong to the off-patent part of the life-cycle. If available, we populated inputs with cost-effectiveness data specific to each period using studies published in the same period. We combined all inputs by calculating weighted averages.

If, for a specific input, there was no available data for a particular time period, we used the data closest to the uncovered period. Inputs for which separating the on- and off-patent parts of the life-cycle were necessary for the analysis, were combined separately. For the rest, we combined data for the whole life-cycle. A detailed description of input selection is shown in Appendix 1.

In addition, we attributed specific cost-effectiveness data to patients treated with Risperdal Long-Acting Injectable (RLAI) (comparator, Haloperidol Long-Acting Injectable (HLAI))[8]. For the oral formulation of risperidone, we used cost-effectiveness data of the generic version since 2008 for the UK and 2009 for Sweden as first generics were introduced in December 2007 and January 2009 respectively in the UK and Sweden.

[8] *RLAI was launched in September 2002 and is still on-patent*

TABLE 3: ARTICLES SELECTED FOR POPULATING MODEL INPUTS

Reference	Inputs	Country of original study	Country of application
Einarson et al. (2014)	Medicine cost: RLAI and HLAI Total direct cost: RLAI and HLAI Total indirect cost: RLAI and HLAI QALY gain: RLAI and HLAI	Sweden	United Kingdom and Sweden
Foster and Goa (1999)	QALY gain: risperidone and haloperidol	Multi-country: United States, Nederland, Germany and United Kingdom	United Kingdom and Sweden
Guest et al. (1996)	Medicine cost: risperidone and haloperidol	Sweden and United Kingdom	Sweden and United Kingdom
Hensen et al. (2010)	Medicine cost: RLAI and HLAI Total direct cost: RLAI and HLAI QALY gain: RLAI and HLAI	Sweden	Sweden
Laux et al. (2005)	Medicine cost: RLAI and HLAI Total direct cost: RLAI and HLAI QALY gain: RLAI and HLAI	Germany	United Kingdom
Lindström et al. (2011)	Medicine cost risperidone and haloperidol Total direct cost: risperidone and haloperidol Total indirect cost: risperidone and haloperidol QALYs gain: risperidone and haloperidol	Sweden	Sweden and United Kingdom
Lindström et al. (2007)	Medicine cost risperidone	Sweden	Sweden
Nicholls, Hale and Freemantle (2003)	Medicine cost: risperidone	United Kingdom	United Kingdom
Zeidler et al. (2013)	Medicine cost: risperidone and haloperidol Total direct cost: risperidone and haloperidol	Germany	United Kingdom and Sweden

Abbreviations: Risperdal Long-Acting Injectable, RLAI; Haloperidol Long-Acting Injectable, HLAI.

2.4. Product life-cycle timeline

The aim of the present research is to quantify the life-cycle value of risperidone which requires capturing all relevant events that played a role in determining its year-by-year value. Three main events that are known to have played a role:

(i) patent expiration time and the entry of generic competition for oral risperidone;

(ii) the approval date of risperidone for other indications (e.g., bipolar disorder and dementia); and

(iii) the launch of new and more effective formulations (e.g., Risperidone Long-Acting Injectable (RLAI)).

In the UK, the branded version of oral risperidone was launched in June 1993 for schizophrenia, having been approved in December 1992, and the patent expired in December 2007 when the first generic versions entered the market. Oral risperidone was approved and launched in May 2004 for treating patients with bipolar disorder and in December 2008 for treating patients with dementia. RLAI was approved and launched for treating patients with schizophrenia in August 2002.

In Sweden, the branded version of oral risperidone was launched in February 1994 for schizophrenia, after its approval in December 1993, and the patent expired in December 2007, although the first generics did not enter in the market until January 2009. Oral risperidone was approved and launched in April 2003 for treating patients with bipolar disorder. It was approved in December 1998, and launched in April 2000, for treating patients with dementia. RLAI was approved in March 2004 and launched in April 2004 for treating patients with schizophrenia.

Detailed timelines including all formulations and approval/launch dates for all indications are shown in Appendix 2.

2.5. Metrics used and assumptions applied for the analysis

We related the cost-effectiveness data from the literature to the number of patients per year to create a set of metrics for the analysis. They can be split into two groups: absolute and incremental metrics. The set of absolute metrics comprised:

- Consumer surplus: the difference between the system's willingness to pay per total QALY gain and the cost (price) of the medicine;
- Producer surplus: commercial benefit obtained by the manufacturer from selling the medicine calculated as the difference between revenue – the price (cost) of the medicine per patient multiplied by the number of patients – less the operating cost (e.g., manufacturing, marketing and distribution). Note this excludes R&D cost;
- Social surplus: the sum of consumer and producer surpluses.

To estimate the consumer surplus, we assumed the consumer willingness to pay to be the lower bound of NICE's assumed cost-effectiveness threshold of £20k/QALY for the UK and the lower bound of Sweden's assumed cost-effectiveness threshold of €70k/QALY. Then, willingness to pay per QALY of each country was multiplied by the number of total (not incremental) QALYs gained in each country and the full cost of the medicine (not the incremental cost) was subtracted. For the UK,

the cost-effectiveness threshold was converted to 2017 Euros by using the average 2017 Sterling to Euro exchange rate.

To provide a measure of the value added by second generation antipsychotics as a new class, we estimated the value added by risperidone as compared to haloperidol which we assumed to be the representative first-generation antipsychotic (old class). We compared risperidone oral with haloperidol oral, and Risperdal long-acting injectable with haloperidol long-acting injectable. When relevant, we present metrics for the two formulations separately. The set of incremental metrics comprised:

- Incremental cost: the difference between the cost of treating patients with risperidone and with haloperidol (includes both, direct and indirect costs);
- Incremental Cost-Effectiveness Ratio (ICER): the incremental cost to incremental health gain ratio per patient as between risperidone and with haloperidol;
- Net Monetary Benefit (NMB): the consumer's willingness to pay – assumed to be the cost-effectiveness threshold of either UK or Sweden – multiplied by the incremental QALY, less the incremental cost;
- Incremental surplus captured by the producer: the additional surplus that the producer of risperidone captures compared to the haloperidol producer under the assumption that both would treat the same number of patients.

For the purpose of the analysis, metrics are shown both aggregated and per patient. Per patient measures are useful to compare the results of time periods of different length. This is the case for instance when comparing the last pre-generic period (2001-2007) and first post-generic period (2008-2012).

Figures of estimates for all metrics by time periods for both, Sweden and UK, are shown in Appendix 3 section.

Additionally, as actual data about operational costs are not available in the public domain, we assumed that the manufacturer's commercial margin represented 80% of the total cost of the medicine whilst still on patent and 20% of the total cost of the medicine after patent expiration when generic versions entered the market (Lindgren and Jönsson, 2012).

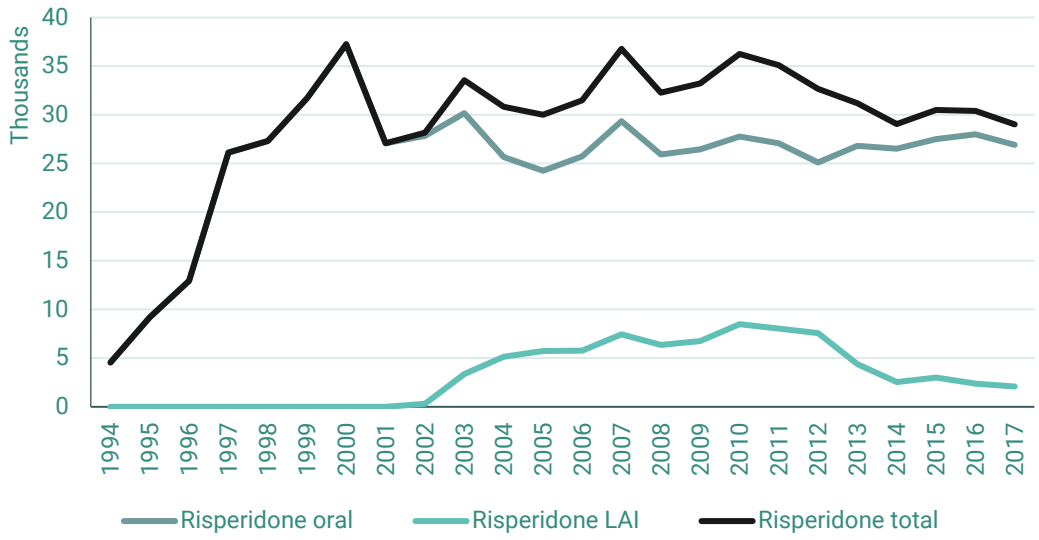
3. Results

Estimates of all metrics defined in methods are presented, separately for the UK and Sweden in following sections.

3.1. Results for UK

The number of patients increases until 2000 and then drops until 2002 when it increases again, with the launch of the RLAI (Figure 1). It remains quite stable from 2003 (with 33,500 patients treated) until 2012 (32,600 patients)9. It then drops again after paliperidone long-acting injectable, a better product of the same class, was launched in 2013. Figure 1 shows the uptake of risperidone in terms of the number of patients for the study period.

FIGURE 1: Number of patients with schizophrenia treated with risperidone, UK



In the next analysis, we compare the total number of patients treated with the total cost of risperidone over time. Results are shown in Figure 2 where cost is measured on the primary axis (left) and patients on the secondary axis (right). The decrease in the total cost for the payer due to generic competition is reflected from 2007. Generic entry produced a positive impact for payers by reducing the total cost while the number of patients treated remained constant. Figure 2 also shows the increase in the cost due to the launch of the long-acting injectable (RLAI) in 2003.

[9] *Total uptake of SGAs would had likely increased during this period as other SGAs were launched after risperidone and competed for the market.*

FIGURE 2: Total cost of risperidone and total patients treated per year, UK

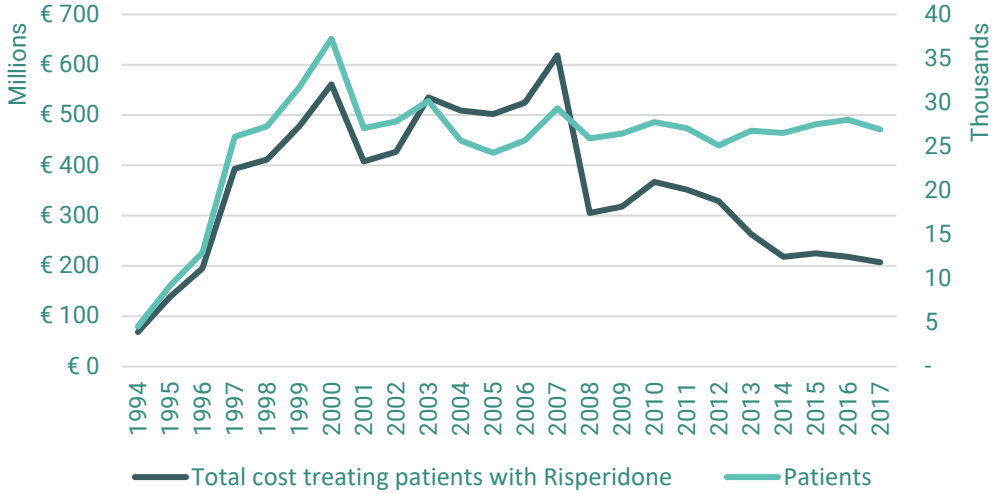
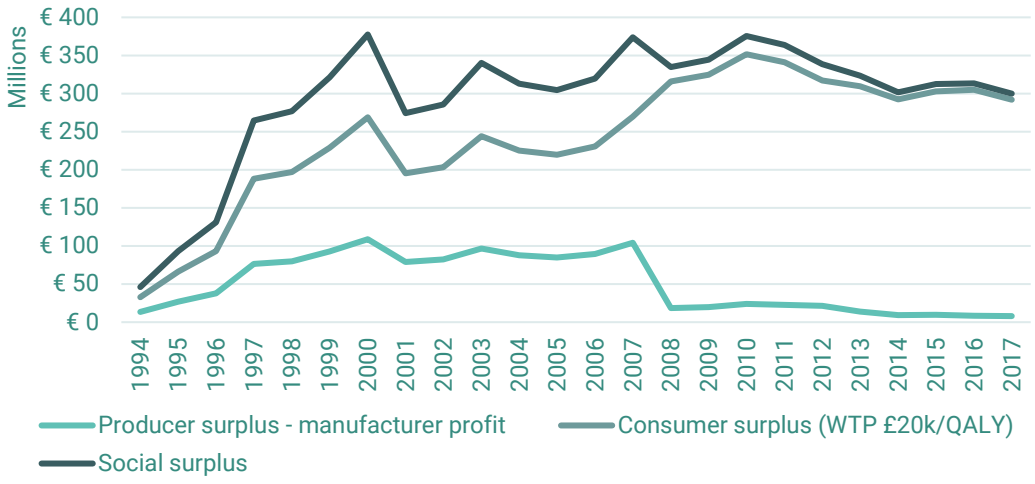


Figure 3 shows the absolute consumer, producer and social surplus over the period of study. The orange line in Figure 3 represents the social surplus, as the sum of consumer and producer surplus, the blue and green lines, respectively. Figure 3 shows that until 2007, when the patent expired and the first generic versions of risperidone entered the market, the producer was able to capture a larger share of the surplus than after 2007. After patent expiration, the producer surplus (the green line) dropped significantly and consequently the consumer surplus increased. The system's ability to capture more monetary value from health gains increased with generic competition. The distance between the blue and green line increased after 2007 to the same extent as the distance between blue and orange line narrowed to the point that almost all the social surplus was captured by the health system in the later periods of the study (2013-2017).

FIGURE 3: Absolute social, consumer and producer surplus in the risperidone market, UK



Abbreviations: Willingness to Pay, WTP; Quality Adjusted of Life Year, QALY.

Figure 4 shows the aggregated consumer and producer surplus by periods of five to seven years, and in total[10]. In total, the UK's health system was able to capture more than five times the surplus of the producer. The grey line in the figure shows the number of patients. For the two time periods after patent expiration (i.e., 2008-2012, 2013-2017), consumer surplus remained reasonably constant while producer surplus was considerably lower as compared to the two periods before patent expiration (i.e., 1994-2000, 2001-2008). This happened even though, (i) the periods after patent expiration are two years shorter, and (ii) the number of patients treated with risperidone decreased.

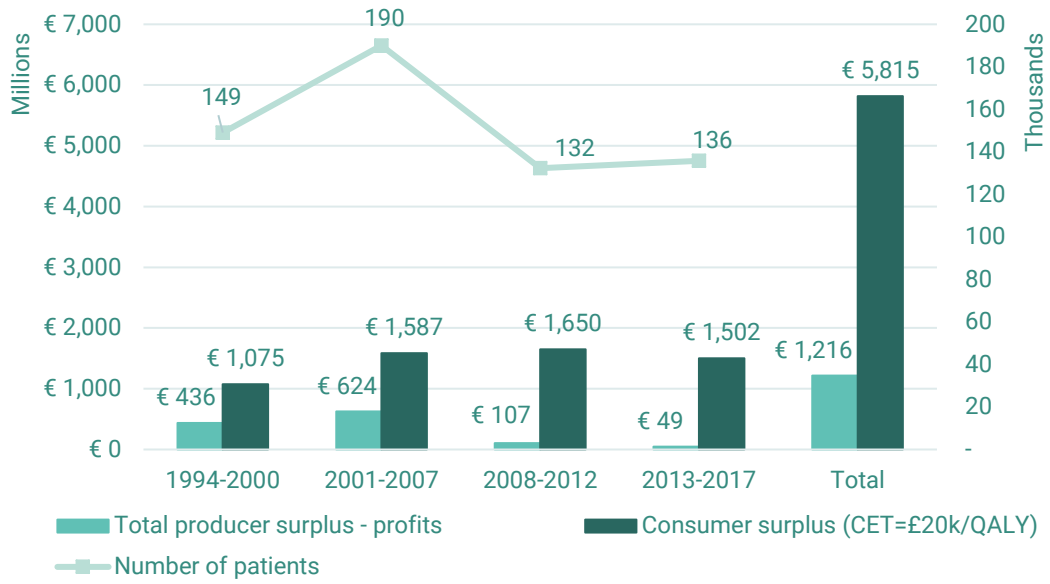
The absolute metrics presented clearly show that generic competition changed the distribution of the social surplus in favour of the health system of the UK (i.e. the consumer, the tax payer). Put in other words, expiration of the patent term allowed the consumer to capture a significantly larger share of the value created by the medical innovation.

We also assess the incremental value created by risperidone and how it changes over time by looking at the set of incremental metrics. Figure 5 shows how incremental cost including both, direct and indirect costs, evolves over time during the period of study.

A first fact worth highlighting is that risperidone dominates haloperidol (comparator) over the entire life-cycle (1994-2017). That means that the incremental cost of risperidone was lower than that of its predecessor, no matter when it occurred.

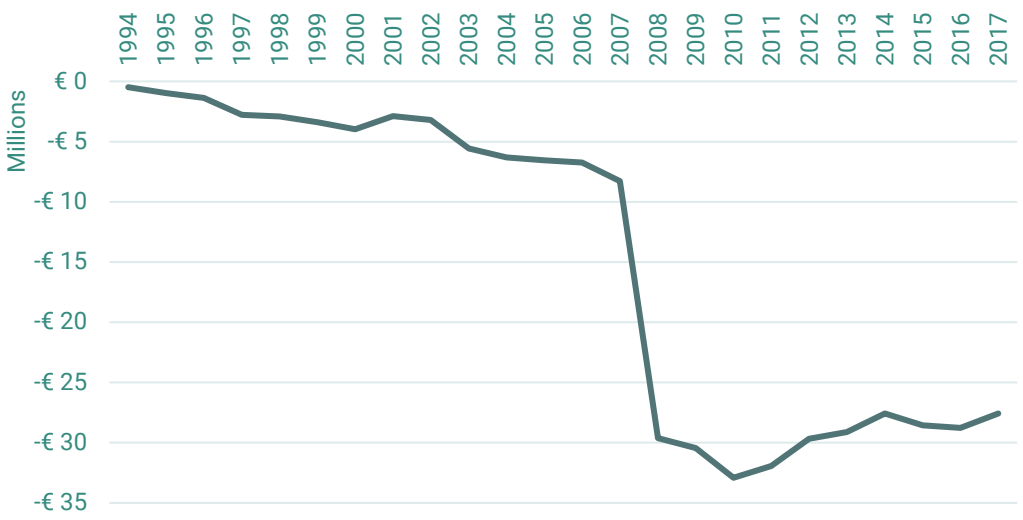
The second most noticeable fact that Figure 5 shows is that the cost per incremental health gain hugely decreased with generic entry after 2007. The launch of RLAI also reduced the cost per incremental health gain. This effect, however, is not immediately apparent in Figure 5 during the period 2003-2007.

FIGURE 4: Number if patients, consumer surplus and producer surplus, UK



[10] To determine the different periods of time, we firstly have split the whole period into pre- and post-generic competition. Then we split each period into two equal size periods for two reasons: to have more granularity and to the extent that data makes it possible, update metrics' values in response of updated data published in the literature. Given that generic entry time varies between the UK (2007) and Sweden (2009), although patent expired in both in 2007, we use different time splits for each country.

FIGURE 5: Incremental cost of risperidone versus haloperidol, UK

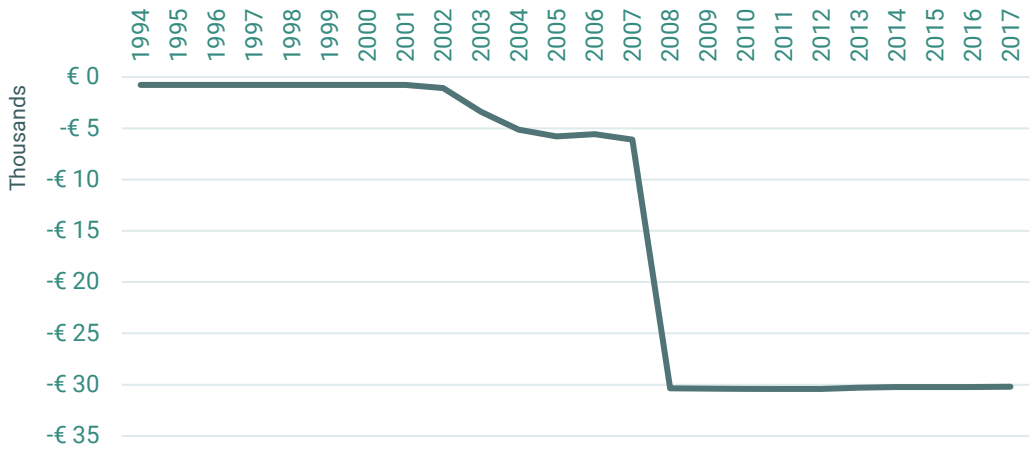


To see how much value risperidone added per incremental health gain, we quantified the total incremental QALYs per year. Total QALY gains considering both, oral and long-acting formulations are positive for the whole period. The incremental QALY gain of risperidone oral versus haloperidol oral was 0.021 while for RLAI compared to HLAI was 0.016.

Figure 6 shows the ICER over the period of study. It specifically shows how the net value added changed over time in relation to key events during the life-cycle.

The ICERs in Figure 6 confirm that risperidone dominates haloperidol over its entire life-cycle. It is negative and constant between 1994 and 2002. This is due to the positive incremental health gain and lower cost of risperidone (-€107). The ICER reduced between 2002 and 2004, and then remained quite stable until 2007. This is because: (i) the healthcare cost per treated patient of RLAI was lower than the cost of long-acting haloperidol to a greater extent than for oral formulations (-€1075); and (ii) uptake of RLAI increased during 2002-2005 and therefore contributed to reducing the ICER.

FIGURE 6: Evolution of the ICER during risperidone's life-cycle, UK



In 2007, the patent of risperidone expired, and generic versions of oral risperidone entered the market. The cost per treated patient with oral risperidone decreased even more. Compared to haloperidol, the difference – in terms of cost per incremental health gain per patient – was larger than with the branded version (-€974). Consequently, the ICER dropped between 2007 and 2008, and thus the value created per treated patient increased hugely after patent expiration.

A decrease in the ICER is observed in 2003 which we can associate with the launch of paliperidone long-acting injectable. The consequent loss of market share of RLAI, reduced its contribution to the total ICER of risperidone.

To assess the net value added to society, its distribution between system/society (consumer) and producer, and how this evolved over the life-cycle, we analysed the NMB for the health system and the incremental surplus captured by the producer of risperidone. Figure 7 shows how the NMB for the health system and the incremental surplus captured by the producer of risperidone changed over the life-cycle.

The NMB – the orange line in Figure 7 – measures the additional value risperidone added to the system per year by multiplying the NMB per patient by number of patients treated. Figure 7 shows that this increased almost continuously between 1994 and 2010. Generic entry pushed it up from an average of €1,043 per patient during the period 2001-2007 to an average of €2,130 per patient during the period 2008-2012, an increase of 104%. This is shown by the trend in the orange line in the graph after 2007 and indicates that the system benefited substantially from generic competition.

The incremental surplus captured by the producer moved in the opposite direction, as Figure 7 shows. The incremental surplus that risperidone generated compared to haloperidol decreased significantly after generic entry in 2007. From €3,107 per patient in the period 2001-2007, it decreased to €625 in the period 2008-2012, a decrease of -80%, and to €215 in the period 2013-2017, an additional decrease of around 65%. The blue line in the figure shows this effect in € millions.

FIGURE 7: NMB and incremental producer surplus, UK

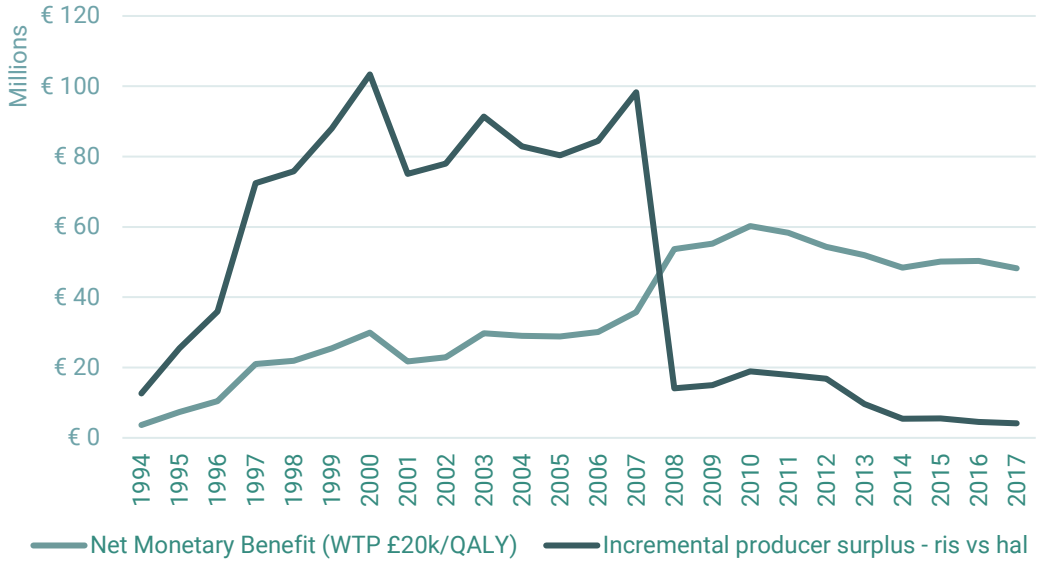
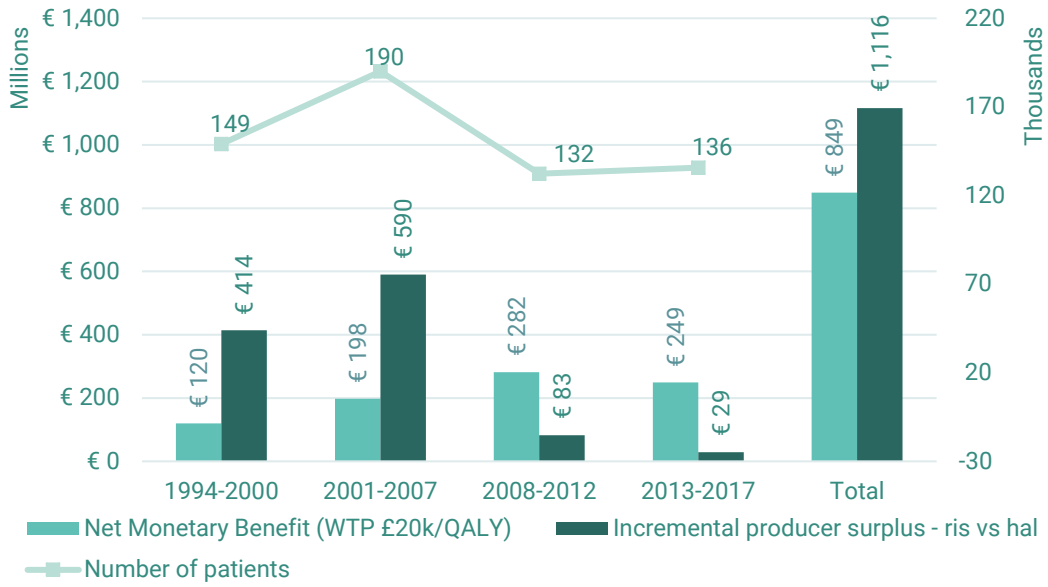


Figure 8 shows the NMB and incremental producer surplus figures in different periods and in total. Comparing the share of incremental value captured by producer and system, the result differs considerably from the absolute figures, although the general message they send is the same. In total, the amount of incremental surplus captured by the producer (€1,116m) is larger than the NMB

(€806m), the benefit captured by patients and the health system. Going period by period, Figure 8 shows that 90% of the incremental producer surplus was generated in the two pre-generic competition periods and that 63% of the NMB was generated in the two post-generic competition periods. This was so despite the fact that the total number of patients treated was considerably lower in the post-patent period which is also four years shorter in total[11].

FIGURE 8: NMB and incremental producer surplus, UK



3.2. Results for Sweden

The number of patients in Sweden increased rapidly until 1997 when it reached 13,800 patients, experienced a peak in 2000 with 15,100 patients, decreased significantly in 2001-2002 to 9,000 patients per annum and then remained quite stable at this level until 201112. It decreased again to 6,000 patients per annum in the period 2012-2017. Figure 9 shows the uptake of risperidone in number of patients for the study period.

[11]Per patient figures that neutralise the effect of comparing estimates belonging to different time lengths are presented in Appendix 3.
[12] Total uptake of SGAs would had likely increased during this period as other SGAs were launched after risperidone and competed for the market.

FIGURE 9: Number of patients treated with schizophrenia treated with risperidone, Sweden

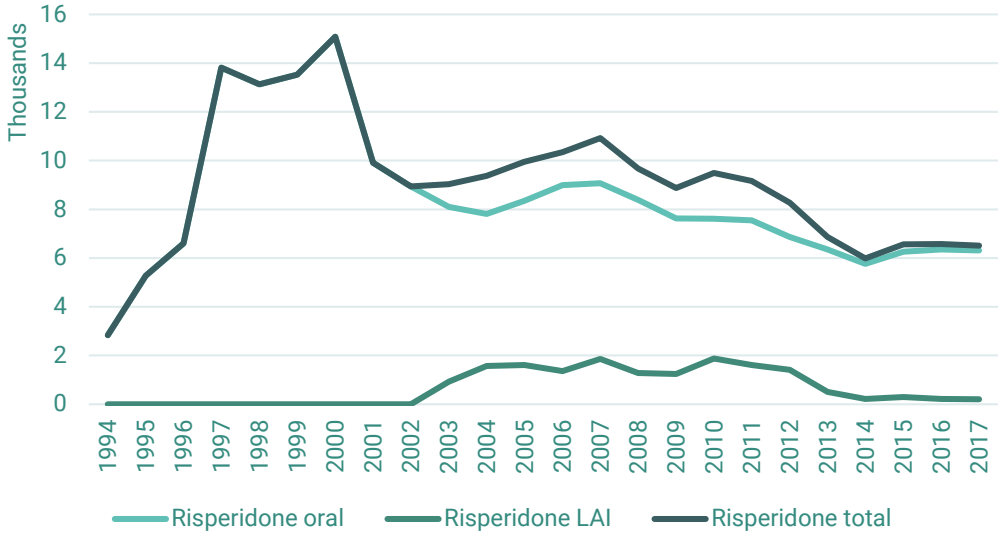
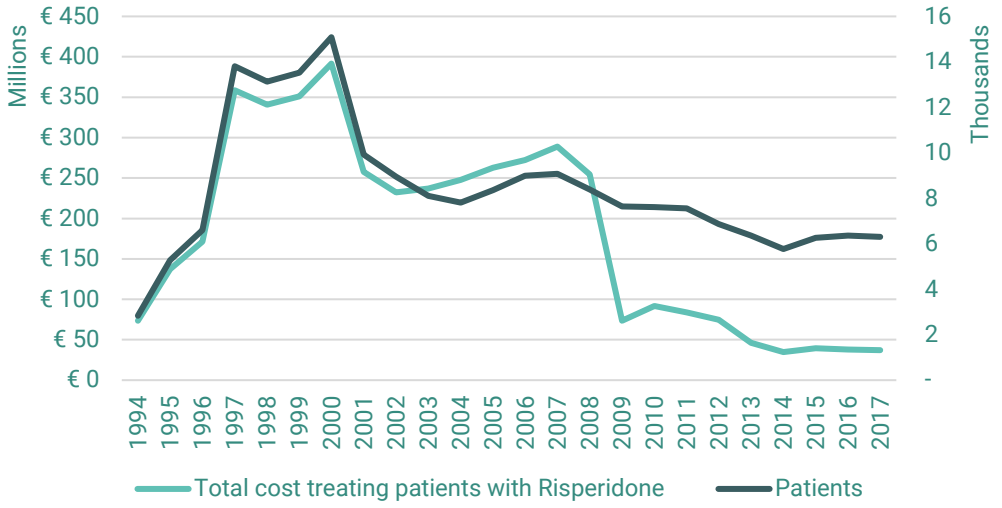


FIGURE 10: Total cost of risperidone and total patients treated per year, Sweden



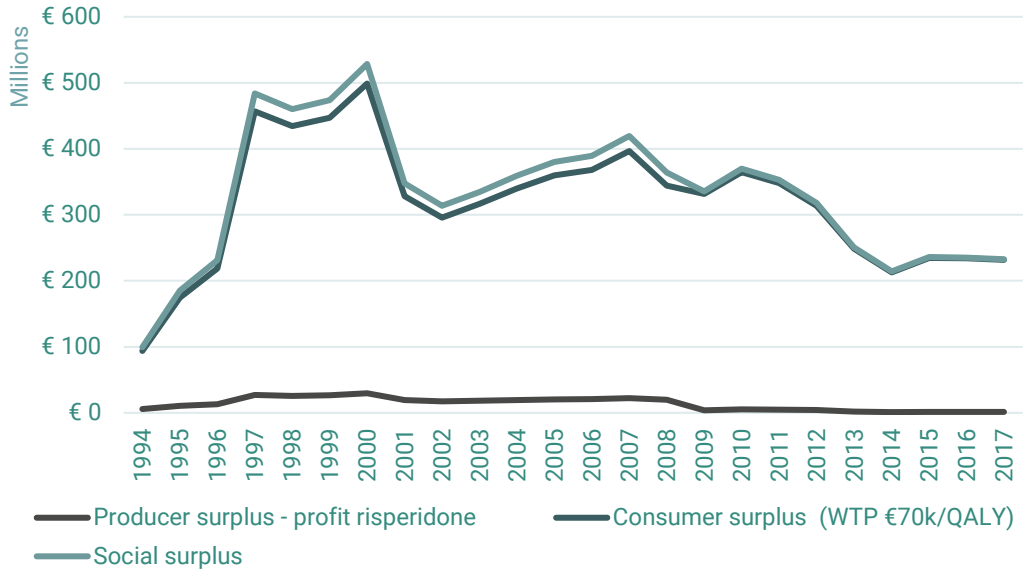
Analyses to assess the life-cycle value added by risperidone in Sweden followed the same approach as was taken for the UK.

Figure 10 compares uptake with the total cost of treating patients with risperidone. The same pattern previously observed for the UK is shown in Figure 10 for Sweden. Generic entry in 2009 reduced the total cost of risperidone, while the number of patients remained stable. The launch of the long acting injectable version in 2004 increased the total cost, although it improved the cost-effectiveness of risperidone, as analyses presented later in this section show.

Figure 11 shows the absolute consumer, producer and social surplus over the period of study. The orange line in Figure 11 represents the social surplus calculated as the sum of both, consumer and producer surplus. Consumer surplus is represented by the blue line. In Sweden, although the risperidone patent expired in 2007, the first generics did not enter the market until January 2009. Figure 11 shows that before the first generics entered the market, the producer was able to capture a

larger share of the surplus (green line). However, it is very difficult to see this change clearly in the graph as the higher willingness to pay of Swedish system leads it to accrue most of the social surplus. If readers scrutinize the green line, they will be able to see a decrease that coincides with the difference between the consumer surplus (blue line) and social surplus (orange line) disappearing.

FIGURE 11: Absolute social, consumer and producer surplus in the risperidone market, Sweden

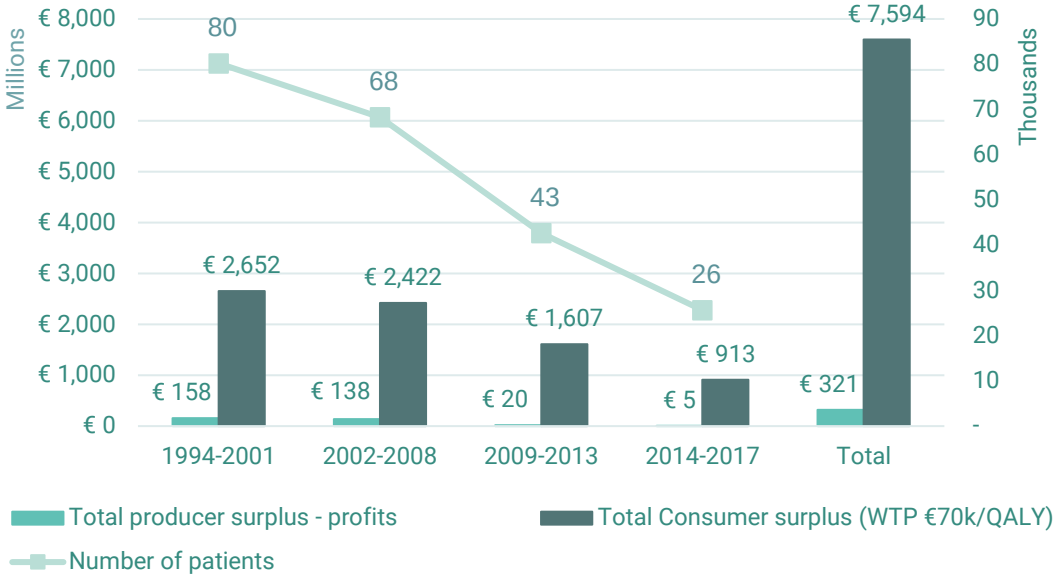


In Figure 12, we also compare the aggregated consumer surplus, producer surplus and social surplus in periods of 4 to 8 years and for the entire life-cycle (1994-2017).

The aggregated consumer surplus for the whole period of the study in Sweden is around 23 times the aggregated producer surplus. Such a huge difference is due to the high willingness to pay of the Swedish system (€70k per QALY) and the producer's inability to exploit it by charging higher prices. The decrease in the producer surplus after patent expiration in 2009 is noticeable. This is in part due to the shorter number of years of each period[13].

[13] *Per patient figures that neutralise the effect of comparing estimates belonging to different time lengths are presented in Appendix 3.*

FIGURE 12: Number of patients, consumer surplus and producer surplus, Sweden



To get a closer measure of this decrease in the producer surplus and in the consumer surplus we related the consumer and producer surplus to the number of patients treated within each period. The number of patients treated decreased by 38% between the period 2002-2008 and 2009-2013, accumulated consumer surplus only decreased by 34% (which means a net increase in the per patient consumer surplus) and the producer surplus decreased by 86% (which means a considerable net decrease in per patient producer surplus). In Sweden, generic competition happened together with a decrease in the number of patients treated, both of which affected negatively the surplus captured by the producer. Comparing the last period before generic competition (2002-2008) with the first period after it (2009-2013), the producer surplus went from being approximately 6% of the total surplus to being approximately 1%. An inverse effect is observed for the health system where the share of total surplus went up from 94% to 99%.

We also assess the incremental value added by risperidone against haloperidol in Sweden. For that purpose, we use the same metrics and procedures as used for the analysis of the UK, explained in the previous section. Figure 13 shows the incremental cost of risperidone compared to haloperidol.

Risperidone dominates haloperidol throughout the entire life-cycle which means the incremental cost was negative for all years and therefore the health system and society were able to treat each patient at a lower cost with risperidone during the whole period of the study (1994-2017). Cost reductions are positively correlated with the number of patients and therefore they increase until the number of patients peaks in 2000 and decreases afterwards. Then, RLAI was launched in 2004 and, whilst patients on oral risperidone remained quite constant after 2001, patients on RLAI were added and consequently incremental cost decreased again. This was due mostly to the fall in the incremental cost per patient treated with RLAI by €2,222, while for oral risperidone this fall was €290 (pre-generics) and €840 (post-generics).

Incremental cost decreased markedly for the system in 2009, the first year of generic competition. In the same way as in the UK, generic competition positively and significantly increased the share of the value added by risperidone captured by the consumer. However, in 2013, the number of patients on RLAI decreased due to the launch of Paliperidone Long-Acting Injectable (PLAI), reducing the reductions in incremental cost contributed by the use of RLAI.

We use the ICER to assess the value that risperidone added to the health system and society per unit of health gain (QALY) in Sweden. Figure 14 shows the per annum evolution of the ICER.

FIGURE 13: Incremental cost of risperidone versus haloperidol, Sweden

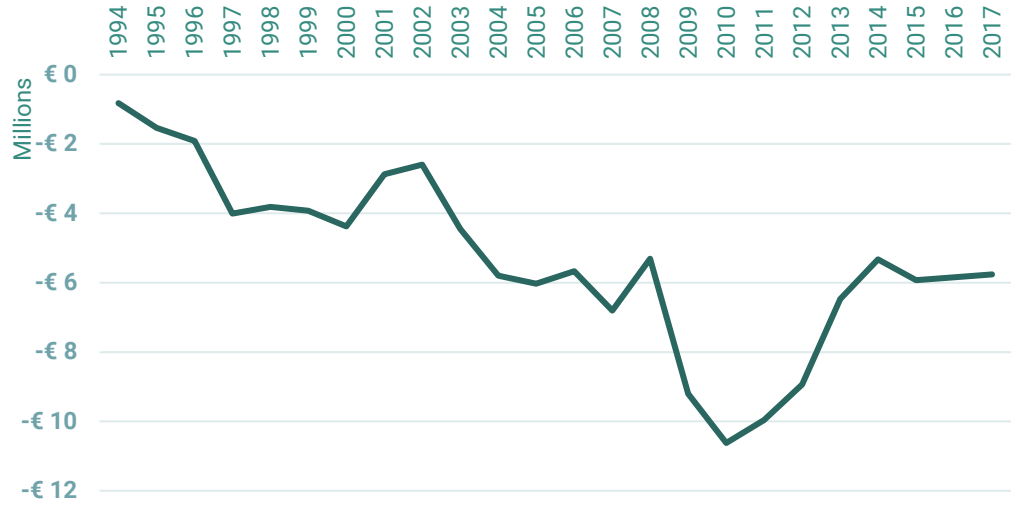
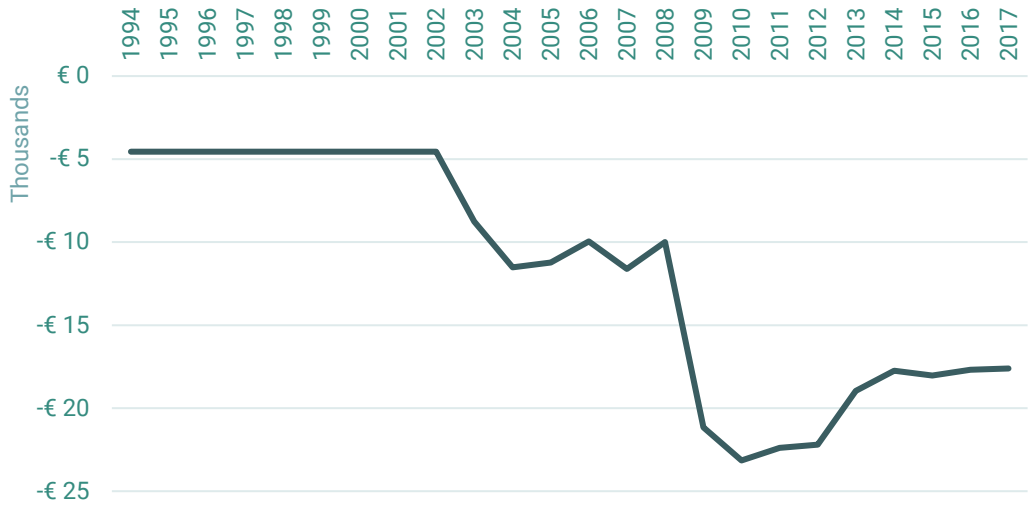


FIGURE 14: Evolution of the ICER during risperidone's life-cycle, Sweden

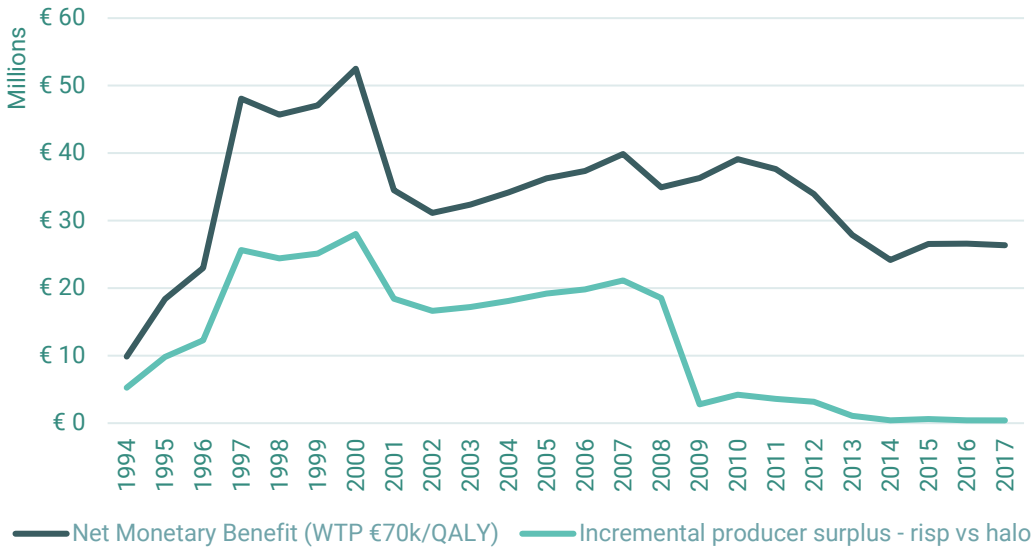


The ICER was negative during the entire life-cycle of risperidone, which means that the health system and society paid less per unit of health gain produced by risperidone compared with producing equivalent health gain with haloperidol. Two events are worth noting: (i) the launch of RLAI in Sweden in 2004; and (ii) the entry of generics in 2009. RLAI produced more incremental QALYs per patient (0.05) than risperidone oral (0.03) at lower system costs per patient (-€2,222 vs -€840) during the on-patent period. Consequently, the ICER decreased after RLAI's launch in 2004 as Figure 14 shows. This means that the incremental value added per patient by risperidone increased on average. The decrease in the ICER in response to generic entry in 2009 was substantial. This was the result of the lower incremental cost of generic risperidone versus haloperidol. Therefore, the value added (or the

lower cost per unit of health gain generated) by risperidone increased significantly with generic entry. However, the loss of market share of RLAI to PLAI later increased the ICER after 2012.

To assess how much net value risperidone added as well as how that value-added was distributed during the life-cycle, we estimated the NMB and the incremental surplus captured by the producer. Both are shown in Figure 15.

FIGURE 15: NMB and incremental producer surplus, Sweden

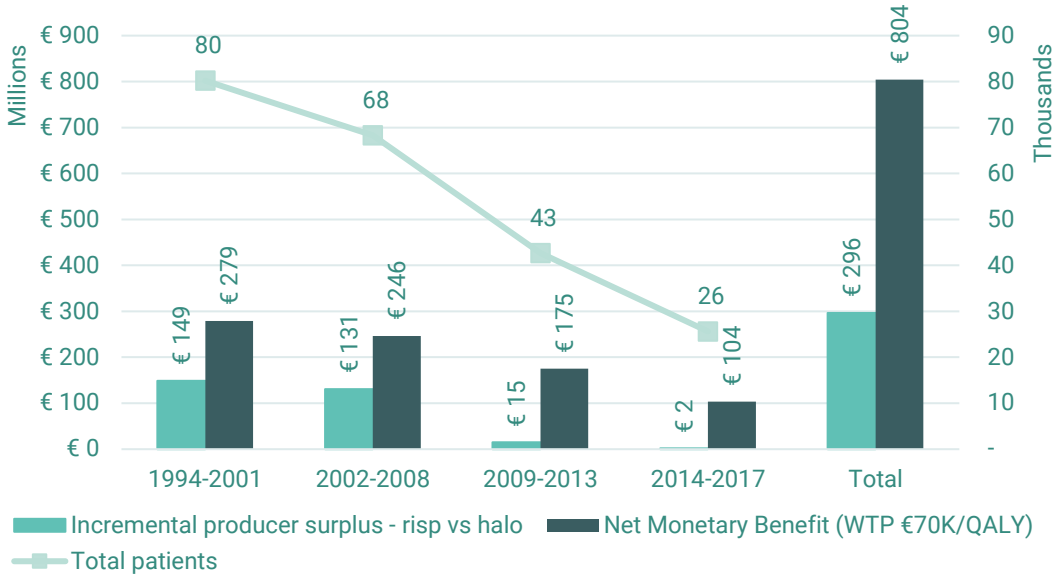


In Sweden, the NMB has always been greater than the additional surplus accrued by the innovator. Once more, this is due to the higher cost-effectiveness threshold in Sweden, which is assumed to be the consumer's willingness to pay per unit of health gain.

Figure 15 also shows that the launch of RLAI generated additional value that both, health system and producer, benefited from. The orange and blue lines grew slightly but steadily in the years just after its launch in 2004. Then, the entry of generics in 2009 significantly redistributed the incremental value added in favour of the health system.

The incremental producer surplus and NMB are shown by time periods and in totals in the bar chart in Figure 16.

FIGURE 16: NMB and incremental producer surplus, Sweden



The health system and society (the consumer) appropriated 2.6 times the incremental surplus of the producer when considering the entire life-cycle of risperidone in Sweden as compared to haloperidol. Looking period by period, Figure 16 clearly shows that the producer lost a great share of the incremental surplus generated when the first generic versions of risperidone entered the market in 2009. The accrued incremental surplus for the period 2009-2013 was 88% lower than that in the period 2002-2008, while the number of patients only decreased by 38% - a per patient loss of incremental surplus. By contrast, the decrease in the NMB between the two same periods was 29% – an increase in the per patient NMB. The incremental producer surplus in the final period, 2014-2017, amounted to only around €2 million because the price of the generic risperidone was close to the price of haloperidol.

3.3. Additional findings

The other two indications for which risperidone was granted a marketing authorisation were bipolar disorder and dementia. Risperidone was launched for bipolar disorder in May 2004 in the UK and May 2003 in Sweden. For dementia, launch dates were April 1998 in Sweden and December 2008 in the UK.

Due to data availability, we have not been able to conduct an analysis of these approved indications for risperidone in as detailed a way as that for schizophrenia. However, for both countries, Sweden and the UK, we have been able to estimate the total number of patients treated with risperidone including bipolar, dementia and off-label prescription. In the UK, during risperidone's life-cycle an estimated 2 million patients other than those with schizophrenia were treated[14]. In Sweden, this figure was estimated at 739,000[15]. It is plausible to assume that patients treated for bipolar disorder and dementia comprised a large share of these additional patients.

[14] It is important to note that this estimate does not reflect treated patients accurately as share of the off-label use, as well as some use in dementia and bipolar indication, is for the temporary treatment of acute symptoms.
[15] For Sweden number of prescriptions were obtained and therefore data are more reliable, although the same problem of acute temporary use also may apply.

Literature on the cost-effectiveness of risperidone for bipolar disorder and dementia is scarce and we were not able to find enough consistent evidence. For bipolar disorder, the only reliable study is by Klok et al., (2007), which estimated the healthcare cost of risperidone to be €12,974, and for olanzapine (SGA) and quetiapine (SGA), €13,326 and €14,017, respectively[16]. The lower cost of risperidone shows, assuming similar QALY gains between treatments, that additional value was likely to have been added by the use of risperidone in treating bipolar patients[17].

For dementia, Rosenheck et al., (2007) estimated an annual healthcare cost of €23,507 per patient treated with risperidone and €27,504 with olanzapine. QALY gains in the same study were estimated at 0.16 and 0.12 respectively for risperidone and olanzapine. Again, assuming that a significant percentage of the additional patients were treated with risperidone for dementia, additional value would have been created with the use of risperidone in this new indication.

[16] In 2017 euros and inflated to UK inflation rates. Other numbers would result for Sweden as country specific inflation rates should be applied.
[17] The reader must note that the study compares risperidone with other SGAs rather than with haloperidol or another FGA.

4. Discussion

In this paper we assessed the value added by medicines over their life-cycle. The aim was to find out whether the short-run cost per QALY estimates at launch are a valid guide to long-term access decisions.

To assess the life-cycle value added by innovative medicines, we firstly estimated the distribution of the absolute consumer (i.e., health system's and tax payers') surplus and producer surplus, and secondly, we compared the performance of risperidone – the SGA class representative – with haloperidol – the FGA class representative – using a set of incremental economic and cost-effectiveness metrics. Analyses for the UK and Sweden were separately conducted and presented.

Currently, governments, national health authorities and/or health technology assessment bodies typically make market access decisions based on technology appraisals (TAs) or cost-effectiveness analyses (CEAs) focused on a medium/short-run time horizon[18] and only for the indication covered in the marketing authorisation licence. Thus, additional value added through on-patent competition (Berdud et al., 2018; Berndt and Dubois, 2016; Kanavos, Font and McGuire, 2007; Berndt, McGuire and Newhouse, 2011) and off-patent generic competition (Aitken et al., 2018; Lakdawalla et al., 2017; McKellar et al., 2012) is not usually considered when making market access and pricing decisions. The findings of the present study demonstrate that generic competition significantly increases the value accrued by health systems and patients (consumers) via lower prices and lower healthcare costs. In the UK, the incremental cost decreased from -€9.0 million to -€30.2 million (-237%) in the first year after patent expiration, while in Sweden, it decreased from -€5.3 million to -€9.2 million (-74%). For both countries, the incremental cost of risperidone compared to haloperidol was negative during the former drug's entire life-cycle. Most of these effects are direct rather than indirect. On average for the entire life-cycle, the share of savings due to incremental direct cost is 93% and 83% in the UK and Sweden respectively.

The ICER shows how much economic value is generated per each unit of health gain measured through QALYs. In the UK, the ICER decreased from an average of -€3,979 in 2001-2007 to an average of -€30,391 in 2008-2012[19]. This means that for each incremental QALY generated by risperidone after its patent expiration, the health system paid around €26,412 less. For Sweden, the figure of reduced cost per unit of health gain amounted to €11,909 in 2009-2013[20]. Between 2013 and 2017, the cost of producing a QALY was €26,259 lower and for Sweden, 2014-2017, it was €8,120 lower, compared to the last pre-generic period. This demonstrates that, in this case, the value added to society is higher looking at the entire life-cycle of a medicine, than that which would be estimated at launch in a conventional HTA. Currently, this additional value is entirely captured by health systems and society, because it is not considered in the market access and reimbursement decisions at launch. How to incorporate this long-run benefit into the decision making process as well as how to share it between the innovator and the health system are questions for debate and further research. It is also likely that not all new medicines will generate similar proportions of long-term verus short term value. Those displaced before the patent expiration by newer and therapeutically superior medicines will not produce such a large benefit. This makes estimation and incorportation in an HTA at launch a hard exercise, but given that the market share of generic drugs in volume terms was 62% in Europe in 2016 (Sheppard, 2017) it is a question worthy of exploration.

[18] Most economic models for technology appraisals consider time horizons within 1-5 years range.
[19] Risperidone patent expired in December 2007 in the UK. First generics entered the market in late November 2007. For more detailed information see Appendix 2.
[20] Risperidone patent expired in December 2007. First generics entered the market in January 2009. For more detailed information see Appendix 2

The launch of new formulations or indications for the same molecule that improve health outcomes of patients during a drug's life-cycle, also affects the value added to the society (i.e., to the health system, patients, citizens and innovators) of a new medicine in the long-run. The launch of RLAI contributed to the total value-added as well as to its distribution across stakeholders. The three main impacts of the RLAI were that: (i) compared against HLAI its incremental QALY gain was higher; (ii) its incremental cost was lower than the incremental cost of oral versions of risperidone versus oral haloperidol[21]; and (iii) compared to oral risperidone, its clinical outcomes were better, with significantly lower relapse and hospitalization rates of patients with schizophrenia. This means that for every patient treated with RLAI, the health system was able to capture higher value than it would have obtained with the oral formulation. The producer also benefited from the launch of RLAI; that is to say, the launch of RLAI created additional value per patient treated which was distributed between producer and consumer.

The average ICER shows a significant decrease in the period of analysis in which RLAI was launched in each country – 2001-2007 in the UK and 2002-2008 in Sweden. Thus, for instance, the ICER decreased from -€773 to -€3,979 in the UK and from –€4552 to -€9,658 in Sweden, reducing the amount of resources needed to increase health gains to patients with schizophrenia in both countries. In aggregate terms, the amount of cost reduced was proportional to the uptake at 12% of total schizophrenia patients treated with risperidone in Sweden and 15% in the UK. Looking at the incremental cost (Figures 5 and 13), both graphs show a decrease in the incremental cost in the same year as the RLAI launch – 2003 in the UK and 2004 in Sweden.

The approval of cost-effective new indications during the life-cycle of an innovative drug also has the potential to generate additional value to the health system, patients and the innovator. We have not been able to collect definitive evidence to measure and show the value added by risperidone through its use in patients with bipolar disorder and dementia. The scarce data we have found, however, indicate that more value was likely to have been created in these two additional indications. However, the quantitative results presented in the paper only show the value of risperidone (standing for SGAs as a class) in schizophrenia and therefore they are underestimates of the total value added during its entire life-cycle.

The methodology and analyses of the present study come with several caveats. Firstly, the data collected from the literature review on life-cycle cost-effectiveness were not fully comprehensive and show some gaps that we covered with assumptions:

- We had to select data from different studies for different time periods. Different studies use different methodologies and time horizons which has required some data homogenisation. Additionally, to avoid different methodologies affecting the results, we have focused analyses on incremental outcomes (e.g. incremental cost, incremental QALY).

- It has not been possible to obtain enough input data from studies performed specifically in Sweden and the UK entirely to populate country-specific models. To solve this problem, we used inputs from studies performed in other countries. We have considered data on QALY gains to be immediately transferable across countries.

- We have also considered generic prices in Germany to be applicable in the UK and Sweden, as country-specific information was not available, which means that we have underestimated the cost reductions, as German generic prices are typically higher than UK and Swedish generic prices (Wouters, Kanavos and McKee, 2017).

[21] *Incremental cost was negative for the entire life-cycle in both countries, UK and Sweden. In such a context, a lower incremental cost means that systems save more money per patient treated.*

- For healthcare costs, it is important to note that transferability is not straightforward, as health systems vary in their structure and their costs. To appropriately transfer inputs from third countries to the UK and Swedish models, we applied recognised transferability criteria as described in section 2.3 of this report.

Secondly, we have had to use assumptions whenever data were not available:

- Following Lindgren and Jönsson (2012), we assume that generic entry reduces the commercial margin over the price from 80% to 20%. This assumption is key in determining the producer surplus and social surplus distribution after generic entry. We performed a sensitivity analysis by using two alternative assumptions – 40% and 50%. Sensitivities show that assuming a larger net profit margin per unit sold after generic entry affects both producer surplus and social surplus distribution significantly, but it does not change either the direction of the results or the conclusions that can be drawn from them. The detailed results of the sensitivity analysis are provided in Appendix 4.

- The other assumption with a significant impact on the results is societal (consumers)willingness to pay. We assume that for Sweden this is €70k per QALY and for the UK it is £20k per QALY. We acknowledge that the large difference between Swedish and UK results is primarily driven by this difference. Essentially, we use threshold values used by the HTA agencies in the two countries as a proxy for consumers' willingness to pay and this could of course be questioned – certainly for the UK but also for Sweden. There is current debate in Sweden based on the fact that the Swedish Road Traffic Authority has increased its valuation of a statistical life saved from SEK 24 million (~£2m) to SEK 40.5 million (~£3.3m) which involves a cost per QALY estimate of SEK 2 million (~£164k)[22]. Analogously, research conducted by Donaldson et al., (2011) estimated the societal valuation of a QALY for the UK to be within the range of £18k to £40k. Although we acknowledge that the current study uses a different set of willingness to pay assumptions, the assumptions used are not so far from the actual social valuation of health benefits in Sweden and the UK (Vallejo-Torres et al., 2016; Ryen and Svensson, 2015).

Thirdly, to fill data gaps on uptake, oral versus RLAI uptake distribution and percentage of risperidone use for schizophrenia, we have also had to make assumptions. We acknowledge that these assumptions may have an impact on the results. However, as we are measuring changes in the absolute and incremental metrics over time, conclusions drawn from observed time trends are not (or minimally) affected by these assumptions. Additionally, to assess the life-cycle value of risperidone, we complemented aggregate cost-effectiveness metrics with per patient metrics based on the per patient inputs collected from the literature. These are shown in Appendix 3 and are not (or only minimally) affected by assumptions made to estimate patient numbers.

Finally, another limitation important to note is the limited scope of the study. This research is an attempt to demonstrate the life-cycle value of innovative medicines using risperidone as a case study. We use risperidone to represent SGAs compared with haloperidol, as representative of FGAs. Though risperidone is only one drug from a larger set of SGAs, analysis of the life-cycle value of risperidone gives sufficient insight to demonstrate the necessity, in principle, to incorporate the long-term view into market access and pricing policy decisions.

We recognise that further research is needed to understand how such considerations should be incorporated into formal decision-making processes for a wide range of innovative medicines. In an ideal world, the optimal cost-effectiveness evaluation of a drug would take into account its life-cycle value ex ante, and this would be factored into decisions on access and price. This raises two questions. Firstly, the question of the evidence needed to perform such assessment exercises. As

[22] *See http://lakartidningen.se/Opinion/Debatt/2018/08/Ett-QALY-ar-vart-mer-an-tva-miljoner-kronor/*

the future cannot be perfectly predicted, the generation of such predictions would presumably depend on payers having access to information of the typical price trajectory over time of similar drugs in the recent past, judging that these data are sufficiently reliable to be used. Alternatively, drugs could be subject to periodic reapraisals including pipeline analysis to anticipate any breakthrough innovation coming. Secondly, agreement would be needed as to the appropriate division of life cycle value between innovators and the health system. Contracts taking the dynamics of value into account would be required at launch. How to design and implement the appropriate mechanism is however a question for further research.

5. Conclusion

Our analysis of the life-cycle value of risperidone versus haloperidol shows that, in this case, health systems and societies in general (consumers) were able to appropriate most of the life-cycle value (surplus) generated. The value added by the SGA significantly increased with the launch of RLAI and even more with the entry of generic competition, as the evolution of the absolute surplus distribution, as well as the incremental NMB and the life cycle ICER show. This suggests that the life-cycle value added by SGAs to the system was higher than the value that would have been estimated using cost-effectiveness analysis at launch. The latter does not consider generic entry, and the launch of new and more effective presentations and indications.

Consequently, we suggest that pricing and reimbursement decisions should consider how to recognise the dynamic nature of pharmaceutical markets and the full life cycle of value added by innovative medicines. This presents a challenge of estimation, but also of assessing the appropriate share of social value that should go to the producer and to the health system.

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Appendix 1.

TABLE A.1.1: INPUTS FOR ORAL RISPERIDONE FOR UK

INPUT	1994-2000	2001-2007	2008-2012	2013-2017	COMBINED	
					BRAND	GENERIC
Medicine cost risperidone	€4,293 (1)	€3,152 (5)	€584 (6)	€584 (6)	€3,654	€584
Medicine cost comparator	€739 (1)	€739 (1)	€643 (6)	€643 (6)	€739*	€643
Direct cost risperidone	€13,763 (2)	€13,763 (2)	€4,656 (6)	€4,656 (6)	€13,763	€4,656
Direct cost comparator	€13,785 (2)	€13,785 (2)	€5,546 (6)	€5,546 (6)	€13,785	€5,546
Indirect cost risperidone	€1,299 (3)	€1,299 (3)	€1,299 (3)	€1,299 (3)	€1,299	€1,299
Indirect cost comparator	€1,405 (3)	€1,405 (3)	€1,405 (3)	€1,405 (3)	€1,405	€1,405
QALY gain risperidone	0.63 (4)	0.426 (3)	0.426 (3)	0.426 (3)	0.48	*NA*
QALY gain comparator	0.52 (4)	0.422 (3)	0.422 (3)	0.422 (3)	0.45	*NA*

References: (1) Guest et al. (1996); (2) Almond and O'donnell (1998); (3) Lindström et al. (2011); (4) Foster and Goa (1999); (5) Nicholls, Hale and Freemantle (2003); (6) Zeidler et al. (2013)
Abbreviations and notes: *generic price of haloperidol selected for risperidone patent term period; Not Applicable, NA.

There is a noticeable difference between the direct cost of boith, risperidone and comparator, estimated by study (2) used for pre-generic competition period and study (6) used for post-generic competition period. This difference is due to several factors including, the difference in risperidone price (brand vs generic), the sterling pound to euro exchange rate applied to (2), different inputs and methods used for the estimation in the two studies and inflation rates used to calculate 2017 monetary values (sterling pound 1999 values used in (2) and euro 2011 values in (6)). However, this variation does not affect results as the direct cost input is relevant only for the estimation of incremental metrics and we consistently use the same study for risperidone and comparator within each subperiod.

For the case of oral formulations, to combine all selected inputs into a single one, we first separated the life-cycle into two clear periods: before and after patent expiration. Put in other words, the brand on-patent period and the generic off-patent period. We then calculate the combined input as the average weighted by the number of patients treated and whenever applies, separately for brand and generic periods. We do not distinguish between on-patent and off-patent period neither to combine QALYs gain nor when the same input is used all over the life-cycle. Inputs therefore, have been combined using the following general equation:

$$y_i = \sum_{t=1}^{4} \left(\frac{q_t}{\sum_{t=1}^{4} q_t} \right) x_i^t \qquad (1)$$

Where y_i is the combined measure of input *i* (e.g., medicine cost, direct cost, indirect cost, QALY gain), q_t is the number of patients treated in each period $\mathrm{t} = 1,2,3,4$ of the study (e.g., 1994-2000, 2001-2007, 2008-2012, 2013-2017), and x_i^t is the value taken for the input *i*, in period *t*.
To combine inputs specifically for on- and off-patent period we use constrained versions of equation one:

$$y_i^P = \sum_{t^P=1}^{2} \left(\frac{q_{t^P}}{\sum_{t=1}^{4} q_{t^P}} \right) x_i^{t^P} \qquad (2)$$

$$y_i^G = \sum_{t^G=3}^{4} \left(\frac{q_{t^G}}{\sum_{t=1}^{4} q_{t^G}} \right) x_i^{t^G} \qquad (3)$$

Where $t^P = 1,2$ refer to on-patent periods or the first two periods of the study (e.g., 1994-2000, 2001-2007), $t^G = 3,4$ refer to generic periods or the last two periods of the study (e.g., 2008-2012, 2013-2017).

Below we show how medicine cost of risperidone has been combined to provide an example to the reader. But previously, table A.1.2 shows number of patients receiving oral risperidone per period of study, during patent term, after patent expiration and in total.

TABLE A.1.2: NUMBER OF PATIENTS TREATED WITH ORAL RISPERIDONE

	1994-2000	2001-2007	2008-2012	2013-2017	ON-PATENT	OFF-PATENT	TOTAL
Patients treated	149,086	190,044	132,324	135,754	339,130	268,078	607,208
Weights on-patent	44%	56%	NA	NA	100%	NA	NA
Weights off-patent	NA	NA	49%	51%	NA	100%	NA
Weights total	25%	31%	22%	22%	NA	NA	100%

Substituting patient-based weights and inputs for the medicine cost into equations (2) and (3), we have:

$$y_i^P = 0.44 \cdot 4{,}293 + 0.56 \cdot 3{,}152 = 3{,}654$$
$$y_i^G = 0.49 \cdot 584 + 0.51 \cdot 584 = 584$$

Inputs for the long-acting risperidone have been combined following the same methodology, although in this case it is not necessary to separate the on- and off-patent periods because the patent has not expired then.

TABLE A.1.3: INPUTS FOR LONG-ACTING RISPERIDONE FOR UK

INPUT	1994-2000	2001-2007	2008-2012	2013-2017	COMBINED
Medicine cost risperidone	*NA*	€2,980(7)	€2,980 (7)	€3,539 (8)	€3,077
Medicine cost comparator	*NA*	€1,077 (7)	€1,077 (7)	€552 (8)	€986
Direct cost risperidone	*NA*	€23,020 (7)	€23,020 (7)	€23,164 (8)	€23,045
Direct cost comparator	*NA*	€23,507 (7)	€23,507 (7)	€25,279 (8)	€23,814
Indirect cost risperidone	*NA*	€692 (8)	€692 (8)	€692 (8)	€692
Indirect cost comparator	*NA*	€999 (8)	€999 (8)	€999 (8)	€999
QALY gain risperidone	*NA*	0.374 (7)	0.374 (7)	0.804 (8)	0.65
QALY gain comparator	*NA*	0.356 (7)	0.352 (7)	0.776 (8)	0.62

References: Laux et al. (2005) (7); Einarson et al. (2014) (8)
Abbreviations: Not Applicable, NA.

TABLE A.1.4: INPUTS FOR ORAL RISPERIDONE FOR SWEDEN

INPUT	1994-2001	2002-2009	2010-2013	2014-2017	COMBINED	
					BRAND	GENERIC
Medicine cost risperidone	€3,201 (1)	€1,456 (4)	€528 (5)	€528 (5)	€2,405	€5528
Medicine cost comparator	€546 (1)	€524 (2)	€580 (5)	€580 (5)	€536	€580
Direct cost risperidone	€29,241 (2)	€24,941 (2)	€3,953 (5)	€3,953 (5)	€24,941	€3,953
Direct cost comparator	€25,149 (2)	€25,149 (2)	€4,711 (5)	€4,711 (5)	€25,149	€4,711
Indirect cost risperidone	€1,021 (2)	€1,021 (2)	€1,021 (2)	€1,021 (2)	€1,021	1,021
Indirect cost comparator	€1,105 (2)	€1,105 (2)	€1,105 (2)	€1,105 (2)	€1,105	1,104
QALY gain risperidone	0.63 (3)	0.426 (2)	0.426 (2)	0.426 (2)	0.48	*NA*
QALY gain comparator	0.52 (3)	0.422 (2)	0.422 (2)	0.422 (2)	0.45	*NA*

References:(1) Guest et al. (1996); (2) Lindström et al., (2011); (3) Foster and Goa (1999); (4) Lindström et al., (2007); (5) Zeidler et al. (2013)
Abbreviations and notes: *generic price of haloperidol selected for risperidone patent term period; Not Applicable, NA.

Again, it is importantto notice estimates of direct healthcare cost for the pre-gerenic periods collected from study (2) and post-generic periods collected from study (5), are subject to a variation that cannot be fully explained only by the generic price reduction. Reasons behind such variation are the same as those explained for the UK: price differene between branded and generic versions of risperidone, the SEK to euro exchange rate and differences between country specific inflation rates used to estimate the present value of inputs.

Inputs have been combined as per the methodology described for the case of the UK. Table A.1.5. shows the weights for oral risperidone for Sweden.

TABLE A.1.5: NUMBER OF PATIENTS TREATED WITH ORAL RISPERIDONE

	1994-2001	2002-2009	2010-2013	2014-2017	ON-PATENT	OFF-PATENT	TOTAL
Patients treated	80,196	59,664	36,022	24,694	139,860	60,717	200,577
Weights on-patent	57%	43%	NA	NA	100%	NA	NA
Weights off-patent	NA	NA	59%	41%	NA	100%	NA
Weights total	40%	30%	18%	12%	NA	NA	100%

Combined inputs for the long-acting risperidone is shown in table A.1.6. below.

TABLE A.1.3: INPUTS FOR LONG-ACTING RISPERIDONE FOR SWEDEN

INPUT	1994-2001	2002-2009	2010-2013	2014-2017	COMBINED
Medicine cost risperidone	*NA*	€2,630 (6)	€3,536 (7)	€3,536 (7)	€3,077
Medicine cost comparator	*NA*	€906 (6)	€551 (7)	€551 (7)	€986
Direct cost risperidone	*NA*	€32,170 (6)	€23,143 (7)	€23,143 (7)	€23,045
Direct cost comparator	*NA*	€33,958 (6)	€25,257 (7)	€25,257 (7)	€23,814
Indirect cost risperidone	*NA*	€692 (7)	€692 (7)	€692 (7)	€692
Indirect cost comparator	*NA*	€999 (7)	€999 (7)	€999 (7)	€999
QALY gain risperidone	*NA*	0.773 (6)	0.804 (7)	0.804 (7)	0.65
QALY gain comparator	*NA*	0.738 (6)	0.776 (7)	0.776 (7)	0.62

References: Laux et al. (2005) (7); Einarson et al. (2014) (8)
Abbreviations: Not Applicable, NA.

Appendix 2

TABLE A.2.1: UNITED KINGDOM – ORIGINAL RISPERDAL MARKETING AUTHORISATION, AUTHORISATION EXTENSIONS OF INDICATIONS, NEW FORMULATIONS, GENERIC COMPETITORS' ENTRY AND PATENT EXPIRY DATES

		Years																											
		89	90	91	92	93	94	95	96	97	98	99	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17
Risperdal FCTs 0.5mg	Schizo-phrenia												6A 8L						3PE	12SPC 11GE										
	Schi. Main.												12A 12L						3PE	12SPC 11GE										
	Bipolar																5A 5L		3PE	12SPC 11GE										
	Dementia																		3PE	12SPC 11GE	12A 12L									
Risperdal FCTs 1mg	Schizo-phrenia				12A	6L													3PE	12SPC 11GE										
	Schi. Main.												12A 12L						3PE	12SPC 11GE										
	Bipolar																5A 5L		3PE	12SPC 11GE										
	Dementia																		3PE	12SPC 11GE	12A 12L									
Risperdal FCTs 2mg	Schizo-phrenia				12A	6L													3PE	12SPC 11GE										
	Schi. Main.												12A 12L						3PE	12SPC 11GE										
	Bipolar																5A 5L		3PE	12SPC 11GE										
	Dementia																		3PE	12SPC 11GE	12A 12L									
Risperdal FCTs 3mg	Schizo-phrenia				12A	6L													3PE	12SPC 11GE										
	Schi. Main.												12A 12L						3PE	12SPC 11GE										
	Bipolar																5A 5L		3PE	12SPC 11GE										
	Dementia																		3PE	12SPC 11GE	12A 12L									

Abbreviations: Film Coated Tablets, FCT; Authorisation, A; Launch, L; Patent Expiration, PE; Supplementary Patent Certificate, SPC; Generic Entry, GE; Schi. Main., maintenance of clinical improvement during continuation therapy in stabilised patients.

Notes: numbers within cells reflect the month of the corresponding year in the column in which the formulation was approved, launched, etc.

Sources: Janssen-Cilag Ltd. and IQVIA.

		89	90	91	92	93	94	95	96	97	98	99	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17
Risperdal FCTs 4mg	Schizo-phrenia				12A	6L													3PE	12SPC 11GE									
	Schi. Main.												12A 12L						3PE	12SPC 11GE									
	Bipolar																5A L		3PE	12SPC 11GE									
	Demen-tia																		3PE	12SPC 11GE	12A 12L								
Risperdal FCTs 6mg	Schizo-phrenia									7A 10L									3PE	12SPC 11GE									
	Schi. Main.												12A 12L						3PE	12SPC 11GE									
	Bipolar																5A L		3PE	12SPC 11GE									
	Demen-tia																		3PE	12SPC 11GE	12A 12L								
Risperdal OS 1mg/ml	Schizo-phrenia							11A	3L										3PE	12SPC 12 GE									
	Schi. Main.												12A 12L						3PE	12SPC 12GE									
	Bipolar																5A L		3PE	12SPC 12GE									
	Demen-tia																		3PE	12SPC 12GE	12A 12L								
Risperdal OT 0.5mg	Schizo-phrenia															1A		1L	3PE	12SPC 11GE									
	Schi. Main.															1A		1L	3PE	12SPC 11GE									
	Bipolar																5A	1L	3PE	12SPC 11GE									
	Demen-tia																		3PE	12SPC 11GE	12A 12L								
Risperdal OT 1mg	Schizo-phrenia															1A 1L			3PE	12SPC 11GE									
	Schi. Main.															1A 1L			3PE	12SPC 11GE									
	Bipolar																5A5L		3PE	12SPC 11GE									
	Demen-tia																		3PE	12SPC 11GE	12A 12L								

Abbreviations: Film Coated Tablets, FCT; Authorisation, A; Launch, L; Patent Expiration, PE; Supplementary Patent Certificate, SPC; Generic Entry, GE; Schi. Main., maintenance of clinical improvement during continuation therapy in stabilised patients.
Notes: numbers within cells reflect the month of the corresponding year in the column in which the formulation was approved, launched, etc.
Sources: Janssen-Cilag Ltd. and IQVIA

		89	90	91	92	93	94	95	96	97	98	99	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17
Risperdal OT 2mg	Schizo-phrenia															1A 1L			3PE	12SPC 11GE										
	Schi. Main.															1A 1L			3PE	12SPC 11GE										
	Bipolar																5A5L		3PE	12SPC 11GE										
	Demen-tia																		3PE	12SPC 11GE	12A 12L									
Risperdal OT 3mg	Schizo-phrenia																		12A 3PE	1L 12SPC 11GE										
	Schi. Main.																		12A 3PE	1L 12SPC 11GE										
	Bipolar																		12A 3PE	1L 12SPC 11GE										
	Demen-tia																		3PE	1L 12SPC 11GE	12A 12L									
Risperdal ODT 4mg	Schizo-phrenia																		12A 3PE	1L 12SPC 11GE										
	Schi. Main.																		12A 3PE	1L 12SPC 11GE										
	Bipolar																		12A 3PE	1L 12SPC 11GE										
	Demen-tia																		3PE	1L 12SPC 11GE	12A 12L									

Abbreviations: Film Coated Tablets, FCT; Authorisation, A; Launch, L; Patent Expiration, PE; Supplementary Patent Certificate, SPC; Generic Entry, GE; Schi. Main., maintenance of clinical improvement during continuation therapy in stabilised patients.
Notes: numbers within cells reflect the month of the corresponding year in the column in which the formulation was approved, launched, etc.
Sources: Janssen-Cilag Ltd. and IQVIA

		89	90	91	92	93	94	95	96	97	98	99	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17
Risperdal CONSTA 25mg	Schizophrenia														8A 8L															
	Schi. Main.														8A 8L															
Risperdal CONSTA 37.5mg	Schizophrenia														8A 8L															
	Schi. Main.														8A 8L															
Risperdal CONSTA 50mg	Schizophrenia														8A 8L															
	Schi. Main.														8A 8L															

Abbreviations: Film Coated Tablets, FCT; Authorisation, A; Launch, L; Patent Expiration, PE; Supplementary Patent Certificate, SPC; Generic Entry, GE; Schi. Main., maintenance of clinical improvement during continuation therapy in stabilised patients.
Notes: numbers within cells reflect the month of the corresponding year in the column in which the formulation was approved, launched, etc.
Sources: Janssen-Cilag Ltd. and IQVIA

TABLE A.2.2: SWEDEN – ORIGINAL RISPERDAL MARKETING AUTHORISATION, AUTHORISATION EXTENSIONS OF INDICATIONS, NEW FORMULATIONS, GENERIC COMPETITORS' ENTRY AND PATENT EXPIRY DATES

		Years																											
		89	90	91	92	93	94	95	96	97	98	99	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17
Risperdal FCTs 0.5mg	Schizo-phrenia										5A		4L						3PE	12SPC		1GE								
	Schi. Main.										5A		4L						3PE	12SPC		1GE								
	Bipolar															4A5L			3PE	12SPC		1GE								
	Dementia										12A		4L						3PE	12SPC		1GE								
Risperdal FCTs 1mg	Schizo-phrenia					12A	2L												3PE	12SPC		1GE								
	Schi. Main.					12A	2L												3PE	12SPC		1GE								
	Bipolar															4A5L			3PE	12SPC		1GE								
	Dementia										12A 12L								3PE	12SPC		1GE								
Risperdal FCTs 2mg	Schizo-phrenia					12A	2L												3PE	12SPC		1GE								
	Schi. Main.					12A	2L												3PE	12SPC		1GE								
	Bipolar															4A5L			3PE	12SPC		1GE								
	Dementia										12A 12L								3PE	12SPC		1GE								
Risperdal FCTs 3mg	Schizo-phrenia					12A	2L												3PE	12SPC		1GE								
	Schi. Main.					12A	2L												3PE	12SPC		1GE								
	Bipolar															4A5L			3PE	12SPC		1GE								
	Dementia										12A 12L								3PE	12SPC		1GE								

Abbreviations: Film Coated Tablets, FCT; Authorisation, A; Launch, L; Patent Expiration, PE; Supplementary Patent Certificate, SPC; Generic Entry, GE; Schi. Main., maintenance of clinical improvement during continuation therapy in stabilised patients.
Notes: numbers within cells reflect the month of the corresponding year in the column in which the formulation was approved, launched, etc.
Sources: Janssen-Cilag Ltd., IQVIA and Godman et al. 2014.

		89	90	91	92	93	94	95	96	97	98	99	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17
Risperdal FCTs 4mg	Schizo-phrenia					12A	2L												3PE	12SPC		1GE								
	Schi. Main.					12A	2L												3PE	12SPC		1GE								
	Bipolar															4A5L			3PE	12SPC		1GE								
	Demen-tia										12A 12L								3PE	12SPC		1GE								
Risperdal FCTs 6mg	Schizo-phrenia																													
	Schi. Main.																													
	Bipolar																													
	Demen-tia																													
Risperdal OS 1mg/ml	Schizo-phrenia							5A	4L										3PE	12SPC		1GE								
	Schi. Main.							5A	4L										3PE	12SPC		1GE								
	Bipolar															4A5L			3PE	12SPC		1GE								
	Demen-tia										12A 12L								3PE	12SPC		1GE								
Risperdal OT 0.5mg	Schizo-phrenia																													
	Schi. Main.																													
	Bipolar																													
	Demen-tia																													
Risperdal OT 1mg	Schizo-phrenia															7A 12L			3PE	12SPC		1GE								
	Schi. Main.															7A 12L			3PE	12SPC		1GE								
	Bipolar															7A 12L			3PE	12SPC		1GE								
	Demen-tia															7A 12L			3PE	12SPC		1GE								

Abbreviations: Film Coated Tablets, FCT; Authorisation, A; Launch, L; Patent Expiration, PE; Supplementary Patent Certificate, SPC; Generic Entry, GE; Schi. Main., maintenance of clinical improvement during continuation therapy in stabilised patients.
Notes: numbers within cells reflect the month of the corresponding year in the column in which the formulation was approved, launched, etc.
Sources: Janssen-Cilag Ltd., IQVIA and Godman et al. 2014.

		89	90	91	92	93	94	95	96	97	98	99	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17
Risperdal OT 2mg	Schizo-phrenia															7A 12L			3PE	12SPC		1GE								
	Schi. Main.															7A 12L			3PE	12SPC		1GE								
	Bipolar															7A 12L			3PE	12SPC		1GE								
	Demen-tia															7A 12L			3PE	12SPC		1GE								
Risperdal OT 3mg	Schizo-phrenia																		10A 3PE	12SPC		1GE								
	Schi. Main.																		3PE	12SPC		1GE								
	Bipolar																		3PE	12SPC		1GE								
	Demen-tia																		3PE	12SPC		1GE								
Risperdal OT 4mg	Schizo-phrenia																		10A 3PE	12SPC		1GE								
	Schi. Main.																		3PE	12SPC		1GE								
	Bipolar																		3PE	12SPC		1GE								
	Demen-tia																		3PE	12SPC		1GE								

Abbreviations: Film Coated Tablets, FCT; Authorisation, A; Launch, L; Patent Expiration, PE; Supplementary Patent Certificate, SPC; Generic Entry, GE; Schi. Main., maintenance of clinical improvement during continuation therapy in stabilised patients.
Notes: numbers within cells reflect the month of the corresponding year in the column in which the formulation was approved, launched, etc.
Sources: Janssen-Cilag Ltd., IQVIA and Godman et al. 2014.

		89	90	91	92	93	94	95	96	97	98	99	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17
Risperdal CONSTA 25mg	Schizophrenia																3A 4L													
	Schi. Main.																3A 4L													
Risperdal CONSTA 37.5mg	Schizophrenia																3A 4L													
	Schi. Main.																3A 4L													
Risperdal CONSTA 50mg	Schizophrenia																3A 4L													
	Schi. Main.																3A 4L													

Abbreviations: Film Coated Tablets, FCT; Authorisation, A; Launch, L; Patent Expiration, PE; Supplementary Patent Certificate, SPC; Generic Entry, GE; Schi. Main., maintenance of clinical improvement during continuation therapy in stabilised patients.
Notes: numbers within cells reflect the month of the corresponding year in the column in which the formulation was approved, launched, etc.
Sources: Janssen-Cilag Ltd., IQVIA and Godman et al. 2014.

Appendix 3

Table A.3.1 shows the key metrics used for the analysis for UK. Columns of the table show estimations of metrics by periods and in total. Off-patent period (2008-2017) is four years shorter than the on-patent period (1994-2007). This effect is removed by comparing the per patient figures. Table A.3.2 reproduces the same information as Table A.3.1 for Sweden.

TABLE A.3.1: THE LIFE-CYCLE VALUE OF RISPERIDONE: KEY METRICS

INPUT	1994-2001	2002-2009	2010-2013	2014-2017	TOTAL/AVERAGE
ICER[1]	-€773	-€3,979	-€30,391	-€30,238	*Not applicable*
Net Monetary Benefit	€119.8m	€198.1m	€281.8m	€249.0m	€848.7m
Net Monetary Benefit per patient	€804	€1,043	€2,130	€1,834	€1,398[2]
Incremental producer surplus	€413.7m	€590.4m	€82.7m	€29.2m	€1,116.1m
Incremental producer surplus per patient	€2,775	€3,107	€625	€215	1,838[2]
Consumer surplus	€1075.2m	€1,587.4m	€1,650.3m	€1,501.7m	€5,814.6m
Producer surplus	€435.8m	€624.0m	€107.0m	€49.3m	€1,216.2m
Total surplus	€1,510.0m	€2,211.4m	€1,757.3m	€1,551.0m	€7,030.8m
Producer surplus as % of total	29%	28%	6%	3%	17%[2]
Consumer surplus per patient	€7,212	€8,353	€12,472	€11,062	€9,576[2]
Producer surplus per patient	€2,923	€3,284	€809	€363	€2,003[2]

[1]Measured in euros pre QALY; [2]Averages reported for per patient metrics

TABLE A.3.2: THE LIFE-CYCLE VALUE OF RISPERIDONE: KEY METRICS

INPUT	1994-2001	2002-2009	2010-2013	2014-2017	TOTAL/AVERAGE
ICER[1]	-€4,552	-€9,658	-€21,567	-€17,778	*Not applicable*
Net Monetary Benefit	€279.1m	€246.1m	€174.9m	€103.7m	€803.9m
Net Monetary Benefit per patient	€3,481	€3,605	€4,099	€4,047	€3709[2]
Incremental producer surplus	€149.0m	€130.6m	€14.9m	€1.9m	€296.4m
Incremental producer surplus per patient	€1,858	€1,913	€349	€74	€1,367[2]
Consumer surplus	€2,652.3m	€2,421.7.4m	€1,607.0m	€913.2m	€7,594.2m
Producer surplus	€157.6m	€138.3m	€20.0m	€4.9m	€320.8m
Total surplus	€2,809.9m	€2,560.0m	€1,627.0m	€918.0m	€7,915.0m
Producer surplus as % of total	6%	5%	1%	1%	4%[2]
Consumer surplus per patient	€33,073	€35,470	€37,661	€35,626	€35,033[2]
Producer surplus per patient	€1,965	€2,025	€470	€191	€1,480[2]

[1]Measured in euros pre QALY; [2]Averages reported for per patient metrics

Appendix 4

We present two sensitivity analyses to show the impact of assumptions on results. We firstly present sensitivities showing how results change in response different impact levels of the generic entry on the commercial margin over the price. We alternatively assume two additional margins (50%, 40%) to the original assumption 20%. Table A.4.1 shows the impact that such alternative assumptions have on the relevant results for the UK (Table A.4.2 present sensitivities for Sweden).

TABLE A.4.1: SENSITIVITY ANALYSIS RESULTS ON GENERIC COMMERCIAL MARGIN ASSUMPTION FOR THE UK

	1994-2000			2001-2007			2008-2012			2013-2017			Total/Average		
Assumption	**20%**	**40%**	**50%**	**20%**	**40%**	**50%**	**20%**	**40%**	**50%**	**20%**	**40%**	**50%**	**20%**	**40%**	**50%**
Incremental producer surplus	€413.7m	€391.7m	€380.7m	€590.4m	€562.4m	€548.3m	€82.7m	€81.1m	€80.3m	€29.2m	€27.6m	€26.8m	€1,116.1m	€1,062m	€1,036.2m
Incremental producer surplus per patient	€2,775	€2,627	€2,554	€3,107	€2,959	€2,885	€625	€613	€607	€215	€203	€197	€1,838[1]	€1,750[1]	€1,707[1]
Producer surplus	€435.8m	*NA*	*NA*	€624.0m	*NA*	*NA*	€107.0m	€122.5m	€130.2m	€49.3m	€65.2m	€73.1m	€1,216.2m	€1247.5m	€1,263.1m
Producer surplus as % of total	29%	*NA*	*NA*	28%	*NA*	*NA*	6%	7%	7%	3%	4%	5%	17%[1]	18%[1]	18%[1]
Producer surplus per patient	€2,923	*NA*	*NA*	€3,284	*NA*	*NA*	€809	€926	€984	€363	€480	€539	€2,003[1]	€2,054[1]	€2,080[1]

[1]Averages reported for per patient metrics

As Table A.4.1 shows, assuming lower impacts of generic competition on net profit per unit sold (50%, 40%) do not affect the general conclusion that may be drawn from results as the life-cycle trend on the percentage of total surplus that the producer appropriates remains the same. Some variation is observed though as the producer surplus increases after generic entry when compared to the original assumption. The impact on the incremental metrics is negligible. The same pattern remains when looking at the Sweden results as Table A.4.2 shows.

TABLE A.4.1: SENSITIVITY ANALYSIS RESULTS ON GENERIC COMMERCIAL MARGIN ASSUMPTION FOR THE UK

	1994-2001			2002-2009			2010-2013			2014-2017			Total/Average		
Assumption	**20%**	**40%**	**50%**	**20%**	**40%**	**50%**	**20%**	**40%**	**50%**	**20%**	**40%**	**50%**	**20%**	**40%**	**50%**
Incremental producer surplus	€148.9m	€140.4m	€136.1m	€130.6m	€122.9m	€119.1m	€14.8m	€13.5m	€12.8m	€1.9m	€1.5m	€1.3m	€296.4m	€278.3m	€269.3m
Incremental producer surplus per patient	€1,858	€1,751	€1,697	€1,913	€1,801	€1,744	€349	€317	€301	€74	€58	€50	€1,367[1]	€1,284[1]	€1,242[1]
Producer surplus	€157.6m	*NA*	*NA*	€138.3m	*NA*	*NA*	€20.0m	€23.8m	€25.7m	€4.9m	€7.5m	€8.8m	€327.2m	€320.8m	€330.4m
Producer surplus as % of total	6%	*NA*	*NA*	5%	*NA*	*NA*	1%	1%	2%	1%	1%	1%	4%[1]	4%[1]	4%[1]
Producer surplus per patient	€1,965	*NA*	*NA*	€2,025	*NA*	*NA*	€470	€559	€603	€191	€293	€344	€1,480[1]	€1,510[1]	€1,524[1]

[1]Averages reported for per patient metrics

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JULY 2019

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