PROPOSAL FOR THE INCLUSION OF RISPERIDONE FOR THE TREATMENT OF PSYCHOTIC DISORDERS IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES

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1. Summary statement of the proposal for inclusion of risperidone:

Section 24.1 (medicines used in psychotic disorders) of the 17th WHO Model List of Essential Medicines includes the following medications: chlorpromazine, fluphenazine, and haloperidol. There have been no new additions to this section of the Model List since its inception in 1977. The three antipsychotics listed above while effective are not well tolerated by many patients owing to potentially serious side effects. Second generation (atypical) antipsychotics have been widely used in developed nations for the past twenty years. Risperidone, an atypical antipsychotic, boasts comparable efficacy as typical antipsychotics and improved tolerability in at least some areas. Risperidone has been off-patent since 2003 and is now produced by numerous manufacturers, of which 17 have been FDA-approved. Importantly, buyer prices of risperidone have decreased significantly since 2008, and we present international as well as country-specific pricing data to demonstrate this. When balancing clinical efficacy with side effects and cost, we believe that risperidone is overall the best choice amongst the atypical antipsychotics currently available on the generic market.

We would like to note that submissions have been made and rejected twice previously for risperidone. An application was first made in 1998 at a time when risperidone had only been on the market for four years and was still on-patent, making its cost exceedingly prohibitive. A second application was made in 2009 several years after generic production of risperidone had commenced. Two expert reviewers at the time stated that an atypical antipsychotic should be on the Model List, though the 2009 application was rejected for incompleteness of literature review and pricing data. Considering this, we endeavor to present a robust application for the addition of risperidone to the Model List with data on clinical efficacy, comparative side effects, cost, and cost-effectiveness.
2. Name of the focal point in WHO submitting or supporting the application: N/A

3. Name of the organizations consulted and/or supporting the application:
   Massachusetts General Hospital Department of Psychiatry
   Young Professionals Chronic Disease Network
   Universities Allied for Essential Medicines
   BasicNeeds

4. International Nonproprietary Name (generic name) of the medicine: Risperidone

5. Formulation proposed for inclusion: (for Adult Model List only)

   Risperidone: Oral tablets containing 0.25 mg, 0.5 mg, 1 mg, 2mg, 3 mg, 4 mg, and 6 mg

6. International availability including manufacturers and trade names:

   Risperidone gained US FDA-approval as a “new molecular entity” under the trade name Risperdal produced by Janssen-Cilag on December 29, 1993 (FDA application number NDA 020272). Risperidone went off-patent on the same date ten years later (December 29, 2003), though Janssen-Cilag retained exclusive marketing rights for the drug until June 29, 2004. Teva Pharmaceuticals was the first company to gain FDA approval for a generic form of Risperidone in June 2008, and some sixteen companies would follow suit over the next three years. See Appendix A for a list of companies who currently have US FDA approval for a generic form of Risperidone (oral tablet formulation).

   Apart from those companies whose products have been FDA approved, numerous other companies are producing generic risperidone. On the MedIndia website for example, 50 “branded” generic versions of risperidone are listed. See Appendix B for full list.

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group: Though risperidone would be the first atypical antipsychotic on the WHO Model List of Essential Medicines, we are requesting its inclusion as an individual medicine and not as an example of its class. As explained in more detail in section 11, risperidone has a more tolerable side effect and safety profile than other atypical antipsychotics currently available on the generic market.

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population):

   The spectrum of psychotic disorders includes schizophrenia, schizoaffective disorder, mania with psychosis, and major depression with psychosis. Here we will mostly focus

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2 “List of Brand Name(s) for Generic Drug Risperidone.” Drug “Risperidone” Price List, MedIndia website. http://www.medindia.net/drug-price/risperidone.htm#
on the public health relevance of schizophrenia, as significantly better epidemiological data exists for schizophrenia compared with that of other psychotic disorders.

Schizophrenia is a significant contributor to the global disease burden, accounting for 1.1% of disability-adjusted life years (DALY’s) lost\(^3\). Within the age group of 15-44 years, schizophrenia is the 8\(^{th}\) leading cause of DALY’s lost\(^4\). Furthermore, people suffering with schizophrenia have significantly lower life expectancies than the general population. One study in the UK for example found that both men and women with schizophrenia had lower life expectancies at birth when compared with the general population (62.8 years versus 77.4 years for men and 71.9 years versus 81.6 years for women)\(^5\). Possible contributors to this decreased life expectancy include higher rates of coronary artery disease, diabetes, and smoking in schizophrenic patients \(^6\)\(^7\)\(^8\). Moreover, schizophrenia carries a higher risk of suicide, with one meta-analysis finding that patients with schizophrenia have an 8.5 times higher risk of suicide than the general population\(^9\).

In addition to morbidity and mortality, schizophrenia also incurs an enormous economic burden. A recent UK study estimates the total cost of schizophrenia nationally to be £6.7 billion\(^10\). Notably, this study found only 30% of total costs attributed to schizophrenia to come from direct costs of treatment and care, while 70% of total costs came from indirect costs to society. An analogous study in the US reported the total cost of schizophrenia in the US to be 62.7 billion USD, of which more than half was attributed to productivity losses (unemployment, reduced workplace productivity), premature mortality from suicide, and family caregiving\(^11\). Only 36% was associated with direct healthcare costs and 12% by non-healthcare services.

Twenty-four million people suffer from schizophrenia globally, though only half receive treatment. It is estimated that 90% of those without access to treatment reside in low and middle-income countries\(^12\). Psychiatry remains a neglected field in developed nations, though it is severely under-resourced in many developing nations. In parallel to

strengthening healthcare systems, developing community health networks, and recruiting healthcare workers, we must provide effective pharmacological and psychological tools to treat psychotic disorders. At present, we believe too little choice exists with regards to antipsychotic medications available in resource-poor settings.

9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostics, treatment or monitoring facilities and skills):

(a) Brief primer on the pathophysiology of psychosis

Various models exist to explain the pathophysiology of psychosis drawing on genetics, development, and biochemistry. There is strong evidence to support a genetic predisposition to schizophrenia, for example; twin studies in Japan and Europe have shown monozygotic twin concordance rates of 41-65% and dizygotic twin rates ranging from 0-28%.

Although a strong genetic component predisposing individuals to schizophrenia has been established, total acquired risk is affected by environmental and developmental factors. From a neurochemical perspective, schizophrenia and all psychotic disorders are thought to be precipitated by a hyperdopaminergic state, as reflected by increases in synthesis and synaptic transmission of dopamine.

Here we would like to introduce Kapur’s model of “aberrant salience,” which is perhaps the most intuitive model for understanding the dopamine hypothesis to date. His model seeks to explain the neurochemistry and clinical presentation of psychosis, as well as pharmacologic efficacy. He argues that dopamine mediates salience, “a process whereby events and thoughts come to grab attention, drive action, and influence goal-oriented behavior.” In hyperdopaminergic states therefore, the brain is hyperaroused and aberrant salience is produced. He explains that “delusions are a cognitive effort by the patient to make sense of these aberrantly salient experiences” and “hallucinations reflect a direct experience of aberrant salience of internal representations.” Apart from genetic predisposition, several factors are known to affect dopamine synthesis and transmission in the brain, including excessive sleep deprivation, medications such as prednisone and amphetamine derivatives, and recreational drugs such as marijuana.

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Kapur’s model of aberrant salience can be used to understand why antipsychotic medications are effective. Importantly, both typical and atypical antipsychotic medications have been shown to antagonise dopamine receptors, lowering levels of dopamine-mediated transmission\textsuperscript{18,19}. That is, antipsychotic medications treat psychosis (and affect aberrant salience) by decreasing dopamine transmission. They are thought to do this by antagonising dopaminergic projections from the ventral tegmental area in the midbrain to the frontal cortex and limbic system\textsuperscript{20}.

(b) Brief primer on the mechanisms of action of typical and atypical antipsychotics

In 1950 chlorpromazine was developed as an anti-histamine and incidentally found to have antipsychotic properties, decreasing both hallucinations and delusions\textsuperscript{21}. It would become the first of the typical (or first generation) antipsychotics, thought to work primarily by antagonising the dopamine D2 receptor\textsuperscript{22}. Typical antipsychotics include haloperidol, fluphenazine, and thioridazine, amongst others. Clozapine, the first atypical antipsychotic was approved by the US FDA in 1989. Atypical (or second generation) antipsychotics have different receptor affinities than typicals, including variable dopamine (D1 and D2) receptor affinities, increased serotonin 5-HT\textsubscript{2A} affinity, and in some cases alpha adrenergic and histamine H1 receptor affinities\textsuperscript{23}. As a result of these differing affinities, atypical antipsychotics confer reduced risks of extrapyramidal side effects than typicals, but increased risks of metabolic side effects\textsuperscript{24}. See section 11 for more information on the differing side effect profiles of antipsychotic medications.

(b) Dosage regimen and duration of treatment: for more details, see section 15.

Risperidone can be started initially in adults at 1 mg once a day or twice daily, and this dose can be increased by 1 mg each day until desired therapeutic effect. The typical dose of risperidone ranges from 2.0-8.0 mg daily, and the average dose is around 4 mg daily. The maximum dose of risperidone is 16 mg daily, though doses higher than 8 mg daily are rarely used. In elderly patients, it is recommended to start risperidone at 0.5 mg initially once or twice daily, and this dose may be increased by 0.5 mg twice daily. The typical dose for elderly patients ranges from 0.5-2.0 mg. Duration of therapy should be based on clinical judgment and natural history of the patient’s psychiatric illness. As


\textsuperscript{19} Farde L, Wiesel FA, Halldin C, Sedvall G: Central D2-dopamine receptor occupancy in schizophrenic patients treated with antipsychotic drugs. Arch Gen Psychiatry. 1998; 45: 71-76.

\textsuperscript{20} Stevens J. An anatomy of schizophrenia? Arch Gen Psychiatry. 1973; 29: 177-189.


discussed in section 10, risperidone can be used to manage acute psychoses, as well as part of maintenance therapy for chronic psychotic illnesses. Importantly, in patients with schizophrenia risperidone has been shown to delay relapse\(^\text{25}\).

(c) Reference to WHO and other clinical guidelines:

The **American Psychiatric Association Practice Guidelines** for the Treatment of Patients with Schizophrenia\(^\text{26}\) recommend selecting medications after considering the following factors, “prior degree of symptom response, past experience of side effects, side effect profile of prospective medications, patient’s preferences for a particular medication, available formulations of medications.” The APA guidelines then go on to recommend, “consider second-generation antipsychotics as first-line medications because of the decreased risk for extrapyramidal side effects and tardive dyskinesia.” An excerpt from these guidelines is included below.

**Excerpt from American Psychiatric Association Practice Guideline (for Schizophrenia):**

Consider second-generation antipsychotics as first-line medications because of the decreased risk for extrapyramidal side effects and tardive dyskinesia. For patients who have had prior treatment success or who prefer first-generation agents, these medications are useful and for specific patients may be the first choice. With the possible exception of clozapine for patients with treatment-resistant symptoms, antipsychotics generally have similar efficacy in treating positive symptoms. Second-generation antipsychotics may have superior efficacy in treating global psychopathology and cognitive, negative, and mood symptoms.

The **National Institute for Health and Clinical Excellence (NICE) guidelines** for the treatment of schizophrenia place a similar emphasis on empowering patients, their caretakers, and clinicians the ability to make informed choices about antipsychotic medications\(^\text{27}\). See excerpt from NICE clinical guideline 82 (Schizophrenia) below.

**Excerpt from NICE Clinical Guideline 82 (for Schizophrenia):**

For people with newly diagnosed schizophrenia, offer oral antipsychotic medication. Provide information and discuss the benefits and side-effect profile of each drug with the service user. The choice of drug should be made by the service user and healthcare professional together, considering: the relative potential of individual antipsychotic drugs to cause extrapyramidal side effects (including akathisia), metabolic side effects


(including weight gain) and other side effects (including unpleasant subjective experiences) [and] the views of the carer where the service user agrees.

The **Mental Health Gap Action Programme Intervention Guide** published by the WHO in 2010 includes a section on the treatment of psychotic disorders\textsuperscript{28}. Though the mhGAP guide only mentions the three antipsychotics currently on the Model List by name (haloperidol, chlorpromazine, and fluphenazine), it does state that if the responses to these medications are inadequate, providers may choose to treat patients with atypical antipsychotics if available and affordable. See excerpt from mhGAP guide below.

**Excerpt from mhGAP Intervention Guide:**

*If the response is inadequate to more than one antipsychotic medication using one medicine at a time at adequate dosage for adequate duration:*

...consider second-generation antipsychotics (with the exception of clozapine), if cost and availability is not a constraint, as an alternative to haloperidol or chlorpromazine.

If added to the WHO Model List, we hope that risperidone will be included in future iterations of the mhGAP guidelines. In sections 10 and 11, we detail the efficacy and safety profile of risperidone when compared with other antipsychotics. In section 12, we provide international and India-specific pricing data for generic versions of risperidone to demonstrate that risperidone is both available and affordable.

(d) Need for special diagnostics, treatment or monitoring facilities and skills:

The following recommendations are adapted from Stahl’s Essential Pharmacology\textsuperscript{29}. It is recommended that a patient’s metabolic profile be assessed at baseline prior to starting risperidone therapy. Weight, body mass index, blood pressure, fasting blood sugar, and fasting lipids are all factors that can help identify patients at the start of therapy who may benefit from lifestyle changes including improved nutrition and increased physical activity. These metabolic indicators can also be monitored over time, ideally within a few months of starting treatment and annually thereafter. Though routine blood tests may not be feasible in resource-limited settings, patients can still be monitored for changes in weight, body mass index, and blood pressure.

**10. Summary of comparative effectiveness in a variety of clinical settings:**

In developed nations, atypical antipsychotics including risperidone have become the first-line drugs for psychotic disorders including schizophrenia, schizoaffective disorder, acute mania, and depression with psychosis. The most robust evidence currently exists for schizophrenia and schizoaffective disorder. See enclosed documents for the Cochrane reviews described below.


(a) Schizophrenia & Schizoaffective disorder

Comparison of Risperidone with Typical Antipsychotics

A 2010 Cochrane review by Hunter et al of 23 randomized controlled trials (RCTs) including nearly 4445 patients found risperidone to be more effective than typical antipsychotics in treating schizophrenia and schizoaffective disorder\(^{30}\). Pooling data from nine RCTs, risperidone was more likely than haloperidol to cause clinical improvement in the short-term as assessed by the Positive and Negative Syndrome Scale (PANSS). The number needed to treat (NNT) was just eight, meaning that for every eight patients given risperidone instead of haloperidol, one patient would be expected to gain clinical improvement than they otherwise would have. According to the same review, risperidone was also more likely than haloperidol to cause clinical improvement in the long-term, with the NNT ranging from 4-11. One RCT involving 367 patients found that risperidone decreased one-year relapse rates compared to haloperidol (RR 0.64 CI 0.41-0.99), with an NNT of seven\(^{31}\). Moreover, when considering data from twenty RCTs, the authors found that fewer patients dropped out in risperidone treatment arms compared with patients in the typical antipsychotic treatment arms. We can infer from this that risperidone has better medication adherence than typical antipsychotics, and as described later adherence is a major challenge in treating chronic psychotic disorders.

Comparison of Risperidone with Other Atypical Antipsychotics

A 2011 Cochrane review by Kamossa et al of 45 randomized controlled trials involving 7760 patients compared risperidone with other atypical antipsychotics including clozapine, olanzapine, quetiapine, aripiprazole, ziprasidone, sertindole, and amisulpride\(^{32}\). As in the 2010 Cochrane review by Hunter et al, variability in clinical improvement between drugs was evaluated by PANSS scores. Compared with medications of its own class, risperidone was more efficacious than both quetiapine and ziprasidone, though less efficacious than clozapine and olanzapine. Importantly, risperidone has a safer side effect profile than both clozapine and olanzapine (see section 11 for more details).

(b) Acute Mania & Depression with Psychosis

A 2009 Cochrane review by Rendell et al of six randomized controlled trials including over 1300 patients found risperidone to be effective in treating the symptoms of acute


mania as assessed by the Young Mania Rating Scale (YMRS)\textsuperscript{33}. In one trial comparing risperidone and haloperidol monotherapy for acute mania, there was no significant difference in efficacy.

Major depressive disorder with psychotic features (or psychotic depression) is commonly treated with a dual regimen of an antidepressant and antipsychotic. Guidelines from the American Psychiatric Association and Canadian Psychiatric Association both recommend treatment of psychotic depression with antipsychotic and antidepressant co-therapy.\textsuperscript{34, 35} A recent meta-analysis of randomised controlled trials suggest antidepressant and antipsychotic co-therapy is more effective than monotherapy with either class alone in the acute treatment of psychotic depression\textsuperscript{36}. In the United States, atypical antipsychotics are commonly used in concert with antidepressants in treating depression with psychosis. Further studies are needed to elucidate the relative efficacies of various combinations of antidepressants and antipsychotics, as comparative evidence in this regard is limited.

11. Summary of comparative evidence on safety:

As discussed in section 9(a), disorders of psychosis (namely, schizophrenia spectrum disorders, bipolar disorder with mania and psychosis, as well as depression with psychosis) are states of aberrant saliency, believed to be caused by increased levels of dopamine in the brain. When a patient’s reality does not match those of their caregivers or healthcare providers, it can be exceedingly difficult to convince patients to take medication at all. Once starting medication, patients sometimes discontinue treatment because of side effects, often leading to a recrudescence of their mental illness. Treatment adherence is therefore a major challenge faced in addressing chronic psychotic illnesses.

For this reason, it is paramount that patients, their caregivers, and their clinicians are offered choices of different antipsychotics from which they can make informed decisions as to which drug would be appropriate for them. Not every patient responds to each drug the same way; that is, some drugs may be more or less efficacious and more or less tolerable for each individual patient. Considering this, we believe that offering at least one atypical antipsychotic medication to patients in the developing world is invaluable. Let us now consider the differing side effect profiles of risperidone compared with both typical antipsychotics and other atypical antipsychotics.

Comparison of Risperidone with Typical Antipsychotics

Typical antipsychotics are more likely than atypicals to cause extrapyramidal side effects including akathisia (the subjective feeling of psychomotor agitation and restlessness), acute dystonic reactions (sustained painful muscle spasms of the face and neck, which can be life-threatening), drug-induced parkinsonism (bradykinesia, shuffling gait, cogwheel rigidity of the arms and legs, resting tremor), as well as the more well known tardive dyskinesia (involuntary, repetitive movements of the face, neck, or other parts of the body). Tardive dyskinesia (TD) most often manifests as repetitive orofacial movements such as tongue protrusion, lip pursing or smacking, and eyebrow raising, but may also affect core muscles, limbs, and fingers/toes. While usually painless, TD is disfiguring, can interfere with speech and swallowing, and can have devastating impacts on a patient’s social relationships. A 2005 systematic review by Hawton et al examining risk factors for suicide among people with schizophrenia found psychomotor agitation (akathisia) to increase suicide risk (OR 2.61 CI 1.54-4.41).\textsuperscript{37}

According to the 2010 Cochrane review by Hunter et al, risperidone caused fewer extrapyramidal side effects than typical antipsychotics.\textsuperscript{38} The number needed to treat was just three, meaning that for every three patients who received risperidone instead of a typical antipsychotic, one extra patient did not develop extrapyramidal symptoms. This is also reflected in the fact that patients taking risperidone were less likely to take antiparkinson medications to combat movement-related side effects than those who were taking typical antipsychotics. Whereas risperidone (and other atypicals) are less likely to cause extrapyramidal side effects than typicals, they are more likely to cause metabolic side effects such as weight gain, hyperlipidemia, and hyperglycemia. However, not all atypical antipsychotics are equal in this regard. See below for more information.

Comparison of Risperidone with Other Atypical Antipsychotics

When balancing clinical efficacy with side effects and cost, risperidone is overall the best choice amongst the atypical antipsychotics currently available on the generic market. There are several issues to consider when comparing risperidone with other medications in its class, including clozapine (trade name Clozaril), olanzapine (Zyprexa), quetiapine (Seroquel), aripiprazole (Abilify), and Ziprasidone (Geodon). See Table 1, which we have adapted from the American Psychiatric Association Practice Guidelines.

As mentioned earlier, the 2011 Cochrane review by Kamossa et al reported that while risperidone was marginally less effective than clozapine and olanzapine, it was found to


be less likely to cause weight gain than both drugs\textsuperscript{39}. Risperidone was also less likely to cause weight gain than sertindole and hypercholesterolemia than quetiapine. It was however found to cause more weight gain than amisulpride and more hyperlipidemia than aripiprazole and ziprasidone, though risperidone was found to be more effective than all three of these drugs. Additionally when compared with other atypicals, risperidone was more likely to cause extrapyramidal side effects, though it remains less likely than typical antipsychotics to do so. Kamossa et al also found that risperidone is more likely to cause hyperprolactinemia than other atypical antipsychotics.

Table 1: Comparison of Side Effects Amongst Typical and Atypical Antipsychotics\textsuperscript{40}

<table>
<thead>
<tr>
<th></th>
<th>Extrapyramidal Side Effects</th>
<th>Prolonged QTc</th>
<th>Sedation</th>
<th>Anti-cholinergic Side Effects</th>
<th>Weight Gain</th>
<th>Elevated Lipids</th>
<th>Elevated Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>None</td>
<td>+</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Rare</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Rare</td>
<td>+</td>
<td>++</td>
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<td>+++</td>
<td>+++</td>
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<td>Quetiapine</td>
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<tr>
<td>Aripiprazole</td>
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<td>Less Likely</td>
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<tr>
<td>Ziprasidone</td>
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<td>None</td>
<td>None</td>
<td>Less Likely</td>
<td>Less Likely</td>
<td>Less Likely</td>
</tr>
</tbody>
</table>

Table 1, adapted from the American Psychiatric Association’s Quick Reference Guide on treating schizophrenia, reinforces these findings. When compared with clozapine and olanzapine, risperidone is less likely to cause weight gain, hyperlipidemia, hyperglycemia, and anti-cholinergic effects. Additionally, clozapine can cause rare but life-threatening side effects including agranulocytosis, myocarditis, and seizures. Patients who are taking clozapine must have their white blood cell counts monitored very


frequently (once a week for the first six months of treatment), which may not be feasible or cost-effective in most resource-poor settings.

While aripiprazole and ziprasidone have better metabolic side effect profiles than risperidone, Kamossa et al conclude that risperidone may be more effective than both. In all fairness we should state that efficacy is relative; that is, while risperidone appears to be more effective than aripiprazole and ziprasidone overall, it does not mean that these drugs would not be effective in a given patient. However, aripiprazole is still on-patent, set to expire in 2014. Ziprasidone went off-patent earlier this year, and currently five generic manufacturers have been FDA-approved. Once multiple generic manufacturers enter the market for both drugs, we would expect their prices to fall and at least aripiprazole may become a good candidate for the WHO Model List.

Lastly, most antipsychotics (including haloperidol and risperidone) can cause delayed repolarization of cardiac myocytes (as reflected by a prolonged QT interval on electrocardiogram), which while rare may lead to life-threatening cardiac arrhythmias. Patients can be monitored for this by routine ECGs upon starting antipsychotics and after dosage increases. A recent review by Wenzel-Seifert and colleagues found that amongst antipsychotics, thioridazine (typical) and ziprasidone (atypical) carried the greatest risk of QT prolongation. Of note, ziprasidone is more likely than both haloperidol and risperidone to cause prolonged QT syndrome.

12. Summary of available data on comparative cost and cost-effectiveness:

(a) Cost of Risperidone: As mentioned in sections 6 and 13, risperidone was developed by Janssen-Cilag, a subsidiary of Johnson & Johnson. Risperidone went off-patent on December 29, 2003, though Janssen-Cilag retained exclusive marketing rights for the drug until June 29, 2004. Teva Pharmaceuticals was the first company to gain FDA approval for a generic form of risperidone in June 2008.

Using the International Drug Price Indicator Guide published by Management Sciences for Health, we have compiled buyer prices for risperidone (2 mg tablets) from 2002-2011. See Appendix C for lowest, highest, and median buyer prices in USD. A comparison of pre- and post-generic production data reveals the impact of generic production on the price of Risperidone. In 2002, the cost of a 2 mg tablet of risperidone ranged from 0.070 USD to 1.33 USD, with the median price being roughly 70 cents. In 2011, however, the cost of a 2 mg tablet of risperidone ranged from 0.0080 USD to 0.067 USD, with the median price being just 0.034 USD, or roughly 3 cents. See figure 1 below for a graphical representation of this data.


In figure 2, we again use median buyer prices from MSH to plot the yearly cost of risperidone for one patient between 2002-2011. We chose the dosing regimen to be 4 mg daily. Whereas the yearly cost of this dosing regimen would have been nearly 512 USD in 2002, it was roughly 25 USD per year per patient in 2011.

We were also able to identify country-specific data for India. We searched the PatientIndia website for branded generic manufacturers of risperidone available in India. PatientIndia identified 12 manufacturers, and the price of 10 units of 1 mg tablets ranged from 7.00 rupees to 19.70 rupees. See Appendix D for full list. By way of comparison, Ethnor Ltd, an affiliate of Johnson & Johnson (the parent company of Janssen-Cilag) markets the same number of branded Risperdal (non-generic) pills for 135 rupees43.

(b) Cost effectiveness of Risperidone:

43 PatientIndia
http://patientindia.com/resultDetails.php?searchC=2&genId=1222&strength=1mg&form=4
A 2012 study in Spain indicated that risperidone and a related drug (paliperidone ER) to be cost-effective compared with other atypical antipsychotics and haloperidol. The average cost-effectiveness ratio in euros/QALY of risperidone was 4,353 versus 4,593 for haloperidol. When comparing incremental cost-effectiveness ratios (ICERs), risperidone and paliperidone were found to be dominant strategies with higher effectiveness and lower cost compared with amisulpride, aripiprazole, olanzapine, and haloperidol. Few studies have been done regarding the cost-effectiveness in low and middle income countries. Here we profile known examples. A recent (2011) Thai study has indicated that the use of risperidone or family/psychosocial interventions is highly cost-effective in Thailand (well below the WHO defined levels 3 x GDP per capita threshold [110,000 Bhat per DALY in Thailand]). The adjunctive therapy of psychosocial interventions is also highly cost-effective in the country.

One study in 2007 in Slovenia that accounted for costs of care (drug plus inpatient costs) suggested the costs of using risperidone were just over 8,000 euros (note: this was for risperidone in depot formulation, which is not yet generic and more expensive). While the older antipsychotics comprised just 6.5% of the cost of the regimen (vs 37.9% for the newer antipsychotics), the authors suggest the improved safety profile of the newer generation antipsychotics was a cost-effective strategy for the treatment of chronic schizophrenia in the context of Slovenia.

An analogous study concerning an “economic evaluation of antipsychotic drugs for schizophrenia treatment within the Brazilian healthcare system” was performed in 2009. These data indicate a 5-year benefit of 4.2 QALYs per US $5,964.57 per patient (haloperidol was 4.1 with cost of $3,935.15 and olanzapine was 4.2 QALYs with cost of $10,423.12). However, utility evaluations in this study showed that the newer antipsychotics, including risperidone, performed better (versus haloperidol) with respect to the adverse side effects, hospitalizations, relapses and overall quality of life.

Here, we would like to reference a major study published in 2008 using WHO Choice methodology that questioned the cost-effectiveness of atypical antipsychotics. The study identified prices for risperidone to be low ($0.06 for 2 mg in Sri Lanka) to moderate ($2.50 for 2 mg in Nigeria). The authors found favorable cost-effectiveness for typical antipsychotics over atypsicals. The cost per DALY averted using the older regimens ranged from I$ 2,350 (international dollars) in WHO African subregion D to I$ 7,158 in WHO Region of the Americas subregion B. Whereas, the cost-effectiveness of newer antipsychotic drugs implemented within a community-based service model without

adjuvant psychosocial treatment was estimated to range between I$ 13,000 and I$ 20,000\textsuperscript{48}.

This led the authors to argue the following:

“…switching first-line treatment to newer antipsychotic drugs has a very modest expected incremental impact on health outcomes but, depending on the price reached for these drugs, has a potentially ruinous effect on the financial feasibility of scaled-up provision of treatment (as would be the case in Nigeria, for example). This conclusion is in line with recent empirical research in Australia, the United Kingdom and the United States of America. The Assessing Cost-Effectiveness in Mental Health (ACE-MH) project in Australia also found an unfavourable level of cost-effectiveness for atypical antipsychotic drugs (an incremental cost of A$ 48,000–92,000 per DALY compared to conventional neuroleptics). However, when generic forms of these medications become more widely available, the picture could change dramatically with regard to cost-effectiveness, so our results should not be taken to imply that low-income countries should permanently exclude these newer medications from their public health systems.”

We wish to alert the Expert Review Committee to fact that a significant price reduction transpired between the time of publication of the above study (2008) and 2011. Perhaps foreshadowed by the concluding statement in the paragraph above, generic risperidone is now widely available and much more affordable. A thorough list of multi-source generic suppliers is provided in Appendices A&B. See pricing data in Appendices C&D.

13. Summary of regulatory status: As discussed in sections 6 and 12, risperidone first gained US FDA-approval under the trade name Risperdal produced by Janssen-Cilag on December 29, 1993 (FDA application number NDA 020272)\textsuperscript{49}. According to the European Medicines Agency website, Janssen-Cilag or its parent company Johnson & Johnson have registered various oral formulations of risperidone (branded versions) in the following European countries: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovak Republic, Spain, Sweden, and the United Kingdom\textsuperscript{50}.

Risperidone went off-patent on December 29, 2003, though Janssen-Cilag retained exclusive marketing rights for the drug until June 29, 2004. Teva Pharmaceuticals was the first company to gain FDA approval for a generic form of Risperidone in June 2008, and some sixteen companies would follow suit over the next three years. See Appendix A for a list of companies who currently have US FDA approval for a generic form of Risperidone (oral tablet formulation).

\textsuperscript{48} http://www.who.int/bulletin/volumes/86/7/07-045377/en/index.html
\textsuperscript{50} European Medicines Agency http://www.emea.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Risperdal/human_referrals_1_000022.jsp&mid=WC0b01ac05805c516fv
Apart from those companies who have gained FDA approval, numerous other companies are producing generic risperidone. On the MedIndia website for example, you can find 50 “branded” generic versions of Risperidone\(^5\). See Appendix B for full list.

14. Availability of pharmacopoeial standards:
(a) British Pharmacopoeia: (Available, Source: British Pharmacopoeia 2012)
(b) European Pharmacopoeia: (Available, Source: European Pharmacopoeia 2008)
(c) United States Pharmacopoeia: (Available, Source: US Pharmacopoeial Convention)
(d) Japan Pharmacopoeia: (Available, Source: Japanese Pharmacopoeia 2011)
(e) International Pharmacopoeia: (Unavailable, Source: WHO Pharmacopoeia Library)

15. Proposed (new) text for the WHO Model List and WHO Model Formulary:

(a) Proposed Model List Text

<table>
<thead>
<tr>
<th>Section 24.1: Medicines Used in Psychotic Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation: Oral tablets containing 0.25 mg, 0.5 mg, 1 mg, 2mg, 3 mg, 4 mg, and 6 mg</td>
</tr>
<tr>
<td>Type of List: Core List</td>
</tr>
<tr>
<td>Disease/Indication: Psychotic disorders including schizophrenia, schizoaffective disorder, mania with psychosis, and depression with psychosis.</td>
</tr>
</tbody>
</table>

(b) Proposed Model Formulary Text

In composing this text, the authors used the 2008 WHO Formulary as a template, and Stahl’s Essential Pharmacology\(^5\) and Dynamed for content\(^3\).

**General information:** Risperidone is a second-generation (atypical) antipsychotic useful in the treatment of schizophrenia, depression with psychotic features, acute mania and mixed episodes. Risperidone functions by antagonizing dopamine D2 receptors and blocking serotonin 5HT-2A receptors.

**Uses:** Psychotic disorders including schizophrenia, schizoaffective disorder, mania with psychosis, and depression with psychosis.

**Contraindications:** Known hypersensitivity to risperidone

\(^5\) “List of Brand Name(s) for Generic Drug Risperidone.” Drug “Risperidone” Price List, MedIndia website. [http://www.medindia.net/drug-price/risperidone.htm](http://www.medindia.net/drug-price/risperidone.htm)
**Precautions:** Risperidone should be used with caution in the elderly particularly those with dementia especially Lewy Body Dementia, as patients with dementia may worsen on anti-psychotic medications and have an increased risk of death and cardiovascular and cerebrovascular events. Risperidone is currently considered in Risk Category C during pregnancy. Patients who become pregnant while taking risperidone should seek the advice of a healthcare professional to weigh the risks and benefits of continuing this medication. Breast-feeding is not advised while taking risperidone.

**Drug Interactions:**
Pharmacokinetic interactions: Risperidone is metabolized by CYP2D6. Drugs that inhibit CYP2D6 may increase blood levels of risperidone; examples include clozapine, fluoxetine, paroxetine, and ranitidine. Drugs that increase CYP2D6 activity may result in decreased blood levels of risperidone; examples include carbamazepine, phenobarbital, and phenytoin. Pharmacodynamic interactions: Dopamine agents, including levodopa and mirapex, may antagonize the antipsychotic effect of risperidone. Hypotensive agents, especially beta-blockers, may contribute to orthostatic hypotension.

**Skilled tasks:** May impair ability to perform skilled tasks, for example operating machinery, driving

**Dose:** Schizophrenia and other psychoses, mania, mixed episode, by mouth, **ADULTS** initially 1mg once daily or twice daily and may increase by 1mg each day until desired therapeutic effect. Typical dose: 2.0-8.0 mg daily (average dose is around 4 mg daily, maximum dose is 16 mg daily, there is an increased risk of extrapyramidal symptoms above 6 mg daily); **ELDERLY** initially 0.5mg once or twice daily, may increase by 0.5 mg twice daily. Typical dose: 0.5-2.0 mg daily.

**Other dosing considerations:** In patients with hepatic or renal impairment, initially 0.5mg twice daily for at least one week, may subsequently increase to 1 mg twice daily. May dose at bedtime to reduce daytime sedation. To avoid abrupt withdrawal symptoms, discontinue gradually over 6-8 weeks.

**Adverse Effects:** May cause dizziness, sedation, constipation, nausea, hypotension, dose-related hyperprolactinemia, galactorrhea, weight gain, increased risk of diabetes, dyslipidemia, neuroleptic malignant syndrome, tardive dyskinesia, tachycardia, dose-related extrapyramidal symptoms including akathisia, acute dystonia.
APPENDIX A: FDA-Approved Generic Manufacturers of Risperidone (Oral Tablet Formulation)

Source: U.S. Food and Drug Administration

<table>
<thead>
<tr>
<th>MANUFACTURER</th>
<th>DRUG NAME</th>
<th>FORMULATION</th>
<th>FDA APPLICATION</th>
<th>APPROVAL DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEVA</td>
<td>Risperidone</td>
<td>Tablet, Oral</td>
<td>ANDA 076228</td>
<td>6/30/08</td>
</tr>
<tr>
<td>MYLAN</td>
<td>Risperidone</td>
<td>Tablet, Oral</td>
<td>ANDA 076288</td>
<td>9/15/08</td>
</tr>
<tr>
<td>APOTEX INC</td>
<td>Risperidone</td>
<td>Tablet, Oral</td>
<td>ANDA 077953</td>
<td>9/15/08</td>
</tr>
<tr>
<td>AUROBINDO PHARMA</td>
<td>Risperidone</td>
<td>Tablet, Oral</td>
<td>ANDA 078269</td>
<td>10/8/08</td>
</tr>
<tr>
<td>WOCKhardt</td>
<td>Risperidone</td>
<td>Tablet, Oral</td>
<td>ANDA 078871</td>
<td>10/9/08</td>
</tr>
<tr>
<td>PLIVA HRVATSKA DOO</td>
<td>Risperidone</td>
<td>Tablet, Oral</td>
<td>ANDA 077769</td>
<td>10/16/08</td>
</tr>
<tr>
<td>ZYDUS PHARMS USA INC</td>
<td>Risperidone</td>
<td>Tablet, Oral</td>
<td>ANDA 078040</td>
<td>10/16/08</td>
</tr>
<tr>
<td>DR REDDYS LABS LTD</td>
<td>Risperidone</td>
<td>Tablet, Oral</td>
<td>ANDA 076879</td>
<td>10/24/08</td>
</tr>
<tr>
<td>TORRENT PHARMS</td>
<td>Risperidone</td>
<td>Tablet, Oral</td>
<td>ANDA 079088</td>
<td>10/30/08</td>
</tr>
<tr>
<td>WATSON LABS</td>
<td>Risperidone</td>
<td>Tablet, Oral</td>
<td>ANDA 077860</td>
<td>12/5/08</td>
</tr>
<tr>
<td>VINTAGE</td>
<td>Risperidone</td>
<td>Tablet, Oral</td>
<td>ANDA 078707</td>
<td>12/29/08</td>
</tr>
<tr>
<td>WEST WARD PHARMS</td>
<td>Risperidone</td>
<td>Tablet, Oral</td>
<td>ANDA 078740</td>
<td>5/29/09</td>
</tr>
<tr>
<td>PROSAM LABS</td>
<td>Risperidone</td>
<td>Tablet, Oral</td>
<td>ANDA 078071</td>
<td>6/17/09</td>
</tr>
<tr>
<td>SANDOZ</td>
<td>Risperidone</td>
<td>Tablet, Oral</td>
<td>ANDA 078528</td>
<td>10/16/09</td>
</tr>
<tr>
<td>CIPLA</td>
<td>Risperidone</td>
<td>Tablet, Oral</td>
<td>ANDA 077543</td>
<td>5/18/11</td>
</tr>
<tr>
<td>AJANTA PHARMA LTD</td>
<td>Risperidone</td>
<td>Tablet, Oral</td>
<td>ANDA 201003</td>
<td>8/24/11</td>
</tr>
<tr>
<td>PRINSTON INC</td>
<td>Risperidone</td>
<td>Tablet, Oral</td>
<td>ANDA 077493</td>
<td>11/29/11</td>
</tr>
</tbody>
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APPENDIX B: List of Branded Generic Producers of Risperidone (Oral Tablet Formulation)\(^{55}\)
Source: MedIndia

<table>
<thead>
<tr>
<th>MANUFACTURER</th>
<th>BRANDED NAME</th>
<th>FORMULATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAN PHARMA PVT LTD</td>
<td>Sperd</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>ALPIC REMEDIES LTD</td>
<td>Ridon</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>ATHENS LABS LTD</td>
<td>Shazone</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>BARODA PHARMA PVT LTD</td>
<td>Sycodone</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>CIPLA LTD (PROTEC)</td>
<td>Risnia</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>CONSERN PHARMA PVT LTD</td>
<td>Riscon</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>CYRIL PHARMACEUTICALS</td>
<td>Respid</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>D.R. JOHN &amp; LAB</td>
<td>Phallus</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>DAGON PHARMACEUTICALS PVT LTD</td>
<td>Respijet</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>DENSAN PHARMACEUTICALS PVT LTD</td>
<td>Riskar</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>EAST AFRICAN I REMEDIES PVT LTD</td>
<td>Risperiv</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>EAST WEST PHARMA</td>
<td>Ridon</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>ECOLITY - DIV OF PANACEA BIOTEC LTD</td>
<td>Rispid</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>ELIKEM PHARMACEUTICALS PVT LTD</td>
<td>Zon</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>ELITE PHARMA PVT LTD</td>
<td>R-Don</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>ESTEEM PHARMACEUTICALS LTD</td>
<td>Retardon</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>GENTECH HEALTHCARE</td>
<td>Genrest</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>INTAS LABORATORIES PVT LTD</td>
<td>Risdone</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>KC LABORATORIES PVT LTD</td>
<td>Eauris</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>KONARK BIOCHEM</td>
<td>Repridon MD</td>
<td>Tablet, Oral</td>
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</tbody>
</table>

\(^{55}\) “List of Brand Name(s) for Generic Drug Risperidone.” Drug “Risperidone” Price List, MedIndia website. [http://www.medindia.net/drug-price/risperidone.htm](http://www.medindia.net/drug-price/risperidone.htm)
<table>
<thead>
<tr>
<th>MANUFACTURER</th>
<th>BRANDED NAME</th>
<th>FORMULATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA PHARMACEUTICALS</td>
<td>Ragrace</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>LA PHARMACEUTICALS</td>
<td>Regrace</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>LIFECARE INNOVATIONS PVT LTD</td>
<td>Rize</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>MANKIND PHARMACEUTICALS PVT LTD</td>
<td>Neudon</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>MEDICO LABS</td>
<td>Respimed</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>MEDO CHEM LAB P LTD</td>
<td>Ristab</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>MICRO LABS LTD (SYNCHRO)</td>
<td>Rispond</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>MOLEKULE PVT LTD</td>
<td>Speridon</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>MOXY LABORATORIES PVT LTD</td>
<td>Benzix</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>ORCHID CHEMICALS &amp; PHARM LTD</td>
<td>Riscalm</td>
<td>Tablet, Oral</td>
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<tr>
<td>OSHO PHARMA PVT LTD</td>
<td>Riposh</td>
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</tr>
<tr>
<td>OSMED FORMULATIONS P LTD</td>
<td>Zodon</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>PHARMACIA INDIA LTD</td>
<td>Zepid</td>
<td>Tablet, Oral</td>
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<td>PIFER PHARMACEUTICALS PVT LTD</td>
<td>Rasin</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>PSYCO REMEDIES</td>
<td>Psudon</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>RAIKAR PHARMACEUTICALS PVT LTD</td>
<td>Riskar</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>RANBAXY LABORATORIES LTD (SOLUS)</td>
<td>Rozidal</td>
<td>Tablet, Oral</td>
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<tr>
<td>RELIANCE FORMULATION PVT LTD</td>
<td>Peridon</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>RPG LIFE SCIENCES LTD</td>
<td>Sizomax</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>SUN RISE INTL LABS LTD</td>
<td>Sizodon</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>TALENT HEALTHCARE</td>
<td>Resqe</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>TALENT LABORATORIES</td>
<td>Ristal</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>TAS MED I PVT LTD</td>
<td>Repid</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>TORRENT LABS P LTD</td>
<td>Respidon</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>UBIT PHARMACEUTICALS PVT LTD</td>
<td>Ubitdon</td>
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<td>Rescalm-DN</td>
<td>Tablet, Oral</td>
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<tr>
<td>UNICHEM LABORATORIES LTD</td>
<td>Zisper MD</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>MANUFACTURER</td>
<td>BRANDED NAME</td>
<td>FORMULATION</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>VGR BIO LABORATORIES</td>
<td>RI</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>ZEE LABORATORIES</td>
<td>Rion</td>
<td>Tablet, Oral</td>
</tr>
<tr>
<td>ZEUS PHARMACEUTICALS</td>
<td>Riszes</td>
<td>Tablet, Oral</td>
</tr>
</tbody>
</table>
**APPENDIX C: Buyer Prices of Risperidone 2 mg Tablet in USD from 2002-2011**
Source: MSH International Drug Price Indicator Guide\(^5\)

<table>
<thead>
<tr>
<th>Year</th>
<th>Lowest Price (USD)</th>
<th>Highest Price (USD)</th>
<th>Median Price (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>0.07</td>
<td>1.332</td>
<td>0.701</td>
</tr>
<tr>
<td>2003</td>
<td>0.7005</td>
<td>1.2234</td>
<td>0.9619</td>
</tr>
<tr>
<td>2004</td>
<td>0.0033</td>
<td>1.188</td>
<td>0.7005</td>
</tr>
<tr>
<td>2005</td>
<td>0.511</td>
<td>1.242</td>
<td>0.8765</td>
</tr>
<tr>
<td>2006</td>
<td>0.3</td>
<td>1.1127</td>
<td>0.7691</td>
</tr>
<tr>
<td>2007</td>
<td>0.3</td>
<td>0.496</td>
<td>0.398</td>
</tr>
<tr>
<td>2008</td>
<td>0.2951</td>
<td>0.9922</td>
<td>0.4208</td>
</tr>
<tr>
<td>2009</td>
<td>0.0099</td>
<td>0.3</td>
<td>0.2981</td>
</tr>
<tr>
<td>2010</td>
<td>0.0467</td>
<td>0.0761</td>
<td>0.0651</td>
</tr>
<tr>
<td>2011</td>
<td>0.008</td>
<td>0.0666</td>
<td>0.0339</td>
</tr>
</tbody>
</table>

APPENDIX D: Prices (Rs) of Branded Generic Versions of Risperidone Available in India (Oral Tablet Formulation)\textsuperscript{57}

Source: PatientIndia

<table>
<thead>
<tr>
<th>MANUFACTURER</th>
<th>BRANDED NAME</th>
<th>PRICE (RUPEES)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIPLA (PROTEC)</td>
<td>Risnia</td>
<td>7.52</td>
</tr>
<tr>
<td>ELITE PHARMA</td>
<td>R-Don</td>
<td>9.00</td>
</tr>
<tr>
<td>INTAS PHARMACEUTICALS</td>
<td>Risdone</td>
<td>13.65</td>
</tr>
<tr>
<td>MICROLABS (SYNCRO)</td>
<td>Rispond</td>
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<td>Sizomax</td>
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<td>UNICHEM LABORATORIES</td>
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*Price in Rs listed above for 10 units of 1mg tablets of risperidone.

\textsuperscript{57} PatientIndia website, \url{http://patientindia.com/resultDetails.php?searchC=2&genId=1222&strength=1mg&form=4}