Australian Government

Department of Health and Ageing

Therapeutic Goods Administration

Australian Public Assessment Report for Risperidone

Proprietary Product Name: Risperdal Consta

Submission No: PM-2008-03495-3-1

Sponsor: Janssen-Cilag Pty Ltd

June 2010

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Extension of Indications
Decision:	Approved
Date of Decision:	18 March 2010
Active ingredient(s):	Risperidone
Product Name(s):	Risperdal Consta
Sponsor's Name and Address:	Janssen-Cilag Pty Ltd Locked Bag 2070 North Ryde NSW 1670
Dose form(s):	Powder for injection
Strength(s):	25 mg, 37.5 mg and 50 mg
Container(s):	5mL vial and a prefilled syringe containing 2mL diluent
Pack size(s):	One dose pack containing vial, syringe, one Alaris SmartSite Needle-Free Vial Access Device for reconstitution and Two Needle-Pro needles for intramuscular injection.
Approved Therapeutic use:	Treatment of schizophrenia and related psychoses. Monotherapy for maintenance treatment to prevent the recurrence of manic or mixed episodes of bipolar I disorder in patients with a manic or mixed episode, following stabilisation with oral risperidone. Adjunctive maintenance treatment with lithium or sodium valproate in treatment refractory patients with bipolar I disorder who have at least 4 relapses in a 12 month period.
Route(s) of administration:	Intramuscular injection
Dosage:	25 mg every two weeks
ARTG Numbers:	81489, 81490, 81491

Product Background

Risperdal Consta is an injectable depot formulation of risperidone, an atypical antipsychotic medication. Currently, Risperdal tablets, orally disintegrating tablets and oral solution are indicated for:

- Treatment of schizophrenia and related psychoses;
- Short-term treatment of acute mania associated with bipolar I disorder;
- Treatment of behavioural disturbances in dementia;
- Treatment of conduct and other disruptive behaviour disorders in children (over 5 years), adolescents and adults with subaverage intellectual functioning or mental retardation in whom destructive behaviours (e.g. aggression, impulsivity and self-injurious behaviours) are prominent (see Actions, Clinical trials for maintenance data);

- Treatment of behavioural disorders associated with autism in children and adolescents (see Actions, Clinical trials).

Risperdal Consta is indicated for:

- Treatment of schizophrenia and related psychoses.

With this submission the sponsor proposed to extend the indications for Risperdal Consta to include maintenance treatment to prevent the recurrence of mood episodes of bipolar disorder.

No atypical antipsychotic agents have a depot formulation registered for use in patients with bipolar I disorder. Haldol Deconate (haloperidol deconate) is registered for maintenance therapy of psychoses. The immediate release form of risperidone is not registered for the proposed indication.

Regulatory Status

Risperdal Consta was registered in Australia in April 2003 for the treatment of schizophrenia and related psychoses. Corresponding submissions based on the same data in the current extension of indications submission have been made in the USA, the European Union (EU), New Zealand, Switzerland, the Philippines, Brazil, Colombia, South Africa and Israel (for monotherapy and adjunctive maintenance treatment) and in Korea (monotherapy maintenance) and Thailand and Turkey (for adjunctive maintenance treatment only). Approval was given in the US on 15 May 2009, in New Zealand on 25 May 2009 and in Brazil on 23 June 2009.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

The submission relates to the modified-release injectable form of risperidone. No formulation changes are proposed in the submission.

Quality Summary and Conclusions

There was no requirement for a quality assessment in a submission of this type.

III. Non-Clinical Findings

Non-Clinical Summary and Conclusions

There was no requirement for a non-clinical assessment in a submission of this type.

IV. Clinical Findings

Introduction

The indications as proposed in the draft PI (new text underlined) are:

Risperdal Consta is indicated for the treatment of schizophrenia and related psychoses.

<u>Risperdal Consta is indicated for maintenance treatment to prevent the recurrence of mood episodes of bipolar disorder.</u>

The recommended dosage for the new indication is 25 mg every two weeks via intramuscular injection. The draft PI states that some patients may benefit from higher doses of 37.5 mg or 50 mg, and that doses above 50 mg were not studied in patients with bipolar disorder. The submission also seeks approval for changes to the Clinical Trials section (related to the new indication) of the PI and to the Adverse Effects section (based on changes to the Company Core Data Sheet (CCDS) for Risperdal Consta, not all of which are related to the new indication) of the PI.[1]

[1] A Company Core Data Sheet (CCDS) is a company-internal global reference labeling document used to direct the

The following aspects of the proposed indication were noted by the clinical evaluator:

It does not specify the use of Risperdal Consta as monotherapy or adjunctive therapy, and by inference includes both.

It refers to "bipolar disorder" without qualification, and thus includes maintenance treatment of both bipolar I and bipolar II disorder.

It refers to "mood disorders" without qualification, and thus includes the prevention of recurrence of manic, depressive and mixed episodes.

It encompasses maintenance treatment with Risperdal Consta in *all* patients with bipolar disorder, irrespective of the medication that was used to treat the *acute* episode.

The submission included:

- RIS-BIM-3003 - A pivotal, randomised-withdrawal, placebo-controlled, recurrence-prevention study of Risperdal Consta monotherapy in subjects with bipolar I disorder.
- RIS-BIP-302 - A supporting, randomised-withdrawal, placebo-controlled, recurrence-prevention study of Risperdal Consta adjunctive therapy in subjects with bipolar I or II disorder and ≥4 mood episodes requiring psychiatric intervention in the previous 12 months. The study is regarded as supporting rather than pivotal for reasons explained in this report.
- A review of the published literature on the efficacy and safety of risperidone (oral and long-acting injection) in the long-term (≥12 week) treatment of bipolar disorder. No randomised controlled trials were identified by this review.
- A 'justification document' supporting proposed changes to the Adverse Effects section of the Risperdal Consta product information.
- A report on 'Post-marketing safety experience with Risperdal Consta in bipolar disorders' dated 10 March 2008, and two updates to that report, dated 19 June 2008 and 27 October 2008.
- A *Clinical Overview*, *Summary of Clinical Efficacy* and *Summary of Clinical Safety* based on the above information.

Pharmacokinetics

There was no requirement for a reassessment of pharmacokinetics in a submission of this type.

Drug Interactions

There was no requirement for a reassessment of drug interactions in a submission of this type.

Pharmacodynamics

There was no requirement for a reassessment of pharmacodynamics in a submission of this type.

Efficacy

Pivotal study

RIS-BIM-3003 was a randomised, double-blind, placebo-controlled study that evaluated the efficacy and safety of Risperdal Consta in the prevention of a mood episode (recurrence[2]) in

content of local (affiliate) labeling.

[2].In both the pivotal study RIS-BIM-3003 and the supportive study RIS-BIP-302, the term 'relapse' was inappropriately used to refer to what the relevant TGA-adopted guideline (*CPMP/EWP/567/98. Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment and Prevention of Bipolar Disorder*) refers to as a 'recurrence'. The *Note for Guidance* makes a clear distinction between a relapse (defined as a resurgence of symptoms during the early period after an acute episode) and a recurrence (defined as a re-emergence of symptoms at a later time, representing a new acute episode). To avoid confusion, the *Note for Guidance* terminology has been used in this evaluation report.

subjects with bipolar I disorder after an initial 26-week (6-month) stabilisation period on Risperdal Consta treatment. The principle inclusion criteria were:

- Age 18-65 years *with*
- A diagnosis of bipolar I disorder as defined by DSM-IV-TR criteria *and*
- An acute manic or mixed episode (YMRS score[3] ≥20) *or* stable (CGI-S[4] score ≤3) for at least 4 weeks on Risperdal Consta alone, *or* stable (CGI-S score ≤3) for at least 4 weeks on another antipsychotic or mood stabiliser but had experienced problems of safety or tolerability with the antipsychotic or mood stabilizer, thereby warranting a change of treatment, *and*
- 2 or more bipolar mood (manic, mixed manic, or depressed) episodes, exclusive of the current episode (if applicable), during the last 2 years. For stable subjects, 1 episode 'occurred within 4 months of enrolment'[5].

There were a large number of exclusion criteria but of note in regard to the generalisability of the efficacy results the trial excluded patients with rapid cycling (>4 mood episodes/year during the last 2 years before screening) or a depressive episode. Of note in regard to the generalisability of the safety results, the trial excluded patients with alanine transaminase (ALT) or aspartate transaminase (AST) levels >2 × the upper limit of normal (ULN).

RIS-BIM-3003 had 5 periods:

- Period I - Screening, up to 1 week.
- Period II (only for patients with an acute episode or stable on another antipsychotic) - Cessation of other antipsychotics / mood stabilisers (if applicable) and 3 weeks of open-label oral risperidone treatment at a dose of 1-6 mg/day.
- Period III - 26 weeks of open-label Risperdal Consta stabilisation. Entry to period III was open to:
  - Patients who had been stable for 4 weeks on Risperdal Consta alone at study entry. These patients entered Period III directly from Period I and continued their previous Risperdal Consta dose of 25, 37.5 or 50 mg once every 2 weeks (q2w).
  - Patients who had an acute episode at study entry that responded to open-label oral risperidone during Period II. Responders had to satisfy *all* of the following criteria:

    (a) Did not meet the DSM-IV-TR criteria for a manic, hypomanic, mixed, or depressive episode;

    (b) Clinical Global Impression - Severity (CGI-S) score ≤3 (mild);

    (c) Discharged from hospital by the end of Week 3 (hospitalisation beyond Day 22 was only allowed for reasons other than bipolar I disorder and only with the prior approval of the sponsor). These patients were started on Risperdal Consta 25 mg q2w at the beginning of

[3].YMRS = Young Mania Rating Scale. The YMRS is a validated measure of the severity of mania, based on the subject's subjective report of their condition over the previous 7 days or since the last visit (whichever was shorter) and the clinician's behavioural observations during the interview, with emphasis on the latter. It consists of 11 items: 7 items (elevated mood, increased motor activity, sexual interest, sleep, language-thought disorder, appearance and insight) are scored on a scale of 0 to 4; 4 items (irritability, speech rate and amount, content, and disruptive-aggressive behaviours) are scored on a scale of 0 to 8. Possible scores range from 0 to 60. A higher score indicates more severe mania.

[4].CGI-S = Clinical Global Impression - Severity. The investigator rates the severity of a subject's condition on a 7-point scale 1=not ill, 2=very mild, 3=mild, 4=moderate, 5=marked, 6=severe, and 7=extremely severe.

[5].It was not clear from the study report whether this meant that 1 episode *could* have occurred within 4 months prior to enrolment, or that 1 episode *must* have occurred within 4 months prior to enrolment.

Period III. They also continued to receive oral risperidone during the first 3 weeks of Period III (to cover the period until release of risperidone from the microspheres in Risperdal Consta).

- Patients who were stabilised on another antipsychotic or mood stabiliser at study entry, who were successfully transferred to oral risperidone and met *all* of the following criteria at the end of Period II:

  (a) Did not meet the DSM-IV-TR criteria for a manic, hypomanic, mixed, or depressive episode;

  (b) CGI-S score ≤3 (mild);

  (c) Did not have a CGI-S score that had increased by ≥2 from study entry. These patients were started on Risperdal Consta 25 mg q2w at the beginning of Period III and also continued to receive oral risperidone during the first 3 weeks of Period III.

Dosage titration (increase or decrease in 12.5-mg increments according to prespecified criteria) was allowed at 4-week intervals during the stabilisation period, as was supplementation with oral risperidone (also according to prespecified criteria). However, no dose adjustments were permitted during the last 8 weeks of open-label Risperdal Consta stabilisation.

Subjects who maintained a treatment response during the stabilisation period and received a stable dose of Risperdal Consta for the last 8 weeks of treatment were eligible to enter the randomised maintenance treatment period (Period IV). Subjects who did not maintain a response, or who did not maintain a stable dose of Risperdal Consta for the last 8 weeks of treatment, were discontinued from the study. A subject was defined as a non-responder during the open-label stabilisation period if they met any of the following criteria: (a) Met DSM-IV-TR criteria for a manic, hypomanic, mixed, or depressive episode; (b) Needed treatment intervention with any mood stabiliser, antipsychotic medication (other than study drug), benzodiazepine (beyond the dosage allowed), or antidepressant medication; (c) Required hospitalisation for any bipolar mood episode; (d) YMRS score >12, MADRS score >12[6], or CGI-S score >4 (marked, severe, or extremely severe) at any single visit.

- Period IV - A randomised, double-blind, maintenance treatment period with either Risperdal Consta or placebo for up to 24 months. Subjects who entered Period IV were randomly assigned, in a 1:1 ratio, to a continuation of the dose of Risperdal Consta they were receiving at the end of Period III (12.5, 25, 37.5, or 50 mg) or placebo injections every 2 weeks for up to 24 months. Subjects remained on double-blind treatment until they met recurrence criteria (see below), withdrew consent, were lost to follow-up, completed the double-blind period, or the study was terminated. Study visits were scheduled every 4 weeks for the first 6 months of Period IV (until Study Week 50) and then every 12 weeks. YMRS, MADRS, CGI-S, SF-36[7], PSP[8] and RUQ[9]

[6] MADRS = Montgomery-Åsberg Depression Rating Scale. The MADRS is a validated depression rating scale with 10 items that cover the core depressive symptoms (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, suicidal thoughts). Each item is scored from 0 (item is not present or is normal) to 6 (severe or continuous presence of the symptom). The total MADRS score can range from 0 to 60, with higher scores representing more severe depression.

[7] SF-36 = Medical Outcomes Short-Form 36. The SF-36 is a validated, patient-based, measure of health-related quality of life. It is a 36-item questionnaire measuring 8 domains (physical functioning, role-physical, role-emotional, social functioning, bodily pain, mental health, vitality, and general health). Responses to questions within each dimension are summed and linearly transformed to scale scores that range from 0 (worst health) to 100 (optimal health) (Ware, 1993). In addition, 2 component scale scores, Standardized Physical Component Summary Scale and the Standardized Mental Component Scale, are computed based on weighted combinations of the 8 domain scores

[8] PSP = Personal and Social Performance scale. The PSP is a validated, clinician-based rating instrument that provides an overall rating of personal and social functioning on a scale of 0 to 100 (higher score indicates better functioning). A

evaluations were performed at each visit. Investigators had been trained and qualified in the use of these instruments.

- Period V - 8 week open-label extension with Risperdal Consta (only for subjects who had received at least 1 dose of double-blind study medication). This period was included to provide for the stabilisation of subjects with a recurrence and ensure an adequate transition to standard care.

The primary efficacy variable was the time from the first injection of double-blind study medication to recurrence of a mood episode during double-blind treatment (Period IV). Subjects met the criteria for a recurrence if they had *any* of the following:

- Met DSM-IV-TR criteria for a manic, hypomanic, mixed, or depressive episode.
- Needed treatment intervention with any mood stabilizer, antipsychotic medication (other than study drug), benzodiazepine (beyond the dosage allowed), or antidepressant medication.
- Required hospitalisation for any bipolar mood episode.
- YMRS score >12, MADRS score >12, or CGI-S score >4 at any single visit.
- Needed a dosage increase or supplementation with oral risperidone or another antipsychotic or mood stabilizer, in the opinion of the investigator.

A large number of secondary efficacy variables were also examined, as outlined below:

- Time to recurrence of a mood episode within various subgroups:
  - Subject category at screening (acute, stable on risperidone, stable on other antipsychotic or mood stabiliser);
  - Sex;
  - Region;
  - Number of previous psychiatric hospitalizations (<5, 5-10, >10);
  - Years since diagnosis (≤5, >5);
  - Dose level (≤25 mg, ≥37.5 mg based on the fixed dose during double-blind treatment);
  - Mental health status at baseline of double-blind treatment (categorised based on quartiles of SF-36 mental health domain score).
- Time to recurrence of an elevated mood episode.
- Time to recurrence of a manic episode (post-hoc).
- Time to recurrence of a hypomanic episode (post-hoc).
- Time to recurrence of a depressed mood episode.
- Time to early discontinuation of study medication for any reason (including recurrence) except termination of the study by the sponsor, as a measure of overall duration of treatment.
- Time to recurrence of a mood episode, including recurrences observed in subjects followed off study medication during double-blind treatment (Period IV) and subjects during open-label extension who did not have a recurrence in Period IV (as a sensitivity analysis for the primary efficacy variable)
- Time to clinically relevant decline in mental health status (ie ≥5-point decrease from baseline in the normalised mental health domain score of the SF-36 score) during double-blind treatment.

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single rating is based on 4 domains of functioning: socially useful activities, including work and study; personal and social relationships; self-care; and disturbing and aggressive behaviour.

[9].RUQ = Resource Use Questionnaire. The RUQ included items related to sociodemographics, productivity, and employment status; use of outpatient services, emergency room visits, or hospitalization during the previous month; and assessment of accommodation status (at home, alone; at home, with family or friends; homeless; psychiatric institution; sheltered living; prison; or other).

- Change in YMRS, MADRS, and CGI-S scores at protocol-specified time points and at end point from the relevant baselines during open-label oral risperidone treatment, open-label Risperdal Consta stabilisation, and double-blind treatment.
- Change in the scores for the 8 domains, Mental Health Component Summary and Physical Component Summary of the SF-36, and change in PSP score, at protocol-specified time points and at the endpoint from the relevant baselines during open-label Risperdal Consta stabilisation and double-blind treatment.
- Number and percentage of responders at each time point during open-label oral risperidone treatment.
- Number and percentage of maintained responders at each time point during open-label Risperdal Consta stabilisation (non-responders defined as subjects with at least 1 YMRS score >12, MADRS score >12, or CGI-S score >4 during open-label Risperdal Consta stabilisation).

The primary efficacy variable and other 'time-to-event' variables were analysed by the Kaplan-Meier method. The statistical comparison between treatment groups was performed using a log-rank test, controlling for country. A *post-hoc* analysis using Cox proportional hazards regression was conducted to estimate the hazard ratio for time to recurrence of a mood episode.

Ordinal variables (YMRS, MADRS, CGI-S, PSP and SF-36 scores) were analysed using an analysis of covariance (ANCOVA) model, with treatment and country as factors, and baseline score for the respective study period as covariate.

Four analysis sets were defined:

- Primary efficacy analysis set: Subjects randomised to double-blind treatment (Period IV) who received at least 1 injection of double-blind medication.
- All treated subjects: Subjects who received at least 1 dose of study medication (oral risperidone or Risperdal Consta).
- Subjects with an injection: subjects who received at least 1 injection of Risperdal Consta during open-label Risperdal Consta stabilisation (Period III).
- Treated in Period V (open-label): subjects who received at least 1 dose of oral or injectable risperidone during open-label extension treatment (Period V).

Approximately 600 subjects were to be enrolled into the study, with the goal of randomising 200 subjects (100 per group) in whom at least 114 recurrence events were expected during double-blind treatment. This sample size was calculated to provide approximately 90% power to detect a 'clinically meaningful difference of 23%' in the recurrence rates of any mood episode between the risperidone and placebo groups (assuming recurrence rates at 9 months of approximately 45% in the risperidone group and 68% in the placebo group).

Because of issues at two sites, discussion of which is beyond the scope of this document, the primary efficacy analysis and all secondary efficacy analyses for RIS-BIM-3003 excluded the 28 subjects who were randomised to Period IV from the two sites. A secondary sensitivity analysis of the primary efficacy variable (time to recurrence during double-blind treatment) was performed including these subjects. All of the 56 subjects enrolled at the two sites noted above were included in the safety analyses.

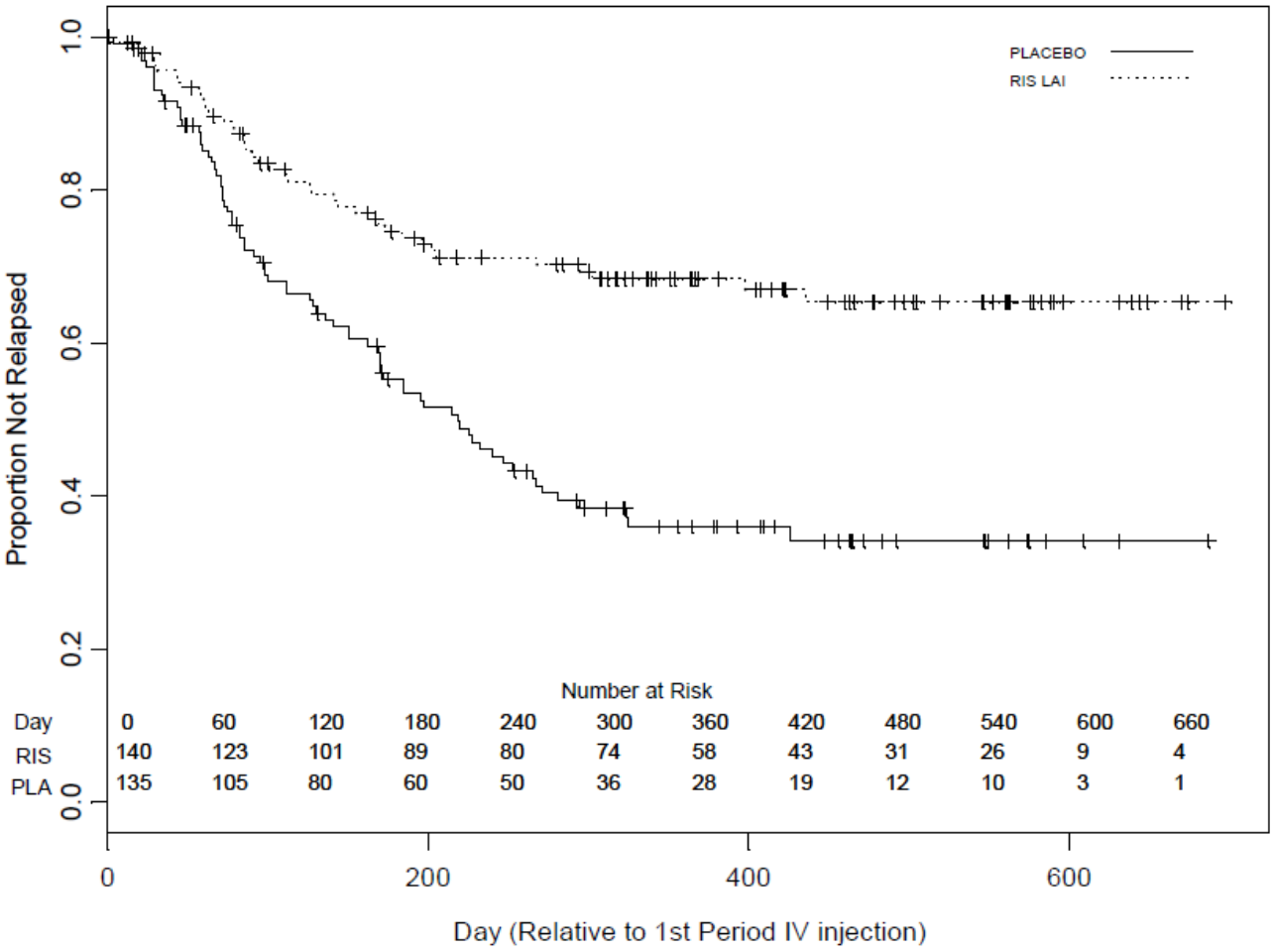
Primary efficacy results

There was a statistically significant difference ($p<0.001$; log-rank test, adjusting for country) between the treatment groups in the time to recurrence during double-blind treatment in favour of Risperdal Consta[10]. The percentage of subjects who had a recurrence during double-blind treatment

[10] The primary analysis excluded data from the GCP non-compliant centre (Centre 221) and the centre with alleged

was 30% (42 of 140 subjects) in the Risperdal Consta group and 56% (76 of 135 subjects) in the placebo group. Kaplan-Meier curves of the time to recurrence for the treatment groups are shown in Figure 1.

Figure 1: RIS-BIM-3003. Kaplan-Meier curves of time to recurrence in Period IV.



In the placebo group, the 25th percentile time to recurrence was 82 days and the median time to recurrence was 219 days. In the Risperdal Consta group, the 25th percentile time to recurrence was 173 days and the median time to recurrence was not reached during the study period.

As can be seen from the Kaplan-Meier curves in Figure 1, most of the recurrences occurred during the first year of follow-up. Kaplan-Meier estimates of the recurrence rate at successive 3 month intervals up to 12 months are shown in Table 1, below. At 12 months, the estimated recurrence rate was 64% in the placebo group and 32% in the Risperdal Consta group, representing an absolute reduction of 32% and a relative reduction of 50% in the recurrence rate in subjects maintained on Risperdal Consta.

research misconduct (Centre 107). A sensitivity analysis including the data from these centres also showed a statistically significant difference in favour of Risperdal Consta (adjusted log-rank p<0.001; percentage of subjects with relapse 29% vs 52%).

Table 1: RIS-BIM-3003: Kaplan-Meier estimate of recurrence rate (%) during double-blind treatment (Randomised subjects).

Time point	Kaplan-Meier estimate of recurrence rate			
	Placebo	Risperdal Consta	Point estimate of treatment effect (Reduction in recurrence rate due to RisperdalConsta) *	
			Absolute	Relative
Month 3 (Day 90)	28%	16%	12%	43%
Month 6 (Day 183)	45%	25%	20%	44%
Month 9 (Day 274)	60%	30%	30%	50%
Month 12 (Day 365)	64%	32%	32%	50%

Excludes subjects from Centres 221/107. *Calculated by the evaluator.

A post-hoc Cox proportional hazards regression analysis of the primary efficacy variable found a hazard ratio of 2.50 (95% confidence intervals (CIs) 1.71 to 3.66; p<0.0001) for recurrence in the placebo group compared to the Risperdal Consta group. This equates to a hazard ratio of 0.40 for recurrence in the Risperdal Consta group compared to the placebo group (95% CIs 0.27 to 0.58), or a 60% relative reduction in the risk of recurrence in the Risperdal Consta group compared to placebo (95% CIs42% to 73%).

Kaplan-Meier curves for the time to recurrence according to subject type at screening showed that Risperdal Consta reduced the risk of recurrence in subjects who had entered the study with an acute episode, subjects who had been stabilised on risperidone at the time of enrolment, and subjects who had been stabilised on another antipsychotic/mood stabiliser at the time of enrolment (noting that subjects in the first 2 categories first had to respond to risperidone either before or during the study, and all subjects had to maintain a response through the 26-week open-label period before being eligible for randomisation).

Recurrence percentages according to the type of recurrence episode (elevated mood or depressive) are summarised in Table 2.

Table 2: RIS-BIM-3003: Number (%) of patients with recurrences during double-blind treatment according to the type of recurrence (Randomised subjects).

Double-blind treatment Period IV Type of Mood Episode	PLACEBO (N=135) Events (%)	RIS LAI (N=140) Events (%)
Elevated mood	62 (46)	22 (16)
Manic	53 (39)	20 (14)
Mixed	9 (7)	2 (1)
Depressive mood	14 (10)	20 (14)

Excludes subjects from Centres 221/107.

Elevated mood recurrences occurred in 46% of the placebo group and 15% of the Risperdal Consta group; depressed mood recurrences occurred in 16% of the Risperdal Consta group and 14% of the placebo group. These findings show that the overall beneficial effect of Risperdal Consta was due primarily to the prevention of elevated mood recurrences, with no effect (possibly a small unfavourable effect) on the prevention of depressed mood recurrences. This conclusion is supported by Kaplan-Meier curves (not shown in this AusPAR) which show a steady divergence in the proportion of patients with an elevated mood recurrence over the course of the first year, leading to

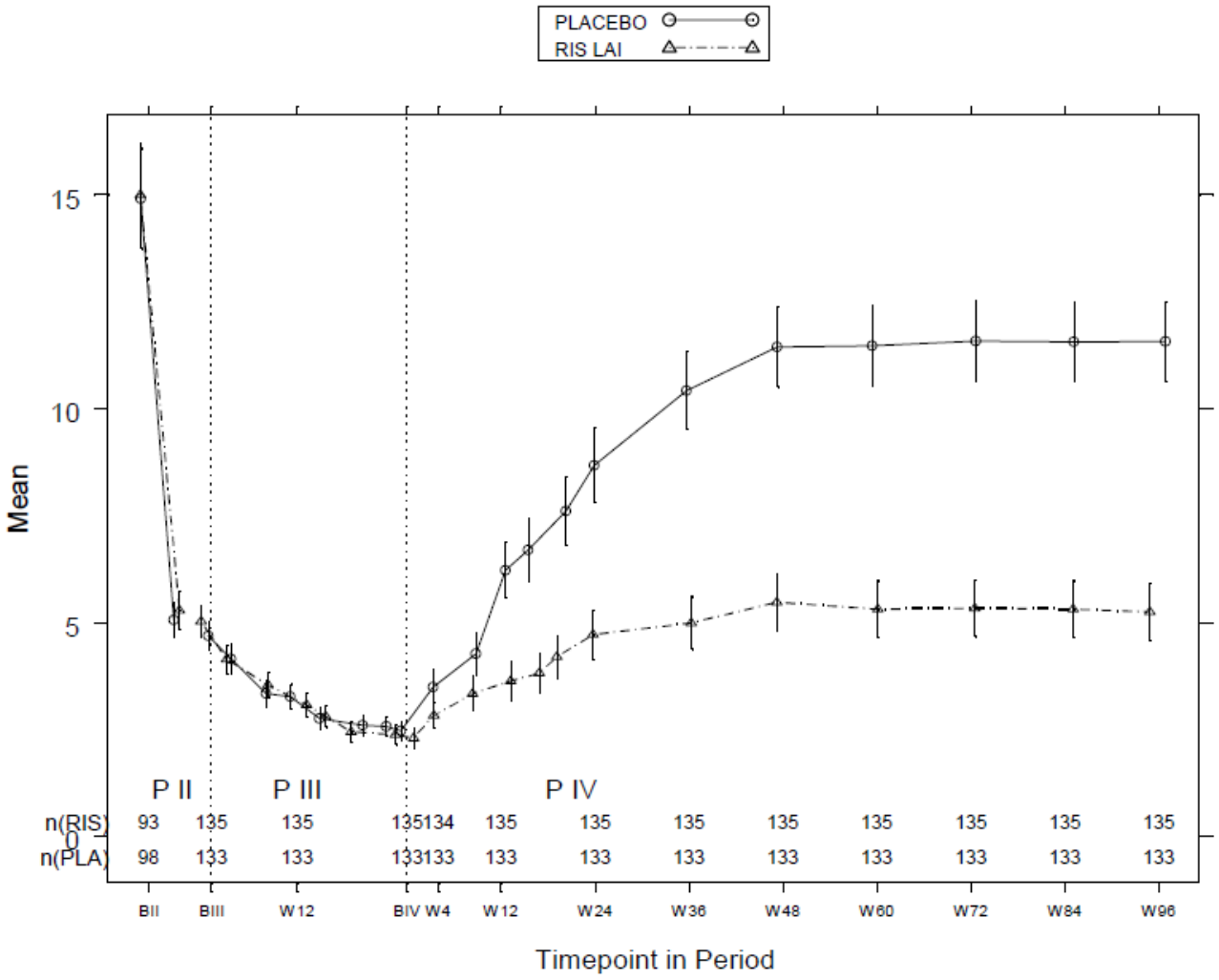
a large difference (about 40%) at the end of the first year in favour of Risperdal Consta that was maintained during subsequent follow-up. For depressed mood recurrences, however, Kaplan-Meier curves (not shown) show no difference between the two treatment groups during the first year of follow-up, but then diverge a little in favour of placebo.

Other efficacy results

Young Mania Rating Scale

The mean YMRS score improved during open-label risperidone treatment (Periods II and III) (Figure 2). As expected, YMRS improvement during open-label treatment was greater in the sustained responders (who went on to randomisation) than in the study population as a whole. Mean YMRS worsened in both treatment groups during double-blind treatment (Period IV), but the worsening was significantly greater with placebo than Risperdal Consta.

Figure 2: RIS-BIM-3003: YMRS score (mean ± SD) during double-blind treatment (Period IV; Randomised subjects).



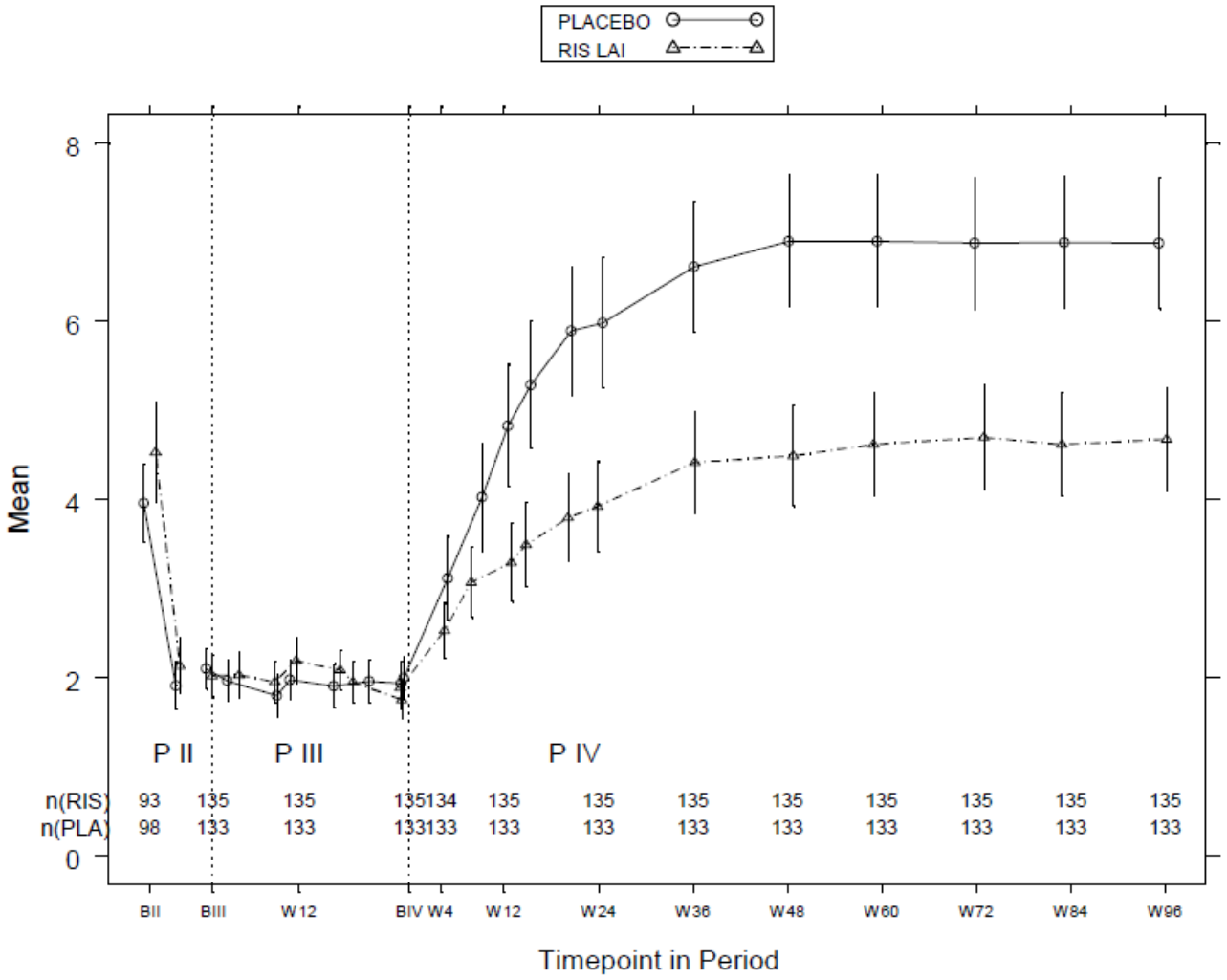
RIS LAI = risperidone long-acting injection (Risperdal Consta);
Includes only patients with data for both baseline and endpoint; Excludes sites 221/107.

Montgomery-Åsberg Depression Rating Scale

The mean MADRS score improved during Period II, mostly due to improvement in patients with an acute episode at screening (Figure 3). The mean MADRS score then worsened during Period III (open-label risperidone stabilisation), due the influence of non-responders. In the sustained

responders (who went on to enter the randomised treatment period), MADRS remained stable during Period III. During randomised treatment, the mean MADRS worsened in both treatment groups, but the worsening was significantly greater with placebo than Risperdal Consta.

Figure 3: RIS-BIM-3003: MADRS score (mean ± SD) during double-blind treatment (Period IV; Randomised subjects).

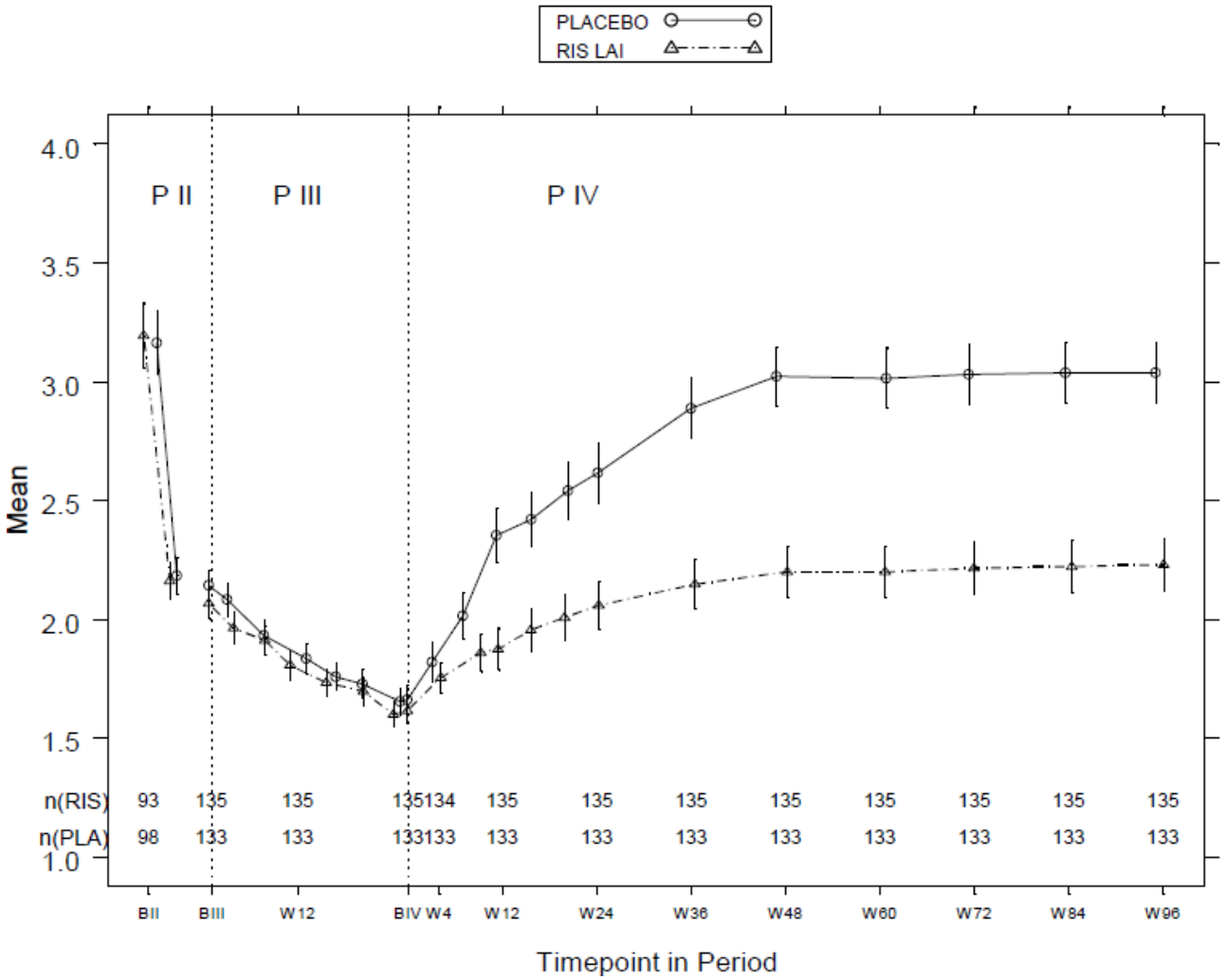


RIS LAI = risperidone long-acting injection (Risperdal Consta);
Includes only patients with data for both baseline and endpoint; Excludes sites 221/107.

Clinical Global Impression - Severity

Mean CGI-S scores during the open label and double-blind periods followed a similar pattern to the MADRS scores (Figure 4). During randomised treatment, the mean CGI-S score worsened in both treatment groups, but the worsening was significantly greater with placebo than Risperdal Consta.

Figure 4: RIS-BIM-3003: CGI-S score (mean ± SD) during double-blind treatment (Period IV; Randomised subjects).

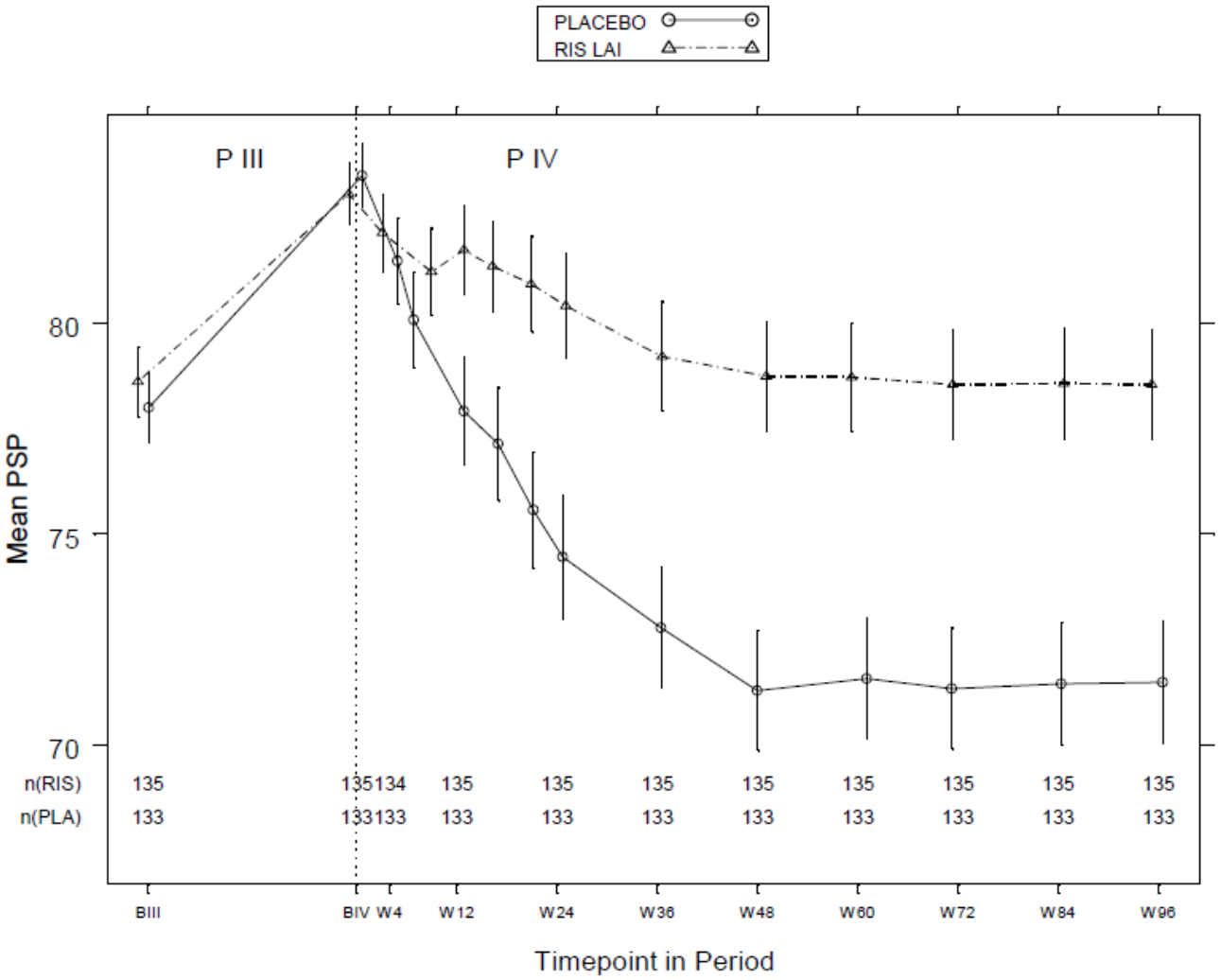


RIS LAI = risperidone long-acting injection (Risperdal Consta);
Includes only patients with data for both baseline and endpoint; Excludes sites 221/107.

Personal and Social Performance scale

The PSP was not assessed during Period II. During open-label stabilisation (Period III), the mean PSP score improved in the overall population and in the sustained responders who went on to randomisation (Figure 5). During randomised treatment, the mean PSP score worsened in both treatment groups, but the worsening was significantly greater with placebo than Risperdal Consta.

Figure 5: RIS-BIM-3003: PSP score (mean ± SD) during double-blind treatment (Period IV; Randomised subjects).



RIS LAI = risperidone long-acting injection (Risperdal Consta);
Includes only patients with data for both baseline and endpoint; Excludes sites 221/107.

Medical Outcomes Short-Form 36

During randomised treatment, significant differences in favour of Risperdal Consta were seen for 2 domains (pain index, role-emotional) and the Standardised Metal Component Scale, but not for the remaining domains (mental health, physical functioning, role-physical, social functioning, vitality, general health perceptions) or the Standardised Physical Component Scale.

With regard to the SF-36 mental health domain, the mean score worsened slightly in the overall population (from 67.5 to 65.4) during open-label stabilisation (Period III) but improved slightly in the sustained responders who went on to randomisation (from 70.6 to 72.7 and from 68.7 to 70.4 in the responders who were subsequently allocated to placebo and Risperdal Consta, respectively. During randomised treatment, the mean score worsened in both treatment groups. The amount of worsening was numerically greater with placebo (7.2 points) than Risperdal Consta (2.0 points), but the between-treatment difference was not statistically significant.

Resource Use Questionnaire

Similar percentages of subjects in both treatment groups reported at least one visit to an outpatient service (22% of in the placebo group and 23% in the Risperdal Consta group), with visits to psychiatrists more common in the placebo group and visits to general practitioners more common in

the Risperdal Consta group. Hospitalisations reported using the RUQ (mostly to psychiatric hospitals) were more common in the placebo group (14%) than the Risperdal Consta group (6%). Fewer than 5% of subjects reported an emergency room visit during double-blind treatment and most visits were for mental health conditions.

Evaluator comments on the pivotal study

The design of the pivotal study was in accordance with the relevant TGA-adopted EU guideline, *CPMP/EWP/567/98. Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment and Prevention of Bipolar Disorder*.[11] The stabilisation period was long enough to ensure that mood episodes during the double-blind period represented true recurrences (new episodes) rather than relapses of the previous acute episode. The statistical methods, including the handling of data from the two suspect study centres, were appropriate.

A statistically and clinically meaningful effect of Risperdal Consta was demonstrated in terms of both a lengthening of the time to recurrence of a mood episode and a reduction of the proportion of patients with recurrence of a mood episode, as recommended in the *Note for Guidance*. Efficacy was demonstrated irrespective of whether the subject had entered the study with an acute episode, stabilised on risperidone or stabilised on another antipsychotic, but with the proviso that in all cases the subject had to first undergo successful stabilisation on Risperdal Consta.

Importantly, Risperdal Consta was primarily effective in preventing elevated mood recurrences. Risperdal Consta did not prevent depressed mood recurrences (and possibly had a small unfavourable effect after the first year) on depressed mood recurrences

The results for the secondary efficacy variables were consistent with those for the primary efficacy variable. Of note, both manic and depressive symptoms were significantly reduced, compared to the placebo group, in patients maintained on Risperdal Consta. There was a trend towards less worsening of the Mental Health domain of the SF-36 in patients maintained on Risperdal Consta, although the effect did not reach statistical significance. This probably reflects a lack of power in the study in relation to demonstrating effects on quality of life.

Supporting study

RIS-BIP-302 was a prospective, randomised, multicentre (India and USA) study that evaluated the efficacy and safety of Risperdal Consta as adjunctive therapy to 'treatment as usual' (TAU) in adults with 'frequently-relapsing' bipolar disorder type I or II (FRBD). FRBD was defined as bipolar I or II disorder according to DSM-IV-TR criteria, with at least 4 episodes of mood disorder requiring psychiatric intervention in the past 12 months.

RIS-BIP-302 is regarded as a supporting, rather than a pivotal, study in relation to the claimed indication because:

- The study only investigated the effect of Risperdal Consta in a restricted subset of patients with bipolar disorder, namely those with FRBD;
- That subset is akin to, but not the same as, the recognised condition of rapid recycling bipolar disorder (RCBD);
- The *Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment and Prevention of Bipolar Disorder* states that 'data from rapid cyclers cannot be extrapolated to the whole group of patients with bipolar disorder', and this would also apply to data from patients with FRBD.

[11] CPMP/EWP/567/98. Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment and Prevention of Bipolar Disorder. http://www.tga.gov.au/docs/pdf/euguide/ewp/056798en.pdf

Enrolled patients entered a 16-week open-label stabilisation period, during which Risperdal Consta was initiated as adjunctive therapy to TAU. Patients taking oral antipsychotics had these tapered within the first 3 weeks of the study. The starting dose of Risperdal Consta was 25 mg q2w, increased to 37.5 mg q2w after 4 weeks and 50 mg q2w after 10 weeks if treatment response was unsatisfactory (YMRS or MADRS total scores >10 or CGI-S ≥3). Patients who achieved stable remission of mood episodes in the open label stabilisation period qualified for a 52-week double-blind, placebo-controlled recurrence-prevention period in which they continued taking their TAU and were randomised to receive injections of either Risperdal Consta (at the same dose as at the end of the stabilisation phase) or placebo every 2 weeks. Patients who did not achieve stable remission during the planned 16-week open-label period were not automatically discontinued but were offered the opportunity, if clinically appropriate, to continue with open-label Risperdal Consta + TAU for up to an additional 36 weeks; these patients were identified as 'non-remitted continuing' (NRC) patients. Patients who discontinued early from the randomised period were offered the opportunity to be followed as 'retrieved dropouts' (RDOs), with treatment determined by the investigator (which may have included open-label Risperdal Consta).

A total of 313 subjects were screened, of whom 275 were enrolled into the open-label Risperdal Consta + TAU stabilisation period. 218 subjects completed the open-label period, of whom 139 (51% of the original 275) were in continued remission and entered the double-blind randomised period. Amongst the remaining 136 enrolled subjects, 57 discontinued during open-label treatment, 9 did not maintain remission during open-label treatment and withdrew from the study, and 70 did not maintain remission during the planned 16-week open-label treatment period but continued open-label treatment as NRC patients.

Of the 139 subjects who entered the randomised treatment period, 72 were assigned to Risperdal Consta + TAU and 67 to placebo + TAU. These subjects constituted the primary, intention-to-treat (ITT) efficacy analysis population.

The primary efficacy variable for the study was time from randomisation to recurrence during the double-blind treatment period, where recurrence was defined as the first occurrence of a mood episode, determined in a blinded manner, by an independent Relapse [sic] Monitoring Board (RMB). A recurrence was recorded if the subject met DSM-IV-TR criteria for an acute mood episode in the setting of adequate compliance with oral TAU, *and also* satisfied at least 1 of the following 3 criteria:

1. The subject clinically worsened and needed the addition of a new mood stabiliser, antidepressant, or antipsychotic; or required a dose increase of >20% of any existing mood stabiliser or antidepressant used by the subject as a part of oral TAU, and also met both of the following criteria:

   - YMRS score >15 or MADRS score >15 (indicating worsening of a mood disorder); and
   - CGI-S[12] score ≥4 or CGI-C [13] score ≥6 or GAF [14] score decreased by >10 points from baseline (indicating worsening of clinical status).

[12] Actually the CGI-BP-S (Clinical Global Impression - Bipolar - Change), but the instrument is the same as the CGI-S used in RIS-BIM-3003 and therefore the same terminology is used for consistency.

[13] Actually the CGI-BP-S (Clinical Global Impression - Bipolar - Change), but the shorter abbreviation is used for consistency with the reporting of the pivotal study. The CGI-[BP]-C scale is a 7-point, clinician-assessed scale that measures *change* in the subject's status compared to a reference visit. Values of 0 to 3 indicate improvement, a value of 4 indicates no change and values of 5 to 7 indicate worsening. The reference visit for the double-blind period of RIS-BIP-302 was Visit 10 (Week 16), at the end of open-label stabilisation.

[14] GAF = Global Assessment of Function scale. The GAF is a validated, clinician-assessed, 100-point, single-item scale that assesses the global functioning of in- or out-patients. Higher scores indicate better functioning.

2. The subject was hospitalised for worsening of manic or depressive symptoms and met the following criteria:

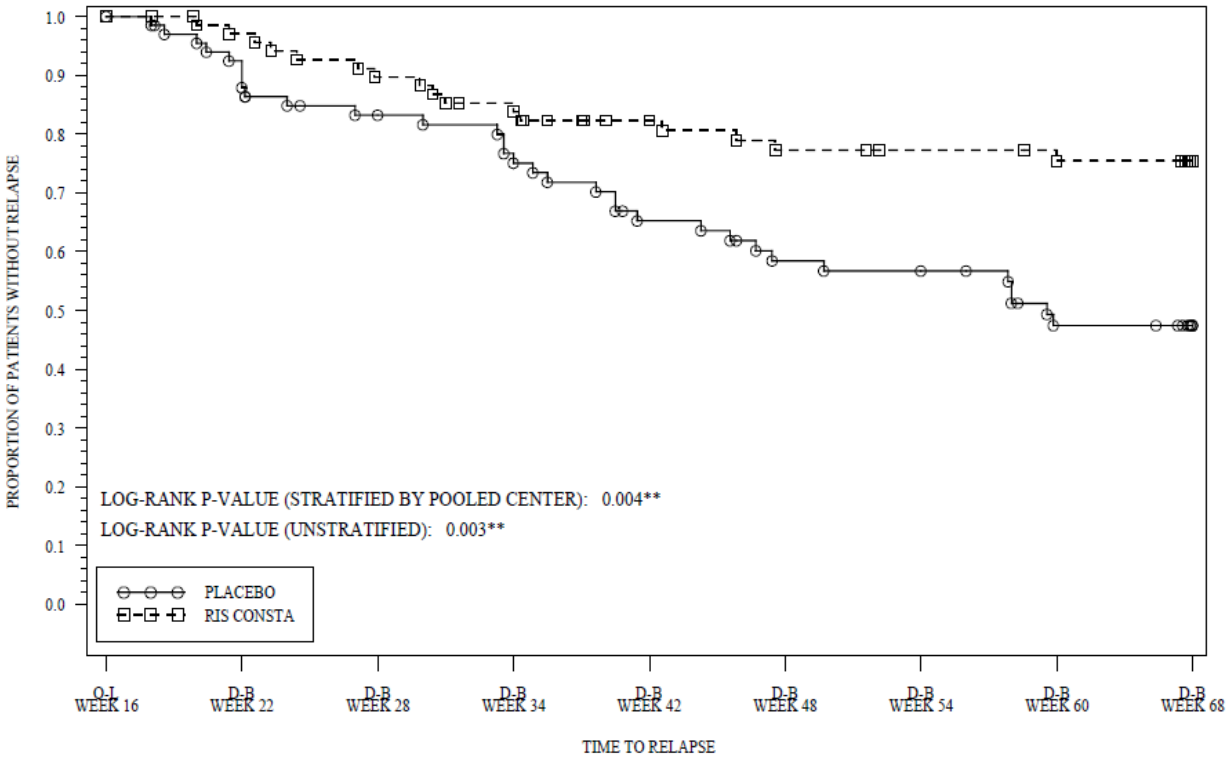
   - YMRS score >15 or MADRS score >15 (indicating worsening of a mood disorder); and
   - CGI-S score ≥4 or CGI-C score ≥6 or GAF score decreased by >10 points from baseline (indicating worsening of clinical status).

3. The subject was hospitalized for worsening of manic or depressive symptoms and the subject had significant suicidal ideation (for example, ISST Revised [15] score of >7).

Results

Maintenance treatment with Risperdal Consta + TAU significantly prolonged the time to recurrence compared to placebo + TAU (Figure 6). Over the course of the 52-week double-blind period, 22% of subjects in the Risperdal Consta + TAU group and 48% of those in the placebo + TAU group were determined to have had a recurrence by the independent RMB. The median time to recurrence was 305 days in the placebo + TAU group and was not reached in the Risperdal Consta + TAU group. The 25th percentile time to recurrence was 134 days in the placebo + TAU group and was not reached in the Risperdal Consta + TAU group.

Figure 6: RIS-BIP-302: Kaplan-Meier analysis of time to recurrence during double-blind treatment (ITT population).



RIS CONSTA (72)72	65	61	55	49	46	44	42	42
PLACEBO (67): 67	57	52	46	39	34	33	25	24

RIS CONSTA = Risperdal Consta + TAU; PLACEBO = placebo + TAU).

[15]ISST Revised = Revised InterSePT Scale for Suicidal Thinking. The ISST is a 12-item instrument developed for the assessment of suicidal ideation and prediction of suicide in patients with schizophrenia and schizoaffective disorders. Each item is rated on a scale of 0 (none), 1 (weak) or 3 (moderate to strong). The ISST has been shown to correlate with other measures of suicidality/depression and independent measures of psychopathology.

In contrast to the pivotal study, Risperdal Consta + TAU in RIS-BIP-302 reduced the recurrence of both elevated and depressed mood recurrences (Table 3).

Table 3: RIS-BIP-302: Number (%) of patients with recurrences during double-blind treatment according to the type of recurrence (ITT population).

Recurrence type	**Risperdal Consta + TAU** (N=72)	**Placebo + TAU** (N=67)
Any recurrence	**16 (22)**	**32 (48)**
Depression	9 (13)	14 (21)
Mania	5 (7)	14 (21)
Mixed	2 (3)	4 (6)

Percentages have been recalculated by the evaluator to show the percentage of *patients* with each recurrence type, rather than the percentage of recurrences represented by each type).

The recurrence rate on Risperdal Consta + TAU was comparable at Indian and US sites (22% and 23%, respectively) but the recurrence rate on placebo was lower in India than in the US (46% and 60%, respectively). The between-treatment difference was thus lower at the Indian sites, which dominated the overall results. Given that the US clinical environment is more likely to reflect the Australian situation, the overall efficacy results may be regarded as conservative. Possible reasons for the difference in the placebo recurrence rate at the Indian and US sites were not discussed in the study report.

Evaluator comments on the supporting study

In the supporting study RIS-BIP-302, Risperdal Consta reduced the risk of both elevated and depressed mood recurrences, when used as adjunctive therapy in adults with frequently recurring, predominantly bipolar I disorder, who had first been successfully stabilised on a combination of Risperdal Consta and 'treatment as usual' for 16 weeks. However:

- In accordance with the *Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment and Prevention of Bipolar Disorder*, the findings of this study cannot be reliably extrapolated to the whole group of patients with bipolar I disorder.
- The population enrolled in the study does not correspond to a recognised DSM-IV diagnostic category.

Literature review

The sponsor performed a 'comprehensive search' of published literature reporting original clinical efficacy and safety data related to the long-term (>12 weeks) use of oral and long-acting injectable risperidone in subjects with bipolar disorder, covering the period from 1 January 1992 to 31 August 2008. Fifty three articles were identified as containing original clinical data relevant to the search terms, and were included in the review. There were 28 fully published reports, 20 abstracts, 3 letters and 2 conference posters. *No randomised controlled trials were identified.* There were 27 prospective, open-label clinical studies, 9 of which were comparative studies. The other articles included 8 retrospective reviews, and 15 case reports. Overall, data were reported for approximately 1,300 subjects treated for bipolar disorder with risperidone for >12 weeks, approximately 190 of whom received Risperdal Consta. Efficacy results were reported in 48 articles, and safety results were reported in 43 articles.

The evaluator noted that the absence of randomised, controlled trials means that the literature review does not provide additional efficacy data that is meaningful in a regulatory context. The literature references are, however, relevant to the consideration of safety and are discussed in that light.

Conclusions regarding efficacy

In the pivotal study RIS-BIM-3003, in adults with bipolar I disorder who had first been successfully stabilised on Risperdal Consta, further treatment with Risperdal Consta monotherapy reduced the subsequent risk of an elevated mood recurrence, but not a depressed mood recurrence.

In the supporting study RIS-BIP-302, Risperdal Consta reduced the risk of both elevated and depressed mood recurrences, when used as adjunctive therapy in adults with frequently recurring, predominantly bipolar I disorder, who had first been successfully stabilised on a combination of Risperdal Consta and 'treatment as usual' for 16 weeks. In accordance with the *Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment and Prevention of Bipolar Disorder*, the findings of this study cannot be extrapolated to the whole group of patients with bipolar I disorder.

The literature review did not provide meaningful efficacy data.

Safety

Limitations of the safety data

The two fully-reported studies excluded patients with a range of safety-related risk factors (clinically significant cardiovascular, renal, hepatic, gastrointestinal, neurological, endocrine, metabolic, or pulmonary disease), not all of which are listed as contraindications or even precautions in the proposed PI for Risperdal Consta. Accordingly, the safety data from the two main studies are not fully representative of safety in the less selected population that would be exposed in clinical practice.

Subject exposure

In the 2 fully-reported studies, a total of 775 subjects with bipolar disorder received at least one dose of Risperdal Consta. 374 subjects had ≥180 days of exposure (229 in RIS-BIM-3003 and 145 in RIS-BIP-302) and 201 subjects had ≥365 days of exposure (91 in RIS-BIM-3003 and 110 in RIS-BIP-302). The vast majority of subjects in both studies were on 25 mg of Risperdal Consta for both the open-label stabilisation and double-blind periods.

Adverse events and adverse drug reactions

Pivotal study RIS-BIM-3003

During open-label oral risperidone treatment, treatment-emergent adverse events (AEs) were reported in 188/440 (43%) subjects (Table 4).The most frequent AEs were headache (8% of subjects), somnolence (5%), and insomnia (5%). Summary information was not provided regarding the percentage of patients with AEs considered by the investigator to be at least possibly related to study treatment (adverse drug reactions; ADRs). The study report stated that 'most AEs were assessed by the investigator as not related, doubtfully related, or possibly related to study drug. In the case of reproductive system and breast disorders events, 9 of 12 subjects had an event assessed as probably or very likely related'.

During open-label Risperdal Consta stabilisation, AEs were reported in 298/501 (59%) subjects (Table 5). The most frequent AEs were insomnia (13%), agitation (6%), and headache (6%). The study report stated that 'most treatment-emergent adverse events were assessed by the investigator as not related, doubtfully related, or possibly related to study drug, with the exception of reproductive system and breast disorders events in whom 19 of 31 subjects had an event assessed as probably related or very likely related'.

During double-blind treatment, AEs were reported in 81/154 (53%) of the Risperdal Consta group and 79/149 (53%) of the placebo group (Table 6). The most common AEs in the Risperdal Consta and placebo groups, respectively, were mania (5% vs 11%), insomnia (8% vs 6%), bipolar I

disorder (2% vs 7%), headache (7% vs 7%), and depression (6% vs 2%). AEs that were noticeably more frequent in the Risperdal Consta group than the placebo group during the double-blind period (≥3% difference) were depression and weight increased. The study report stated that 'most treatment-emergent adverse events were assessed by the investigator as not related or possibly related to study drug'.

During the open-label Risperdal Consta extension period, AEs were reported in 40/160 (25%) of the patients taking open-label Risperdal Consta (Table 7). The most frequent AEs were insomnia (4%) and agitation (3%). The study report stated that 'most treatment-emergent adverse events were assessed by the investigator as not related, doubtfully related, or possibly related to study drug'.

Table 4: RIS-BIM-3003: AEs in ≥2% of subjects during open-label oral risperidone treatment (Safety population).

Period II Open-label Oral Risperidone		Stable on	Stable on	
	Acute	RIS	Other AP	Total
Body System or Organ Class	(N=275)	(N=4)	(N=161)	(N=440)
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)
Total no. subjects with adverse events	137 (50)	2 (50)	49 (30)	188 (43)
Nervous system disorders	67 (24)	2 (50)	25 (16)	94 (21)
Headache	23 (8)	1 (25)	9 (6)	33 (8)
Somnolence	15 (5)	1 (25)	8 (5)	24 (5)
Dizziness	8 (3)	0	4 (2)	12 (3)
Tremor	9 (3)	0	3 (2)	12 (3)
Akathisia	7 (3)	0	3 (2)	10 (2)
Sedation	6 (2)	0	1 (1)	7 (2)
Gastrointestinal disorders	37 (13)	0	16 (10)	53 (12)
Constipation	10 (4)	0	3 (2)	13 (3)
Nausea	7 (3)	0	6 (4)	13 (3)
Dry mouth	6 (2)	0	1 (1)	7 (2)
Salivary hypersecretion	6 (2)	0	1 (1)	7 (2)
Dyspepsia	5 (2)	0	0	5 (1)
Psychiatric disorders	31 (11)	1 (25)	17 (11)	49 (11)
Insomnia	14 (5)	0	9 (6)	23 (5)
Anxiety	3 (1)	0	3 (2)	6 (1)
Aggression	0	1 (25)	0	1 (<1)
Musculoskeletal and connective tissue disorders	26 (9)	0	5 (3)	31 (7)
Muscle rigidity	7 (3)	0	2 (1)	9 (2)
Musculoskeletal stiffness	4 (1)	0	3 (2)	7 (2)
Infections and infestations	16 (6)	0	7 (4)	23 (5)
Nasopharyngitis	2 (1)	0	4 (2)	6 (1)
General disorders and administration site conditions	16 (6)	0	3 (2)	19 (4)
Fatigue	5 (2)	0	1 (1)	6 (1)
Eye disorders	4 (1)	0	4 (2)	8 (2)
Vision blurred	0	0	3 (2)	3 (1)
Injury, poisoning and procedural complications	3 (1)	1 (25)	0	4 (1)
Contusion	0	1 (25)	0	1 (<1)

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

Table 5: RIS-BIM-3003: AEs in ≥2% of subjects during open-label Risperdal Consta stabilisation (Safety population).

Period III Open-Label RISPERDAL CONSTA		Stable on	Stable on	
	Acute	RIS	Other AP	Total
Body System or Organ Class	(N=235)	(N=115)	(N=151)	(N=501)
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)
Total no. subjects with adverse events	142 (60)	70 (61)	86 (57)	298 (59)
Psychiatric disorders	76 (32)	35 (30)	41 (27)	152 (30)
Insomnia	32 (14)	14 (12)	21 (14)	67 (13)
Agitation	13 (6)	8 (7)	7 (5)	28 (6)
Depression	16 (7)	3 (3)	7 (5)	26 (5)
Anxiety	10 (4)	7 (6)	7 (5)	24 (5)
Libido decreased	8 (3)	3 (3)	2 (1)	13 (3)
Bipolar I disorder	8 (3)	2 (2)	2 (1)	12 (2)
Suicidal ideation	1 (<1)	2 (2)	1 (1)	4 (1)
Nervous system disorders	48 (20)	19 (17)	27 (18)	94 (19)
Headache	16 (7)	3 (3)	9 (6)	28 (6)
Akathisia	9 (4)	4 (3)	2 (1)	15 (3)
Dizziness	4 (2)	4 (3)	6 (4)	14 (3)
Somnolence	7 (3)	3 (3)	3 (2)	13 (3)
Tremor	3 (1)	3 (3)	5 (3)	11 (2)
Parkinsonism	4 (2)	1 (1)	1 (1)	6 (1)
Sedation	5 (2)	0	1 (1)	6 (1)
General disorders and administration site conditions	27 (11)	10 (9)	12 (8)	49 (10)
Irritability	9 (4)	6 (5)	4 (3)	19 (4)
Fatigue	9 (4)	1 (1)	4 (3)	14 (3)
Asthenia	2 (1)	2 (2)	1 (1)	5 (1)
Pyrexia	4 (2)	1 (1)	0	5 (1)
Infections and infestations	22 (9)	10 (9)	17 (11)	49 (10)
Nasopharyngitis	6 (3)	4 (3)	11 (7)	21 (4)
Bronchitis	4 (2)	1 (1)	0	5 (1)
Urinary tract infection	0	2 (2)	0	2 (<1)
Investigations	29 (12)	12 (10)	6 (4)	47 (9)
Weight increased	17 (7)	8 (7)	2 (1)	27 (5)
Blood glucose increased	5 (2)	0	0	5 (1)
Gastrointestinal disorders	21 (9)	6 (5)	7 (5)	34 (7)
Nausea	5 (2)	2 (2)	1 (1)	8 (2)
Constipation	3 (1)	0	4 (3)	7 (1)
Diarrhoea	6 (3)	1 (1)	0	7 (1)
Dry mouth	6 (3)	0	0	6 (1)
Reproductive system and breast disorders	13 (6)	12 (10)	6 (4)	31 (6)
Amenorrhoea	6 (3)	3 (3)	0	9 (2)
Erectile dysfunction	0	4 (3)	3 (2)	7 (1)
Galactorrhoea	3 (1)	2 (2)	0	5 (1)
Menstruation irregular	2 (1)	2 (2)	0	4 (1)
Musculoskeletal and connective tissue disorders	19 (8)	6 (5)	4 (3)	29 (6)
Back pain	4 (2)	3 (3)	1 (1)	8 (2)
Pain in extremity	4 (2)	2 (2)	1 (1)	7 (1)
Muscle rigidity	4 (2)	0	2 (1)	6 (1)
Arthralgia	4 (2)	0	1 (1)	5 (1)
Musculoskeletal stiffness	3 (1)	2 (2)	0	5 (1)
Metabolism and nutrition disorders	8 (3)	7 (6)	11 (7)	26 (5)
Increased appetite	5 (2)	2 (2)	4 (3)	11 (2)
Decreased appetite	2 (1)	3 (3)	0	5 (1)
Respiratory, thoracic and mediastinal disorders	10 (4)	3 (3)	3 (2)	16 (3)
Cough	4 (2)	1 (1)	0	5 (1)

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

Table 6: RIS-BIM-3003: AEs in ≥2% of subjects during randomised treatment (Randomised population).

Period IV Double-Blind **Body System or Organ Class** Dictionary-derived Term	RISPERDAL CONSTA (N=154) n (%)	Placebo (N=149) n (%)
Total no. subjects with adverse events	81 (53)	79 (53)
Psychiatric disorders	37 (24)	51 (34)
Insomnia	12 (8)	9 (6)
Depression	10 (6)	3 (2)
Mania	7 (5)	16 (11)
Anxiety	4 (3)	6 (4)
Bipolar I disorder	3 (2)	11 (7)
Agitation	2 (1)	7 (5)
Bipolar disorder	0	3 (2)
Nervous system disorders	20 (13)	22 (15)
Headache	11 (7)	10 (7)
Dizziness	4 (3)	2 (1)
Infections and infestations	19 (12)	17 (11)
Nasopharyngitis	6 (4)	4 (3)
Upper respiratory tract infection	3 (2)	5 (3)
Viral infection	3 (2)	1 (1)
General disorders and administration site conditions	14 (9)	12 (8)
Fatigue	6 (4)	4 (3)
Asthenia	3 (2)	2 (1)
Irritability	1 (1)	6 (4)
Gastrointestinal disorders	13 (8)	4 (3)
Diarrhoea	3 (2)	1 (1)
Nausea	3 (2)	2 (1)
Investigations	13 (8)	9 (6)
Weight increased	7 (5)	1 (1)
Weight decreased	1 (1)	3 (2)
Musculoskeletal and connective tissue disorders	8 (5)	7 (5)
Back pain	5 (3)	5 (3)
Reproductive system and breast disorders	5 (3)	4 (3)
Dysmenorrhoea	0	3 (2)
Cardiac disorders	4 (3)	5 (3)
Sinus tachycardia	1 (1)	3 (2)
Vascular disorders	4 (3)	2 (1)
Hypertension	4 (3)	2 (1)

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

Table 7: RIS-BIM-3003: AEs in ≥2% of subjects during the open-label extension.

Period V Open-label Extension Body System or Organ Class Dictionary-derived Term	RIS/RIS (N=90) n (%)	PLA/RIS (N=70) n (%)	Total (N=160) n (%)
Total no. subjects with adverse events	20 (22)	20 (29)	40 (25)
Psychiatric disorders	3 (3)	9 (13)	12 (8)
Insomnia	2 (2)	4 (6)	6 (4)
Agitation	0	4 (6)	4 (3)
Bipolar I disorder	0	3 (4)	3 (2)
Depressed mood	0	2 (3)	2 (1)
Investigations	6 (7)	3 (4)	9 (6)
Blood creatine phosphokinase increased	2 (2)	0	2 (1)
Nervous system disorders	4 (4)	5 (7)	9 (6)
Dizziness	0	2 (3)	2 (1)
Somnolence	2 (2)	0	2 (1)
Cardiac disorders	5 (6)	3 (4)	8 (5)
Sinus tachycardia	2 (2)	1 (1)	3 (2)
General disorders and administration site conditions	2 (2)	3 (4)	5 (3)
Irritability	0	2 (3)	2 (1)
Metabolism and nutrition disorders	1 (1)	3 (4)	4 (3)
Diabetes mellitus	0	2 (3)	2 (1)

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

Supporting Study RIS-BIP-302

During open-label Risperdal Consta + TAU stabilisation 212/275 (77%) subjects had one or more AEs. AEs were reported in ≥2% of subjects (Table 8). The most common AEs (incidence ≥5%) were tremor (23% of subjects), muscle rigidity (15%), weight increased (13%), insomnia (10%), headache (9%), sedation (8%), somnolence (6%), akathisia (6%) and bradykinesia (5%). ADRs were reported in 55% of subjects during open-label Risperdal Consta + TAU stabilisation. The most common ADRs (in ≥5% of subjects) were tremor (20% of subjects), weight increased (13%), muscle rigidity (12%), sedation (7%) and insomnia (6%) (Table 9).

During double-blind treatment, AEs were reported in 51/72 (71%) of the Risperdal Consta group and 51/67 (76%) of the placebo + TAU group (Table 10). The most common AEs in the Risperdal Consta + TAU and placebo + TAU groups, respectively, were tremor (23.6% vs 16.4%), insomnia (19.4% vs 23.9%), muscle rigidity (11.1% vs 6.0%), and mania (4.2% vs 11.9%). AEs that were noticeably more frequent in the Risperdal Consta + TAU group than the placebo + TAU group during the double-blind period (≥3% difference) were tremor, muscle rigidity, weight increased, sedation, increased appetite, decreased appetite, disturbance in attention, gait abnormal, and hypokinesia. AEs that that were noticeably more frequent in the placebo + TAU group (≥3% difference) were insomnia, headache, fatigue, nausea, pyrexia, depression, mania, suicidal ideation, hypertension, and injury.

Table 8: RIS-BIP-302: AEs in ≥2% of subjects during open-label stabilisation.

AE	N (%) subjects with AE (N=275)
ANY AE	212 (77.1)
tremor	64 (23.3)
muscle rigidity	40 (14.5)
weight increased	35 (12.7)
insomnia	28 (10.2)
headache	24 (8.7)
sedation	21 (7.6)
somnolence	17 (6.2)
akathisia	15 (5.5)
bradykinesia	14 (5.1)
fatigue	13 (4.7)
oedema peripheral	13 (4.7)
arthralgia	11 (4.0)
dyskinesia	11 (4.0)
increased appetite	11 (4.0)
nausea	11 (4.0)
pyrexia	11 (4.0)
back pain	10 (3.6)
dizziness	10 (3.6)
salivary hypersecretion	10 (3.6)
anxiety	9 (3.3)
constipation	9 (3.3)
decreased appetite	9 (3.3)
upper respiratory tract infection	9 (3.3)
depression	8 (2.9)
dystonia	8 (2.9)
dry mouth	8 (2.9)
mania	8 (2.9)
pain	8 (2.9)
vision blurred	8 (2.9)
vomiting	8 (2.9)
galactorrhoea	7 (2.5)
myalgia	7 (2.5)
suicidal ideation	7 (2.5)
pollakiuria	7 (2.5)
amenorrhoea	6 (2.2)
diarrhoea	6 (2.2)

Table 9: RIS-BIP-302: ADRs in ≥2% of subjects during open-label stabilisation.

ADR	% subjects with ADR
ANY ADR	55.3
tremor	20.4
weight increased	12.7
muscle rigidity	11.6
sedation	6.5
insomnia	5.8
bradykinesia	4.7
fatigue	4.4
akathisia	4.4
somnolence	4.4
headache	4
dyskinesia	3.6
salivary hypersecretion	3.3
increased appetite	2.9
dystonia	2.9
constipation	2.5
dizziness	2.5
galactorrhoea	2.5
vision blurred	2.2

ADR = Treatment-emergent adverse event that was considered by the investigator to be at least possibly related to study treatment.

Table 10: RIS-BIP-302: AEs in ≥2% of subjects during double-blind treatment.

AE	N (%) subjects with AE	
	RISPERDAL CONSTA + TAU	Placebo + TAU
ANY AE	51 (70.8)	51 (76.1)
Insomnia	14 (19.4)	16 (23.9)
Tremor	17 (23.6)	11 (16.4)
Muscle rigidity	8 (11.1)	4 (6.0)
Mania	3 (4.2)	8 (11.9)
Pyrexia	4 (5.6)	6 (9.0)
Akathisia	4 (5.6)	4 (6.0)
Dizziness	3 (4.2)	4 (6.0)
Upper respiratory tract infection	4 (5.6)	2 (3.0)
Oedema peripheral	3 (4.2)	3 (4.5)
Weight increased	5 (6.9)	1 (1.5)
Arthralgia	3 (4.2)	2 (3.0)
Decreased appetite	4 (5.6)	1 (1.5)
Depression	0	5 (7.5)
Dyskinesia	3 (4.2)	2 (3.0)
Dystonia	2 (2.8)	3 (4.5)
Headache	0	5 (7.5)
Hypokinesia	5 (6.9)	0
Memory impairment	3 (4.2)	2 (3.0)
Restlessness	2 (2.8)	3 (4.5)
Amenorrhoea	3 (4.2)	1 (1.5)
Cough	3 (4.2)	1 (1.5)
Fatigue	0	4 (6.0)
Irritability	2 (2.8)	2 (3.0)
Loose stools	3 (4.2)	1 (1.5)
Nasopharyngitis	2 (2.8)	2 (3.0)
Salivary hypersecretion	2 (2.8)	2 (3.0)
Sedation	4 (5.6)	0
Sleep disorder	2 (2.8)	2 (3.0)
Suicidal ideation	1 (1.4)	3 (4.5)
Asthenia	1 (1.4)	2 (3.0)
Bipolar I disorder	1 (1.4)	2 (3.0)
Bronchitis	1 (1.4)	2 (3.0)
Disturbance in attention	3 (4.2)	0
Gait abnormal	3 (4.2)	0
Increased appetite	3 (4.2)	0
Hypertension	0	3 (4.5)
Injury	0	3 (4.5)
Myalgia	1 (1.4)	2 (3.0)
Nausea	0	3 (4.5)
Urinary tract infection	2 (2.8)	1 (1.5)
Alopecia	2 (2.8)	0
Bradykinesia	2 (2.8)	0
Diarrhoea	0	2 (3.0)
Dry mouth	0	2 (3.0)
Dyspnoea exertional	2 (2.8)	0
Musculoskeletal stiffness	2 (2.8)	0
Orthostatic hypotension	2 (2.8)	0
Pharyngeal pain	0	2 (3.0)
Visual acuity reduced	2 (2.8)	0
Weight decreased	0	2 (3.0)

During double-blind treatment, ADRs were reported in 46% and 43% of the Risperdal Consta + TAU and placebo + TAU groups, respectively (Table 11). The most common ADRs in the Risperdal Consta + TAU group (in ≥5% of subjects) were tremor (19%), muscle rigidity (10%),

insomnia (8%), weight increased (6%) and hypokinesia (6%). The most common ADRs in the placebo + TAU group were tremor (15%), mania (9%) and insomnia (6%).

Table 11: RIS-BIP-302: ADRs in ≥2% of subjects during double-blind treatment.

ADR	% Subjects with ADR	
	RIS + TAU	PLAC + TAU
tremor	19.4	14.9
muscle rigidity	9.7	1.5
insomnia	8.3	5.8
weight increased	5.6	1.5
hypokinesia	5.6	0 .0
akathisia	4.2	4.5
dyskinesia	4.2	3.0
gait abnormal	4.2	0.0
dystonia	2.8	4.5
salivary hypersecretion	2.8	3.0
increased appetite	2.8	0.0
bradykinesia	2.8	0.0
disturbance in attention	2.8	0.0
restlessness	2.8	0.0
sleep disorder	2.8	0.0
amenorrhoea	2.8	0.0
orthostatic hypotension	2.8	0.0
bipolar I disorder	1.4	3.0
irritability	1.4	3.0
mania	0.0	9.0
depression	0.0	3.0
suicidal ideation	0.0	3.0

RIS + TAU = Risperdal Consta plus treatment-as-usual; PLAC + TAU = Placebo plus treatment-as usual
ADR = Treatment-emergent adverse event that was considered by the investigator to be at least possibly related to study treatment.

In the 'non-remitted continuing' (NRC) population of 70 subjects who did not maintain remission during the planned 16 week open-label treatment period but elected to continue open-label treatment with Risperdal Consta + TAU, 69 subjects (99%) reported at least one AE. The most common AEs (incidence ≥10%) in the NRC population were tremor (40%), muscle rigidity (30%), insomnia (24%), weight increased (24%), sedation 19%, arthralgia 17%, back pain and headache (16% each), dizziness and nausea (14% each), constipation, peripheral oedema, somnolence, suicidal ideation and upper respiratory tract infection (11% each), akathisia and bradykinesia (10% each).

In the 'retrieved dropout' (RDO) population of 41 subjects who discontinued double-blind treatment and commenced open-label Risperdal Consta + TAU, 28 subjects (68%) reported at least one AE. AEs in the RDO population were more common amongst subjects who had come from the placebo + TAU group (AEs reported in 77% of 20 subjects) than in subjects who had come from the Risperdal Consta + TAU group (53% of 15 subjects). The most common AEs (incidence ≥10%) in the RDO population were tremor (29%) and insomnia (12%).

Deaths and other serious adverse events

A total of 6/775 subjects (0.8%) died in the two fully-reported studies: 3 subjects during RIS-BIM-3003 (all during open-label stabilisation), and 3 during RIS-BIP-302 (2 during the double-blind, relapse prevention phase and 1 in the 'retrieved dropouts' population). AEs leading to death were duodenal ulcer perforation with peritonitis, accidental death (n=2), completed suicide (n=2), and hypertensive heart disease. One of the accidental deaths (due to a fall from a fifth floor window) was considered to be possibly related to Risperdal Consta by the investigator, who thought that the subject might have experienced vertigo precipitating the fall. The remaining fatal AEs were considered by the investigator to be unrelated or of doubtful relationship to study drug.

RIS-BIM-3003

Serious treatment-emergent adverse events (SAEs) were reported in 8/440 (2%) subjects during open-label oral risperidone treatment. The SAEs judged by investigators as possibly related to study drug were gastritis (1 subject); and chest pain plus tachycardia (1 subject).

SAEs were reported in 38/501 (8%) subjects during open-label Risperdal Consta stabilisation, including 23 (10%) subjects with an acute episode at screening. The majority of these SAEs appeared to be related to the underlying psychiatric disorder. Twelve subjects had a total of 13 SAEs that investigators judged as possibly related to Risperdal Consta. These were bipolar I disorder or bipolar disorder (8 subjects), depression (2 subjects), accidental death (1 subject) and depression and suicidal ideation (1 subject).

During double-blind treatment, the incidence of SAEs was lower in the Risperdal Consta group than the placebo group. The most frequent SAEs in the Risperdal Consta and placebo groups, respectively, were mania (2% vs 7%) and bipolar I disorder (2% vs 6%). Three subjects in the Risperdal Consta group had SAEs during the double-blind period that investigators judged as possibly or probably related to study drug. These were bipolar I disorder (2 subjects) and mania (1 subject).

During the open-label Risperdal Consta extension period, 5/160 subjects (3%) reported SAEs. 2 subjects had SAEs that were assessed as at least possibly treatment-related: bipolar I disorder (n=1) and cardiac arrest (n=1).

RIS-BIP-302

SAEs were reported in 25 (9%) subjects during open-label Risperdal Consta + TAU stabilisation. The majority of these SAEs appeared to be related to the underlying psychiatric disorder. Three subjects had SAEs that investigators judged as at least possibly related to study drug (Risperdal Consta and/or TAU). These were transient ischaemic attack, depression and suicidal ideation (1 subject each).

During double-blind treatment, the incidence of SAEs was lower in the Risperdal Consta group than the placebo group. The most frequent SAEs in the Risperdal Consta and placebo groups, respectively, were mania (4% vs 6%), depression (0% vs 6%) and bipolar I disorder (0% vs 3%). Suicide attempt was reported in 1 subject in the Risperdal Consta + TAU group, and suicidal ideation was reported in 1 subject in the placebo group. Two subjects in the Risperdal Consta group had SAEs during the double-blind period that investigators judged as at least possibly related to study drug. These were tardive dyskinesia and hypokinesia (1 subject each).

In the 'non-remitted continuing' population 15/70 (21%) subjects reported SAEs during open-label Risperdal Consta + TAU, mostly related to the psychiatric disorders System Organ Class (SOC). SAEs reported by more than 1 subject included depression (7% of subjects), suicidal ideation (7%), mania (4%), aggression (3%) and agitation (3%). The SAEs were regarded to be at least possibly treatment-related in 2 subjects: suicidal ideation (1 subject); and suicidal depression with suicide attempt (1 subject).

In the 'retrieved dropout' population 3/41 (7%) subjects reported 4 SAEs during open-label Risperdal Consta + TAU. Three SAEs were related to the psychiatric disorders SOC (depression, intentional self-injury and completed suicide) and the remaining SAE was pneumonia. The relationship of most of these SAEs to study treatment was not stated, but the case of completed suicide was assessed as unlikely to be treatment-related.

Withdrawals due to adverse events

RIS-BIM-3003

Fourteen of 440 (3%) subjects withdrew due to AEs during open-label oral risperidone treatment, including 10/275 (4%) of subjects with an acute episode at screening. No AE caused discontinuation in more than 1 subject during open-label oral risperidone treatment. Non-psychiatric AEs of interest that resulted in discontinuation during open-label oral risperidone treatment included galactorrhea (1 subject), erectile dysfunction (1 subject), tardive dyskinesia (1 subject), chest pain and tachycardia (both events in 1 subject and both were serious). One subject, stable on another antipsychotic at screening, discontinued treatment and died on Day 15 due to the serious events of duodenal ulcer perforation and peritonitis, which were not considered to be related to study treatment.

Fourteen of 501 (3%) subjects withdrew due to AEs during open-label Risperdal Consta stabilisation. The most common AEs leading to discontinuation were insomnia (2 subjects), fatigue (2 subjects) and weight increased (2 subjects). Non-psychiatric AEs of interest that resulted in discontinuation during open-label Risperdal Consta stabilisation were weight increased (2 subjects), ALT increased (1 subject) and allergic dermatitis (1 subject). None of these events were serious. Two subjects ceased treatment when they died during open-label Risperdal Consta stabilisation: One subject due to the serious events of chemical poisoning and completed suicide (not regarded as treatment-related) and one subject due to serious events of accidental death, fall, haemorrhage, hepatic rupture and multiple injuries (regarded as possibly treatment-related due to suspected but unconfirmed vertigo preceding the fall).

One of 149 (1%) and 1/154 (1%) subjects in the Risperdal Consta and placebo groups, respectively, withdrew due to AEs during double-blind treatment. The subject in the Risperdal Consta group withdrew due to hyperglycaemia and the subject in the placebo group withdrew due to weight increased.

Six of 160 subjects withdrew due to AEs during the open-label Risperdal Consta extension period. The AEs were bipolar I disorder (2 subjects), mania (2 subjects), cardiac arrest (1 subject) and QT prolongation/left bundle branch block (1 subject).

RIS-BIP-302

Twenty (7%) subjects withdrew due to AEs that began during open-label Risperdal Consta + TAU stabilisation. AEs leading to treatment discontinuation in more than one subject were weight increased (0.7% of patients), dizziness (0.7%), tremor (0.7%), depression (0.7%) and galactorrhoea (0.7%).

Three of 72 (4%) and 2/67 (3%) subjects in the Risperdal Consta + TAU and in the placebo + TAU groups, respectively, withdrew due to AEs during double-blind treatment. The AEs leading to treatment discontinuation in the Risperdal Consta + TAU group were hypokinesia, tardive dyskinesia and hypertensive heart disease (1 subject each). The AEs leading to treatment discontinuation in the placebo + TAU group was mania (2 subjects).

Five (7%) subjects in the 'non-remitted continuing' population withdrew due to AEs. The AEs were akathisia, amenorrhea, galactorrhea, hypotension, suicidal ideation, and weight increased (each in 1 subject), and anaemia and thrombocytopenia (both in 1 subject)

One (2%) subject in the 'retrieved dropout' population withdrew due to an AE. The AE was depression.

Other safety-related assessments

Clinical laboratory evaluations

With the exception of prolactin, there were no clinically relevant mean changes from baseline to end point during any treatment period for the laboratory analyses, including haematology, renal function, liver function, fasting glucose, or fasting lipids (cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL], or triglycerides) when Risperdal Consta was administered as monotherapy (RIS-BIM-3003) or as adjunctive therapy to TAU (RIS-BIP-302).

In RIS-BIM-3003, mean serum prolactin concentrations increased by approximately 25 to 26 ng/mL from open-label Risperdal Consta stabilisation baseline to endpoint in subjects who were not previously stable on risperidone at screening, compared with a decrease of 12 ng/mL in subjects who were previously stable on risperidone. During double-blind treatment, mean ± SD prolactin concentrations were decreased from double-blind baseline in the placebo group (27.3 ± 49.86 ng/mL) and the Risperdal Consta group (8.8 ± 39.45 ng/mL).

In RIS-BIP-302, mean (SD) changes in prolactin from open-label baseline to double-blind endpoint (Week 68 of the study) were +18.5 (36.7) ng/mL for the Risperdal Consta group and −16.6 (49.0) ng/mL for the placebo group.

During the double-blind treatment periods of both studies, there were no noteworthy differences between the placebo and the Risperdal Consta groups in the types of events or percentage of subjects with laboratory-related adverse events.

Vital signs

There were no notable changes in mean systolic and diastolic blood pressure, heart rate, and temperature in any phase or treatment group of either study. No subjects had orthostatic hypotension as assessed by orthostatic changes in blood pressure and pulse rate, however orthostatic hypotension was reported as an AE in a small number of subjects.

ECG

There were no clinically significant changes in mean electrocardiogram (ECG) parameters (heart rate, pulse rate [PR] interval, QRS interval, QT interval, QT interval corrected for Fridericia [QTcF], and QT interval corrected for linear derived factors [QTcLD]) in any phase or treatment group of either study. A QTcF increase >60 milliseconds (ms) from baseline was not reported during RIS-BIM-3003, but reported during RIS-BIP-302 in 3 subjects: 1 subject in the Risperdal Consta + TAU group and 2 subjects in the placebo + TAU group. No subjects had a QTcB, QTcF, or QTcLD interval of ≥500 ms in either study.

Body weight

In RIS-BIM-3003, mean increases in body weight from baseline to end point were noted during Risperdal Consta stabilisation (1.6 kg), and in subjects treated with Risperdal Consta in the double-blind period (1.14 kg). Mean body weight also increased after the addition of Risperdal Consta to TAU in RIS-BIP-302.

In RIS-BIM-3003, clinically significant individual changes in body weight from double-blind baseline to end point (body weight increases ≥7% from baseline) were more common in the Risperdal Consta group than in the placebo group (11.6% vs. 2.8%). In RIS-BIP-302, clinically significant individual changes in body weight during randomised treatment were more common in

the monotherapy study, but were similar in the Risperdal Consta and placebo groups (26.8% vs. 27.3%).

Extrapyramidal symptoms

There were no meaningful changes from baseline to study endpoint for mean Extrapyramidal Symptom Rating Scale (ESRS) [16] total score during any phase of the monotherapy study

RIS-BIP-302

In the adjunctive therapy study RIS-BIP-302, there were no meaningful changes from baseline to study endpoint in respect of dyskinetic symptoms (measured using the Abnormal Involuntary Movement Scale), akathisia symptoms (measured using the Barnes Akathisia Scale), or Parkinsonian symptoms (measured using the Simpson-Angus Rating Scale).

Nevertheless, extrapyramidal symptoms were reported as AEs in a substantial proportion of subjects during treatment with Risperdal Consta.

Post-marketing experience

The sponsor reviewed the postmarketing database for adverse events with Risperdal Consta in patients with bipolar disorder. The initial review and two updates covered the period from initial marketing until 31 August 2008. In total, 234 cases involving the use of Risperdal Consta to treat bipolar disorders were retrieved from the sponsor's database. The review did not identify any unexpected safety issues in patients receiving Risperdal Consta for the treatment of bipolar disorders. The most frequently reported adverse events (≥6 cases) were weight increased, drug administration error, somnolence, anxiety, insomnia, drug ineffective, tremor, blood prolactin increased and extrapyramidal disorder. All of these except drug administration error and drug ineffective are listed as ADRs in the current CCDS.

In addition, a review of cases with fatal outcome, suicidality, overdose, medication error and the cases reported in special patient populations (paediatric and elderly) did not identify any new safety signal in patients receiving Risperdal Consta for the treatment of bipolar disorders.

Literature review

There was a considerable degree of variation in the reporting of adverse events. In general, the AEs reported in the published articles were consistent with the known AE profile of risperidone. The most frequently reported AEs, all of which are listed in the PI as potential adverse effects of risperidone, were:

- weight increase (13 articles, all oral risperidone);
- sedation/somnolence (8 articles);
- extrapyramidal symptoms such as tremor (6 articles), akathisia (4 articles), unspecified extrapyramidal symptoms (4 articles), parkinsonism (3 articles), neuroleptic malignant syndrome (1 article reporting a single case) and tardive dyskinesia (1 article reporting a single case after 'years' of treatment), 'buccolingual movements' (1 article) and dystonia (1 article);
- hyperprolactinaemia/prolactin increased (8 articles).

Discontinuation of risperidone because of AEs was reported in 16 articles. The most frequently reported treatment-limiting AE was weight gain. No deaths were reported in the literature. A total

[16]. The ESRS assesses the overall severity of extrapyramidal symptoms. The total ESRS score is the sum of the parkinsonism, dystonia, and dyskinetic movement clusters. The ESRS rating instrument also contains a questionnaire and behavioural cluster and a CGI of overall severity of dyskinesia, parkinsonism, and dystonia as well as staging of parkinsonism. Low scores indicate normal performance or absence of symptoms.

of 6 SAEs were reported but details were only provided for one of these: postoperative haemorrhage following tubal ligation and curettage, which was considered not related to study drug by the investigator, and from which the subject recovered.

Conclusions regarding safety

An overall appreciation of the safety profile of Risperdal Consta in the fully-reported studies is hindered somewhat by the sponsor's decision to report the safety data separately for the different treatment periods within each study, with no amalgamated reporting of safety data for the full duration of Risperdal Consta treatment in either trial.

However, apart from events related to the underlying psychiatric condition (mania, agitation, insomnia and depression), there were no obvious differences in the type and frequency of AEs reported in the two studies in patients with bipolar I disorder and those documented in the PI for short- and long-term studies in patients with schizophrenia. The effect of Risperdal Consta on prolactin and body weight in the new studies was consistent with previous information.

Noteworthy gaps in the safety information for Risperdal Consta (irrespective of the indication) include a lack of data in the elderly, in children and adolescents and in pregnant women.

The post-marketing database review and literature review did not identify any significant new safety issues.

Clinical Summary and Conclusions

In the pivotal study RIS-BIM-3003, in adults with bipolar I disorder who had first been successfully stabilised on Risperdal Consta, further treatment with Risperdal Consta monotherapy reduced the subsequent risk of an elevated mood recurrence, but not a depressed mood recurrence.

In the supporting study RIS-BIP-302, Risperdal Consta reduced the risk of both elevated and depressed mood recurrences, when used as adjunctive therapy in adults with frequently recurring, predominantly bipolar I disorder, who had first been successfully stabilised on a combination of Risperdal Consta and 'treatment as usual' for 16 weeks. In accordance with the *Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment and Prevention of Bipolar Disorder*, the findings of this study cannot be extrapolated to the whole group of patients with bipolar I disorder.

Importantly, there is a gap between the period for which efficacy and safety in bipolar disorder have been demonstrated for Risperdal (acute mania in studies of only 3 weeks duration) and the period for which efficacy was demonstrated for Risperdal Consta in the pivotal study (maintenance treatment *in patients who had first been successfully stabilised on Risperdal Consta*).

As outlined in the *Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment and Prevention of Bipolar Disorder*, the demonstration of the effectiveness of a proposed treatment for bipolar disorder involves three successive phases:

- Demonstration of effectiveness in the control of an acute episode. This requires randomised, placebo- (and preferably active-) controlled studies of 3-4 weeks duration, demonstrating a satisfactory response rate for the candidate drug in patients with an acute mood episode.
- Demonstration of maintenance of effect (ie successful stabilisation of the acute episode, as evidenced by the prevention of a *relapse* of the acute episode). This requires active-controlled studies of 12 weeks duration, showing that the initial response is maintained through the 12 weeks in a satisfactory proportion of subjects. Such studies are usually performed as extensions of the short-term 3 week studies used to show initial response.
- Demonstration of the prevention of *recurrences* during long-term maintenance therapy. The *Note for Guidance* makes a clear distinction between a *relapse*, a resurgence of symptoms during the

early period after an acute episode) and a *recurrence* (re-emergence of symptoms at a later time, representing new acute episode).

In the case of risperidone, the studies supporting the existing bipolar disorder indication for Risperdal demonstrate efficacy in the first of the above three treatment phases. The studies in the current submission demonstrate efficacy in the last of the above three phases, but *only in patients who were successfully stabilised on Risperdal Consta*. However, no adequate controlled studies have been submitted, for either Risperdal or Risperdal Consta, to demonstrate efficacy in the middle (stabilisation) phase.

Thus, the use of Risperdal Consta in a manner supported by the studies in the current submission is based on the prior use of Risperdal Consta *in an unapproved manner*, namely for the stabilisation of patients whose acute episode has responded to Risperdal, or who have been transferred from another antipsychotic agent.

Accordingly, approval of the current submission cannot be recommended at this time. Before Risperdal Consta can be approved for the prevention of recurrences of bipolar disorder, the sponsor first needs to show, in adequate controlled studies of the recommended 12-week duration, that Risperdal Consta is effective in preventing a relapse of the acute episode.

The evaluator indicated that should the Delegate decide to approve the submission despite the absence of controlled efficacy and safety data covering the stabilisation period, the indication in the PI should reflect at least three major limitations of the pivotal study, namely:

- The study only enrolled patients with bipolar I disorder, not bipolar II.
- Risperdal Consta was used as monotherapy, not as adjunctive therapy. The use of Risperdal Consta as adjunctive therapy in patients with bipolar I or II disorder should not be approved on the basis of RIS-BIP-302, because the findings of that study cannot be reliably extrapolated to the general population of patients with bipolar I or II disorder, and the population enrolled in that study does not correspond to a recognised DSM-IV diagnostic category.
- Risperdal Consta was only shown to be effective in preventing elevated mood recurrences, not depressed mood recurrences.
- Arguably, the fact that efficacy has only been demonstrated in adults should also be reflected in the bipolar disorder indication, although this was not done in the existing schizophrenia indication.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Efficacy

With respect to efficacy, the clinical evaluator concluded that:

There is a gap between the period for which efficacy and safety in bipolar disorder have been demonstrated for Risperdal (acute mania in studies of only 3 weeks duration) and the period for which efficacy was demonstrated for Risperdal Consta in the pivotal study (maintenance treatment *in patients who had first been successfully stabilised on Risperdal Consta*).

As outlined in the *Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment and Prevention of Bipolar Disorder*, the demonstration of the effectiveness of a proposed treatment for bipolar disorder involves three successive phases:

- Demonstration of effectiveness in the control of an acute episode. This requires randomised, placebo- (and preferably active-) controlled studies of 3-4 weeks duration, demonstrating a satisfactory response rate for the candidate drug in patients with an acute mood episode.
- Demonstration of maintenance of effect (that is,. successful stabilisation of the acute episode, as evidenced by the prevention of a *relapse* of the acute episode). This requires active-controlled studies of 12 weeks duration, showing that the initial response is maintained through the 12 weeks in a satisfactory proportion of subjects. Such studies are usually performed as extensions of the short-term 3 week studies used to show initial response.
- Demonstration of the prevention of *recurrences* during long-term maintenance therapy. The *Note for Guidance* makes a clear distinction between a *relapse* a resurgence of symptoms during the early period after an acute episode) and a *recurrence* (re-emergence of symptoms at a later time, representing new acute episode).

In the case of risperidone, the studies supporting the existing bipolar disorder indication for Risperdal demonstrate efficacy in the first of the above three treatment phases. The studies in the current submission demonstrate efficacy in the last of the above three phases, but *only in patients who were successfully stabilised on Risperdal Consta*.

However, no adequate controlled studies have been submitted, for either Risperdal or Risperdal Consta, to demonstrate efficacy in the middle (stabilisation) phase. Thus, the use of Risperdal Consta in a manner supported by the studies in the current submission is based on the prior use of Risperdal Consta *in an unapproved manner*, namely for the stabilisation of patients whose acute episode has responded to Risperdal or who have been transferred from another antipsychotic agent.

For this reason, the evaluator concluded that approval of the current submission cannot be recommended at this time. Before Risperdal Consta can be approved for the prevention of recurrences of bipolar disorder, the sponsor first needs to show, in adequate controlled studies of the recommended 12-week duration, that Risperdal Consta is effective in preventing a relapse of the acute episode.

In response to the clinical evaluation report the sponsor has noted that efficacy of Risperdal in the treatment of acute mania was demonstrated in a 12 week study which is described in the PI for Risperdal. The sponsor considers this sufficient to demonstrate efficacy of Risperdal in the stabilisation phase between acute treatment and maintenance treatment.

The clinical evaluator considered that the data from adjunctive treatment study RIS-BIP-302 could not be extrapolated to the general bipolar disorder population because the study subjects had frequently cycling episodes which did not correspond to a separate DSM IV diagnostic group. The sponsor responded to the effect that while the *Guideline on Clinical Investigation of Medicinal Products for the Treatment and Prevention of Bipolar Disorder* states that data from rapid cyclers cannot be extrapolated subjects in this study were not rapid cyclers but frequent cyclers. This group (with at least 4 episodes in the 12 months prior to study entry) was selected in order to ensure a degree of clinical severity and potential relapse tendency. Data from this group would be generalisable to the bipolar population.

The clinical evaluator noted that the pivotal monotherapy study enrolled only patients with bipolar I disorder and that patients with bipolar II disorder comprised only 11% of subjects in the adjunctive treatment study. The sponsor has responded by proposing to limit the indications to bipolar I disorder.

The clinical evaluator also noted that Risperdal Consta was only shown to be effective in preventing elevated mood recurrences, not depressed mood recurrences. In its response, the sponsor noted that this was the case in the monotherapy study but that in the adjunctive study efficacy of Risperdal Consta in preventing depressive episode recurrences was demonstrated with 13% of subjects

receiving Risperdal Consta + TAU vs. 21% of subjects receiving placebo + TAU experiencing a depressive recurrence.

The sponsor proposed the amended indications of:

Risperdal Consta is indicated for adjunctive maintenance treatment to prevent the recurrence of ***mood episodes of bipolar I disorder*** *in patients stabilised on oral treatments*

Risperdal Consta is indicated as monotherapy for maintenance treatment to prevent the recurrence of ***manic or mixed episodes of bipolar I disorder*** *in patients stabilised on oral treatments.*

Safety

The clinical evaluation contains a thorough review of safety information contained in the submission. No new safety information concerning risperidone was identified. In the pivotal study 11.6% of subjects given Risperdal Consta vs. 2.8% given placebo during the double-blind period had a weight gain of ≥ 7% from baseline. Mean increases in body weight were relatively modest (1.14 kg in subjects given Risperdal Consta during the double-blind period).

With the exception of elevations in serum prolactin there were no clinically significant changes to laboratory parameters including cholesterol and serum lipids and no clinically significant ECG changes or changes in vital signs.

Risk-Benefit Analysis

The sponsor has responded to the clinical evaluator's primary concerns proposing to amend the patient group in which maintenance treatment with Risperdal Consta is indicated to patients with bipolar I disorder who are stabilised on oral treatments. Monotherapy maintenance is further proposed to be indicated for prevention of recurrence of manic or mixed episodes only (and not depressive episodes). For adjunctive maintenance the nature of the episode to be prevented (depressive, mixed or manic) is not proposed to be specified.

Limiting the indications to patients stabilised on oral therapy is consistent with the demonstration of efficacy of Risperdal in stabilisation in patients with acute mania, provided data obtained from Risperdal can be extrapolated to Risperdal Consta. A gap remains for those patients who had depressive or mixed episodes for their initial presentation, as there has been no randomised, controlled trial of stabilisation for this patient group.

The sponsor's proposal to limit all indications to patients with bipolar 1 disorder is acceptable and consistent with the study populations. The proposal to indicate monotherapy maintenance treatment for prevention of recurrence of manic or mixed episodes is also consistent with the available data and is acceptable. Efficacy in prevention of total recurrences and recurrences of depressive episodes was demonstrated for adjunctive maintenance therapy and is also acceptable.

The issue now of most concern is the lack of demonstration of stabilisation in patients with an initial episode which was not acute mania. The Delegate noted that the sponsor has not specified any treatment other than "oral treatment" that patients are required to be stabilised on prior to commencing Risperdal Consta for maintenance treatment. This is not consistent with the clinical trials, where patients where stabilised on Risperdal Consta. There is no evidence that patients stabilised on other oral treatments would have a maintenance response similar to that seen in these clinical studies.

The Delegate considered that there is sufficient evidence to allow mono and adjunctive maintenance treatment with Risperdal Consta for those patients with previous episodes of acute mania that have responded to Risperdal but this does require extrapolation and the assumption that those who respond to Risperdal would respond in a similar manner to Risperdal Consta.

The Delegate proposed to approve Risperdal Consta for:

Adjunctive maintenance treatment to prevent the recurrence of mood episodes in bipolar I disorder in patients with previous manic episodes which have responded to oral risperidone and

Monotherapy for maintenance treatment to prevent the recurrence of manic or mixed episodes of bipolar I disorder in patients with previous manic episodes which have responded to oral risperidone.

The advice of the Australian Drug Evaluation Committee (ADEC) was requested particularly on:

- Whether it is acceptable to extrapolate stabilisation of patients with an acute episode of mania with Risperdal to Risperdal Consta;
- Whether the demonstration of efficacy of Risperdal Consta in achieving stabilisation after a manic, mixed or depressive episode in the open, uncontrolled phases of the submitted studies is sufficient to support use in patients with past mixed or depressive episodes.

ADEC recommended approval of the application for the indication:

Monotherapy for maintenance treatment to prevent the recurrence of manic or mixed episodes of bipolar I disorder in patients with a manic or mixed episode, following stabilisation with oral risperidone.

In making this recommendation, ADEC agreed with the clinical evaluator and Delegate in considering that monotherapy with risperidone modified release injection should be restricted to the prevention of recurrence of mixed or manic episodes in patients with a mixed or manic episode. This is because no patients with acute depression were enrolled in the monotherapy trial, RIS-BIM-3003, and no reduction in the number of depressive events was observed in the risperidone group (20/140, 14%) versus the placebo treated patients (14/135, 10%).

The ADEC also agreed there is a gap in the evidence of the efficacy and safety of risperidone in bipolar disorder because no adequate controlled studies have been submitted for either Risperdal or Risperdal Consta demonstrating efficacy in the stabilisation phase of treatment[17]. However the Committee considered that this gap can be addressed in practice by limiting maintenance treatment with Risperdal Consta to patients stabilised on oral risperidone.

ADEC recommended rejection of the application for use as adjunctive maintenance treatment to prevent the recurrence of mood episodes in bipolar I disorder in patients with previous manic episodes on the grounds that efficacy and safety in the adjunctive setting has not been satisfactorily established.

In making this recommendation the Committee noted that data have been presented from a single study, RIS-BIP-302, that evaluated the efficacy and safety of Risperdal Consta as adjunctive therapy to 'treatment as usual' (TAU) in adults with 'frequently-relapsing' bipolar disorder type I or II (FRBD). FRBD overlaps with, but is not the same as the DSM-IV-TR condition, Rapid Cycling Bipolar Disorder (RCBD). Thus the population enrolled in Study 302 does not correspond to a recognised DSM-IV diagnostic category. Additionally, the *Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment and Prevention of Bipolar Disorder* states that 'data from rapid cyclers cannot be extrapolated to the whole group of patients with bipolar disorder'.

The Committee was also concerned about possible biases in the results from Study 302 arising from differences in the usage of mood stabilisers and antidepressants in the Risperdal Consta + TAU versus the placebo + TAU groups in the Intent to Treat (ITT) population. Additionally, there were

[17] The *Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment and Prevention of Bipolar Disorder* requires the effectiveness of a proposed treatment for bipolar disorder to be demonstrated in three successive phases: control of an acute episode, maintenance of effect, and prevention of recurrences.

differences between the US and Indian sites in Study 302 in terms of TUA and placebo recurrence rates. The unknown overall effect of these various confounders further reduces the Committee's preparedness to rely upon the results of this study to support approval of the adjunctive therapy indication.

Further Risk-Benefit Analysis

The sponsor was advised that the Delegate intended to accept the ADEC's recommendation regarding adjuvant maintenance treatment for bipolar 1 disorder. The sponsor responded to the above ADEC recommendation with commentary on issues raised by the ADEC. The Delegate requested consideration of these comments at a subsequent meeting by the Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC). Each issue is summarised below with the Delegate's current view.

1. Evidence of efficacy and safety of Risperdal Consta as adjunctive maintenance treatment to "treatment as usual" (TAU) was provided from a single study, RIS-BIP-302, which assessed patients with "frequently-relapsing" bipolar disorder. The clinical evaluator noted that this patient group did not correspond to a recognised subgroup of patients with bipolar disorder. Additionally the guidance document states that data from rapid cyclers cannot be extrapolated to the whole group of patients with bipolar disorder.[18]

Summary of sponsor's response

The sponsor noted that study RIS-BIP-302 included patients with either bipolar I disorder or bipolar II disorder and that patients were required to have at least 4 mood episodes in the previous 12 months. The requirement for at least 4 episodes was intended to be an indicator of disease severity only and was an attempt to enrich the study population and ensure a sufficient number of relapses, thereby allowing for a meaningful relapse prevention study. The sponsor believes this population to be representative of all patients with bipolar disorder as these patients do not otherwise qualitatively differ from others with the illness.

Delegate's current view

Differences between "frequently cycling" and "rapid cycling" are reproduced in Table 12.

The DSM-IV states that the essential feature of rapid cycling bipolar disorder is the occurrence of 4 or more mood episodes during the previous 12 months.[19] These episodes can occur in any combination and order. The episodes must meet both the duration and symptom criteria for a Major Depressive, Manic, Mixed or Hypomanic Episode and must be demarcated by either a period of full remission for at least 2 months or by a switch to an episode of the opposite polarity. Manic, Hypomanic and Mixed Episodes are counted as being on the same pole.

Study RIS-BIP-302 combined patients with bipolar I and bipolar II disorder and included only those patients with at least 4 mood episodes in the preceding 12 months. As shown in Table 12, patients with rapid cycling were a subgroup of "frequent cyclers". The remaining patients included as "frequent cyclers" would have had ultra-rapid cycling or unresolved episodes. The Delegate therefore does not consider this group representative of the general population of patients with bipolar disorder and data obtained from this group should, consistent with the recommendation in the guideline, not be extrapolated to the general bipolar disorder population.

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[18] The *Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment and Prevention of Bipolar Disorder* requires the effectiveness of a proposed treatment for bipolar disorder to be demonstrated in three successive phases: control of an acute episode, maintenance of effect, and prevention of recurrences.

[19] Diagnostic and statistical manual of mental disorders / prepared by the Task Force on DSM-IV and other committees and work groups of the American Psychiatric Association Washington, DC Publisher: American Psychiatric Association. Fourth edition, 1994.

Table 32: RIS-BIP-302: Comparison of Rapid Cycling Bipolar Disorder and 'Frequently Relapsing Bipolar Disorder'.

Specifier	Rapid Cycling Bipolar Disorder	Frequently Relapsing Bipolar Disorder
Type	Course specifier for Type I and Type II bipolar disorder	Empirical definition of a subpopulation of patients with Type I or Type II bipolar disorder
Criterion	At least 4 episodes of mood disorder in the previous 12 months • Episodes are demarcated either by partial or full remission for at least 2 months or a switch to an episode of opposite polarity	At least 4 episodes of mood disorder in the previous 12 months • Episodes require psychiatric/clinical intervention
Patient Diagnosis	Narrow definition—excludes many frequently relapsing patients with ultra-rapid and ultradian mood cycling	Includes patients with current diagnosis of RCBD, and those who relapse, or whose disease recurs, any number of times in the past 12 months.
Durability of Diagnosis	Unclear when RCBD course specifier label is lost	FRBD descriptor is lost when patients no longer fit the empirical definition, ie, when they have had fewer than 4 episodes in the previous 12 months

The Delegate considered that there are insufficient patients with bipolar II disorder in this study for those patients to be further considered for maintenance adjuvant treatment. The Delegate did not propose to accept this study as sufficient evidence of efficacy and safety of Risperdal Consta for adjuvant maintenance treatment of either bipolar I or bipolar II disorder.

2. ADEC was concerned about possible biases in the results from Study RIS-BIP-302 arising from differences in the usage of mood stabilisers and antidepressants in the Risperdal Consta + TAU vs. the placebo + TAU groups in the ITT population.

Summary of Sponsor's response

The sponsor provided a table of the TAU medicines taken by patients with bipolar I disorder only, during the double-blind period of the study. Patients were randomised and not permitted to change their TAU regimen during the double-blind relapse prevention phase of the study.

Both groups were similar in the percentage of patients taking one, two or three TAU bipolar medications and the distribution of TAU medications at double-blind baseline between treatment groups was similar. The majority of patients were taking mood stabilisers only: 65% Risperdal Consta vs. 78% placebo. Twenty six per cent of patients randomised to Risperdal Consta vs. 17% randomised to placebo were taking both mood stabilisers and antidepressants as their TAU regimen at double-blind baseline. The sponsor regards these differences as minor and expected, due to the variability in prescribing practices for bipolar treatment.

Delegate's current view

There is a difference of 9% in the number of patients taking both antidepressants and mood stabilisers in the two treatment groups in study RIS-BIP-302, with those randomised to Risperdal Consta more likely to be receiving both an antidepressant and a mood stabiliser in addition to study treatment. The concern that this difference may have biased the results in favour of the Risperdal Consta group was justified. However, the sponsor has tabulated outcome by TAU subgroup in their

response and, although there were few patients in each of the TAU subgroups in each treatment group (Risperdal Consta or placebo), efficacy of Risperdal Consta was consistently greater than placebo in each of these small subgroups. Additional statistical analysis was performed which showed no significant treatment-by-medication interaction. The Delegate accepted that Risperdal Consta demonstrated additional efficacy over TAU in the subgroup of patients with bipolar 1 disorder who were enrolled in this study.

3. There were differences between the USA and Indian sites in study RIS-BIP-302 in terms of TAU and placebo recurrence rates.

Summary of sponsor's response

The sponsor referred only to patients with bipolar I disorder in response to the above concern. Of the 240 patients with bipolar disorder who entered to open-label stabilisation phase of study RIS-BIP-302, 82 (34%) were from the USA and 158 (66%) were from India. 21/82 (26%) of patients from the USA achieved remission in the 16 week open-label stabilisation phase in which all patients received Risperdal Consta compared with 103/158 (65%) of patients from India.

Of patients who achieved stabilisation and who were then randomised to the double-blind phase, 12/21 USA patients received Risperdal Consta and 9/21 received placebo while 53/103 Indian patients received Risperdal Consta and 50/103 received placebo. In these patients relapse rates were similar in India and the USA with relapse in 3/12 (25%) USA patients and 12/53 (22.6%) Indian patients given Risperdal Consta. Relapse rates in the placebo groups were 5/9 (55.6%) and 22/50 (44.0%) in the USA and India respectively.

The sponsor noted that relapse rates and estimated delay in time to relapse were similar between countries and the results do not support a significant difference between the USA and Indian sites in terms of TAU and placebo recurrence rates.

Delegate's current view

The ADEC's concern was about the difference in the percentage of patients in the USA and India who achieved stabilisation during the 16 week open-label stabilisation period where all patients received Risperdal Consta. Only 34% of patients in the USA were stabilised during that period compared with 66% of patients in India. It was that restricted and now unbalanced group of patients that was randomised for the maintenance period of study RIS-BIP-302.

The ADEC considered that the Australian population was likely to more closely follow the pattern in the USA rather than in India and the Delegate agreed. Given the low rate of stabilisation of bipolar I disorder achieved with Risperdal Consta in patients enrolled in the USA, the indication for maintenance treatment proposed by the sponsor should, if it is accepted by the ADEC, be restricted to those patients who are able to be stabilised on risperidone and TAU. The Delegate noted that the sponsor has not proposed Risperdal Consta for stabilisation after an acute mood disorder. Given the USA results from study RIS-BIP-302, it is likely that only a minority of patients who could not be stabilised on current TAU will achieve stabilisation with the addition of risperidone. However, given that the study population was not representative of the general group of patients with bipolar disorder or bipolar I disorder and results from this subgroup cannot reasonably be extrapolated to the general bipolar or bipolar I disorder population, this point is not relevant.

The Delegate proposed to accept the previous advice of the ADEC and restrict the indication Risperdal Consta in bipolar disorder to Monotherapy for maintenance treatment to prevent the recurrence of manic or mixed episodes of bipolar I disorder in patients with a manic or mixed episode, following stabilisation with oral risperidone.

The ACPM confirmed the previous recommendation. The new data submitted by the sponsor did not support the proposed indication of maintenance treatment to prevent the recurrence of mood episodes of bipolar disorder. However, the Committee agreed with the Delegate that Risperdal Consta did demonstrate additional efficacy over "treatment as usual" (TAU) in the subgroup of patients with bipolar 1 disorder who were enrolled in the study RIS-BIP-302. Therefore, the Committee recommended approval may be possible for a highly targeted subset of the population; specifically as adjunctive maintenance treatment with lithium or valproate in treatment refractory patients with bipolar I disorder with a history of at least 4 relapses in a 12 month period.

Outcome

Based on review of safety and efficacy, TGA approved the registration of Risperdal Consta containing risperidone 25mg powder for injection vial with diluent syringe, Risperdal Consta containing risperidone 37.5mg powder for injection vial with diluent syringe and Risperdal Consta containing risperidone 50mg powder for injection vial with diluent syringe for the following new indications:

Monotherapy for maintenance treatment to prevent the recurrence of manic or mixed episodes of bipolar I disorder in patients with a manic or mixed episode, following stabilisation with oral risperidone.

Adjunctive maintenance treatment with lithium or sodium valproate in treatment refractory patients with bipolar I disorder who have at least 4 relapses in a 12 month period.

Attachment 1. Product Information

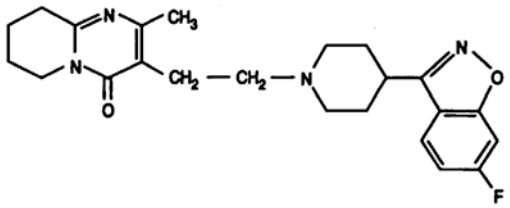
The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

RISPERDAL CONSTA® (risperidone) Intramuscular Injection

PRODUCT INFORMATION

NAME OF THE MEDICINE

Risperidone is chemically identified as 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, and has the following structural formula:



CAS-106266-06-2 $C_{23}H_{27}FN_4O_2$ MW=410.49

DESCRIPTION

RISPERDAL CONSTA is an extended release microspheres formulation of risperidone micro-encapsulated in polyglactin for intramuscular injection, in strengths of 25mg, 37.5mg and 50mg when suspended in 2mL diluent. The diluent contains carmellose sodium 40 mPa.s, anhydrous citric acid, sodium phosphate-dibasic dihydrate, polysorbate 20, sodium chloride, sodium hydroxide and water for injection.

PHARMACOLOGY

Pharmacodynamics

Risperidone is a selective monoaminergic antagonist with a high affinity for serotoninergic 5-HT_2 and dopaminergic D_2 receptors. Risperidone binds also to alpha$_1$-adrenergic receptors, and with lower affinity, to H_1-histaminergic and alpha$_2$-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. The antipsychotic activity of risperidone is considered to be attributable to both risperidone and its active metabolite 9-hydroxy risperidone.

Central dopamine D_2 receptor antagonism is considered to be the mechanism of action by which conventional neuroleptics improve the positive symptoms of schizophrenia, but also induce extrapyramidal symptoms and release of prolactin.

Although risperidone antagonises dopamine D_2 receptors and causes release of prolactin, it is less potent than classical neuroleptics for depression of motor activity and for induction of catalepsy in animals.

Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

Due to the alpha-blocking activity of risperidone, orthostatic hypotension can occur, especially during the initial dose-titration period. This alpha-blocking activity may also induce nasal mucosal swelling, which is probably related to the observed incidence of rhinitis associated with the use of risperidone.

Antagonism of serotoninergic and histaminergic receptors may induce body weight gain.

In controlled clinical trials, risperidone was found to improve positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), as well as negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech). Risperidone may also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

Pharmacokinetics

Disposition of risperidone after administration of RISPERDAL CONSTA

After a single i.m. injection with RISPERDAL CONSTA the release profile consists of a small initial release of drug (<1% of the dose), followed by a lag time of 3 weeks. Following i.m. injection, the main release of drug starts from 3 weeks onwards, is maintained from 4 to 6 weeks and subsides by week 7. Oral antipsychotic supplementation should therefore be given during the first 3 weeks of RISPERDAL CONSTA treatment.

The combination of the release profile and the dosage regimen (i.m injection every two weeks) result in sustained therapeutic plasma concentrations. Therapeutic plasma concentrations remain until 4 to 6 weeks after the last RISPERDAL CONSTA injection. The elimination phase is complete approximately 7 to 8 weeks after the last injection.

The absorption of risperidone from RISPERDAL CONSTA is presumably complete following breakdown of the microspheres.

Risperidone is rapidly distributed following oral administration. The volume of distribution is 1- 2 L/kg. In plasma, risperidone is bound to albumin and alphal-acid glycoprotein. The plasma protein binding of risperidone is 90% and that of 9-hydroxy-risperidone is 77%.

Risperidone plus 9-hydroxy risperidone and risperidone clearances were 5.0 and 13.7 L/h in extensive metabolisers, respectively, and 3.2 and 3.3 L/h in poor metabolisers of CYP2D6, respectively.

After repeated i.m. injections with 25 or 50mg RISPERDAL CONSTA every two weeks, median trough and peak plasma concentrations of risperidone plus 9-hydroxy risperidone fluctuated between 9.9 – 19.2 ng/mL and 17.9 – 45.5 ng/mL respectively. The pharmacokinetics of risperidone are linear in the dose range of 25-50 mg injected every 2 weeks. No accumulation of risperidone was observed during long-term use (12 months) in patients who were injected with 25-50 mg every two weeks.

The above studies were conducted with gluteal intramuscular injection. Deltoid and gluteal intramuscular injections at the same doses are bioequivalent and, therefore, interchangeable.

In vitro data suggests that drugs that inhibit the metabolism of risperidone to 9-hydroxyrisperidone by inhibition of cytochrome P450 2D6 would increase the plasma concentration of risperidone and lower the plasma concentration of 9-hydroxyrisperidone. Drugs metabolised by other P450 isoenzymes are only weak inhibitors of risperidone metabolism *in vitro*. Although *in vitro* studies suggest that risperidone can inhibit cytochrome P4502D6, substantial inhibition of the clearance of drugs metabolised by this enzymatic pathway would not be expected at therapeutic risperidone plasma concentrations. However, clinical data to confirm this expectation are not available.

Risperidone has an elimination half-life of about 3 hours in extensive metabolisers and 17 hours in poor metabolisers. Clinical studies do not suggest that poor and extensive metabolisers have different rates of adverse effects.

One week after administration of oral risperidone, 70% of the dose is excreted in the urine and 14% in faeces. In urine, risperidone and 9-hydroxyrisperidone represent 35-45% of the dose.

An oral, single-dose study showed higher active plasma concentrations and a slower elimination of risperidone by 30% in the elderly and 60% in patients with renal insufficiency. Risperidone plasma concentrations were normal in patients with liver insufficiency, but the unbound risperidone was somewhat increased by about 35% due to diminished concentration of both alpha$_1$-acid glycoprotein and albumin.

Pharmacokinetic/pharmacodynamic relationship.

There was no apparent relationship between the plasma concentrations of risperidone plus 9-hydroxy risperidone and the change in total PANSS (Positive and Negative Syndrome Scale) and total ESRS (Extrapyramidal Symptom Rating Scale) scores across the assessment visits in any of the phase-III trials where efficacy and safety was examined.

Clinical trials

Schizophrenia

The effectiveness of RISPERDAL CONSTA (25 mg and 50 mg) in the management of the manifestations of psychotic disorders (schizophrenia/schizoaffective) was established in one 12-week, placebo-controlled trial in adult psychotic inpatients and outpatients who met the DSM-IV criteria for schizophrenia (RIS-USA-121-see figure 1).

Further trials included a 12 week non-inferiority comparative trial in stable patients with schizophrenia, in which RISPERDAL CONSTA was shown to be as effective as the oral tablet formulation (RIS-INT-61). The long-term (50 weeks) safety and efficacy of RISPERDAL CONSTA was also evaluated in an open-label trial of stable psychotic inpatients and outpatients who met the DSM IV criteria for schizophrenia or schizoaffective disorder (RIS-INT-57-see figure 2). Over time efficacy was maintained with RISPERDAL CONSTA.

These efficacy trials used the internationally recognised PANSS scale. The total score (30 items) is divided into subscales: 8 items covering positive symptoms (e.g. hallucinations and delusions), 7 covering negative symptoms (e.g. blunted affect), 7 covering disorganised thought, 4 covering uncontrolled hostility/excitement and 4 covering anxiety/depression. Each item is scored on a seven point item-specific Likert scale ranging from 1 to 7.

The safety information is available in the safety section of this document.

Figure 1. Change from Baseline to Endpoint in Total PANSS (Positive and Negative Syndrome Scale) Score in Schizophrenic Patients During a 12-Week, Placebo-Controlled Trial (RIS-USA-121) (Last Observation Carried Forward)

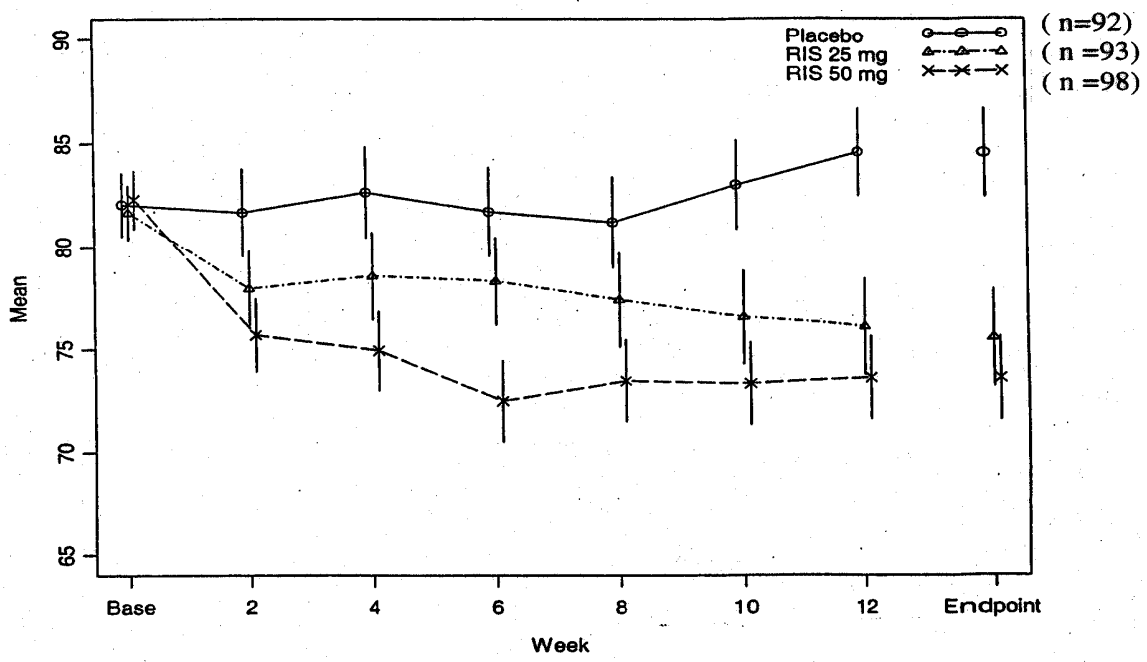
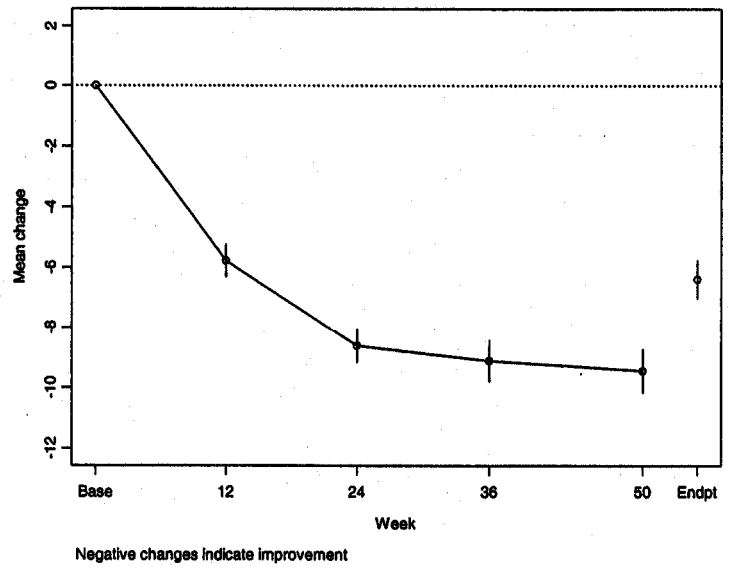


Figure 2.

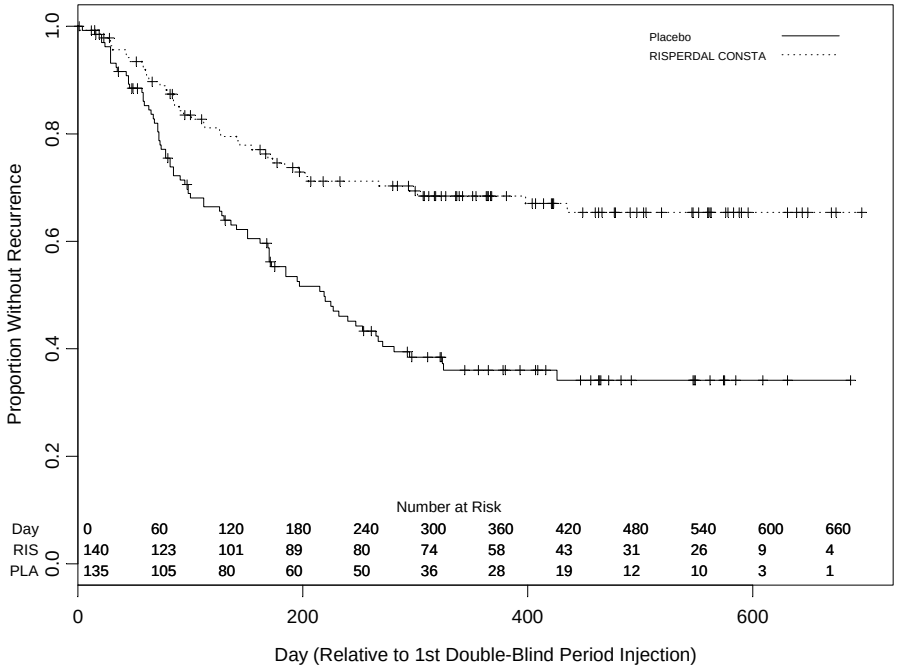
Mean Change in Total PANSS (Positive and Negative Syndrome Scale) Score in Patients with Schizophrenia and Schizoaffective Disorder in a 50-Week, Open-Label Trial (RIS-INT-57) (Observed Case, All Treatments Combined) (n = 725)



***Bipolar I disorder**

In a pivotal 24-month placebo-controlled trial (RIS-BIM-3003) male and female patients aged 18 to 65 with Bipolar Disorder Type I who achieved remission on RISPERDAL CONSTA during an open-label 26-week initial stabilisation phase were randomised to receive either RISPERDAL CONSTA as monotherapy or placebo during a 2-year, double-blind treatment period. A total of 559 patients were enrolled in the study, of which a total of 303 subjects (54%) were randomly assigned to double-blind treatment with RISPERDAL CONSTA (n=154) or placebo (n=149). Patients receiving RISPERDAL CONSTA demonstrated superiority over placebo in preventing recurrence of a mood episode. There was a statistically significant difference ($p<0.001$; log-rank test) between treatment groups in the time to recurrence during double-blind treatment in favour of RISPERDAL CONSTA, with 30% of patients experiencing a recurrence in the RISPERDAL CONSTA group versus 56% in the placebo group during the 2-year double-blind follow-up period. The relative reduction in risk of recurrence, as reflected by the treatment:placebo hazard ratio [95% CI], was 0.40 [0.27, 0.59]. The majority of recurrences were due to manic rather than depressive symptoms. RISPERDAL CONSTA was not effective in delaying the time to occurrence of a depressed mood episode.

Figure 3. Kaplan-Meier Curves of Time to Recurrence in Double-Blind Period (Study RIS-BIM-3003)



In a supporting 52-week placebo-controlled study (RIS-BIP-302), male and female patients, aged 18 to 70, with primarily Bipolar disorder Type I (87%, with 13% Bipolar Disorder Type II) who had at least 4 episodes of mood disorder requiring psychiatric/clinical intervention in the 12 months prior to study entry (at least 2 of which were in the 6 months prior to study entry) were enrolled. Patients entered a 16-week open-label stabilization period prior to randomisation and received RISPERDAL CONSTA as adjunctive therapy to their usual treatments for bipolar disorder. The usual treatments for bipolar disorder included one or more of the following: valproic acid derivatives, lithium carbonate, lamotrigine, benzodiazepines, and/or antidepressants (serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, mirtazapine, bupropion, trazodone). Patient taking carbamazepine, oxcarbazepine, paroxetine or fluoxetine were excluded from the study. A total of 275 patients were enrolled, of which 139 (51%) patients were randomized to receive either RISPERDAL CONSTA plus treatment-as-usual (n=72) or placebo plus treatment-as-usual (n=67) in the 52-week double-blind follow-up period. Treatment-as-usual was valproate or lithium (or both) for 89% of patients in the RISPERDAL CONSTA group and 96% of patients in the placebo group. There was a statistically significant

difference (p<0.004; log-rank test) between treatment groups in the time to recurrence during double-blind treatment in favour of RISPERDAL CONSTA, with 22% of patients in the RISPERDAL CONSTA group versus 48% in the placebo group experiencing a recurrence. RISPERDAL CONSTA as adjunctive therapy to treatment-as-usual demonstrated superiority over placebo plus treatment-as-usual in preventing recurrence of both elevated and depressed mood episodes.

INDICATIONS

RISPERDAL CONSTA is indicated for:

- Treatment of schizophrenia and related psychoses.

- **Adjunctive maintenance treatment with lithium or sodium valproate in treatment refractory patients with bipolar I disorder who have at least 4 relapses in a 12 month period.*

- *Monotherapy for maintenance treatment to prevent the recurrence of manic or mixed episodes of bipolar I disorder in patients with a manic or mixed episode, following stabilisation with oral risperidone.*

CONTRAINDICATIONS

RISPERDAL CONSTA is contraindicated in patients with a known hypersensitivity to the medicine or any of its excipients.

PRECAUTIONS

Elderly Patients with Dementia

Overall Mortality:
Elderly patients with dementia treated with atypical antipsychotic medicines have an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic medicines, including risperidone. In placebo-controlled trials with oral risperidone in this population, the incidence of mortality was 4.0% (40/1009) for risperidone treated patients and 3.1% (22/712) for placebo-treated patients. The mean age (range) of patients who died was 86 years (range 67-100).

Concomitant use with Frusemide:
In the oral risperidone placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with frusemide plus risperidone (7.3%[15/206]; mean age 89 years, range 75-97) compared to treatment with risperidone alone (3.1% [25/803]; mean age 84 years, range 70-96) or frusemide alone (4.1% [5/121]; mean age 80 years, range 67-90). The Odds Ratio (95% exact confidence interval) was 1.82 (0.65, 5.14). The increase in mortality was observed in two of the four clinical trials.

No pathophysiological mechanism has been clearly identified to explain this finding and no consistent pattern for cause of death was observed. Nevertheless, caution should be exercised and the risks and benefits of this combination should be considered prior to the decision to treat. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

Cerebrovascular Adverse Events:
In placebo-controlled trials in elderly patients with dementia there was a significantly higher incidence of cerebrovascular adverse events, such as stroke (including fatalities) and transient ischaemic attacks in patients (mean age 85 years, range 73-97) treated with oral risperidone compared to patients treated with placebo. The pooled data from six placebo-controlled trials in

mainly elderly patients (>65 years of age) with dementia showed that cerebrovascular adverse events (serious and non-serious combined) occurred in 3.3%(33/989) of patients treated with risperidone and 1.2% (8/693) of patients treated with placebo. The Odds Ratio (95% exact confidence interval) was 2.96 (1.33, 7.45).

Alpha-blocking activity

Due to the alpha-blocking activity of risperidone, orthostatic hypotension can occur, especially during the initial dose-titration period. Clinically significant hypotension has been observed postmarketing with concomitant use of risperidone and antihypertensive treatment. The risk-benefit of further treatment with RISPERDAL CONSTA should be assessed if clinically relevant orthostatic hypotension persists with oral treatment.

Patients with a history of clinically significant cardiac disorders were excluded from clinical trials. Risperidone should be used with caution in patients with known cardiovascular disease (e.g. heart failure, myocardial infarction, conduction abnormalities) and other conditions (such as dehydration, hypovolaemia, hypokalaemia or cerebrovascular disease). In these patients the dosage should be gradually increased.

Tardive dyskinesia (TD)

A syndrome consisting of potentially irreversible, involuntary dyskinetic movements may develop in patients treated with conventional neuroleptics. Although this syndrome of TD appears to be most prevalent in the elderly, especially elderly females, it is impossible to predict at the onset of treatment which patients are likely to develop TD.

It has been suggested that the occurrence of parkinsonian side effects is a predictor for the development of TD. In clinical studies, the observed incidence of drug-induced Parkinsonism was lower with risperidone than with haloperidol. In the optimal clinical dose-range, the difference between risperidone and haloperidol was significant. Therefore the risk of developing tardive dyskinesia may be less with risperidone. The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic medicines administered to the patient increase. However, the syndrome can develop, although less commonly, after relatively brief periods of treatment at low doses. There is no known treatment for an established case of TD. The syndrome may remit partially or completely if antipsychotic medicine treatment is withdrawn.

Antipsychotic drug treatment itself, however, may suppress the signs and symptoms of TD, thereby masking the underlying process. The effect of symptom suppression upon the long-term course of TD is unknown. In view of these considerations, RISPERDAL CONSTA should be prescribed in a manner that is most likely to minimise the risk of TD. As with any antipsychotic drug, RISPERDAL CONSTA should be reserved for patients who appear to be obtaining substantial benefit from the drug. In such patients, the smallest dose and the shortest duration of treatment should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of TD appear in a patient on antipsychotics, medicine discontinuation should be considered. However, some patients may require treatment despite the presence of this syndrome.

Neuroleptic Malignant Syndrome (NMS)

This is a potentially fatal symptom complex that has been reported in association with antipsychotic medicines, including risperidone.

Clinical manifestations of NMS are hyperthermia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, cardiac arrhythmias and diaphoresis). Additional signs may include elevated creatine phosphokinase (CPK) levels, myoglobinuria (rhabdomyolysis), and acute renal failure.

In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (eg pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of all antipsychotic medicines and other medicines not essential to concurrent therapy. After the last administration of RISPERDAL CONSTA, plasma levels of risperidone are measurable for at least 6 weeks; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic medicine treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Physicians should weigh the risks versus benefits when prescribing antipsychotics, including risperidone, to patients with Parkinson's Disease or Dementia with Lewy Bodies (DLB) since both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Patients with Epilepsy

Classical neuroleptics are known to lower the seizure threshold. RISPERDAL CONSTA has not been studied in patients who also have epilepsy. In clinical trials, seizures have occurred in a few risperidone treated patients. Therefore, caution is recommended when treating patients having a history of seizures or other predisposing factors.

Hyperglycaemia and Diabetes Mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL CONSTA. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with atypical antipsychotics. Precise risk estimates for hyperglycaemia related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect medicine.

QT Interval

As with other antipsychotics, caution should be exercised when RISPERDAL CONSTA is prescribed in patients with a history of cardiac arrhythmias, in patients with congenital long QT syndrome, and in concomitant use with drugs known to prolong the QT interval.

Premenopausal women with secondary amenorrhoea

Premenopausal women who develop secondary amenorrhoea of greater than six months duration should receive appropriate preventive therapy to avoid hypo-oestrogenic bone loss.

Effects on mental alertness

RISPERDAL CONSTA may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

Weight gain

Patients may be advised to refrain from excessive eating in view of the possibility of weight gain.

Administration

Care must be taken to avoid inadvertent injection of RISPERDAL CONSTA into a blood vessel (see **ADVERSE EFFECTS**).

Carcinogenicity

Risperidone was administered in the diet to Swiss albino mice for 18 months and to Wistar rats for 25 months at doses equivalent to 0.3, 1.3 and 5 times the maximum human dose of 10 mg/day (mice) or 0.6, 2.5 and 10 times the maximum human dose (rats) on a mg/m^2 basis. There were statistically significant increases in pituitary gland adenomas in female mice and endocrine pancreas adenomas in male rats at the two highest dose levels, and in mammary gland adenocarcinomas at all dose levels in female mice and female rats and at the highest dose in male rats.

Antipsychotic medicines have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5 to 6-fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary and endocrine pancreas neoplasms has been found in rodents after chronic administration of other dopamine receptor antagonists and is considered to be prolactin mediated.

In a 2 year IM carcinogenicity study in rats, increased incidences of mammary gland adenocarcinoma, pancreatic islet-cell adenoma, adrenal gland phaeochromocytoma, pituitary gland adenoma and renal corticotubular adenoma were observed with systemic exposure (plasma AUC) to risperidone plus 9-hydroxy risperidone about twice that anticipated in humans at the maximal recommended clinical dose of RISPERDAL CONSTA. Increased incidences of mammary adenocarcinoma were also observed at doses for which the plasma AUC of risperidone plus 9-hydroxy risperidone was less than anticipated clinical exposure, a no-effect dose for this finding was not determined. Elevated plasma concentrations of prolactin were present after one year of treatment, but the relationship between the renal tubular tumours and prolactin is uncertain. The increase in phaeochromocytomas was associated with hypercalcemia but there was no evidence for a causal relationship. However, phaeochromocytomas associated with hypercalcemia is a common finding in rats and is likely to be of low relevance to humans.

The relevance for human risk of the findings of prolactin-mediated endocrine tumours in rodents is unknown. In controlled clinical trials, risperidone elevated serum prolactin levels more than haloperidol, although to date neither clinical studies nor epidemiological studies have shown an association between chronic administration of these medicines and mammary tumorigenesis. However, since tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, risperidone should be used cautiously in patients with previously detected breast cancer or in patients with pituitary tumours. Possible manifestations associated with elevated prolactin levels are amenorrhoea, galactorrhoea and menorrhagia (see **ADVERSE EFFECTS**).

Local irritation at the injection site was observed in dogs and rats after administration of RISPERDAL CONSTA. In a 2 year IM carcinogenicity study in rats, no increased incidence of injection site tumours was seen in either the vehicle or active drug groups.

Genotoxicity

No evidence of genotoxicity was observed in assays for DNA damage, gene mutations or chromosomal damage.

Effects on Fertility

Risperidone impaired mating, but not fertility, in Wistar rats at doses 0.2 to 5 times the maximum human dose on a mg/m^2 basis. The effect appeared to be in females since the oestrus cycle in rats was disrupted by risperidone and impaired mating behaviour was not noted when males only were treated. In repeat dose toxicity studies in Beagle dogs, risperidone at dose of 1 to 17 times the maximum human dose on a mg/m^2 basis was associated with adverse effects on the male reproductive system (inhibited ejaculation, incomplete spermatogenesis, reduced sperm motility and concentration, reduced gonadal and prostatic weight, prostatic immaturity, decreased serum testosterone). Serum testosterone and sperm parameters partially recovered but remained decreased after treatment was discontinued. No-effect doses were not determined in either rat or dog.

Use in the elderly

The recommended dose is 25mg intramuscular every two weeks. Sufficient antipsychotic coverage should be ensured during the three-week lag period following the first RISPERDAL CONSTA injection (see **Pharmacokinetics**).

Use in patients with hepatic and renal impairment

RISPERDAL CONSTA has not been studied in hepatically and renally impaired patients.

In case hepatically or renally impaired patients would require treatment with RISPERDAL CONSTA, a starting dose of 0.5mg b.i.d. oral risperidone is recommended during the first week. The second week 1 mg b.i.d. or 2 mg o.d. can be given. If an oral dose of at least 2 mg is well tolerated, an intrasmuscular injection of 25mg RISPERDAL CONSTA can be administered every 2 weeks.

Use in pregnancy - Category B3

Risperidone has only been taken by a limited number of pregnant women or women of childbearing age. No increases in the frequency of malformation or other direct or indirect harmful effects on the human fetus have been observed. Reversible extrapyramidal symptoms in the neonate were observed following postmarketing use of risperidone during the last trimester of pregnancy.

In rats and rabbits, oral administration of risperidone during the period of organogenesis did not increase the incidence of malformations in offspring at doses of up to 10 times the maximum

human dose on a mg/m^2 basis. In an embryofetal development study in rats, intramuscular administration of RISPERDAL CONSTA delayed ossification in the metatarsals and mandible at risperidone plus 9-hydroxy risperidone levels less than those achieved at the maximal human dose. This is unlikely to be clinically relevant. There was no effect on the incidence of malformations. RISPERDAL CONSTA should only be used during pregnancy if the benefits outweigh the risks.

Use during lactation

It has been demonstrated that risperidone and 9-hydroxyrisperidone are excreted in human breast milk. It is recommended that women receiving risperidone should not breast feed.

Risperidone and 9-hydroxyrisperidone are excreted in milk in lactating dogs. In rats, administration of risperidone during late gestation and lactation was associated with an increase in pup deaths during the first 4 days of lactation at doses 0.2 to 5 times the maximum human dose on a mg/m^2 basis. A no-effect dose was not determined. It is not known whether these deaths were due to a direct effect on the foetuses or pups or to effects on the dams. In one such study there was an increase in stillborn rat pups at a dose 2.5 times the maximum human dose on a mg/m^2 basis.

Use in children

RISPERDAL CONSTA has not been studied in adolescents and children younger than 18 years.

Interactions with other medicines

Given the primary CNS effects of risperidone, it should be used with caution in combination with other centrally acting medicines. Risperidone may antagonise the effect of levodopa and other dopamine-agonists. Tricyclic antidepressants may potentiate the postural hypotensive effect of risperidone.

Clinically significant hypotension has been observed postmarketing with concomitant use of risperidone and antihypertensive treatment.

Caution is advised when prescribing RISPERDAL CONSTA with drugs known to prolong the QT interval.

Carbamazepine has been shown to decrease the plasma levels of risperidone plus 9-hydroxy risperidone. Similar effects may be observed with other CYP 3A4 hepatic enzyme inducers. When carbamazepine or other CYP 3A4 hepatic enzyme inducers are initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL CONSTA.

Paroxetine and fluoxetine are potent CYP2D6 inhibitors. Co-administration of fluoxetine produced relative increases of 1.63±0.43, 1.54±0.54 and 1.40±0.24 in Cmin, Cmax and AUC0-12hr of risperidone plus 9-hydroxy risperidone. Administration of paroxetine 20mg/day for 4 weeks to patients stabilised on 4-8mg risperidone/day produced a relative increase of 1.51±0.34 in Cmin of risperidone plus 9-hydroxy risperidone. When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dose of risperidone.

Topiramate modestly reduced the bioavailability of risperidone, but not that of risperidone plus 9-hydroxy risperidone.

Quinidine, phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentrations of risperidone but not those of risperidone plus 9-hydroxyrisperidone (see **Pharmacokinetics**).

In patients with schizophrenia receiving risperidone 3mg twice daily for 28 days, the addition of amitryptiline initially at 50mg twice daily, increasing to 100mg twice daily for the last 6 days of the study produced relative increases in the 0-12 hr AUC of 1.21±0.35, 1.15±0.36 and 1.16±0.34 and Cmax of 1.17±0.33, 1.11±0.43 and 1.11±0.38 for risperidone, 9-hydroxy-risperidone and risperidone plus 9-hydroxy risperidone respectively. These modest increases do not necessitate dose modification.

In volunteer studies, a single 1mg risperidone dose was administered with cimetidine 400mg twice daily or ranitidine 150mg twice daily. Cimetidine produced a relative increase in AUC 0-Inf of 1.95±0.78, 1.01±0.25 and 1.15±0.28 for risperidone, 9-hydroxy-risperidone and risperidone plus 9-hydroxy risperidone respectively. Relative C max increases were 1.90±0.95, 0.95±0.21 and 1.24±0.27. Co-administration of ranitidine produced a relative increase of 1.35±0.32, 1.23±0.44 and 1.25±0.39 in the AUC 0-Inf and of Cmax of 1.45±0.61, 1.28±0.37 and 1.36±0.35. Dose modification is not considered to be necessary.

Erythromycin, a CYP3A4 inhibitor, does not change the pharmacokinetics of risperidone and risperidone plus 9-hydroxy risperidone. The cholinestease inhibitors galantamine and donepezil, do not show a clinically relevant effect on the pharmacokinetics of risperidone and risperidone plus 9-hydroxy risperidone.

Risperidone does not show a clinically relevant effect on the pharmacokinetics of lithium, valproate, digoxin or topiramate.

In vitro studies, in which risperidone was given in the presence of various, highly protein-bound agents, indicated that clinically relevant changes in protein binding would not occur either for risperidone or for any of the medicines tested.

ADVERSE EFFECTS

Clinical Trial Data

The safety of RISPERDAL CONSTA was evaluated from a clinical trial database consisting of 2392 patients exposed to one or more doses of RISPERDAL CONSTA for the treatment of schizophrenia. Of these 2392 patients, 332 were patients who received RISPERDAL CONSTA while participating in a 12-week double-blind, placebo-controlled trial. A total of 202 of the 332 were schizophrenic patients who received 25 mg or 50 mg RISPERDAL CONSTA. The conditions and duration of treatment with RISPERDAL CONSTA varied greatly and included (in overlapping categories) double-blind, fixed- and flexible-dose, placebo- or active-controlled studies and open-label phases of studies, inpatients and outpatients, and short-term (up to 12 weeks) and longer-term (up to 4 years) exposures.

The majority of all adverse reactions were mild to moderate in severity.

Double-Blind, Placebo-Controlled Data – Schizophrenia

Adverse drug reactions (ADRs) reported by ≥ 2% of RISPERDAL CONSTA-treated patients with schizophrenia in one 12-week double-blind, placebo-controlled trial are shown in Table 1.

Table 1. Adverse Drug Reactions Reported by ≥ 2% of RISPERDAL CONSTA-Treated Patients with Schizophrenia in a 12-Week Double-Blind, Placebo-Controlled Trial

System/Organ Class Adverse Reaction	**RISPERDAL CONSTA 25 mg (n=99) %**	**RISPERDAL CONSTA 50 mg (n=103) %**	**Placebo (n=98) %**
Infections and Infestations			
Upper respiratory tract infection	2	0	1
Nervous System Disorders			
Headache	15	21	12
Parkinsonism*	8	15	9
Dizziness	7	11	6
Akathisia*	4	11	6
Somnolence	4	4	0
Tremor	0	3	0
Sedation	2	2	3
Syncope	2	1	0
Hypoesthesia	2	0	0
Eye Disorders			
Vision blurred	2	3	0
Respiratory, Thoracic And Mediastinal Disorders			
Cough	4	2	3
Sinus congestion	2	0	0
Gastrointestinal Disorders			
Constipation	5	7	1
Dry mouth	0	7	1
Dyspepsia	6	6	0
Nausea	3	4	5
Toothache	1	3	0
Salivary hypersecretion	4	1	0
Skin And Subcutaneous Tissue Disorders			
Acne	2	2	0
Dry skin	2	0	0
Musculoskeletal and Connective Tissue Disorders			
Pain in extremity	6	2	1
General Disorders And Administration Site Conditions			
Fatigue	3	6	0
Asthenia	0	3	0
Edema peripheral	2	3	1
Pain	4	1	0
Pyrexia	2	1	0
Investigations			
Weight increased	5	4	2
Weight decreased	4	1	1

*Parkinsonism includes extrapyramidal disorder, musculoskeletal stiffness, muscle rigidity, and bradykinesia. Akathisia includes akathisia and restlessness.

**Double-Blind, Placebo-Controlled Data – Bipolar Disorder*

Adverse drug reactions (ADRs) reported by ≥ 1% of RISPERDAL CONSTA-treated patients with bipolar disorder in the 24-month double-blind, placebo-controlled period in one monotherapy recurrence prevention trial are shown in Table 2.

Table 2. *Adverse Drug Reactions Reported by ≥ 1% of Bipolar Disorder Patients Treated with RISPERDAL CONSTA as Monotherapy in a 24-Month Double-Blind, Placebo-Controlled Trial*

System/Organ Class *Adverse Reaction*	***RISPERDAL CONSTA (N=154) %***	***Placebo (N=149) %***
Infections and infestations		
Viral infection	*2*	*1*
Metabolism and nutrition disorders		
Hyperglycaemia	*1*	*0*
Psychiatric disorders		
Libido decreased	*1*	*0*
Nervous system disorders		
Dizziness	*3*	*1*
Parkinsonism[a]	*1*	*0*
Dyskinesia[a]	*1*	*0*
Akathisia[a]	*1*	*0*
Cardiac disorders		
Bundle branch block right	*1*	*0*
Vascular disorders		
Hypertension	*3*	*1*
Gastrointestinal disorders		
Diarrhoea	*2*	*1*
Reproductive system and breast disorders		
Erectile dysfunction	*1*	*0*
Sexual dysfunction	*1*	*0*
Investigations		
Weight increased	*5*	*1*
Electrocardiogram QT prolonged	*1*	*1*

[a] *Parkinsonism includes hypokinesia and muscle rigidity; Dyskinesia includes dyskinesia and muscle twitching; Akathisia includes akathisia and restlessness.*

Adverse drug reactions (ADRs) reported by ≥ 1% of RISPERDAL CONSTA-treated patients with bipolar disorder in the 52-week double-blind, placebo-controlled period in one adjunctive therapy recurrence prevention trial are shown in Table 3.

Table 3. *Adverse Drug Reactions Reported by ≥ 1% of Bipolar Disorder Patients Treated with RISPERDAL CONSTA as Adjunctive Therapy in a 52-Week Double-Blind, Placebo-Controlled Trial*

System Organ Class *Adverse Reaction*	***RISPERDAL® CONSTA® + Treatment as Usual[a] (N=72) %***	***Placebo + Treatment as Usual[a] (N=67) %***
Infections and infestations		
Upper respiratory tract infection	*6*	*3*
Urinary tract infection	*3*	*1*
Metabolism and nutrition disorders		
Decreased appetite	*6*	*1*
Increased appetite	*4*	*0*
Anorexia	*1*	*0*
Psychiatric disorders		

Libido decreased	*1*	*0*
Nervous system disorders		
Tremor	*23*	*16*
Hypokinesia	*7*	*0*
Sedation	*6*	*0*
Disturbance in attention	*4*	*0*
Dyskinesia	*4*	*3*
Bradykinesia	*3*	*0*
Cogwheel rigidty	*1*	*0*
Drooling	*1*	*0*
Muscle twitching	*1*	*0*
Posture abnormal	*1*	*0*
Tardive dyskinesia	*1*	*0*
Eye disorders		
Visual acuity reduced	*3*	*0*
Vascular disorders		
Orthostatic hypotension	*3*	*0*
Respiratory, thoracic and mediastinal disorders		
Cough	*4*	*1*
Musculoskeletal and connective tissue disorders		
Muscle rigidity	*11*	*6*
Arthralgia	*4*	*3*
Muscle twitching	*1*	*0*
Reproductive system and breast disorders		
Amenorrhoea	*4*	*1*
Menstrual Disorder	*1*	*0*
General disorders and administration site conditions		
Gait abnormal	*4*	*0*
Investigations		
Weight increased	*7*	*1*

[a] *Adjunctive therapy to patients treated with Treatment as Usual (TAU), i.e. other psychotropic medications, including benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), atypical antipsychotics (including olanzepine), valproate, and/or lithium.*

Other Clinical Trial Data

ADRs reported by < 2% of the RISPERDAL CONSTA-treated patients in the 12-week, double-blind, placebo-controlled schizophrenia trial, by <1% of the RISPERDAL CONSTA-treated patients in the 24-month double-blind, placebo-controlled period of the monotherapy bipolar disorder trial, and by <1% of the RISPERDAL CONSTA-treated patients in the 52-week double-blind, placebo-controlled period of the adjunctive therapy bipolar disorder trial are shown in Table 4. Table 4 also includes ADRs reported at any rate in RISPERDAL CONSTA-treated patients who participated in other studies, including double-blind, active-controlled and open-label studies in schizophrenia and in the open-label phases in bipolar disorder studies.

Table 4. Adverse Drug Reactions Reported by < 2% of RISPERDAL CONSTA-Treated Patients in the 12-Week Double-Blind, Placebo-Controlled SchizophreniaTrial, by < 1% of RISPERDAL® CONSTA®-Treated Patients in the 24-Month Double-Blind, Placebo-Controlled Period of the Monotherapy Bipolar I Disorder Trial, by <1% of RISPERDAL® CONSTA®-Treated Patients in the 52-Week Double-Blind, Placebo-Controlled Phase of the Adjunctive Therapy Bipolar Disorder Trial, or At Any Rate in Other Studies, Including Double-Blind, Active-Controlled and Open-Label Studies in Schizophrenia and in the Open-Label Phases in Bipolar Disorder Studies.

Infections and Infestations
Nasopharyngitis, Influenza, Bronchitis, Rhinitis, Ear infection, Pneumonia, Lower respiratory tract infection, Pharyngitis, Sinusitis, Infection, Localized infection, Cystitis, Gastroenteritis, Subcutaneous abscess

Blood and Lymphatic System Disorders
Anemia, Neutropenia

Immune System Disorders
Hypersensitivity

Endocrine Disorders
Hyperprolactinemia

Psychiatric Disorders
Insomnia, Anxiety, Agitation, Depression, Sleep disorder, Nervousness

Nervous System Disorders
Coordination abnormal, Dystonia, Lethargy, Paresthesia, Dizziness postural, Hypersomnia, Convulsion, Akinesia, Dysarthria

Eye Disorders
Conjunctivitis

Ear and Labyrinth Disorders
Ear pain, Vertigo

Cardiac Disorders
Tachycardia, Atrioventricular block first degree, Palpitations, Sinus bradycardia, Bundle branch block left, Bradycardia, Sinus tachycardia

Vascular Disorders
Hypotension

Respiratory, Thoracic and Mediastinal Disorders
Nasal congestion, Pharyngolaryngeal pain, Dyspnea, Rhinorrhea

Gastrointestinal Disorders
Vomiting, Abdominal pain, Stomach discomfort, Gastritis

Skin and Subcutaneous Disorders
Rash, Eczema, Pruritus

Musculoskeletal, Connective Tissue, and Bone Disorders
Back pain, Myalgia, Musculoskeletal chest pain, Buttock pain, Muscular weakness, Neck pain

Renal and Urinary Disorders
Urinary incontinence

Reproductive System and Breast Disorders
Oligomenorrhea, Galactorrhea, Ejaculation disorder, Gynecomastia, Breast discomfort, Menstruation irregular, Menstruation delayed

General Disorders and Administration Site Conditions
Injection site pain, Chest discomfort, Chest pain, Influenza like illness, Sluggishness, Malaise, Induration, Injection site induration, Injection site swelling Injection site reaction, Face edema

Investigations
Blood prolactin increased, Alanine aminotransferase increased, Electrocardiogram abnormal, Gamma-glutamyl transferase increased, Blood glucose increased, Hepatic enzyme increased, Aspartate aminotransferase increased

Injury, Poisoning and Procedural Complications
Fall, Procedural pain

The following is a list of additional ADRs that have been reported with oral risperidone:

Infections and Infestations: Tonsillitis, Eye infection, Cellulitis, Otitis media, Onychomycosis, Acarodermatitis, Bronchopneumonia, Respiratory tract infection, Tracheobronchitis, Otitis media chronic
Blood and Lymphatic Disorders: Granulocytopenia
Immune System Disorders: Drug hypersensitivity
Metabolism and Nutrition Disorders: Polydipsia
Psychiatric Disorders: Blunted affect, Confusional state, Middle insomnia, Listless, Anorgasmia
Nervous System Disorders: Hypertonia, Balance disorder, Unresponsive to stimuli, Depressed level of consciousness, Movement disorder, Parkinsonian rest tremor, Transient ischemic attack, Cerebrovascular accident, Masked facies, Speech disorder, Loss of consciousness, Muscle contractions involuntary, Cerebral ischemia, Cerebrovascular disorder, Neuroleptic malignant syndrome, Diabetic coma
Eye Disorders: Ocular hyperemia, Eye discharge, Eye rolling, Eyelid edema, Eye swelling, Eyelid margin crusting, Dry eye, Lacrimation increased, Photophobia, Glaucoma,
Ear and Labyrinth Disorders: Tinnitus
Cardiac Disorders: Atrioventricular block
Vascular Disorders: Flushing
Respiratory, Thoracic, and Mediastinal Disorders: Epistaxis, Wheezing, Pneumonia aspiration, Dysphonia, Productive cough, Pulmonary congestion, Respiratory tract congestion, Rales, Respiratory disorder, Hyperventilation, Nasal edema
Gastrointestinal Disorders: Abdominal pain upper, Dysphagia, Fecaloma, Abdominal discomfort, Fecal incontinence, Lip swelling, Cheilitis, Aptyalism
Skin and Subcutaneous Tissue Disorders: Erythema, Skin discoloration, Skin lesion, Skin disorder, Rash erythematous, Rash papular, Hyperkeratosis, Dandruff, Seborrheic dermatitis, Rash generalised, Rash maculo-papular
Musculoskeletal, Connective Tissue, and Bone Disorders: Joint stiffness, Rhabdomyolysis, Torticollis
Renal and Urinary Disorders: Enuresis, Dysuria, Pollakiuria
Reproductive System and Breast Disorders: Vaginal discharge, Retrograde ejaculation, Ejaculation failure, Breast enlargement
General Disorders and Administration Site Conditions: Thirst, Feeling abnormal, Gait disturbance, Pitting edema, Edema, Chills, Discomfort, Generalised edema, Drug withdrawal syndrome, Peripheral coldness,
Investigations: Body temperature increased, Heart rate increased, Eosinophil count increased, White blood cell count decreased, Hemoglobin decreased, Blood creatine phosphokinase increased, Hematocrit decreased, Body temperature decreased, Blood pressure decreased, Transaminases increased

Postmarketing Data

Adverse events first identified as ADRs during postmarketing experience with risperidone based on spontaneous reporting rates are included in Table 5. The frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥1/10,000 to <1/1,000
Very rare	<1/10,000, including isolated reports

Table 5. Adverse Drug Reactions Identified During Postmarketing Experience with Risperidone by Frequency Category Estimated from Spontaneous Reporting Rates	
Blood and Lymphatic Disorders	
Very rare	Agranulocytosis
Very rare	Thrombocytopenia[a]
Immune System Disorders	
Very rare	Anaphylactic reaction
Endocrine Disorders	
Very rare	Inappropriate antidiuretic hormone secretion
Metabolism and Nutrition Disorders	
Very rare	Diabetic ketoacidosis
Very rare	Water intoxication
Psychiatric Disorders	
Very rare	Mania
Eye Disorders	
Very rare	Retinal artery occlusion[b]
Cardiac Disorders	
Very rare	Atrial fibrillation
Respiratory, Thoracic, and Mediastinal Disorders	
Very rare	Sleep apnea syndrome
Gastrointestinal Disorders	
Very rare	Intestinal obstruction
Very rare	Pancreatitis
Hepatobiliary Disorders	
Very rare	Jaundice
Skin and Subcutaneous Tissue Disorders	
Very rare	Angioedema[c]
Very rare	Alopecia
Reproductive System and Breast Disorders	
Very rare	Priapism
General Disorders and Administration Site Conditions	
Very rare	Hypothermia
Very rare	Injection site reaction including injection site abscess, cellulitis, cyst, haematoma, necrosis, nodule, and ulcer[d]

[a] Search terms included Thrombocytopenia, Platelet count decreased, Plateletcrit decreased, Platelet production decreased

[b] RISPERDAL CONSTA formulation only, reported in the presence of an intracardiac defect predisposing to a right-to-left shunt (e.g., a patent foramen ovale)

[c] Search terms included Angioneurotic oedema, C1 esterase deficiency acquired, Circumoral oedema, Eyelid edema, Face edema, Hereditary angioedema, Laryngeal oedema, Laryngotracheal oedema, Oculo-respiratory syndrome, Oedema mouth, Periorbital edema, Small bowel angioedema, Tongue oedema

[d] These events were reported as serious. Isolated cases required surgical intervention.

DOSAGE AND ADMINISTRATION

Treatment initiation: For risperidone naïve patients, it is recommended to establish tolerability with immediate release oral formulations of risperidone prior to initiating treatment with RISPERDAL CONSTA

RISPERDAL CONSTA should be administered every two weeks by deep intramuscular deltoid or gluteal injection using the enclosed appropriate safety needle. For deltoid administration, use the 1-inch needle alternating injections between the two arms. For gluteal administration, use the 2-inch needle alternating injections between the two buttocks. Prior to each administration, the site of injection should be examined for any signs of inflammation. If such signs exist, an alternative site should be chosen for injection. Do not administer intravenously (see **PRECAUTIONS and ADVERSE EFFECTS**). This product does not contain an antimicrobial agent. It is for single use in one patient only. Any residue is to be discarded.

Adults

The recommended dose is 25mg intramuscularly every two weeks. Some patients may benefit from the higher doses of 37.5 mg or 50 mg. No additional benefit was observed with 75 mg in clinical trials in patients with schizophrenia. **Doses above 50 mg were not studied in patients with bipolar disorder*. Doses higher than 50 mg every 2 weeks are not recommended.

Sufficient antipsychotic coverage should be ensured during the three week lag period following the first RISPERDAL CONSTA injection (see **Pharmacokinetics**)**.**

Upward dosage adjustment should not be made more frequently than every 4 weeks. The effect of this dose adjustment should not be anticipated earlier than 3 weeks after the first injection with the higher dose.

Elderly

The recommended dose is 25 mg intramuscular every two weeks. Sufficient antipsychotic coverage should be ensured during the three week lag period following the first RISPERDAL CONSTA injection (see **Pharmacokinetic**).

Hepatic and renal impairment

RISPERDAL CONSTA has not been studied in hepatically and renally impaired patients.

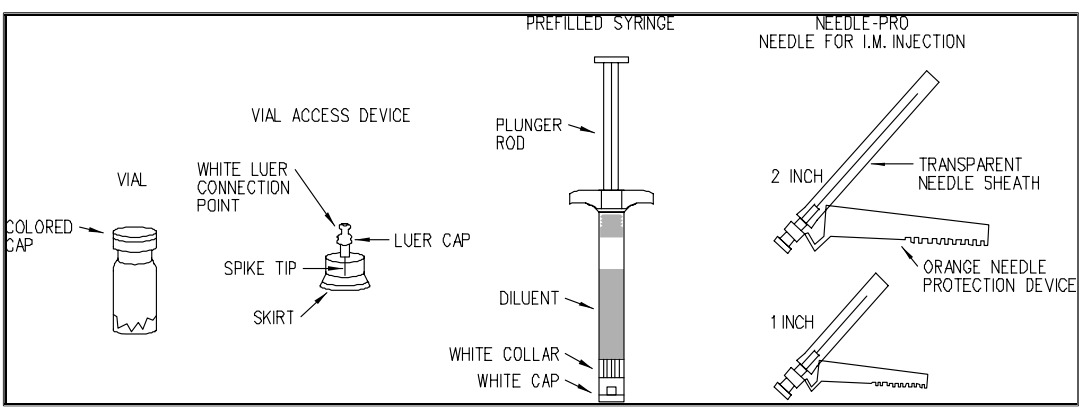
In case hepatically or renally impaired patients would require treatment with RISPERDAL CONSTA, a starting dose of 0.5 mg twice daily oral risperidone is recommended during the first week. The second week 1 mg twice daily or 2 mg once daily can be given. If an oral total daily dose of at least 2 mg is well tolerated, an injection of 25 mg RISPERDAL CONSTA can be administered every 2 weeks.

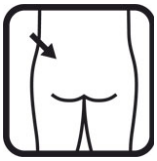
Children

RISPERDAL CONSTA has not been studied in adolescents and children younger than 18 years.

Instruction for use and handling

RISPERDAL CONSTA in the vial must **only** be reconstituted in the diluent in the syringe supplied in the dose pack and must be administered with **only** the appropriate needle supplied in the dose pack for gluteal (2-inch needle) or deltoid (1-inch needle) administration. Do not substitute any components in the dose pack. To assure that the intended dose of risperidone is delivered, the full contents from the vial must be administered. Administration of partial contents may not deliver the intended dose of risperidone.



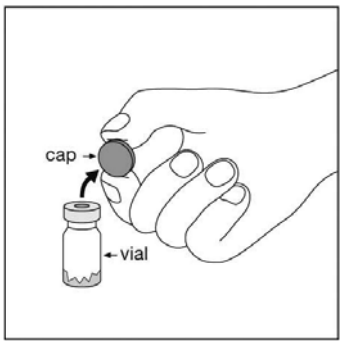


Remove the dose pack of RISPERDAL CONSTA from the refrigerator and allow it to come to room temperature prior to reconstitution.

Contents of the dose pack:

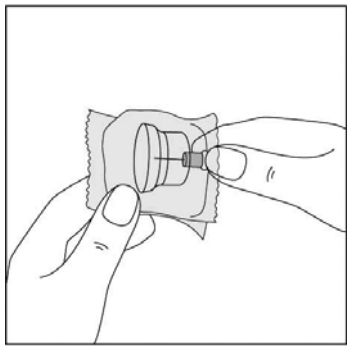
- One vial containing RISPERDAL CONSTA extended release microspheres
- One Alaris ™ SmartSite® needle-free vial access device for reconstitution
- One prefilled syringe containing the diluent for RISPERDAL CONSTA
- Two needles for intramuscular injection (a 21G UTW 1-inch safety needle with Needle-Pro® safety device for deltoid administration and a 20G TW 2-inch safety needle with Needle-Pro® safety device for gluteal administration)

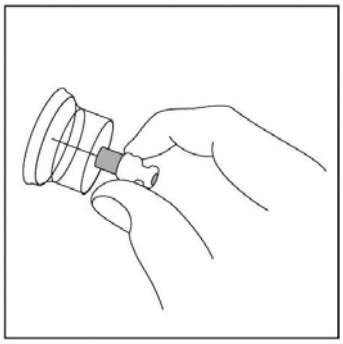
1. Flip off the plastic coloured cap from the vial



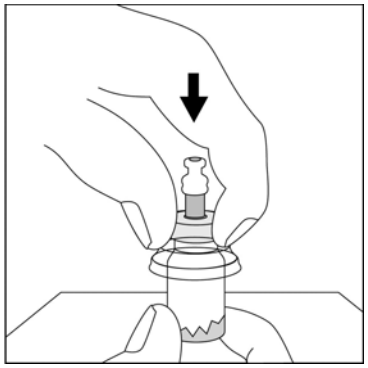
2. Peel back the blister pouch and remove the vial access device by holding the white luer cap.

Do not touch the spike tip of the access device at any time.





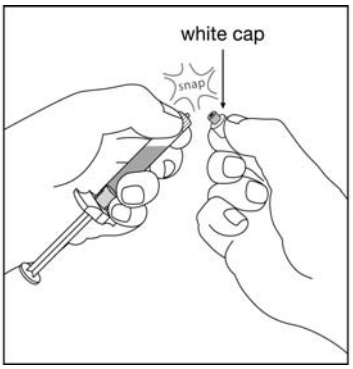
3. Place vial on a hard surface. With a straight push down movement press the spike tip of the vial access device through the centre of the vial's rubber stopper until the device securely snaps onto the vial top.



4. Swab the syringe connection point (blue circle) of the vial access device with preferred antiseptic prior to attaching the syringe to the vial access device.

5. The prefilled syringe has a white tip consisting of 2 parts: a white collar and a smooth white cap. To open the syringe, hold the syringe by the white collar and **snap** off the smooth white cap **(DO NOT TWIST OFF THE WHITE CAP)**. Remove the white cap together with the rubber tip cap inside.

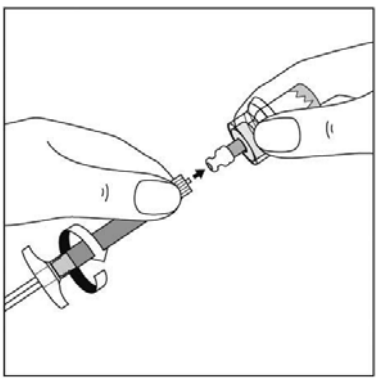
   For all assembly steps, hold the syringe only by the white collar located at the tip of the syringe. Be careful not to overtighten components when assembling. Overtightening connections may cause syringe component parts to loosen from the syringe body.



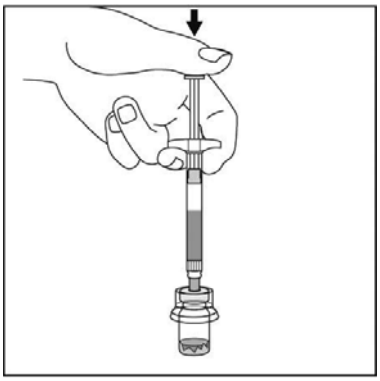
6. While holding the **white collar** of the syringe, insert and **press** the syringe tip into the blue circle of the vial access device and **twist** in a clockwise motion to secure the connection of the syringe to the vial access device (avoid over twisting).

   Hold the skirt of the access device during attachment to prevent it from spinning.

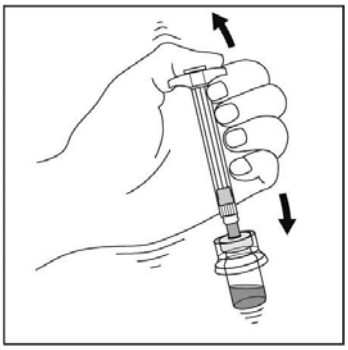
   Keep the syringe and the vial access device aligned.



7. Inject the entire contents of the syringe containing the diluent into the vial.

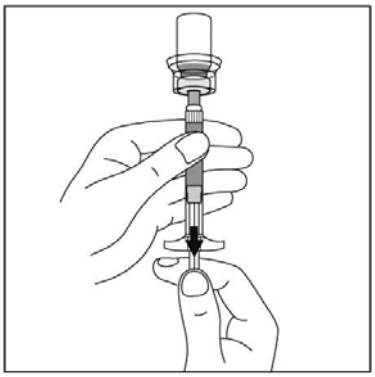


8. Shake the vial vigorously while holding the plunger rod down with the thumb for a minimum of 10 seconds to ensure a homogeneous suspension. When properly mixed the suspension appears uniform, thick, and milky in color. The microspheres will be visible in liquid, but no dry microspheres remain.

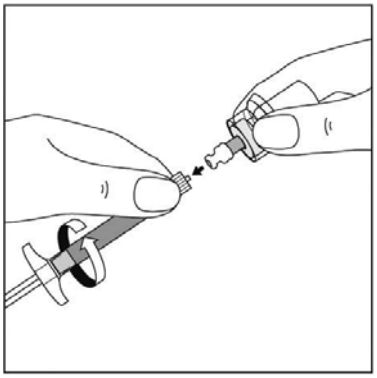


9. DO NOT STORE THE VIAL AFTER RECONSTITUTION OR THE SUSPENSION MAY SETTLE.

10. Invert the vial completely and slowly withdraw the entire contents of the suspension from the vial into the syringe.
Tear section of the vial label at the perforation and apply detached label to syringe for identification purposes.



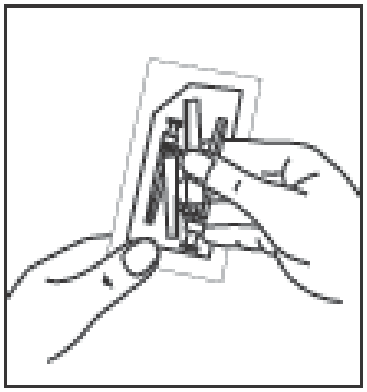
11. While holding the **white collar** of the syringe, unscrew the syringe from the vial access device. Discard both the vial and vial access device appropriately.



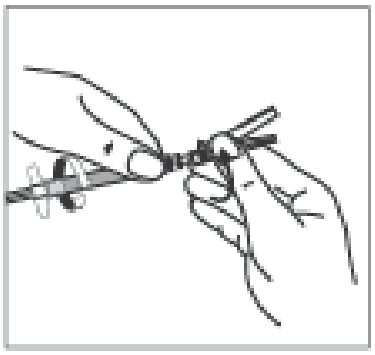
12. Open the needle pack and select the appropriate needle. Do NOT touch the connection part of the needle, only touch the transparent sheath of the needle:

    For GLUTEAL injection, select the **20G** TW **2-inch** needle (longer needle with **yellow** coloured hub).

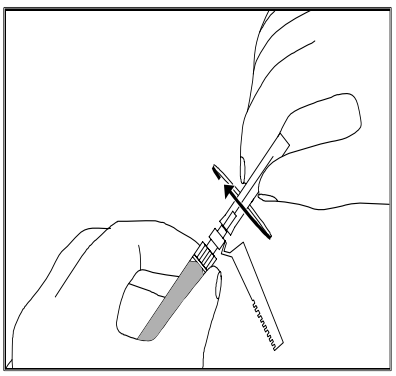
    For DELTOID injection, select the **21G** UTW **1-inch** needle (shorter needle with **green** coloured hub).



13. While holding the **white collar** of the syringe, attach the Luer connection of the orange Needle-Pro® safety device to the syringe with an easy clockwise twisting motion.

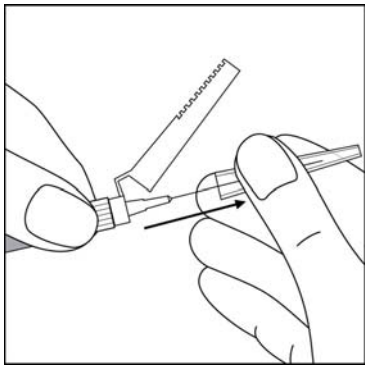


14. While continuing to hold the **white collar** of the syringe, grasp the transparent needle sheath and seat the needle firmly on the orange Needle-Pro® safety device with a push and a clockwise twist.



15. **RESUSPENSION OF RISPERDAL CONSTA WILL BE NECESSARY PRIOR TO ADMINISTRATION AS SETTLING WILL OCCUR OVER TIME ONCE PRODUCT IS RECONSTITUTED. RESUSPEND THE MICROSPHERES IN THE SYRINGE BY SHAKING VIGOROUSLY.**

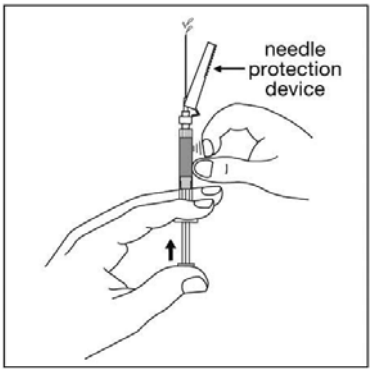
16. While holding the **white** collar of the syringe, pull the transparent needle sheath straight away from the needle. DO NOT TWIST the sheath as the Luer connections may be loosened.



17. Tap the syringe gently to make any air bubbles rise to the top.

    Remove air in syringe by depressing the plunger rod while holding the needle in an upright position. Inject the entire contents of the syringe intramuscularly into the selected gluteal or deltoid muscle of the patient. Gluteal injection should be made into the upper-outer quadrant of the gluteal area.

    DO NOT ADMINISTER INTRAVENOUSLY.

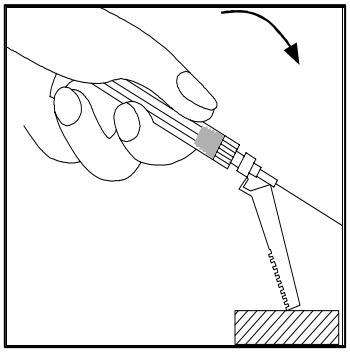


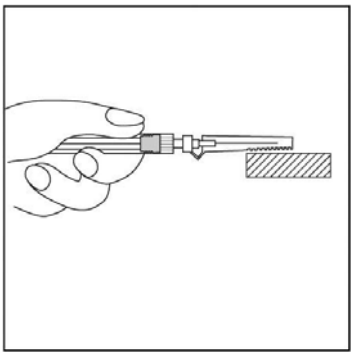
WARNING: To avoid a needle stick injury with a contaminated needle:

- Do not use free hand to press the Needle-Pro® safety device over the needle.
- Do not intentionally disengage the Needle-Pro® safety device
- Do not attempt to straighten the needle or engage Needle-Pro® safety device if the needle is bent or damaged
- Do not mishandle the Needle-Pro® safety device as it may cause the needle to protrude from the Needle-Pro® safety device.

18. After injection is completed, press the needle into the orange Needle-Pro® safety device using a one-handed technique. Perform a one-handed technique by GENTLY pressing the orange Needle-Pro® safety device against a table top or other hard, flat surface. AS THE ORANGE NEEDLE-PRO® SAFETY DEVICE IS PRESSED, THE NEEDLE WILL FIRMLY ENGAGE INTO THE ORANGE NEEDLE-PRO® SAFETY DEVICE. Visually confirm that the needle is fully engaged into the orange Needle-Pro® safety device before discarding. Discard needle appropriately. Also discard the

other (unused) needle provided in the dose pack.





OVERDOSAGE

Symptoms:

In general, reported signs and symptoms have been those resulting from an exaggeration of known pharmacological effects of risperidone. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms.
QT prolongation and convulsions have been reported. Torsades de pointes has been reported in association with combined overdose of oral risperidone and paroxetine.

Treatment:

Establish and maintain a clear airway, and ensure adequate oxygenation and ventilation. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to risperidone. Therefore appropriate supportive measures should be instituted. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers. Due to the lag period with absorption of RISPERDAL CONSTA, adverse effects may not be seen for 2-6 weeks after the overdose.

As strategies for the management of overdose are continually evolving, it is advisable to contact the Poisons Information Centre to determine the latest recommendations for the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

RISPERDAL CONSTA contains either 25 mg, 37.5 mg or 50 mg risperidone and is presented as a white to off-white free-flowing powder in a 5mL vial and a prefilled syringe containing 2mL diluent, together with:

- One Alaris™ SmartSite® Needle-Free Vial Access Device for reconstitution and
- Two Needle-Pro® needles for intramuscular injection (a 21G UTW 1-inch safety needle with needle protection device for deltoid administration and a 20G TW 2-inch safety needle with needle protection device for gluteal administration). (“Rx-only” = device to be sold with prescription medicines only).

Before reconstitution, the entire dose pack should be stored in the refrigerator (2-8°C) and protected from light. It should not be exposed to temperatures above 25°C.

If refrigeration is unavailable, RISPERDAL CONSTA can be stored at temperatures not exceeding 25° for no more than 7 days prior to administration. Do not expose unrefrigerated product to temperatures above 25°C.

After reconstitution, the product should be used immediately. The maximum allowable storage time at room temperature is 6 hours. If the product is not used right away it should be shaken vigorously to re-suspend. Do not refrigerate or refreeze.

Keep out of the reach of children.

NAME AND ADDRESS OF THE SPONSOR

JANSSEN-CILAG Pty Ltd
1-5 Khartoum Road North Ryde NSW 2113 Australia
NZ Office: Auckland, New Zealand

POISON SCHEDULE OF THE MEDICINE

S4 - Prescription Only Medicine

Date of TGA approval: 18 March 2010

Please note changes (presented as **italicised text*) in Product Information.

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