

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

19 February 2014

RISPERDAL 1 mg, scored film-coated tablet

B/60 (CIP: 34009 338 948 7 0)

RISPERDAL 2 mg, scored film-coated tablet

B/60 (CIP: 34009 338 950 1 3)

RISPERDAL 4 mg, scored film-coated tablet

B/30 (CIP: 34009 344 273 8 1)

RISPERDAL 1 mg/ml, oral solution

B/1 30 ml bottle (CIP: 34009 343 980 2 5)

B/1 60 ml bottle (CIP: 34009 343 981 9 3)

B/1 120 ml bottle (CIP: 34009 343 984 8 3)

RISPERDALORO 0.5 mg, orodispersible tablet

B/28 (CIP: 34009 363 738 2 2)

RISPERDALORO 1 mg, orodispersible tablet

B/28 (CIP: 34009 363 743 6 2)

RISPERDALORO 2 mg, orodispersible tablet

B/28 (CIP: 34009 363 747 1 3)

RISPERDALORO 3 mg, orodispersible tablet

B/28 (CIP: 34009 368 153 2 2)

RISPERDALORO 4 mg, orodispersible tablet

B/28 (CIP: 34009 368 157 8 0)

RISPERDALCONSTA L.P. 25 mg/2 ml, powder and solvent for prolonged-release suspension for injection in prefilled syringe

B/1 (CIP: 34009 362 491 3 4)

RISPERDALCONSTA L.P. 37.5 mg/2 ml, powder and solvent for prolonged-release suspension for injection in prefilled syringe

B/1 (CIP: 34009 362 493 6 3)

RISPERDALCONSTA L.P. 50 mg/2 ml, powder and solvent for prolonged-release suspension for injection in prefilled syringe

B/1 (CIP: 34009 362 494 2 4)

Applicant: JANSSEN-CILAG

INN	Risperidone
ATC code	N05AX08 (Antipsychotics)
Reason for the review	Renewal of inclusion Extension of indication in the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non pharmacological approaches and when there is a risk of harm to self or others.
Lists concerned	National Health Insurance (French Social Security Code L.162-17) Hospital use (French Public Health Code L.5123 2)
Indications concerned	<p>"RISPERDAL/RISPERDALORO is indicated for the treatment of schizophrenia."</p> <p>"RISPERDAL/RISPERDALORO is indicated for the treatment of moderate to severe manic episodes associated with bipolar disorders."</p> <p>"RISPERDAL/RISPERDALORO is indicated for the short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviours requires pharmacologic treatment."</p> <p>"RISPERDAL/RISPERDALORO is indicated for the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non pharmacological approaches and when there is a risk of harm to self or others."</p> <p>"RISPERDALCONSTA L.P. is indicated for the maintenance treatment of schizophrenia in patients currently stabilised with oral antipsychotics."</p>

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation	Initial dates (mutual recognition procedure): RISPERDAL: 2 May 1995 RISPERDALORO: 10 March 2004 RISPERDALCONSTA L.P. : 7 October 2003 Date of indication extension (European standardisation): RISPERDAL and RISPERDALORO: 5 March 2009
Prescribing and dispensing conditions/special status	List I

ATC Classification	2012 N N05 N05A N05AX N05AX08	Nervous system Psycholeptics Antipsychotics Other antipsychotics risperidone
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02 BACKGROUND

For purposes of renewal of inclusion of RISPERDAL, RISPERDALORO and RISPERDALCONSTA L.P. on the list of reimbursable proprietary medicinal products (renewed inclusion as of 02/07/2011), the Transparency Committee assessed the extension of indication in the "short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others". This indication was obtained on 5 March 2009 following a European standardisation procedure of the SPCs for these proprietary medicinal products.

The manufacturer does not claim the inclusion of this extension of indication on the list of reimbursable proprietary medicinal products and the list of medicinal products approved for hospital use.

03 THERAPEUTIC INDICATIONS

"RISPERDAL/RISPERDALORO is indicated for the treatment of schizophrenia."

"RISPERDAL/RISPERDALORO is indicated for the treatment of moderate to severe manic episodes associated with bipolar disorders."

"RISPERDAL/RISPERDALORO is indicated for the short term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviours requires pharmacologic treatment."

"RISPERDAL/RISPERDALORO is indicated for the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non pharmacological approaches and when there is a risk of harm to self or others."

"RISPERDALCONSTA L.P. is indicated for the maintenance treatment of schizophrenia in patients currently stabilised with oral antipsychotics."

04 DOSAGE

"Persistent aggression in patients with moderate to severe Alzheimer's dementia

A starting dose of 0.25 mg twice daily is recommended. This dosage can be individually adjusted by increments of 0.25 mg twice daily, not more frequently than every other day, if needed. The optimum dose is 0.5 mg twice daily for most patients. Some patients, however, may benefit from doses up to 1 mg twice daily.

RISPERDAL/RISPERDALORO should not be used more than 6 weeks in patients with persistent aggression in Alzheimer's dementia. During treatment, patients must be evaluated frequently and regularly, and the need for continuing treatment reassessed."

Other indications: see SPC.

05 EXTENSION OF INDICATION IN THE TREATMENT OF PERSISTENT AGGRESSION IN ALZHEIMER'S DISEASE

05.1 Therapeutic need

Aggressive behaviour may be observed in Alzheimer's disease, in particular in progressive forms of the disease where the deterioration of cognitive functions is combined with deterioration of functional autonomy. Aggressive behaviours are of multifactorial origin and may reflect:

- a defence reaction by the patient in a situation that he cannot control or understand,
- a problem specific to the disease (cognitive deficit, delirium, hallucination),
- the expression of a somatic problem (urine retention, infection, acute pain, faecal impaction, etc.),
- the expression of a psychiatric comorbidity, etc.

These behaviour problems may have major consequences on quality of life and the adjustment of patients to their environment, the quality of the care and treatment and the quality of life of caregivers.

The management of disruptive behaviours in Alzheimer's disease is comprehensive. The first-line treatment relies on care techniques adapted to the patients.

The role of psychotropics is controversial, due to the fact that their nature is not well suited to the origin of the problem and its context, their low efficacy and the major risk of adverse effects. The HAS guidelines of 2009 reserve the use of antipsychotics to short-term treatment of severe psychotic disorders not otherwise controllable, after failure of care techniques and non-drug interventions or in an emergency.¹

Risperidone is the only medicinal treatment to have a Marketing Authorisation in the "the short-term treatment of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others".

¹ HAS. Good practice guidelines. Alzheimer's disease and related conditions: Management of behavioural disorders. May 2009.

05.2 Clinically relevant comparators

The management of disruptive behaviours in Alzheimer's disease is comprehensive. The first-line treatment relies on care techniques adapted to patients with dementia. Non-drug interventions on quality of life, speech, cognition, sensory stimulation, motor activity and occupational activities are also elements of care and treatment.

Antipsychotics are used in current practice but do not have a Marketing Authorisation in this indication.

Risperidone is the only antipsychotic to have a Marketing Authorisation in the "the short-term treatment of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others".

► Conclusion

After failure of non-pharmacological approaches, there is no clinically relevant comparator with a Marketing Authorisation. Other antipsychotics are used in this indication.

05.3 Analysis of available data

5.3.1 Efficacy

A Cochrane meta-analysis from 2006 evaluated second-generation antipsychotics including risperidone in the treatment of aggression in patients with Alzheimer's disease.²

Three other meta-analyses that evaluated second-generation antipsychotics on behaviour disorders and/or psychotic symptoms in patients with dementia were identified:

- a meta-analysis by Schneider *et al.*, 2006;³
- a NICE-SCIE meta-analysis from 2006 conducted as part of recommendations on dementia management;⁴
- a meta-analysis by Maher *et al.*, 2011.⁵

The results of these meta-analyses, which rely on the same studies as the Cochrane meta-analysis, will not be discussed in detail.

5.3.1.1 Cochrane meta-analysis²

5.3.1.1.1 Study design

The objective was to evaluate the efficacy and safety of second generation antipsychotics in the treatment of aggressive behaviours and psychotic symptoms in Alzheimer's disease.

The authors searched for randomised, double-blind, placebo-controlled studies of at least 6 weeks. The endpoints evaluated were: aggressive behaviour, psychotic symptoms, treatment discontinuations and adverse effects.

In all, 16 studies met the inclusion criteria and 10 of them contributed to the meta-analysis: five studies concerned risperidone, four concerned olanzapine and one concerned aripiprazole.

5.3.1.1.2 Results concerning risperidone

Five studies concerning risperidone were included in the meta analysis: RIS-INT-24,⁶ RIS-USA-63,⁷ RIS-AUS 5,^{8,9} F1D MC-HGGU,¹⁰ RIS USA 232.¹¹

In all, 1977 patients received risperidone at a dosage of 0.5 to 2 mg/day over a period comprised between 10 and 13 weeks depending on the study. Two studies exclusively included patients with Alzheimer's disease.

² Ballard C, et al. Atypical antipsychotics for aggression and psychosis in Alzheimer's disease (Review). Cochrane Database Syst Rev. 2006;(1):CD003476.

³ Schneider L, et al. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomised, placebo-controlled trials. *Am J Geriatr Psychiatry*. 2006; 14(3): 191-210.

⁴ NICE (National Institute for Health and Clinical Excellence) & SCIE (Social Care Institute for Excellence). Dementia - The NICE-SCIE guideline on supporting people with dementia and their carers in health and social care. November 2006. Last modified October 2012. www.nice.org.uk.

⁵ Maher A, et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. *JAMA*. 2011; 306(12): 1359-69.

⁶ De Deyn P, et al. A randomised trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. *Neurology*. 1999; 53(5): 946-55. [RIS-INT-24 study].

⁷ Katz I, et al. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. Risperidone Study Group. *J Clin Psychiatry*. 1999; 60(2): 107-15. [RIS-USA-63 study].

⁸ Brodaty H, et al. A randomised placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. *J Clin Psychiatry*. 2003; 64(2): 134-43. [RIS-AUS-5 study].

⁹ Brodaty H, et al. Risperidone for psychosis of Alzheimer's disease and mixed dementia: results of a double-blind, placebo-controlled trial. *Int J Geriatr Psychiatry*. 2005; 20(12): 1153-7. [RIS-AUS-5 study].

¹⁰ Deberdt W, et al. Comparison of olanzapine and risperidone in the treatment of psychosis and associated behavioral disturbances in patients with dementia. *Am J Geriatr Psychiatry*. 2005; 13(8): 722-30. [F1D-MC-HGGU study].

¹¹ Mintzer J, et al. Risperidone in the treatment of psychosis of Alzheimer disease: results from a prospective clinical trial. *Am J Geriatr Psychiatry*. 2006; 14(3): 280-91. [RIS-USA-232 study].

The mean age of the patients was between 81 and 83 years of age. In four studies, the patients were cared for in an institution. The mean baseline MMSE scores were comprised between 5.3 and 13.2.

a) Aggressive behaviour

Risperidone (1 to 2 mg/day) showed a better efficacy than placebo on aggressive behaviour. In three studies, aggression was evaluated on the CMAI¹² scale and in two studies on the BEHAVE AD¹³ scale subscore for aggression:

- On the CMAI scale:
 - o risperidone 1 mg/day versus placebo:
three studies; n = 809; mean variation -1.17; 95% CI [-2.02; -0.32].
- BEHAVE-AD aggression score:
 - o risperidone 1 mg/day versus placebo:
two studies; n = 538; mean variation -0.84; 95% CI [-1.28; -0.40];
 - o risperidone 2 mg/day versus placebo:
one study; n = 323; mean variation -1.50; 95% CI [-2.05; -0.95].

In one study, 2 mg/day risperidone showed a better efficacy compared with 1 mg/day risperidone on the BEHAVE-AD aggression score: n = 310; mean variation -0.70; 95% CI [-1.25; -0.15].

b) Other endpoints

- Psychotic symptoms:

Risperidone 1 mg was more effective than placebo on psychotic symptoms evaluated on the BEHAVE-AD¹³ or NPI¹⁴ scale: four studies; n = 1304; mean variation -0.14; 95% CI [-0.25; -0.03].

- Premature discontinuations:

Premature discontinuations for adverse effects in the risperidone 1 and 2 mg groups were more common than with placebo:

- o risperidone 1 mg/day versus placebo:
four studies; 88/764 versus 61/665; OR 1.43; 95% CI [1.01; 2.03];
- o risperidone 2 mg/day versus placebo:
One study; 69/165 versus 44/163; OR 1.94; 95% CI [1.22; 3.09].

5.3.1.1.3 Authors' conclusion

Risperidone has a modest efficacy in the treatment of aggressive behaviours and psychotic symptoms in patients with dementia.

This conclusion also applies to olanzapine. The data concerning other second-generation antipsychotics are very limited.

However, risperidone and olanzapine are not suited to routine use in patients with dementia given the risks, in particular, of cerebral vascular accidents and extrapyramidal adverse effects (see adverse effects section) and should be reserved for cases of major distress or of threat to the physical integrity of caregivers.

5.3.2 Adverse effects

5.3.2.1 Data from meta-analyses

¹² The CMAI (Cohen-Mansfield Agitation Inventory) scale: the total agitation score (physical and verbal, aggressive and non-aggressive) is composed of 29 items, each scored from 1 to 7 points, or a total score of 29 to 203 points; the subscore of aggressive agitation is composed of 14 items, including 11 items on physical aggression (items 1-11) and 3 items on verbal aggression (items and 22 to 24), each scored from 1 to 7 points, i.e. a total score of 14-98 points.

¹³ The BEHAVE-AD (Behavioral Pathology in Alzheimer's Disease) scale: the subscore for aggression is composed of 3 items (items 16-18), each scored from 0 to 3 points, i.e. a total score of 0-9 points.

¹⁴ The NPI (Neuro Psychiatric Inventory) scale is an inventory of 12 symptoms among the most common in Alzheimer's disease and related diseases, which evaluates their frequency and severity, and the impact on the caregiver or professional.

Three meta-analyses evaluated the adverse effects of second-generation antipsychotics compared with placebo in patients with dementia.^{2,3,5}

The adverse effects most commonly reported with second generation anti-psychotics compared with placebo were: drowsiness, sedation, extrapyramidal effects, an increase in appetite or weight, urinary tract infections and peripheral oedema and cerebral vascular events.

According to the meta-analysis by Maher *et al.*, 2011,⁵ the most commonly reported adverse effects with risperidone compared with placebo were:

- Sedation: six studies; n = 2182; OR: 2.30; 95% CI [1.79 to 3.05];
- Extrapyramidal effects: five studies; n = 2477; OR: 3.00; 95% CI [1.96 to 4.70];
- An increase in appetite or weight: two studies; n = 517; OR: 3.40; 95% CI [1.08 to 12.75];
- Cardiovascular events (including oedema and vasodilation): six studies; n = 2767; OR: 2.10; 95% CI [1.38 to 3.22];
- Cerebral vascular events: four studies; n = 1852; OR: 3.12; 95% CI [1.32 to 8.21];
- Urinary tract infections: four studies; n = 1725; OR: 1.60; 95% CI [1.13 to 2.13];

There is no evidence of a difference between risperidone and placebo on the incidence of falls.

5.3.2.2 Specific risks

5.3.2.2.1 Cerebral vascular events

In the meta-analyses of placebo-controlled clinical studies in patients with dementia, an increase of the risk of adverse cerebral vascular events was observed in patients treated with antipsychotics compared with placebo.^{2,3,5,15}

According to the SPC for RISPERDAL/RISPERDALORO, grouped analysis of six placebo-controlled trials conducted with RISPERDAL in elderly patients (above age 65) with dementia showed an incidence of cerebral vascular accidents (serious and non-serious, combined) of 3.3% (33/1009) in patients treated with risperidone and 1.2% (8/712) in patients treated with placebo (OR: 2.96; 95% CI [1.34 to 7.50]). The origin of this increased risk is not known.

The risk of adverse cerebral vascular events was significantly higher in patients with mixed or vascular type dementia compared with patients with Alzheimer's disease.

A warning on the risk of cerebral vascular events was added to the SPC for all antipsychotics.

The warnings and recommendations added to the SPC for RISPERDAL/RISPERDALORO are as follows:

- patients with other types of dementias than Alzheimer's should not be treated with risperidone.
- Physicians are advised to assess the risks and benefits of the use of RISPERDAL/RISPERDALORO in elderly patients with dementia, taking into account risk predictors for stroke in the individual patient.
- Patients/caregivers should be cautioned to immediately report signs and symptoms of potential cerebral vascular accidents such as sudden weakness or numbness in the face, arms or legs, and speech or vision problems. All treatment options should be considered without delay, including discontinuation of risperidone.
- Patients should be reassessed regularly, and the need for continuing treatment reassessed.

5.3.2.2.2 Increase in mortality

In 2005, the FDA documented an increase in mortality for elderly dementia patients treated with second-generation antipsychotics compared with placebo in a meta-analysis of 17 controlled studies.¹⁶ Observational studies also showed that elderly people with dementia treated with

¹⁵ SPCs for the proprietary medicinal products RISPERDAL and RISPERDALORO

¹⁶ FDA Public Health Advisory: Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances. 11/2005. www.fda.gov.

conventional antipsychotics had a slightly increased risk of mortality compared with untreated people.^{17,18,19}

A warning on the increased mortality in elderly people with dementia was added to the SPCs for all antipsychotics.

In a meta-analysis by Schneider *et al.*, 2005²⁰ on the risk of death associated with second-generation antipsychotics in patients with dementia, 15 placebo-controlled studies (5110 patients) were included, 5 for risperidone (1954 patients). The duration of the studies was between 10 and 12 weeks. The results of this meta-analysis, consistent with those of the FDA, show an increase in the risk of death in patients exposed to second-generation antipsychotics compared with placebo: OR = 1.54; 95% CI [1.06 to 2.23]; The increase in the risk of death was evidenced in the global meta analysis but not in the individual meta-analyses of the antipsychotics evaluated. For risperidone, the result versus placebo was as follows: OR = 1.30; 95% CI [0.76 to 2.23];

Currently, additional data on this risk remain necessary.

5.3.3 Summary & discussion

In a Cochrane meta-analysis using five short-term (fewer than 13 weeks) studies, a statistical difference versus placebo in favour of risperidone was observed on aggressive behaviours in patients with dementia (predominantly Alzheimers dementia):

- On the CMAI scale:
 - o risperidone 1 mg/day versus placebo:
three studies ; n = 809; mean variation -1.17; 95% CI [-2.02; -0.32].
- BEHAVE-AD aggression score:
 - o risperidone 1 mg/day versus placebo:
two studies; n = 538; mean variation -0.84; 95% CI [-1.28; -0.40]
 - o risperidone 2 mg/day versus placebo:
one study; n = 323; mean variation -1.50; 95% CI [-2.05; -0.95].

The clinical relevance of this effect is unknown.

In the meta-analyses, the adverse effects most commonly reported with second-generation antipsychotics compared with placebo were: drowsiness, sedation, extrapyramidal effects, an increase in appetite or weight, urinary tract infections and peripheral oedema. Antipsychotics were also associated in patients with dementia with an increased risk of cerebral vascular events and an increased risk of death.

05.4 Therapeutic use

According to the HAS 2009 guidelines on the management of behavioural disorders in patients with Alzheimer's disease and related diseases:¹

►The management of disruptive behavioural disorders in Alzheimer's disease is comprehensive. In the first place, it relies on a precise assessment of the reasons for and context of these symptoms. The first-line treatment relies on care techniques adapted to patients with dementia. Non-drug interventions on quality of life, speech, cognition, sensory stimulation, motor activity and occupational activities may also be proposed (see Figure 1).

¹⁷ Kales HC. *et al.* Mortality risk in patients with dementia treated with antipsychotics versus other psychiatric medications. *Am J Psychiatry* 2007; 164: 1568-76.

¹⁸ Hollis J. *et al.* Antipsychotic medication dispensing and risk of death in veterans and war widows 65 years and older. *Am J Psychiatry* 2007; 15: 932-41.

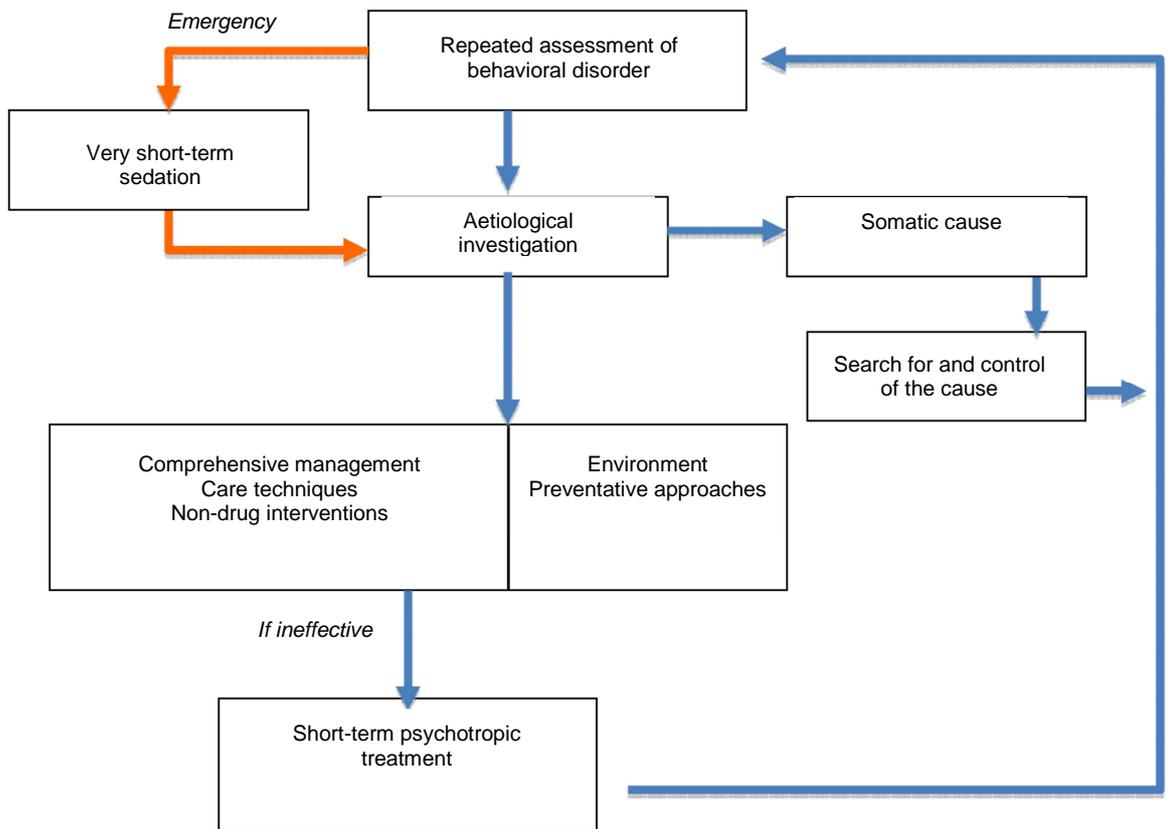
¹⁹ Wang PS. *et al.* Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med* 2005; 353: 2335-41.

²⁰ Schneider LS. *et al.* Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomised placebo-controlled trials. *JAMA* 2005; 294: 1934-43.

- ▶ The use of antipsychotics is not recommended in persons with Alzheimer's disease or a related disease.
- ▶ It is recommended to only prescribe an antipsychotic in case of severe and otherwise uncontrollable psychotic problems, after failure of other non-drug measures or in an emergency.
- ▶ It is necessary to assess the risk/benefit ratio of the treatment for each patient and each antipsychotic by taking account of:
 - the increased risk of death and cerebral vascular events,
 - adverse extrapyramidal neurological effects (akathisia, parkinsonism, tardive dyskinesia),
 - the risk of falls, choking on food, excessive sedation, metabolic disorders, orthostatic hypotension, arrhythmias, heart conduction disorders and possible anticholinergic effects (risk of cognitive problems, constipation and urine retention).
- ▶ When deciding to prescribe an antipsychotic, it is recommended to follow the rules below:
 - systematically assess the risk of cerebral vascular, cardiac, neurological, cognitive and metabolic events;
 - systematically identify, document and quantify the target symptoms to correct;
 - choose antipsychotics after individual analysis of the risks/benefits: short half-life, weak anticholinergic effect.
 - always inform the patient or caregiver of the risk/benefit ratio of the treatment;
 - always use the lowest possible initial dose, of around a quarter of the usual doses in young adults, then progressively increase it as necessary;
 - prescribe the treatment for a very limited duration;
 - systematically re-assess, at least once a week, physical, neurological and cognitive safety and symptomatic efficacy;
 - discontinue antipsychotics as soon as the clinical condition permits it or as soon as other therapeutic measures become effective.

Due to the importance of non-drug therapy, the fact that use of antipsychotics in people with Alzheimer's disease or a related disorder is not recommended, the adverse effects of risperidone and its low efficacy in aggressive behaviour, and the difficulty in setting up short-term treatment, the Transparency Committee considers that risperidone has no role in the management of aggressive behaviours in patients with Alzheimer's dementia.

Figure 1. Decision tree for treatment of behavioural disorders (HAS, 2009)¹



06 RENEWAL OF INCLUSION

06.1 Efficacy

The company has not provided new clinical efficacy data concerning the indications treated.

06.2 Safety/Adverse effects

The changes of the SPCs that took place since the previous Transparency Committee opinions of 21 July 2010 and 30 November 2011 are as follows:

- addition of intraoperative floppy iris syndrome to 4.4 and 4.8 of the SPC. An information letter to ophthalmologists was sent out in September 2013,
- addition of rhabdomyolysis to 4.8 for RISPERDALCONSTA L.P..

06.3 Usage/prescription data

According to the GERS [Group for the Development and Production of Statistics] sales data, 2,125,020 boxes of oral risperidone (RISPERDAL, RISPERDALORO and generics) and 581,050 boxes of RISPERDALCONSTA L.P. were sold in community pharmacies between November 2012 and October 2013.

06.4 Therapeutic use

6.4.1 Treatment of schizophrenia^{21,22,23,24}

Antipsychotics are the standard treatment for schizophrenia. Oral risperidone remains a therapeutic option in the treatment of schizophrenia. Injectable PR risperidone remains a therapeutic option in the maintenance treatment of schizophrenia in patients stabilised by oral antipsychotics.

6.4.2 Treatment of moderate to severe manic episodes associated with bipolar disorders^{25,26,27}

First-line drug treatment of moderate to severe manic episodes associated with bipolar disorders relies on monotherapy with lithium, divalproex sodium or a second-generation antipsychotic (including risperidone). Combined treatments must be reserved for severe manic disorders or if monotherapy fails.

²¹ HAS (Haute Autorité de Santé). Avis de la Commission de la Transparence sur les antipsychotiques de seconde génération par voie orale dans le traitement de la schizophrénie chez l'adulte [Opinion of the Transparency Committee on second-generation oral antipsychotics in the treatment of schizophrenia in adults]. November 2011.

²² HAS (Haute Autorité de Santé). Schizophrénies [Schizophrenia]. Guide - Affection de longue durée [Chronic Conditions Guide]. June 2007.

²³ NICE (National Institute for Health and Clinical Excellence). Schizophrenia - Core interventions in the treatment and management of schizophrenia in adults in primary and secondary care. NICE clinical guideline 82. March 2009

²⁴ APA (American Psychiatric Association). Practice guideline for the treatment of patients with schizophrenia. 2nd edition. Lehman AF, Lieberman JA, Dixon LB, *et al.* Am J Psychiatry. 2004; 161(2 Suppl): 1-56.

²⁵ HAS (Haute Autorité de Santé). Troubles bipolaires [Bipolar disorders]. Guide médecin - Affection de longue durée [Chronic Conditions Physician's Guide]. May 2009.

²⁶ NICE (National Institute for Health and Clinical Excellence). Bipolar disorder - The management of bipolar disorder in adults, children and adolescents, in primary and secondary care. NICE clinical guideline 38. July 2006.

²⁷ APA (American Psychiatric Association). Practice guideline for the treatment of patients with bipolar disorder (revision). Hirschfeld RM, Bowden CL, Gitlin MJ, *et al.* Am J Psychiatry. 2002; 159(4 Suppl): 1-50.

6.4.3 Short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviours require pharmacologic treatment^{28,29}

The appearance of aggressive or impulsive behavioural problems in children with mental retardation requires first ruling out organic or iatrogenic aetiology.

Drug treatment is generally a second-line treatment when non drug treatment is ineffective (psychological, educational and social measures) or in emergency situations if there is a danger to the child or those around him/her. An in-depth clinical evaluation by a specialist in childhood behaviour disorders is indispensable before initiating drug treatment. Pharmacological treatment depends on the underlying syndrome and may make use of antipsychotics (including risperidone), psychostimulants or mood regulators. Currently, additional studies on the efficacy and safety of antipsychotics in this indication are necessary.

²⁸ INSERM (Institut National de la Santé et de la Recherche Médicale [French National Institute of Health and Medical Research]). Trouble des conduites chez l'enfant et l'adolescent. Expertise collective. September 2005.

²⁹ D'Ambrogio T, Speranza M. Psychopharmacological approach to behavioral disorders in children and adolescents. *Neuropsychiatr Enfance Adolesc.* 2012; 60(1): 52-61.

07 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

07.1 Actual benefit

7.1.1 In the extension of indication in the treatment of persistent aggression in Alzheimer's disease

► Aggressive behaviour may be observed in Alzheimer's disease, in particular in progressive forms of the disease where the degradation of cognitive functions is combined with degradation of functional independence. Aggressive behaviours are of multifactorial origin and may reflect:

- a defence reaction by the patient in a situation that he cannot control or understand,
- a problem specific to the disease (cognitive deficit, delirium, hallucination),
- the expression of a somatic problem (urine retention, infection, acute pain, faecal impaction, etc.),
- the expression of a psychiatric comorbidity, etc.

These behaviour problems may have major consequences on quality of life and the adjustment of patients to their environment, the quality of the care and treatment and the quality of life of caregivers.

► Risperidone is intended as symptomatic treatment.

► The clinical relevance of the effect of risperidone relative to placebo on aggressive behaviour in patients with Alzheimer's dementia is not established. In addition, antipsychotics expose patients to the risks of significant adverse effects: extrapyramidal effects, falls, choking on food, excessive sedation, metabolic disorders, orthostatic hypotension, anticholinergic effects (risk of cognitive impairment, constipation and urine retention). Antipsychotics also seemed to be associated, in patients with dementia, with an increased risk of cerebral vascular events and death.

► The management of aggressive behaviour in Alzheimer's disease is comprehensive. Firstly, it includes care techniques adjusted to the dementia patient. Non-drug interventions on quality of life, speech, cognition, sensory stimulation, motor activity and occupational activities are also elements of care and treatment. The use of antipsychotics is not recommended. Risperidone does not have a role in the management strategy for aggressive behaviour in patients with Alzheimer's dementia.

Given the importance of non-drug therapy, the fact that the use of antipsychotics in people with Alzheimer's or a related disease is not recommended, the adverse effects of risperidone and its low efficacy in case of aggressive behaviour and the difficulty in implementing short-term treatment, the Committee considers that the actual benefit of the proprietary medicinal products RISPERDAL and RISPERDALORO is sufficient in "the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non pharmacological approaches and when there is a risk of harm to self or others".

7.1.2 In the other indications for the RISPERDAL products

In view of all the above information, and following the debate and vote, the Committee believes that the conclusions of its previous opinions of 21 July 2010 and 30 November 2011 do not need to be changed.

7.1.2.1 Treatment of schizophrenia

► Schizophrenia is characterised by the presence of a collection of positive or negative signs and symptoms combined with clear social dysfunction or dysfunction in activities. The disease progression varies. Some patients have exacerbations and remissions, while others remain chronically affected; some patients have a relatively stable progression, while others have progressive aggravation associated with severe disability.

► RISPERDAL and RISPERDALORO are symptomatic treatments for acute episodes of schizophrenia and long-term recurrences preventative treatments for schizophrenia. RISPERDALCONSTA PR is a preventative treatment for long-term recurrences of schizophrenia.

► The efficacy/adverse effects ratio for these medicinal products is high in this indication.

► Several other antipsychotics are indicated in the treatment of schizophrenia.

► These medicinal products are first-line therapies in this indication, as are other antipsychotics.

The actual benefit of RISPERDAL and RISPERDALORO remains substantial in the "treatment of schizophrenia".

The actual benefit of RISPERDALCONSTA L.P. remains substantial for the "maintenance treatment of schizophrenia in patients currently stabilised with oral antipsychotics".

7.1.2.2 Treatment of moderate to severe manic episodes associated with bipolar disorder.

► Bipolar disorders are characterised by a propensity for recurrent and pronounced mood swings, notably with the occurrence of one or more manic episodes. For the patient, bipolar disorder leads to chronic vulnerability due to the more or less constant mood swings and requires lifetime support. Bipolar disorders can mean a marked deterioration in quality of life and result in a social handicap. The major risk incurred is suicide.

► RISPERDAL and RISPERDALORO are symptomatic treatments for moderate to severe manic episodes associated with bipolar disorders.

► The efficacy/adverse effects ratio for these medicinal products is high in this indication.

► Several other second-generation antipsychotics are indicated in the treatment of manic episodes in bipolar disorder.

► These medicinal products are first-line therapies in the treatment of moderate to severe manic episodes associated with bipolar disorders, as are other second-generation antipsychotics.

The actual benefit of RISPERDAL and RISPERDALORO remains substantial for the "treatment of moderate to severe manic episodes associated with bipolar disorders".

7.1.2.3 Short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviours require pharmacologic treatment

- ▶ Behaviour problems in children and adolescents with below average intellectual function or mental retardation can lead to additional substantial impairment of familial, academic and/or social functioning.
- ▶ RISPERDAL and RISPERDALORO are symptomatic short term treatment (up to 6 weeks) of persistent aggression in conduct disorder in children and adolescents with below average intellectual functioning or mental retardation.
- ▶ The efficacy/adverse effects ratio for these medicinal products is modest in this indication.
- ▶ There are treatment alternatives to these proprietary medicinal products in this indication, including other antipsychotics, psychostimulants and mood regulators.
- ▶ These medicinal products are second-line therapies when non drug measures are ineffective (psychological, educational and social measures) or in emergency situations if there is a danger to the child or those around him/her.

The actual benefit of RISPERDAL and RISPERDALORO remains substantial for "the short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviours require pharmacologic treatment."

08 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance in the indications in the Marketing Authorisation, except for the "short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non pharmacological approaches and when there is a risk of harm to self or others."

▶ **Proposed reimbursement rate: 65%**

▶ **Packaging:**

The packaging for RISPERDAL and RISPERDALCONSTA L.P. is appropriate for the prescribing conditions.

The packaging for RISPERDALORO is not appropriate for the prescribing conditions as regards the indication, dosage and treatment duration. The Committee wishes to reiterate that, in accordance with its deliberations of 20 July 2005, standardisation of pack size to 30 days is recommended for treatments lasting one month.