# Rapidly Disintegrating Risperidone in Subjects with Schizophrenia or Schizoaffective Disorder: A Summary of Ten Phase I Clinical Trials Assessing Taste, Tablet Disintegration Time, Bioequivalence, and Tolerability

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## ABSTRACT

**Background:** Schizophrenia and schizoaffective disorder are severe and chronic psychiatric illnesses for which treatment compliance is important in the prevention of relapse. Atypical antipsychotic drugs, such as risperidone, have been found to be effective in the treatment of a range of psychiatric disorders. Although the oral route of administration is generally preferable to injection, some patients (eg, elderly patients or children) find swallowing physically difficult and thus refuse oral treatments. Rapidly disintegrating (RD) oral formulations of these drugs have been developed to improve their acceptability to patients and thus improve compliance.

**Objective:** The aim of this report was to describe the results from clinical studies that have assessed the taste, time to disintegration, and tolerability of RD risperidone tablets, and bioequivalence of RD risperidone tablets (2 × 0.5 mg, 2 mg, and reduced-size 4 mg) versus conventional (CV) risperidone tablets.

**Methods:** This study used data from 10 clinical trials conducted between 1996 and 2003. Eight trials were open-label, crossover trials; 2 were pilot trials, and all of the trials were short-term. The results from 2 trials were published previously; the remainder are unpublished trials. Taste, time to dissolution, and tolerability of RD risperidone tablets were assessed, and bioequivalence (based on the guidelines from the European and US health care evaluation agencies) of RD versus CV risperidone tablets were determined for risperidone, the active metabolite (9-hydroxy-risperidone), and the total antipsychotic fraction (sum of risperidone and the active moiety, 9-hydroxy-risperidone).

**Results:** In total, these trials included 264 subjects (160 patients with schizophrenia or schizoaffective disorder, 104 healthy volunteers; 173 men, 91 women; age range, 20–61 years). The taste of the RD risperidone tablets was rated as "nice" in 54.2% of subjects compared with 18.3% of subjects who rated CV risperidone as "nice." Totals of 28.8% and 49.2% of subjects described the RD risperidone tablets as "sweet" or "other taste" (commonly mint), respectively. A total of 66.7% of subjects rated the 4-mg RD risperidone tablets as "acceptable, but could be improved," while 85.7% rated the lower-dose RD risperidone tablets as "good." The median time to complete disintegration of the RD risperidone tablet was 38.0 seconds. The mean plasma concentration–time profiles of risperidone and the active moiety of RD or CV risperidone tablets were similar, and these 2 risperidone formulations were found to be bioequivalent. The RD and CV risperidone tablets were well tolerated; there were no serious adverse events reported.

**Conclusions:** In the 10 studies analyzed, the taste of RD risperidone tablets was found to be acceptable in the majority of healthy subjects and patients with schizophrenia or schizoaffective disorder. In addition, RD risperidone tablets were found to be bioequivalent

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**Key words:** schizophrenia, psychiatric disorders, treatment compliance, rapidly disintegrating tablets, risperidone.

## INTRODUCTION

Schizophrenia and schizoaffective disorder are severe and chronic psychiatric disorders that occur with varying prevalence (1.6–2.4 cases per 10,000 population and per year) worldwide.[1] In the long-term management of schizophrenia, treatment compliance is important in the prevention of relapse.[2] In addition to patients' awareness of the need for compliance with treatment and the efficacy and tolerability of a treatment, the ease and convenience of the drug regimen (eg, route of administration) affect patients' treatment compliance and, thus, outcomes.[3]

Atypical antipsychotic treatments of a variety of psychiatric diseases, including (acute) psychosis and/or agitation associated with schizophrenia, are available in different formulations (eg, oral tablets, oral solutions, intramuscular injections, and long-acting depot formulations). Although the oral route of administration is generally preferable to injection, some patients (eg, elderly patients or children) find swallowing physically difficult and thus may refuse oral treatments.[4,5] Therefore, rapidly disintegrating (RD) oral formulations of some antipsychotics (eg, clozapine, olanzapine, risperidone) have been developed in recent years.[5–7]

The efficacy of RD formulations has been found in previous studies.[7,8] In a pilot study in 85 acutely ill schizophrenic patients, a significant improvement from baseline in Positive and Negative Syndrome Scale[9] total score was found at 1 week and subsequent treatment with 10 to 20 mg/d RD olanzapine tablets for up to 6 weeks ($P < 0.001$).[8] In a small pilot study by Chue et al,[7] in 10 patients who were stable for ≥10 days while receiving monotherapy with conventional (CV) risperidone tablets (2–4 mg once daily), stable clinical status was maintained as measured using the Clinical Global Impression–Severity (CGI-S) scale[10] after the patients were switched to 7-day treatment with an equivalent dosage of RD tablets (in 1- and 2-mg tablets). In that study, RD risperidone tablets were well tolerated and rated as "very acceptable"; mean patient acceptance of RD tablets was 9.61 as rated on a visual analog scale (0 = "not acceptable" to 10 = "very acceptable"). With regard to bioequivalence, 0.5- and 2-mg tablets of RD and CV risperidone were found to be bioequivalent in 2 Phase I clinical trials.[11,12]

Expert consensus guidelines[13] for optimizing pharmacologic treatment of psychiatric disorders mention risperidone as the first-line choice for first-episode and multiepisode schizophrenia. In elderly patients, atypical antipsychotics, and more specifically risperidone, is the first-line recommendation for the treatment of agitated dementia, delusional disorder, geriatric psychotic major depression, late-life schizophrenia, and/or mania with psychosis.[14]

In a meta-analysis of atypical antipsychotics (aripiprazole, olanzapine, quetiapine, and risperidone) used to treat dementia-related psychosis in elderly patients, an increased risk for mortality was found compared with placebo (3.5% vs 2.3%; $P = 0.02$).[15]

This article focuses on various aspects of the RD risperidone tablet, in particular the acceptability of taste, in patients with schizophrenia or schizoaffective disorder and healthy volunteers. Bioequivalence of RD to CV risperidone tablets is reviewed for the 0.5-, 2-, and 4-mg doses and discussed for the parent compound (risperidone) and the active antipsychotic fraction (active moiety), which includes both risperidone and its active metabolite 9-hydroxy-risperidone. In this analysis of the results from 10 clinical trials[7,12,16–23] in patients with schizophrenia or schizoaffective disorder and healthy volunteers, taste, time to disintegration, bioequivalence (pharmacokinetic [PK] properties), and tolerability were assessed.

## MATERIALS AND METHODS

This analysis used data from 10 clinical trials[7,12,16–23] conducted between 1996 and 2003 in patients with schizophrenia or schizoaffective disorder and healthy volunteers. Eight of the 10 trials were of open-label, randomized, 2-way, crossover design conducted at centers in the United States,[12] The Netherlands,[16] Belgium,[18–21,23] and South Africa[22]; 2 were pilot trials conducted in Canada[7] and Belgium.[17] Descriptions of all 10 trials are shown in **Table I.** All trials were conducted in accordance with the Good Clinical Practice guideline[24] and the Declaration of Helsinki and its amendments.[25] The trial protocols and informed-consent documents were reviewed and approved by independent ethics committees. Data are on file at Johnson & Johnson Pharmaceutical Research and Development, Beerse, Belgium, and Titusville, New Jersey.