

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must

continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

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24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.



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Fax 301-827-3843

(Division of Communication and Consumer Affairs, CBER)

Drug studies:

Call 301-594-0020

Fax 301-594-1204

(Division of Scientific Investigations, Office of Medical Policy, CDER)

Medical Device studies:

Call 240-276-0125

Fax 240-276-0128

(Division of Bioresearch Monitoring, Office of Compliance, CDRH)

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Label and Approval History

Drug Name(s) **RISPERDAL (Brand Name Drug)**

FDA Application No. **(NDA) 021444**

Active Ingredient(s) **RISPERIDONE**

Company **JANSSEN PHARMA**

[Go to Approval History](#)

Label Information

What information does a label include?

Note: Not all labels are available in electronic format from FDA.

View the label approved on 08/17/2005 for RISPERDAL, NDA no. 021444

- To see older, previously-approved labels, go to the "[Approval History](#)" section of this page. **Older labels are for historical information only and should not be used for clinical purposes.**

Approval History

Note: Not all reviews are available in electronic format from FDA.

Older labels are for historical information only, and should not be used for clinical purposes.

Action dates can only be verified from 1984 to the present.

Action Date	Supplement Number	Approval Type	Letters, Reviews, Labels, Patient Package Insert	Note
08/17/2005	016	Labeling Revision	Label Letter	
12/23/2004	012	Formulation Revision	Label Letter	
12/04/2003	003	New or Modified Indication	Label Letter	
12/04/2003	002	New or Modified Indication	Label Letter	
11/21/2003	007	Labeling Revision	Letter	Label is not available on this site.

10/29/2003	005	Labeling Revision	Letter 	Label is not available on this site.
09/10/2003	004	Labeling Revision	Letter 	Label is not available on this site.
04/02/2003	000	Approval	Label  Letter  Review	

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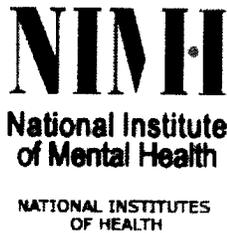
- **There are no Therapeutic Equivalents**
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Questions And Answers About The NIMH Clinical Antipsychotic Trials Of Intervention Effectiveness Study (CATIE) – Phase 2 Results

April 1, 2006

1. Q. What is the goal of phase 2 of the CATIE study?

A. The primary purpose of the CATIE study was to provide information to guide the everyday treatment of people with schizophrenia. The goal of *phase 2* of CATIE was to provide guidance for doctors and patients facing the dilemma of choosing which antipsychotic medication to try next if the first antipsychotic medication was not satisfactory.

Two articles in the April 1, 2006 issue of the American Journal of Psychiatry (1, 2) describe results from phase 2 of CATIE, the National Institute of Mental Health's (NIMH) Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study.

In phase 1 of CATIE, people with schizophrenia were randomly assigned to receive treatment with one of the newer (introduced in the last decade), "atypical" antipsychotic medications: olanzapine (Zyprexa®), quetiapine (Seroquel®), risperidone (Risperdal®), or ziprasidone (Geodon®), or an older "conventional" medication, perphenazine (Trilafon®). Approximately one-quarter of all the participants were satisfied with the level of symptom relief they experienced from this first antipsychotic medication, were able to tolerate its side effects, and stayed on it for the entire 18 months of the study. However, three-quarters of the participants stopped taking their first antipsychotic medication before the end of 18 months. The study investigators recorded why a participant stopped taking a medication: if the medication did not control symptoms, if the side effects were not tolerable or, if the patient chose to stop treatment for some other reason.

2. Q. What treatments were available in phase 2 of CATIE?

A. Two different treatment pathways were available to the participants who stopped medication for any reason during phase 1 yet wanted to continue with the study. Participants in phase 2 collaborated with their doctors to determine the pathway that was best for them.

The **efficacy** pathway was designed for participants who discontinued their phase 1 medication because of inadequate symptom control. This pathway examined the question: *if a patient stops taking an atypical antipsychotic because it was not effective enough, what are the benefits of clozapine (Clozaril®) versus another atypical antipsychotic medication as the next treatment?* The efficacy pathway compared clozapine to the other newer atypical antipsychotic medications. Participants who chose this pathway were randomly assigned to receive either clozapine or an atypical antipsychotic (olanzapine, risperidone, or



DEPARTMENT OF HEALTH & HUMAN SERVICES

FOI

Food and Drug Administration
Rockville MD 20857

JAN 5 1999

TRANSMITTED VIA FACSIMILE

Todd McIntyre, Ph.D.
Director, Regulatory Affairs
Janssen Research Foundation
1125 Trenton-Harbourton Rd.
Titusville, NJ 08560-0200

RE: NDA #20-272, 20-588
Risperdal (risperidone) Tablets
Risperdal (risperidone) Oral Solution
MACMIS #6908

Dear Dr. McIntyre:

This letter concerns Janssen Research Foundation's (Janssen) promotional materials and activities for the marketing of Risperdal (risperidone) Tablets that have been reviewed by the Division of Drug Marketing, Advertising and Communications (DDMAC) as part of its monitoring and surveillance program. In particular, DDMAC is concerned with a campaign that markets Risperdal for geriatric patients. These materials include, but are not limited to sales aids (ID# RS-420, RS-422, RS-473, RS-494), journal ads (ID# RS-470-1, RS-470-1-C, RS-470-1RB, RS-470-2, RS-470-2RB), a display panel (ID# RS-468), brochures (ID# RS-459, RS-469), and a letter (ID #RS-308). Other recent materials include journal ads (ID # RS-450-2, RS-451-2, RS-451-2A, RS-451-C, RS-470-1R, RS-470-2R), letters (ID # RS-462S, RS-477-1, RS-477-1R), a flashcard (ID # RS-518), a calendar (ID #RS-474), and a computer program (ID #RS-463). DDMAC has concluded that these materials are false, misleading, and/or lacking in fair balance, and in violation of the Federal Food, Drug, and Cosmetic Act and the regulations promulgated thereunder.

Specifically, DDMAC has the following objections:

Geriatric Campaign

1. Janssen is disseminating materials that state or imply that Risperdal has been determined to be safe and effective for the elderly population in particular. There is limited data on the use of Risperdal in the elderly, and the elderly population was not specifically studied in the clinical trials for Risperdal. Thus, presentations that focus on this population are

misleading in that they imply that the drug has been found to be specifically effective in the elderly population.

Also, according to the approved product labeling (PI), there are safety considerations for Risperdal in the elderly population. In healthy elderly subjects, the clearance of both risperidone and its active metabolite was decreased, and the elimination half-lives were prolonged. Hepatic impairment would further increase the mean free fraction of plasma risperidone. Risperdal should be used cautiously in healthy elderly individuals because of the potential for decreased clearance of drug, potential drug interactions, hepatic and renal dysfunction, and cardiovascular sensitivity. The safety of Risperdal in "fragile" individuals or individuals with concomitant illnesses has not been evaluated in adequate and well-controlled studies.

2. Risperdal is indicated for the management of the manifestations of psychotic disorders. However, Janssen is disseminating materials that imply, without adequate substantiation, that Risperdal is safe and effective in specifically treating hostility in the elderly.

Efficacy

Materials that claim that Risperdal is indicated "for psychotic symptoms associated with a broad range of disorders," including schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar disorder, and elderly psychosis, are false or misleading because the adequate and well-controlled clinical studies for Risperdal were not designed to examine the efficacy of Risperdal in this broad range of disorders.

Fair Balance

1. Janssen is disseminating materials that are lacking in fair balance because the risk information appears in pale and tiny font at the bottom or back of a journal ad or other presentation, or after the closing of a letter. Thus, the risk information is not presented with a prominence and readability that is reasonably comparable to the presentation of efficacy information.

2. Janssen is disseminating materials that are lacking in fair balance because they emphasize that Risperdal has a low incidence of certain side effects while minimizing or ignoring important risk information for Risperdal. For example, the sales aid ID# RS-420 has bolded headlines that state that Risperdal has a "low incidence of excessive sedation" and "low incidence of anticholinergic side effects," but the precaution concerning orthostatic hypertension is located in plain text in the "Dosing/Formulations" section, the ninth page of the ten-page piece. Further, the warning regarding tardive dyskinesia is minimized and the common adverse events, which occurred up to 34% of the time, have been reduced to a small paragraph with no quantification beneath a half-page table of common events associated with discontinuation (showing discontinuations were infrequent). Treatment-emergent extrapyramidal symptoms occurred 17-34% of patients on Risperdal (16% placebo). The dose-relationship of extrapyramidal symptoms is important risk information that is not included in many of the materials including this sales aid.
3. Materials that state or imply that Risperdal has a low incidence of movement disorders are false or misleading. According to the PI for Risperdal, adverse events that would cause movement disorders were common in the clinical studies for Risperdal and were often dose-related, as in the treatment-emergent extrapyramidal symptoms.
4. Materials that state or imply Risperdal has a low incidence of excessive sedation are false or misleading. According to the PI, the incidence of somnolence was 3% for 10 mg/day and 8% for 16 mg/day Risperdal (placebo = 1%). Sleepiness, increased duration of sleep, accommodation disturbances, asthenia, lassitude, and increased fatigability were all dose-related adverse events.
5. Materials that state or imply that Risperdal has a low incidence of anticholinergic effects are false or misleading. According to the PI, the incidence of constipation was 7% for the 10 mg/day and 13% for the 16 mg/day dose of Risperdal (placebo = 3%), and cognitive impairment (Precautions section of the PI) and reduced salivation are frequent adverse events. Furthermore, this claim is lacking in fair balance because there is no similar emphasis on adverse events that do occur with Risperdal.
6. Claims of low incidence of adverse events coupled with presentations of adverse events associated with discontinuation are false or misleading

because it implies that the events associated with discontinuation were the extent of the adverse events experienced with Risperdal.

Comparative Claims

1. Materials that state or imply that Risperdal has superior safety or efficacy to other antipsychotics due to its receptor antagonist profile are false or misleading because the mechanism of action of Risperdal is unknown, as is the correlation of the specific receptor antagonism to the clinical effectiveness and safety of the drug.
2. Presentations that compare the efficacy or safety of Risperdal to an active control make false and misleading superiority claims in the absence of substantiation from adequate and well-controlled comparative data (see for example, sales aid #RS-422).

Quality of Life Claims

1. Materials that claim that Risperdal can "enhance daily living" or that it offers "quality control of symptoms for daily living" are considered to be false or misleading in the absence of adequate and well-controlled studies using validated instruments to determine benefit to health-related quality of life.
2. The tagline "Quality control" is false or misleading because it is used out of context and can be interpreted to mean, without adequate substantiation, that Risperdal can control health-related quality of life.

The materials and promotional messages Janssen has disseminated contain false and/or misleading information about the safety and effectiveness of Risperdal. The violations discussed above do not necessarily constitute an exhaustive list. Accordingly, Janssen should immediately discontinue the use of all materials that state, suggest, or imply false, misleading, or unbalanced claims of the type discussed in this letter. Janssen should provide a written response to DDMAC stating its intent to comply with this request. The letter should also include a complete listing of the materials that Janssen will discontinue as a result of this letter, including the dates that the materials were discontinued, as well as a list of those materials that will remain in use.

Dr. Tod McIntyre
Janssen
NDA 20-272 (MACMIS 6908)

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Janssen's response should be received no later than January 19, 1999. If Janssen has any questions or comments, please contact the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, rm.17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS 6908 in addition to the NDA number.

Sincerely,

Lisa L. Stockbridge, Ph.D.
Regulatory Reviewer
Division of Drug Marketing,
Advertising and Communications

JANSSEN
PHARMACEUTICA
PRODUCTS, L.P.

RISPERDAL®
(RISPERIDONE)
TABLETS/ORAL SOLUTION

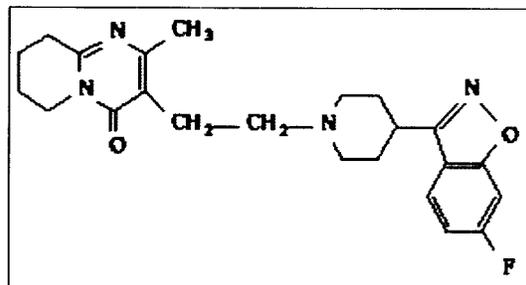
RISPERDAL® M-TAB®
(RISPERIDONE)
ORALLY DISINTEGRATING TABLETS

Increased Mortality in Elderly Patients with Dementia –Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. RISPERDAL® (risperidone) is not approved for the treatment of patients with Dementia-Related Psychosis.

DESCRIPTION

RISPERDAL® (risperidone) is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 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. Its molecular formula is C₂₃H₂₇FN₄O₂ and its molecular weight is 410.49. The structural formula is:



Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL[®] tablets are available in 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green) strengths. Inactive ingredients are colloidal silicon dioxide, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 0.25, 0.5, 2, 3, and 4 mg also contain talc and titanium dioxide. The 0.25 mg tablets contain yellow iron oxide; the 0.5 mg tablets contain red iron oxide; the 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

RISPERDAL[®] is also available as a 1 mg/mL oral solution. The inactive ingredients for this solution are tartaric acid, benzoic acid, sodium hydroxide, and purified water.

RISPERDAL[®] M-TAB[®] Orally Disintegrating Tablets are available in 0.5 mg, 1 mg, and 2 mg strengths and are light coral in color.

RISPERDAL[®] M-TAB[®] Orally Disintegrating Tablets contain the following inactive ingredients: Amberlite[®] resin, gelatin, mannitol, glycine, simethicone, carbomer, sodium hydroxide, aspartame, red ferric oxide, and peppermint oil.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL[®] (risperidone), as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D₂) and serotonin Type 2 (5HT₂) receptor antagonism. Antagonism at receptors other than D₂ and 5HT₂ may explain some of the other effects of RISPERDAL[®].

RISPERDAL[®] is a selective monoaminergic antagonist with high affinity (K_i of 0.12 to 7.3 nM) for the serotonin Type 2 (5HT₂), dopamine Type 2 (D₂), α₁ and α₂ adrenergic, and H₁ histaminergic receptors. RISPERDAL[®] acts as an antagonist at other receptors, but with lower potency. RISPERDAL[®] has low to moderate affinity (K_i of 47 to 253 nM) for the serotonin 5HT_{1C}, 5HT_{1D}, and 5HT_{1A} receptors, weak affinity (K_i of 620 to 800 nM) for the dopamine D₁ and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations >10⁻⁵ M) for cholinergic muscarinic or β₁ and β₂ adrenergic receptors.

Pharmacokinetics

Absorption

Risperidone is well absorbed. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) when compared to a solution.

Pharmacokinetic studies showed that RISPARDAL[®] M-TAB[®] Orally Disintegrating Tablets and RISPARDAL[®] Oral Solution are bioequivalent to RISPARDAL[®] Tablets.

Plasma concentrations of risperidone, its major metabolite, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg BID). Following oral administration of solution or tablet, mean peak plasma concentrations of risperidone occurred at about 1 hour. Peak concentrations of 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady-state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Food Effect

Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and α 1-acid glycoprotein. The plasma protein binding of risperidone is 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites. High therapeutic concentrations of sulfamethazine (100 mcg/mL), warfarin (10 mcg/mL), and carbamazepine (10mcg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Metabolism

Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, CYP 2D6. A minor metabolic pathway is through N-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug (e.g., the active moiety) results from the combined concentrations of risperidone plus 9-hydroxyrisperidone.

CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6%-8% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of the active moiety, after single and multiple doses, are similar in extensive and poor metabolizers.

Risperidone could be subject to two kinds of drug-drug interactions (see PRECAUTIONS – Drug Interactions). First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone. This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The therapeutic benefits and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n=70) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. Second, co-administration of known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely.

In a drug interaction study in schizophrenic patients, 11 subjects received risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment (see PRECAUTIONS – Drug Interactions and DOSAGE AND ADMINISTRATION – Co-Administration of RISPARDAL[®] with Certain Other Medications).

Fluoxetine (20 mg QD) and paroxetine (20 mg QD) have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone an average of 13% (see PRECAUTIONS -Drug Interactions and DOSAGE AND ADMINISTRATION – Co-Administration of RISPERDAL[®] with Certain Other Medications).

Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13) (see PRECAUTIONS – Drug Interactions).

Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone (see PRECAUTIONS – Drug Interactions).

There were no significant interactions between risperidone (1 mg QD) and erythromycin (500 mg QID) (see PRECAUTIONS – Drug Interactions).

Excretion

Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. As illustrated by a mass balance study of a single 1 mg oral dose of ¹⁴C-risperidone administered as solution to three healthy male volunteers, total recovery of radioactivity at 1 week was 84%, including 70% in the urine and 14% in the feces.

The apparent half-life of risperidone was 3 hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. The pharmacokinetics of the active moiety, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours.

Special Populations

Renal Impairment

In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. RISPERDAL[®] doses should be reduced in patients with renal disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment

While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α 1-acid glycoprotein. RISPERDAL[®] doses should be reduced in patients with liver disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly

In healthy elderly subjects, renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients (see DOSAGE AND ADMINISTRATION).

Race and Gender Effects

No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

CLINICAL TRIALS

Schizophrenia

Short-Term Efficacy

The efficacy of RISPERDAL[®] in the treatment of schizophrenia was established in four short-term (4- to 8-week) controlled trials of psychotic inpatients who met DSM-III-R criteria for schizophrenia.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS) were employed.

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=160) involving titration of RISPERDAL[®] in doses up to 10 mg/day (BID schedule), RISPERDAL[®] was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

(2) In an 8-week, placebo-controlled trial (n=513) involving 4 fixed doses of RISPERDAL[®] (2, 6, 10, and 16 mg/day, on a BID schedule), all 4 RISPERDAL[®] groups were generally superior to placebo on the BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL[®] dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses.

(3) In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL[®] (1, 4, 8, 12, and 16 mg/day, on a BID schedule), the four highest RISPERDAL[®] dose groups were generally superior to the 1 mg RISPERDAL[®] dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

(4) In a 4-week, placebo-controlled dose comparison trial (n=246) involving 2 fixed doses of RISPERDAL[®] (4 and 8 mg/day on a QD schedule), both RISPERDAL[®] dose groups were generally superior to placebo on several PANSS measures, including a response measure (>20% reduction in PANSS total score), PANSS total score, and the BPRS psychosis cluster (derived from PANSS). The results were generally stronger for the 8 mg than for the 4 mg dose group.

Long-Term Efficacy

In a longer-term trial, 365 adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medication were randomized to RISPERDAL[®] (2-8 mg/day) or to an active comparator, for 1 to 2 years of observation for relapse. Patients receiving RISPERDAL[®] experienced a significantly longer time to relapse over this time period compared to those receiving the active comparator.

Bipolar Mania

Monotherapy

The efficacy of RISPERDAL[®] in the treatment of acute manic or mixed episodes was established in 2 short-term (3-week) placebo-controlled trials in patients who met the

DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the Y-MRS total score. The results of the trials follow:

- (1) In one 3-week placebo-controlled trial (n=246), limited to patients with manic episodes, which involved a dose range of RISPERDAL[®] 1-6 mg/day, once daily, starting at 3 mg/day (mean modal dose was 4.1 mg/day), RISPERDAL[®] was superior to placebo in the reduction of Y-MRS total score.
- (2) In another 3-week placebo-controlled trial (n=286), which involved a dose range of 1-6 mg/day, once daily, starting at 3 mg/day (mean modal dose was 5.6 mg/day), RISPERDAL[®] was superior to placebo in the reduction of Y-MRS total score.

Combination Therapy

The efficacy of risperidone with concomitant lithium or valproate in the treatment of acute manic or mixed episodes was established in one controlled trial in patients who met the DSM-IV criteria for Bipolar I Disorder. This trial included patients with or without psychotic features and with or without a rapid-cycling course.

- (1) In this 3-week placebo-controlled combination trial, 148 in- or outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms were randomized to receive RISPERDAL[®], placebo, or an active comparator, in combination with their original therapy. RISPERDAL[®], in a dose range of 1-6 mg/day, once daily, starting at 2 mg/day (mean modal dose of 3.8 mg/day), combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.4 mEq/L or 50 mcg/mL to 120 mcg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.
- (2) In a second 3-week placebo-controlled combination trial, 142 in- or outpatients on lithium, valproate, or carbamazepine therapy with inadequately controlled manic or mixed symptoms were randomized to receive

RISPERDAL[®] or placebo, in combination with their original therapy. RISPERDAL[®], in a dose range of 1-6 mg/day, once daily, starting at 2 mg/day (mean modal dose of 3.7 mg/day), combined with lithium, valproate, or carbamazepine (in therapeutic ranges of 0.6 mEq/L to 1.4 mEq/L for lithium, 50 mcg/mL to 125 mcg/mL for valproate, or 4-12 mcg/mL for carbamazepine, respectively) was not superior to lithium, valproate, or carbamazepine alone in the reduction of Y-MRS total score. A possible explanation for the failure of this trial was induction of risperidone and 9-hydroxyrisperidone clearance by carbamazepine, leading to subtherapeutic levels of risperidone and 9-hydroxyrisperidone.

INDICATIONS AND USAGE

Schizophrenia

RISPERDAL[®] (risperidone) is indicated for the treatment of schizophrenia.

The efficacy of RISPERDAL[®] in schizophrenia was established in short-term (6- to 8-weeks) controlled trials of schizophrenic inpatients (see CLINICAL PHARMACOLOGY).

The efficacy of RISPERDAL[®] in delaying relapse was demonstrated in schizophrenic patients who had been clinically stable for at least 4 weeks before initiation of treatment with RISPERDAL[®] or an active comparator and who were then observed for relapse during a period of 1 to 2 years (see CLINICAL PHARMACOLOGY -Clinical Trials). Nevertheless, the physician who elects to use RISPERDAL[®] for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Bipolar Mania

Monotherapy

RISPERDAL[®] is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

The efficacy of RISPERDAL[®] was established in two placebo-controlled trials (3-week) with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL PHARMACOLOGY).

Combination Therapy

The combination of RISPERDAL[®] with lithium or valproate is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

The efficacy of RISPERDAL[®] in combination with lithium or valproate was established in one placebo-controlled (3-week) trial with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL PHARMACOLOGY).

The effectiveness of RISPERDAL[®] for longer-term use, that is, for more than 3 weeks of treatment of an acute episode, and for prophylactic use in mania, has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use RISPERDAL[®] for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

RISPERDAL[®] (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. RISPERDAL[®](risperidone) is not approved for the treatment of dementia-related psychosis (see Boxed Warning).

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., 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 antipsychotic drugs and other drugs not essential to concurrent therapy; (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 drug 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.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL[®] (risperidone) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated on RISPERDAL[®], drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL[®] despite the presence of the syndrome.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia-Related Psychosis

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. RISPERDAL[®] is not approved for the treatment of patients with dementia-related psychosis. (See also **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.**)

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL[®]. 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 hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-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 hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued;

however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

General

Orthostatic Hypotension

RISPERDAL[®] (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL[®]-treated patients in Phase 2 and 3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (see DOSAGE AND ADMINISTRATION). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL[®] should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL[®] and antihypertensive medication.

Seizures

During premarketing testing, seizures occurred in 0.3% (9/2607) of RISPERDAL[®]-treated patients, two in association with hyponatremia. RISPERDAL[®] should be used cautiously in patients with a history of seizures.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL[®] and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. (See also **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.**)

Hyperprolactinemia

As with other drugs that antagonize dopamine D2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of

these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (see **PRECAUTIONS – Carcinogenesis, Mutagenesis, Impairment of Fertility**). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event associated with RISPERDAL[®] treatment, especially when ascertained by direct questioning of patients. This adverse event is dose-related, and in a study utilizing a checklist to detect adverse events, 41% of the high-dose patients (RISPERDAL[®] 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL[®] 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERDAL[®] has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL[®] therapy does not affect them adversely.

Priapism

Rare cases of priapism have been reported. While the relationship of the events to RISPERDAL[®] use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that RISPERDAL[®] may share this capacity. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP)

A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL[®] in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL[®] therapy is unknown.

Antiemetic Effect

Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation

Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral RISPERDAL[®] use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide

The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for RISPERDAL[®] should be written for the smallest quantity of tablets, consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients With Concomitant Illness

Clinical experience with RISPERDAL[®] in patients with certain concomitant systemic illnesses is limited. Patients with Parkinson's Disease or Dementia with Lewy Bodies who receive antipsychotics, including RISPERDAL[®], 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.

Caution is advisable in using RISPERDAL[®] in patients with diseases or conditions that could affect metabolism or hemodynamic responses. RISPERDAL[®] has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing.

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m²), and an increase in the free fraction of risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL[®]:

Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

Interference With Cognitive and Motor Performance

Since RISPERDAL[®] has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL[®] therapy does not affect them adversely.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing

Patients should be advised not to breast-feed an infant if they are taking RISPERDAL[®].

Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol

Patients should be advised to avoid alcohol while taking RISPERDAL[®].

Phenylketonurics

Phenylalanine is a component of aspartame. Each 2 mg RISPERDAL[®] M-TAB[®] Orally Disintegrating Tablet contains 0.56 mg phenylalanine; each 1 mg RISPERDAL[®] M-TAB[®] Orally Disintegrating Tablet contains 0.28 mg phenylalanine; and each 0.5 mg RISPERDAL[®] M-TAB[®] Orally Disintegrating Tablet contains 0.14 mg phenylalanine.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The interactions of RISPERDAL[®] and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL[®] is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, RISPERDAL[®] may enhance the hypotensive effects of other therapeutic agents with this potential.

RISPERDAL[®] may antagonize the effects of levodopa and dopamine agonists.

Amytriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increased the bioavailability of risperidone, but only marginally increased the plasma concentration of the active antipsychotic fraction.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Carbamazepine and Other Enzyme Inducers

In a drug interaction study in schizophrenic patients, 11 subjects received risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. The dose of risperidone may need to be titrated accordingly for patients receiving carbamazepine, particularly during initiation or discontinuation of carbamazepine therapy. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment.

Fluoxetine and Paroxetine

Fluoxetine (20 mg QD) and paroxetine (20 mg QD) have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone an average of 13%. When either concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL[®]. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied.

Lithium

Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13).

Valproate

Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone.

Digoxin

RISPERDAL[®] (0.25 mg BID) did not show a clinically relevant effect on the pharmacokinetics of digoxin.

Drugs That Inhibit CYP 2D6 and Other CYP Isozymes

Risperidone is metabolized to 9-hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (see CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n@70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C9, 2C19, and 3A4, are only weak inhibitors of risperidone metabolism.

There were no significant interactions between risperidone and erythromycin (see CLINICAL PHARMACOLOGY).

Drugs Metabolized by CYP 2D6

In vitro studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, RISPERDAL[®] is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, risperidone did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the maximum recommended human dose (MRHD) (16 mg/day) on a mg/kg basis or 0.2, 0.75, and 3 times the MRHD (mice) or

0.4, 1.5, and 6 times the MRHD (rats) on a mg/m² basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m² (mg/kg) basis at which these tumors occurred.

Tumor Type	Species	Sex	Multiples of Maximum Human Dose in mg/m ² (mg/kg)	
			Lowest Effect Level	Highest No-Effect Level
Pituitary adenomas	mouse	female	0.75 (9.4)	0.2 (2.4)
Endocrine pancreas adenomas	rat	male	1.5 (9.4)	0.4 (2.4)
Mammary gland adenocarcinomas	mouse	female	0.2 (2.4)	None
	rat	female	0.4 (2.4)	none
	rat	male	6.0 (37.5)	1.5 (9.4)
Mammary gland neoplasm, Total	rat	male	1.5 (9.4)	0.4 (2.4)

Antipsychotic drugs 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 5-6 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 antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see PRECAUTIONS, General -Hyperprolactinemia).

Mutagenesis

No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma assay, in vitro rat hepatocyte DNA-repair assay, in vivo micronucleus test in mice, the sex-linked recessive lethal test in *Drosophila*, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility

Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1 to 3 times the maximum recommended human dose (MRHD) on a mg/m² basis. The effect appeared to be in females, since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in Beagle dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the MRHD on a mg/m² basis. Dose-related decreases were also noted in

serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered, but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

Pregnancy

Pregnancy Category C

The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the maximum recommended human dose [MRHD] on a mg/m² basis) and in one Segment II study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the MRHD on a mg/m² basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the MRHD on a mg/m² basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5 mg/kg or 0.1 to 3 times the MRHD on a mg/m² basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams.

There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the MRHD on a mg/m² basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Day 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the MRHD on a mg/m² basis.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone in utero. The causal relationship to RISPARDAL[®] therapy is unknown.

RISPARDAL[®] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of RISPARDAL[®] on labor and delivery in humans is unknown.

Nursing Mothers

In animal studies, risperidone and 9-hydroxyrisperidone are excreted in milk. Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving risperidone should not breast-feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical studies of RISPARDAL® in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by careful titration (see PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

Concomitant use with Furosemide in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%; mean age 89 years, range 75-97) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70-96) or furosemide alone (4.1%; mean age 80 years, range 67-90). The increase in mortality in patients treated with furosemide plus risperidone was observed in two of the four clinical trials.

No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination should be considered prior to

the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant medication with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia-related psychosis. RISPERDAL[®] is not approved for the treatment of patients with dementia-related psychosis (See also **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.**)

ADVERSE REACTIONS

The following findings are based on the short-term, placebo-controlled, North American, premarketing trials for schizophrenia and acute bipolar mania. In patients with Bipolar I Disorder, treatment-emergent adverse events are presented separately for risperidone as monotherapy and as adjunctive therapy to mood stabilizers.

Certain portions of the discussion below relating to objective or numeric safety parameters, namely dose-dependent adverse events, vital sign changes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia. However, this information is also generally applicable to bipolar mania.

Associated With Discontinuation of Treatment

Schizophrenia

Approximately 9% (244/2607) of RISPERDAL[®] (risperidone)-treated patients in Phase 2 and 3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events (≥0.3%) associated with discontinuation and considered to be possibly or probably drug-related included:

Adverse Event	RISPERDAL [®]	Placebo
Extrapyramidal symptoms	2.1%	0%
Dizziness	0.7%	0%
Hyperkinesia	0.6%	0%
Somnolence	0.5%	0%
Nausea	0.3%	0%

Suicide attempt was associated with discontinuation in 1.2% of RISPERDAL[®]-treated patients compared to 0.6% of placebo patients, but, given the almost 40-fold greater exposure time in RISPERDAL[®] compared to placebo patients, it is unlikely that suicide attempt is a RISPERDAL[®]-related adverse event (see PRECAUTIONS). Discontinuation for extrapyramidal symptoms was 0% in placebo patients, but 3.8% in active-control patients in the Phase 2 and 3 trials.

Bipolar Mania

In the US placebo-controlled trial with risperidone as monotherapy, approximately 8% (10/134) of RISPERDAL[®]-treated patients discontinued treatment due to an adverse event, compared with approximately 6% (7/125) of placebo-treated patients. The adverse events associated with discontinuation and considered to be possibly, probably, or very likely drug-related included paroniria, somnolence, dizziness, extrapyramidal disorder, and muscle contractions involuntary. Each of these events occurred in one RISPERDAL[®]-treated patient (0.7%) and in no placebo-treated patients (0%).

In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, there was no overall difference in the incidence of discontinuation due to adverse events (4% for RISPERDAL[®] vs. 4% for placebo).

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials

Schizophrenia

In two 6- to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL[®] groups and at least twice that of placebo were anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial comparing RISPERDAL[®] at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events occurred at an incidence of at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgasmic dysfunction.

Bipolar Mania

In the US placebo-controlled trial with risperidone as monotherapy, the most commonly observed adverse events associated with the use of RISPERDAL[®] (incidence of 5% or greater and at least twice that of placebo) were somnolence, dystonia, akathisia, dyspepsia, nausea, parkinsonism, vision abnormal, and saliva increased. In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, the most commonly observed adverse events associated with the use

of RISPERDAL[®] were somnolence, dizziness, parkinsonism, saliva increased, akathisia, abdominal pain, and urinary incontinence.

**Adverse Events Occurring at an Incidence of 1% or More Among
RISPERDAL[®]-Treated Patients - Schizophrenia**

The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent among RISPERDAL[®]-treated patients treated at doses of ≤ 10 mg/day than among placebo-treated patients in the pooled results of two 6- to 8-week controlled trials. Patients received RISPERDAL[®] doses of 2, 6, 10, or 16 mg/day in the dose comparison trial, or up to a maximum dose of 10 mg/day in the titration study. This table shows the percentage of patients in each dose group (≤ 10 mg/day or 16 mg/day) who spontaneously reported at least one episode of an event at some time during their treatment. Patients given doses of 2, 6, or 10 mg did not differ materially in these rates. Reported adverse events were classified using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Table 1. Incidence of Treatment-Emergent Adverse Events in 6- to 8-Week Controlled Clinical Trials¹

Body System/ Preferred Term	RISPERDAL [®]		
	≤10mg/day (N=324)	16 mg/day (N=77)	Placebo (N=142)
Psychiatric			
Insomnia	26%	23%	19%
Agitation	22%	26%	20%
Anxiety	12%	20%	9%
Somnolence	3%	8%	1%
Aggressive reaction	1%	3%	1%
Central & peripheral nervous system			
Extrapyramidal symptoms ²	17%	34%	16%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%
Abdominal pain	4%	1%	0%
Saliva increased	2%	0%	1%
Toothache	2%	0%	0%
Respiratory system			
Rhinitis	10%	8%	4%
Coughing	3%	3%	1%
Sinusitis	2%	1%	1%
Pharyngitis	2%	3%	0%
Dyspnea	1%	0%	0%
Body as a whole - general			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Seborrhea	1%	0%	0%
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculo-Skeletal			
Arthralgia	2%	3%	0%

(continued)

Table 1. Incidence of Treatment-Emergent Adverse Events in 6- to 8-Week Controlled Clinical Trials¹

Body System/ Preferred Term	RISPERDAL [®]		
	≤10mg/day (N=324)	16 mg/day (N=77)	Placebo (N=142)
Cardiovascular			
Tachycardia	3%	5%	0%

¹ Events reported by at least 1% of patients treated with RISPERDAL[®] ≤10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPERDAL[®] 16 mg/day and placebo are provided as well. Events for which the RISPERDAL[®] incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

² Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia, and extrapyramidal disorders. Although the incidence of 'extrapyramidal symptoms' does not appear to differ for the '10 mg/day' group and placebo, the data for individual dose groups in fixed dose trials do suggest a dose/response relationship (see ADVERSE REACTIONS – Dose Dependency of Adverse Events).

Adverse Events Occurring at an Incidence of 2% or More Among RISPERDAL[®]-Treated Patients - Bipolar Mania

Tables 2 and 3 display adverse events that occurred at an incidence of 2% or more, and were more frequent among patients treated with flexible doses of RISPERDAL[®] (1-6 mg daily as monotherapy and as adjunctive therapy to mood stabilizers, respectively) than among patients treated with placebo. Reported adverse events were classified using the World Health Organization preferred terms.

Table 2. Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial - Monotherapy in Bipolar Mania¹

Body System/ Preferred Term	RISPERDAL [®] (N=134)	Placebo (N=125)
Central & peripheral nervous system		
Dystonia	18%	6%
Akathisia	16%	6%
Dizziness	11%	9%
Parkinsonism	6%	3%
Hypoaesthesia	2%	1%
Psychiatric		
Somnolence	28%	7%
Agitation	8%	6%
Manic reaction	8%	6%
Anxiety	4%	2%
Concentration impaired	2%	1%
Gastrointestinal system		
Dyspepsia	11%	6%

(continued)

Table 2. Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial - Monotherapy in Bipolar Mania¹

Body System/ Preferred Term	RISPERDAL[®] (N=134)	Placebo (N=125)
Nausea	11%	2%
Saliva increased	5%	1%
Mouth dry	3%	2%
Body as a whole - general		
Pain	5%	3%
Fatigue	4%	2%
Injury	2%	0%
Respiratory system		
Sinusitis	4%	1%
Rhinitis	3%	2%
Coughing	2%	2%
Skin and appendages		
Acne	2%	0%
Pruritus	2%	1%
Musculo-Skeletal		
Myalgia	5%	2%
Skeletal pain	2%	1%
Metabolic and nutritional		
Weight increase	2%	0%
Vision disorders		
Vision abnormal	6%	2%
Cardiovascular, general		
Hypertension	3%	1%
Hypotension	2%	0%
Heart rate and rhythm		
Tachycardia	3%	2%

¹Events reported by at least 2% of patients treated with RISPERDAL[®] are included and are rounded to the nearest %. Events reported by at least 2% of patients treated with RISPERDAL[®] that were less than the incidence reported by patients treated with placebo are not listed in the table, but included the following: headache, tremor, insomnia, constipation, back pain, upper respiratory tract infection, pharyngitis, and arthralgia.

Table 3. Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial - Adjunctive Therapy in Bipolar Mania¹

Body System/ Preferred Term	RISPERDAL [®] + Mood Stabilizer (N=52)	Placebo Mood Stabilizer (N=51)
Gastrointestinal system		
Saliva increased	10%	0%
Diarrhea	8%	4%
Abdominal pain	6%	0%
Constipation	6%	4%
Mouth dry	6%	4%
Tooth ache	4%	0%
Tooth disorder	4%	0%
Central & peripheral nervous system		
Dizziness	14%	2%
Parkinsonism	14%	4%
Akathisia	8%	0%
Dystonia	6%	4%
Psychiatric		
Somnolence	25%	12%
Anxiety	6%	4%
Confusion	4%	0%
Respiratory system		
Rhinitis	8%	4%
Pharyngitis	6%	4%
Coughing	4%	0%
Body as a whole - general		
Asthenia	4%	2%
Urinary system		
Urinary incontinence	6%	2%
Heart rate and rhythm		
Tachycardia	4%	2%
Metabolic and nutritional		
Weight increase	4%	2%
Skin and appendages		
Rash	4%	2%

¹Events reported by at least 2% of patients treated with RISPERDAL[®] are included and are rounded to the nearest %. Events reported by at least 2% of patients treated with RISPERDAL[®] that were less than the incidence reported by patients treated with placebo are not listed in the table, but included the following: dyspepsia, nausea, vomiting, headache, tremor, insomnia, chest pain, fatigue, pain, skeletal pain, hypertension, and vision abnormal.

Dose Dependency of Adverse Events

Extrapyramidal Symptoms

Data from two fixed-dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 4 fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale, and (2) incidence of spontaneous complaints of EPS:

Dose Groups	Placebo	Ris 2	Ris 6	Ris 10	Ris 16
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	13%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 5 fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day):

Dose Groups	Ris 1	Ris 4	Ris 8	Ris 12	Ris 16
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	18%	18%	21%

Other Adverse Events

Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p < 0.05$) for the following adverse events: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction, asthenia/lassitude/increased fatigability, and increased pigmentation.

Vital Sign Changes

RISPERDAL® is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS).

Weight Changes

The proportions of RISPERDAL® and placebo-treated patients meeting a weight gain criterion of $\geq 7\%$ of body weight were compared in a pool of 6- to 8-week, placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%).

Laboratory Changes

A between-group comparison for 6- to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL® administration was associated with increases in serum prolactin (see PRECAUTIONS).

ECG Changes

Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant differences between risperidone and placebo in mean changes

from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. When all RISPERDAL[®] doses were pooled from randomized controlled trials in several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenia trials, higher doses of risperidone (8-16 mg/day) were associated with a higher mean increase in heart rate compared to placebo (4-6 beats per minute).

Other Events Observed During the Premarketing Evaluation of RISPERDAL[®]

During its premarketing assessment, multiple doses of RISPERDAL[®] were administered to 2607 patients in Phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL[®] varied greatly, and included (in overlapping categories) open-label and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology. (Note: These events are marked with an asterisk in the listings that follow.)

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 2607 patients exposed to multiple doses of RISPERDAL[®] who experienced an event of the type cited on at least one occasion while receiving RISPERDAL[®]. All reported events are included, except those already listed in Table 1, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL[®], they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders

Frequent: increased dream activity*, diminished sexual desire*, nervousness. *Infrequent:* impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. *Rare:* emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders

Frequent: increased sleep duration*. *Infrequent:* dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare:* aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastrointestinal Disorders

Frequent: anorexia, reduced salivation*. *Infrequent:* flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders

Frequent: fatigue. *Infrequent:* edema, rigors, malaise, influenza-like symptoms. *Rare:* pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders

Infrequent: hyperventilation, bronchospasm, pneumonia, stridor. *Rare:* asthma, increased sputum, aspiration.

Skin and Appendage Disorders

Frequent: increased pigmentation*, photosensitivity* *Infrequent:* increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. *Rare:* bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria.

Cardiovascular Disorders

Infrequent: palpitation, hypertension, hypotension, AV block, myocardial infarction. *Rare:* ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders

Infrequent: abnormal accommodation, xerophthalmia. *Rare:* diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders

Infrequent: hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare:* decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Urinary System Disorders

Frequent: polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare:* urinary retention, cystitis, renal insufficiency.

Musculo-Skeletal System Disorders

Infrequent: myalgia. *Rare:* arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female

Frequent: menorrhagia*, orgasmic dysfunction*, dry vagina* *Infrequent:* nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders

Infrequent: increased SGOT, increased SGPT. *Rare:* hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding, and Clotting Disorders

Infrequent: epistaxis, purpura. *Rare:* hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders

Rare: tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders

Infrequent: anemia, hypochromic anemia. *Rare:* normocytic anemia.

Reproductive Disorders, Male

Frequent: erectile dysfunction* *Infrequent:* ejaculation failure.

White Cell and Resistance Disorders

Rare: leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.

Endocrine Disorders

Rare: gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses

Rare: bitter taste.

* Incidence based on elicited reports.

Postintroduction Reports

Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL[®] therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, including cerebrovascular accident, hyperglycemia, diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL[®]. A causal relationship with RISPERDAL[®] has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

RISPERDAL[®] (risperidone) is not a controlled substance.

Physical and Psychological Dependence

RISPERDAL[®] has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL[®] misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Premarketing experience included eight reports of acute RISPERDAL[®] (risperidone) overdose with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT,

and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure.

Postmarketing experience includes reports of acute RISPERDAL[®] overdosage, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia, hypotension, and extrapyramidal symptoms. Other adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL[®] overdose, include torsade de pointes, prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

Management of Overdosage

In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. Because of the rapid disintegration of RISPERDAL[®] M-TAB[®] Orally Disintegrating Tablets, pill fragments may not appear in gastric contents obtained with lavage.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to RISPERDAL[®]. Therefore, appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Schizophrenia

Usual Initial Dose

RISPERDAL[®] (risperidone) can be administered on either a BID or a QD schedule. In early clinical trials, RISPERDAL[®] was generally administered at 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. Subsequent controlled trials have indicated that total daily risperidone doses of up to 8 mg on a QD regimen are also safe and effective. However, regardless of which regimen is employed, in some patients a slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1-2 mg are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 4 to 16 mg/day in the clinical trials supporting effectiveness of RISPERDAL[®]; however, maximal effect was generally seen in a range of 4 to 8 mg/day. Doses above 6 mg/day for BID dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. In a single study supporting QD dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Maintenance Therapy

While there is no body of evidence available to answer the question of how long the schizophrenic patient treated with RISPERDAL[®] should remain on it, the effectiveness of RISPERDAL[®] 2 mg/day to 8 mg/day at delaying relapse was demonstrated in a controlled trial in patients who had been clinically stable for at least 4 weeks and were then followed for a period of 1 to 2 years. In this trial, RISPERDAL[®] was administered on a QD schedule, at 1 mg QD initially, with increases to 2 mg QD on the second day, and to a target dose of 4 mg QD on the third day (see CLINICAL PHARMACOLOGY – Clinical Trials). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment with an appropriate dose.

Reinitiation of Treatment in Patients Previously Discontinued

Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off RISPERDAL[®], the initial titration schedule should be followed.

Switching From Other Antipsychotics

There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to RISPERDAL[®], or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some schizophrenic patients, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching schizophrenic patients from depot antipsychotics, if medically appropriate, initiate RISPERDAL[®] therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be re-evaluated periodically.

Bipolar Mania

Usual Dose

Risperidone should be administered on a once daily schedule, starting with 2 mg to 3 mg per day. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments/decrements of 1 mg per day, as studied in the short-term, placebo-controlled trials. In these trials, short-term (3 week) anti-manic efficacy was demonstrated in a flexible dosage range of 1-6 mg per day (see CLINICAL PHARMACOLOGY – Clinical Trials). RISPERDAL[®] doses higher than 6 mg per day were not studied.

Maintenance Therapy

There is no body of evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during treatment of an acute manic episode with risperidone. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of risperidone in such longer-term treatment (i.e., beyond 3 weeks).

Pediatric Use

Safety and effectiveness of RISPERDAL[®] in pediatric patients with schizophrenia or acute mania associated with Bipolar I Disorder have not been established.

Dosage in Special Populations

The recommended initial dose is 0.5 mg BID in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of no more than 0.5 mg BID.

Increases to dosages above 1.5 mg BID should generally occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate.

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL[®] than normal adults. Patients with impaired hepatic function may have increases in the free fraction of risperidone, possibly resulting in an enhanced effect (see CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (see PRECAUTIONS). If a once-a-day dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be titrated on a twice-a-day regimen for 2-3 days at the target dose. Subsequent switches to a once-a-day dosing regimen can be done thereafter.

Co-Administration of RISPERDAL[®] with Certain Other Medications

Co-administration of carbamazepine and other enzyme inducers (e.g., phenytoin, rifampin, phenobarbital) with risperidone would be expected to cause decreases in the plasma concentrations of active moiety (the sum of risperidone and 9-hydroxyrisperidone), which could lead to decreased efficacy of risperidone treatment. The dose of risperidone needs to be titrated accordingly for patients receiving these enzyme inducers, especially during initiation or discontinuation of therapy with these inducers (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

Fluoxetine and paroxetine have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone an average of 13%. The dose of risperidone needs to be titrated accordingly when fluoxetine or paroxetine is co-administered (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

Directions for Use of RISPERDAL[®] M-TAB[®] Orally Disintegrating Tablets

RISPERDAL[®] M-TAB[®] Orally Disintegrating Tablets are supplied in blister packs of 4 tablet units each.

Tablet Accessing

Do not open the blister until ready to administer. For single tablet removal, separate one of the four blister units by tearing apart at the perforations. Bend the corner where indicated. Peel back foil to expose the tablet. DO NOT push the tablet through the foil because this could damage the tablet.

Tablet Administration

Using dry hands, remove the tablet from the blister unit and immediately place the entire RISPERDAL[®] M-TAB[®] Orally Disintegrating Tablet on the tongue. The RISPERDAL[®] M-TAB[®] Orally Disintegrating Tablet should be consumed immediately, as the tablet cannot be stored once removed from the blister unit. RISPERDAL[®] M-TAB[®] Orally Disintegrating Tablets disintegrate in the mouth within seconds and can be swallowed subsequently with or without liquid. Patients should not attempt to split or to chew the tablet.

HOW SUPPLIED

RISPERDAL[®] (risperidone) tablets are imprinted "JANSSEN", and either "Ris" and the strength "0.25", "0.5", or "R" and the strength "1", "2", "3", or "4".

0.25 mg dark yellow tablet: bottles of 60 NDC 50458-301-04, bottles of 500 NDC 50458-301-50, hospital unit dose packs of 100 NDC 50458-301-01.

0.5 mg red-brown tablet: bottles of 60 NDC 50458-302-06, bottles of 500 NDC 50458-302-50, hospital unit dose packs of 100 NDC 50458-302-01.

1 mg white tablet: bottles of 60 NDC 50458-300-06, blister pack of 100 NDC 50458-300-01, bottles of 500 NDC 50458-300-50.

2 mg orange tablet: bottles of 60 NDC 50458-320-06, blister pack of 100 NDC 50458-320-01, bottles of 500 NDC 50458-320-50.

3 mg yellow tablet: bottles of 60 NDC 50458-330-06, blister pack of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.

4 mg green tablet: bottles of 60 NDC 50458-350-06, blister pack of 100 NDC 50458-350-01.

RISPERDAL[®] (risperidone) 1 mg/mL oral solution (NDC 50458-305-03) is supplied in 30 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL.

Tests indicate that RISPERDAL[®] (risperidone) oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with either cola or tea, however.

RISPERDAL[®] M-TAB[®] (risperidone) Orally Disintegrating Tablets are etched on one side with "R0.5", "R1", and "R2", respectively, and are packaged in blister packs of 4 (2 X 2) tablets.

0.5 mg light coral, round, biconvex tablets: 7 blister packages per box, NDC 50458-395-28, long-term care packaging of 30 tablets NDC 50458-395-30.

1 mg light coral, square, biconvex tablets: 7 blister packages per box, NDC 50458-315-28, long-term care packaging of 30 tablets NDC 50458-315-30.

2 mg light coral, round, biconvex tablets: 7 blister packages per box, NDC 50458-325-28.

Storage and Handling

RISPERDAL[®] tablets should be stored at controlled room temperature 15o-25oC (59o-77oF). Protect from light and moisture.

Keep out of reach of children.

RISPERDAL[®] 1 mg/mL oral solution should be stored at controlled room temperature 15o-25oC (59o-77oF). Protect from light and freezing.

Keep out of reach of children.

RISPERDAL[®] M-TAB[®] Orally Disintegrating Tablets should be stored at controlled room temperature 15o-25oC (59o-77oF).

Keep out of reach of children.

7503228

US Patent 4,804,663

Revised February 2005

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RISPERDAL[®] tablets are manufactured by:

JOLLC, Gurabo, Puerto Rico or

Janssen-Cilag, SpA, Latina, Italy

RISPERDAL[®] oral solution is manufactured by:

Janssen Pharmaceutica N.V.

Beerse, Belgium

RISPERDAL[®] M-TAB[®] Orally Disintegrating Tablets are manufactured by:

JOLLC, Gurabo, Puerto Rico

JANSSEN
PHARMACEUTICA
PRODUCTS, L.P.

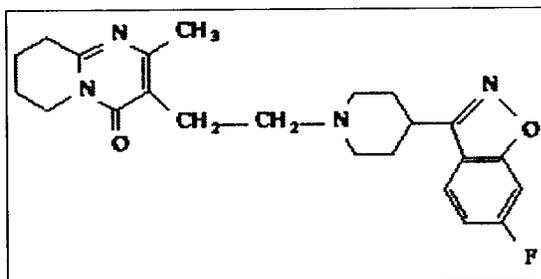
RISPERDAL® CONSTA®
(risperidone)
LONG-ACTING INJECTION

Increased Mortality in Elderly Patients with Dementia –Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. RISPERDAL® CONSTA® (risperidone) is not approved for the treatment of patients with Dementia-Related Psychosis.

DESCRIPTION

RISPERDAL® (risperidone) is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 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. Its molecular formula is C₂₃H₂₇FN₄O₂ and its molecular weight is 410.49. The structural formula is:



Risperidone is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL® CONSTA® (risperidone) Long-Acting Injection is a combination of extended release microspheres for injection and diluent for parenteral use.

The extended release microspheres formulation is a white to off-white, free-flowing powder that is available in dosage strengths of 25, 37.5, or 50 mg risperidone per vial.

Risperidone is micro-encapsulated in 7525 polylactide-co-glycolide (PLG) at a concentration of 381 mg risperidone per gram of microspheres.

The diluent for parenteral use is a clear, colorless solution. Composition of the diluent includes polysorbate 20, sodium carboxymethyl cellulose, disodium hydrogen phosphate dihydrate, citric acid anhydrous, sodium chloride, sodium hydroxide, and water for injection. The microspheres are suspended in the diluent prior to injection.

RISPERDAL[®] CONSTA[®] is provided as a dose pack, consisting of a vial containing the microspheres, a pre-filled syringe containing the diluent, a SmartSite[®] Needle-Free Vial Access Device, and one Needle-Pro[®] 20 G TW safety needle.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL[®] (risperidone), as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D₂) and serotonin Type 2 (5HT₂) receptor antagonism. Antagonism at receptors other than D₂ and 5HT₂ may explain some of the other effects of RISPERDAL[®].

RISPERDAL[®] is a selective monoaminergic antagonist with high affinity (K_i of 0.12 to 7.3 nM) for the serotonin Type 2 (5HT₂), dopamine Type 2 (D₂), α₁ and α₂ adrenergic, and H₁ histaminergic receptors. RISPERDAL[®] acts as an antagonist at other receptors, but with lower potency. RISPERDAL[®] has low to moderate affinity (K_i of 47 to 253 nM) for the serotonin 5HT_{1C}, 5HT_{1D}, and 5HT_{1A} receptors, weak affinity (K_i of 620 to 800 nM) for the dopamine D₁ and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations >10⁻⁵ M) for cholinergic muscarinic or β₁ and β₂ adrenergic receptors.

Pharmacokinetics

Absorption

After a single intramuscular (gluteal) injection of RISPERDAL[®] CONSTA[®] (risperidone), there is a small initial release of the drug (<about 1% of the dose), followed by a lag time of 3 weeks. The main release of the drug starts from 3 weeks onward, is maintained from 4 to 6 weeks, and subsides by 7 weeks following the intramuscular (IM) injection. Therefore, oral antipsychotic supplementation should be given during the first 3 weeks of treatment with RISPERDAL[®] CONSTA[®] to maintain therapeutic levels until the main release of risperidone from the injection site has begun (see DOSAGE AND ADMINISTRATION).

The combination of the release profile and the dosage regimen (IM injections every 2 weeks) of RISPERDAL[®] CONSTA[®] results in sustained therapeutic concentrations. Steady-state plasma concentrations are reached after 4 injections and are maintained for 4 to 6 weeks after the last injection. Plasma concentrations of risperidone, 9-hydroxyrisperidone (the major metabolite), and risperidone plus 9-hydroxyrisperidone are linear over the dosing range of 25 mg to 50 mg.

Distribution

Once absorbed, risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and α 1-acid glycoprotein. The plasma protein binding of risperidone is approximately 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites. High therapeutic concentrations of sulfamethazine (100 mcg/mL), warfarin (10 mcg/mL), and carbamazepine (10 mcg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and of 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Metabolism

Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, CYP 2D6. A minor metabolic pathway is through N-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug (i.e., the active moiety) results from the combined concentrations of risperidone plus 9-hydroxyrisperidone.

CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6%-8% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of the active moiety, after single and multiple doses, are similar in extensive and poor metabolizers.

The interactions of RISPERDAL[®] CONSTA[®] and other drugs have not been systematically evaluated in human subjects. Risperidone could be subject to two

kinds of drug-drug interactions (see PRECAUTIONS - Drug Interactions). First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone. This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The therapeutic benefits and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number ($n \approx 70$) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. Second, co-administration of carbamazepine and other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone (see PRECAUTIONS - Drug Interactions). It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely.

In a drug interaction study in schizophrenic patients, 11 subjects received oral risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment (see PRECAUTIONS - Drug Interactions and DOSAGE AND ADMINISTRATION - Co-Administration of RISPERDAL[®] CONSTA[®] with Certain Other Medications).

Fluoxetine (20 mg QD) and paroxetine (20 mg QD) have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone an average of 13% (see PRECAUTIONS - Drug Interactions and DOSAGE AND ADMINISTRATION - Co-Administration of RISPERDAL[®] CONSTA[®] with Certain Other Medications).

Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium ($n=13$) (see PRECAUTIONS - Drug Interactions).

Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone (see PRECAUTIONS – Drug Interactions).

There were no significant interactions between oral risperidone (1 mg QD) and erythromycin (500 mg QID) (see PRECAUTIONS – Drug Interactions).

Excretion

Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. As illustrated by a mass balance study of a single 1 mg oral dose of ^{14}C -risperidone administered as solution to three healthy male volunteers, total recovery of radioactivity at 1 week was 84%, including 70% in the urine and 14% in the feces.

The apparent half-life of risperidone plus 9-hydroxyrisperidone following RISPERDAL[®] CONSTA[®] administration is 3 to 6 days, and is associated with a monoexponential decline in plasma concentrations. This half-life of 3-6 days is related to the erosion of the microspheres and subsequent absorption of risperidone. The clearance of risperidone and risperidone plus 9-hydroxyrisperidone was 13.7 L/h and 5.0 L/h in extensive CYP 2D6 metabolizers, and 3.3 L/h and 3.2 L/h in poor CYP 2D6 metabolizers, respectively. No accumulation of risperidone was observed during long-term use (up to 12 months) in patients treated every 2 weeks with 25 mg or 50 mg RISPERDAL[®] CONSTA[®]. The elimination phase is complete approximately 7 to 8 weeks after the last injection.

Special Populations

Renal Impairment

In patients with moderate to severe renal disease treated with oral RISPERDAL[®], clearance of the sum of risperidone and its active metabolite decreased by 60% compared with young healthy subjects. Although patients with renal impairment were not studied with RISPERDAL[®] CONSTA[®], it is recommended that patients with renal impairment be carefully titrated on oral RISPERDAL[®] before treatment with RISPERDAL[®] CONSTA[®] is initiated (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment

While the pharmacokinetics of oral RISPERDAL[®] in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of

both albumin and α_1 -acid glycoprotein. Although patients with hepatic impairment were not studied with RISPERDAL[®] CONSTA[®], it is recommended that patients with hepatic impairment be carefully titrated on oral RISPERDAL[®] before treatment with RISPERDAL[®] CONSTA[®] is initiated (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly

In an open-label trial, steady-state concentrations of risperidone plus 9-hydroxyrisperidone in otherwise healthy elderly patients (≥ 65 years old) treated with RISPERDAL[®] CONSTA[®] for up to 12 months fell within the range of values observed in otherwise healthy nonelderly patients. Dosing recommendations are the same for otherwise healthy elderly patients and nonelderly patients (see DOSAGE AND ADMINISTRATION).

Race and Gender Effects

No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether or not corrected for body weight) or race.

CLINICAL TRIALS

The effectiveness of RISPERDAL[®] CONSTA[®] (risperidone) in the treatment of schizophrenia was established, in part, on the basis of extrapolation from the established effectiveness of the oral formulation of risperidone. In addition, the effectiveness of RISPERDAL[®] CONSTA[®] in the treatment of schizophrenia was established in a 12-week, placebo-controlled trial in adult psychotic inpatients and outpatients who met the DSM-IV criteria for schizophrenia.

Efficacy data were obtained from 400 patients with schizophrenia who were randomized to receive injections of 25, 50, or 75 mg RISPERDAL[®] CONSTA[®] or placebo every 2 weeks. During a 1-week run-in period, patients were discontinued from other antipsychotics and were titrated to a dose of 4 mg oral RISPERDAL[®]. Patients who received RISPERDAL[®] CONSTA[®] were given doses of oral RISPERDAL[®] (2 mg for patients in the 25-mg group, 4 mg for patients in the 50-mg group, and 6 mg for patients in the 75-mg group) for the 3 weeks after the first injection to provide therapeutic plasma concentrations until the main release phase of risperidone from the injection site had begun. Patients who received placebo injections were given placebo tablets.

Efficacy was evaluated using the Positive and Negative Syndrome Scale (PANSS), a validated, multi-item inventory, composed of five subscales to evaluate positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression.

The primary efficacy variable in this trial was change from baseline to endpoint in the total PANSS score. The mean total PANSS score at baseline for schizophrenic patients in this study was 81.5.

Total PANSS scores showed significant improvement in the change from baseline to endpoint in schizophrenic patients treated with each dose of RISPERDAL[®] CONSTA[®] (25 mg, 50 mg, or 75 mg) compared with patients treated with placebo. While there were no statistically significant differences between the treatment effects for the three dose groups, the effect size for the 75 mg dose group was actually numerically less than that observed for the 50 mg dose group.

Subgroup analyses did not indicate any differences in treatment outcome as a function of age, race, or gender.

INDICATIONS AND USAGE

RISPERDAL[®] CONSTA[™] (risperidone) is indicated for the treatment of schizophrenia.

The efficacy of RISPERDAL[®] CONSTA[®] is based in part on a 12-week, placebo-controlled trial in schizophrenic inpatients or outpatients, along with extrapolation from the established efficacy of oral RISPERDAL[®] in this population.

The effectiveness of RISPERDAL[®] CONSTA[®] in longer-term use, that is, more than 12 weeks, has not been systematically evaluated in controlled trials. However, oral risperidone has been shown to be effective in delaying time to relapse in longer-term use. Patients should be periodically reassessed to determine the need for continued treatment (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

RISPERDAL[®] CONSTA[®] (risperidone) is contraindicated in patients with a known hypersensitivity to the product or any of its components.

WARNINGS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo.

RISPERDAL[®] CONSTA[®] (risperidone) is not approved for the treatment of dementia-related psychosis (see **Boxed Warning).**

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., 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 antipsychotic drugs and other drugs not essential to concurrent therapy; (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 drug 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.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome

can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL[®] CONSTA[®] should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with RISPERDAL[®] CONSTA[®], drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL[®] CONSTA[®] despite the presence of the syndrome.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of oral risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with oral risperidone compared to patients treated with placebo. RISPERDAL[®] CONSTA[®] is not approved for the treatment of patients with dementia-related psychosis. (See also **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.**)

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL[®]. 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 hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-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 hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

General

Orthostatic Hypotension

RISPERDAL[®] CONSTA[®] (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.8% (12/1499 patients) of patients treated with RISPERDAL[®] CONSTA[®] in multiple-dose studies. Patients should be instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position).

RISPERDAL[®] CONSTA[®] should be used with particular caution in (1) patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia, and (2) in the elderly and patients with renal or hepatic impairment. Monitoring of orthostatic vital signs should be considered in all such patients, and a dose reduction

should be considered if hypotension occurs. Clinically significant hypotension has been observed with concomitant use of oral RISPERDAL[®] and antihypertensive medication.

Seizures

During premarketing testing, seizures occurred in 0.3% (5/1499 patients) of patients treated with RISPERDAL[®] CONSTA[®]. Therefore, RISPERDAL[®] CONSTA[®] should be used cautiously in patients with a history of seizures.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL[®] CONSTA[®] and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. (See also **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.**)

Osteodystrophy and Tumors in Animals

RISPERDAL[®] CONSTA[®] produced osteodystrophy in male and female rats in a 1-year toxicity study and a 2-year carcinogenicity study at a dose of 40 mg/kg administered IM every 2 weeks.

RISPERDAL[®] CONSTA[®] produced renal tubular tumors (adenoma, adenocarcinoma) and adrenomedullary pheochromocytomas in male rats in the 2-year carcinogenicity study at 40 mg/kg administered IM every 2 weeks. In addition, RISPERDAL[®] CONSTA[®] produced an increase in a marker of cellular proliferation in renal tissue in males in the 1-year toxicity study and in renal tumor-bearing males in the 2-year carcinogenicity study at 40 mg/kg administered IM every 2 weeks. (Cellular proliferation was not measured at the low dose or in females in either study.)

The effect dose for osteodystrophy and the tumor findings is 8 times the IM maximum recommended human dose (MRHD) (50 mg) on a mg/m² basis and is associated with a plasma exposure (AUC) 2 times the expected plasma exposure (AUC) at the IM MRHD. The no-effect dose for these findings was 5 mg/kg (equal to the IM MRHD on a mg/m² basis). Plasma exposure (AUC) at the no-effect dose was one third the expected plasma exposure (AUC) at the IM MRHD.

Neither the renal or adrenal tumors, nor osteodystrophy, were seen in studies of orally administered risperidone. Osteodystrophy was not observed in dogs at doses up to 14 times (based on AUC) the IM MRHD in a 1-year toxicity study.

The renal tubular and adrenomedullary tumors in male rats and other tumor findings are described in more detail under PRECAUTIONS, Carcinogenicity, Mutagenesis, Impairment of Fertility.

The relevance of these findings to human risk is unknown.

Hyperprolactinemia

As with other drugs that antagonize dopamine D₂ receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients.

As has been observed with other compounds that increase prolactin release, an increase in the incidence of pituitary gland, mammary gland, and endocrine pancreatic islet cell hyperplasias and/or neoplasias, was observed in rodent carcinogenicity studies with RISPERDAL[®] Tablets and RISPERDAL[®] CONSTA[®] (see PRECAUTIONS – Carcinogenesis. Mutagenesis. Impairment of Fertility). Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment

Somnolence was reported by 5% of patients treated with RISPERDAL[®] CONSTA[®] in multiple-dose trials. Since risperidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that treatment with RISPERDAL[®] CONSTA[®] does not affect them adversely.

Priapism

No cases of priapism have been reported in patients treated with RISPERDAL[®] CONSTA[®]. However, rare cases of priapism have been reported in patients treated with oral RISPERDAL[®]. While the relationship of these events to oral RISPERDAL[®] use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that RISPERDAL[®] may share this capacity. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP)

A single case of TTP was reported in a 28 year-old female patient receiving oral RISPERDAL[®] in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL[®] therapy is unknown.

Antiemetic Effect

Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdose with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation

Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral RISPERDAL[®] use. Caution is advised when prescribing RISPERDAL[®] CONSTA[®] for patients who will be exposed to temperature extremes.

Suicide

The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy. RISPERDAL[®] CONSTA[®] is to be administered by a health care professional (see DOSAGE and ADMINISTRATION); therefore, suicide due to an overdose is unlikely.

Use in Patients with Concomitant Illness

Clinical experience with RISPERDAL[®] CONSTA[®] in patients with certain concomitant systemic illnesses is limited. Patients with Parkinson's Disease or Dementia with Lewy Bodies who receive antipsychotics, including RISPERDAL[®] CONSTA[®], 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.

Caution is advisable when using RISPERDAL[®] CONSTA[®] in patients with diseases or conditions that could affect metabolism or hemodynamic responses. RISPERDAL[®] CONSTA[®] has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing.

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m²) treated with oral RISPERDAL[®]; an increase in the free fraction of risperidone is also seen in

patients with severe hepatic impairment. Patients with renal or hepatic impairment should be carefully titrated on oral RISPERDAL[®] before treatment with RISPERDAL[®] CONSTA[®] is initiated (see DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL[®] CONSTA[®].

Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension and instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position).

Interference With Cognitive and Motor Performance

Because RISPERDAL[®] CONSTA[®] has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that treatment with RISPERDAL[®] CONSTA[®] does not affect them adversely.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy and for at least 12 weeks after the last injection of RISPERDAL[®] CONSTA[®].

Nursing

Patients should be advised not to breast-feed an infant during treatment and for at least 12 weeks after the last injection of RISPERDAL[®] CONSTA[®].

Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol

Patients should be advised to avoid alcohol during treatment with RISPERDAL[®] CONSTA[®].

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The interactions of RISPERDAL[®] CONSTA[®] and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL[®] CONSTA[®] is administered in combination with other centrally-acting drugs or alcohol.

Because of its potential for inducing hypotension, RISPERDAL[®] CONSTA[®] may enhance the hypotensive effects of other therapeutic agents with this potential.

RISPERDAL[®] CONSTA[®] may antagonize the effects of levodopa and dopamine agonists.

Amytriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increased the bioavailability of risperidone, but only marginally increased the plasma concentration of the active antipsychotic fraction.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Carbamazepine and Other Enzyme Inducers

In a drug interaction study in schizophrenic patients, 11 subjects received oral risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment. At the initiation of therapy with carbamazepine or other known hepatic enzyme inducers, patients should be closely monitored during the first 4-8 weeks, since the dose of RISPERDAL[®] CONSTA[®] may need to be adjusted. A dose increase, or additional oral RISPERDAL[®], may need to be considered. On discontinuation of carbamazepine or other hepatic enzyme inducers, the dosage of RISPERDAL[®] CONSTA[®] should be re-evaluated and, if necessary, decreased. Patients may be placed on a lower dose of RISPERDAL[®] CONSTA[®] between 2 to 4 weeks before the planned discontinuation of carbamazepine therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone. For patients treated with the lowest available dose (25 mg) of RISPERDAL[®] CONSTA[®], it is

recommended to continue treatment with the 25-mg dose unless clinical judgment necessitates interruption of treatment with RISPERDAL[®] CONSTA[®].

Fluoxetine and Paroxetine

Fluoxetine (20 mg QD) and paroxetine (20 mg QD), which inhibits CYP 2D6, have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone an average of 13%. When either concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosage of RISPERDAL[®] CONSTA[®]. When initiation of fluoxetine or paroxetine is considered, patients may be placed on a lower dose of RISPERDAL[®] CONSTA[®] between 2 to 4 weeks before the planned start of fluoxetine or paroxetine therapy to adjust for the expected increase in plasma concentrations of risperidone. For patients treated with the lowest available dose (25 mg), it is recommended to continue treatment with the 25-mg dose unless clinical judgment necessitates interruption of treatment with RISPERDAL[®] CONSTA[®]. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied.

Lithium

Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13).

Valproate

Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone.

Digoxin

RISPERDAL[®] (0.25 mg BID) did not show a clinically relevant effect on the pharmacokinetics of digoxin.

Drugs that Inhibit CYP 2D6 and Other CYP Isozymes

Risperidone is metabolized to 9-hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (see CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers

(n=70 patients) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C9, 2C19, and 3A4, are only weak inhibitors of risperidone metabolism.

There were no significant interactions between risperidone and erythromycin (see CLINICAL PHARMACOLOGY).

Drugs Metabolized by CYP 2D6

In vitro studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, RISPERDAL[®] CONSTA[®] is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, oral risperidone did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis - Oral

Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the oral maximum recommended human dose (MRHD) (16 mg/day) on a mg/kg basis, or 0.2, 0.75, and 3 times the oral MRHD (mice) or 0.4, 1.5, and 6 times the oral MRHD (rats) on a mg/m² basis. A maximum tolerated dose was not achieved in male mice. There was a significant increase in pituitary gland adenomas in female mice at doses 0.75 and 3 times the oral MRHD on a mg/m² basis. There was a significant increase in endocrine pancreatic adenomas in male rats at doses 1.5 and 6 times the oral MRHD on a mg/m² basis. Mammary gland adenocarcinomas were significantly increased in female mice at all doses tested (0.2, 0.75, and 3 times the oral MRHD on a mg/m² basis), in female rats at all doses tested (0.4, 1.5, and 6 times the oral MRHD on a mg/m² basis), and in male rats at a dose 6 times the oral MRHD on a mg/m² basis.

Carcinogenesis - IM

RISPERDAL[®] CONSTA[®] was evaluated in a 24-month carcinogenicity study in which SPF Wistar rats were treated every 2 weeks with IM injections of either 5 mg/kg or 40 mg/kg of risperidone. These doses are 1 and 8 times the MRHD (50 mg) on a mg/m² basis. A control group received injections of 0.9% NaCl, and a vehicle control group was injected with placebo microspheres. There was a significant increase in pituitary gland adenomas, endocrine pancreas adenomas, and

adrenomedullary pheochromocytomas at 8 times the IM MRHD on a mg/m² basis. The incidence of mammary gland adenocarcinomas was significantly increased in female rats at both doses (1 and 8 times the IM MRHD on a mg/m² basis). A significant increase in renal tubular tumors (adenoma, adenocarcinomas) was observed in male rats at 8 times the IM MRHD on a mg/m² basis. Plasma exposures (AUC) in rats were 0.3 and 2 times (at 5 and 40 mg/kg, respectively) the expected plasma exposure (AUC) at the IM MRHD.

Dopamine D₂ receptor antagonists have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the carcinogenicity studies of oral risperidone; however, measurements taken during subchronic toxicity studies showed that oral risperidone elevated serum prolactin levels 5- to 6-fold in mice and rats at the same doses used in the oral carcinogenicity studies. Serum prolactin levels increased in a dose-dependent manner up to 6- and 1.5-fold in male and female rats, respectively, at the end of the 24-month treatment with RISPERDAL[®] CONSTA[®] every 2 weeks. Increases in the incidence of pituitary gland, endocrine pancreas, and mammary gland neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and may be prolactin-mediated.

The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see PRECAUTIONS - Hyperprolactinemia).

Mutagenesis

No evidence of mutagenic potential for oral risperidone was found in the *in vitro* Ames reverse mutation test, *in vitro* mouse lymphoma assay, *in vitro* rat hepatocyte DNA-repair assay, *in vivo* oral micronucleus test in mice, the sex-linked recessive lethal test in *Drosophila*, or the *in vitro* chromosomal aberration test in human lymphocytes or in Chinese hamster cells.

In addition, no evidence of mutagenic potential was found in the *in vitro* Ames reverse mutation test for RISPERDAL[®] CONSTA[®].

Impairment of Fertility

Oral risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two mating and fertility studies and a multigenerational study) at doses 0.1 to 3 times the oral maximum recommended human dose (MRHD) (16 mg/day) on a mg/m² basis. The effect appeared to be in females, since impaired mating behavior was not noted in the mating and fertility study in which males only were treated. In a subchronic study in Beagle dogs in which oral risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the oral MRHD on a mg/m² basis. Dose-related

decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm values partially recovered, but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

No mating and fertility studies were conducted with RISPERDAL[®] CONSTA[®].

Pregnancy

Pregnancy Category C

The teratogenic potential of oral risperidone was studied in three embryofetal development studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the oral maximum recommended human dose [MRHD] on a mg/m² basis) and in one embryofetal development study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the oral MRHD on a mg/m² basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the oral MRHD on a mg/m² basis. In three reproductive studies in rats (two peri/post-natal development studies and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5 mg/kg or 0.1 to 3 times the oral MRHD on a mg/m² basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams.

There was no no-effect dose for increased rat pup mortality. In one peri/post-natal development study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the oral MRHD on a mg/m² basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Days 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the oral MRHD on a mg/m² basis.

No studies were conducted with RISPERDAL[®] CONSTA[®].

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone *in utero*. The causal relationship to oral RISPERDAL[®] therapy is unknown.

RISPERDAL[®] CONSTA[®] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of RISPERDAL[®] CONSTA[®] on labor and delivery in humans is unknown.

Nursing Mothers

In animal studies, risperidone and 9-hydroxyrisperidone are excreted in milk. Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women should not breast-feed during treatment with RISPERDAL[®] CONSTA[®] and for at least 12 weeks after the last injection.

Pediatric Use

RISPERDAL[®] CONSTA[®] has not been studied in children younger than 18 years old.

Geriatric Use

In an open-label study, 57 clinically stable, elderly patients (≥65 years old) with schizophrenia or schizoaffective disorder received RISPERDAL[®] CONSTA[®] every 2 weeks for up to 12 months. In general, no differences in the tolerability of RISPERDAL[®] CONSTA[®] were observed between otherwise healthy elderly and nonelderly patients. Therefore, dosing recommendations for otherwise healthy elderly patients are the same as for nonelderly patients. Because elderly patients exhibit a greater tendency to orthostatic hypotension than nonelderly patients, elderly patients should be instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position). In addition, monitoring of orthostatic vital signs should be considered in elderly patients for whom orthostatic hypotension is of concern (see CLINICAL PHARMACOLOGY, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Concomitant use with Furosemide in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus oral risperidone (7.3%; mean age 89 years, range 75-97) when compared to patients treated with oral risperidone alone (3.1%; mean age 84 years, range 70-96) or furosemide alone (4.1%; mean age 80 years, range 67-90). The increase in mortality in patients treated with furosemide plus oral risperidone was observed in two of the four clinical trials.

No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant medication with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia-related psychosis. RISPERDAL[®] CONSTA[®] is not approved for the treatment of patients with dementia-related psychosis. (See also **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.**)

ADVERSE REACTIONS

Adverse findings were assessed by spontaneous reports of adverse events, laboratory tests, vital signs, body weight, and ECGs. Adverse events were classified using the World Health Organization preferred terms. Treatment-emergent adverse events were defined as those events with an onset between the first dose and 49 days after the last dose.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Associated with Discontinuation of Treatment

In the 12-week, placebo-controlled trial, the incidence of schizophrenic patients who discontinued treatment due to an adverse event was lower with RISPERDAL[®] CONSTA[®] (11%; 22/202 patients) than with placebo (13%; 13/98 patients).

Incidence in Controlled Trials

The incidence of adverse reactions in the placebo-controlled trial was based on 202 schizophrenic patients treated with 25 or 50 mg RISPERDAL[®] CONSTA[®] and 98 schizophrenic patients treated with placebo for up to 12 weeks.

Commonly Observed Adverse Events in Controlled Clinical Trials

Spontaneously reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL[®] CONSTA[®] groups (25 mg or 50 mg)

and at least twice that of placebo were: somnolence, akathisia, parkinsonism, dyspepsia, constipation, dry mouth, fatigue, weight increase.

Adverse Events Occurring at an Incidence of 2% or More in Patients Treated with RISPERDAL® CONSTA®:

Table 1 enumerates adverse events that occurred at an incidence of 2% or more, and were at least as frequent among patients treated with 25 mg or 50 mg RISPERDAL® CONSTA™ as patients treated with placebo in the 12-week, placebo-controlled trial. This table shows the percentage of patients in each dose group who spontaneously reported at least one episode of an event at some time during double-blind treatment. All patients were titrated to a dose of 4 mg oral RISPERDAL® during a 1-week run-in period. Patients who received RISPERDAL® CONSTA® were given doses of oral RISPERDAL® (2 mg for patients in the 25-mg group, and 4 mg for patients in the 50-mg group) during the 3 weeks after the first injection to provide therapeutic levels until the main release phase of risperidone from the injection site had begun. Patients who received placebo injections were given placebo tablets.

Table 1. Incidence (% of Patients) of Treatment-Emergent Adverse Events in a 12-Week, Placebo-Controlled Clinical Trial

WHO Body System Disorder/ Preferred Term	RISPERDAL® CONSTA®		Placebo (N=98)
	25 mg (N=99)	50 mg (N=103)	
Psychiatric			
Insomnia	16	13	14
Hallucination	7	6	5
Somnolence	5	6	3
Suicide attempt	1	4	3
Abnormal thinking	0	3	2
Abnormal dreaming	2	0	0
Central & peripheral nervous system			
Headache	15	22	12
Dizziness	8	11	6
Akathisia	2	9	4
Parkinsonism ^a	4	10	3
Tremor	0	3	0
Hypoaesthesia	2	0	0
Gastrointestinal			
Dyspepsia	7	7	2
Constipation	5	7	1
Mouth dry	0	7	1
Toothache	1	3	0
Saliva increased	6	2	1
Tooth disorder	4	2	0
Diarrhea	5	1	3
Body as a whole - general			
Fatigue	3	7	0
Pain	10	3	4
Peripheral edema	2	3	1
Leg pain	4	1	1
Fever	2	1	0
Syncope	2	0	0
Respiratory system			
Rhinitis	14	4	8
Coughing	5	2	4
Sinusitis	3	1	0
Upper respiratory tract infection	2	0	1
Metabolic & nutritional			
Weight increase	5	4	2
Weight decrease	4	1	1
Cardiovascular			
Hypertension	3	3	2
Hearing & vestibular			
Ear disorder (NOS)	0	3	0
Vision			
Vision abnormal	2	3	0
Skin & appendages			
Acne	2	2	0
Skin dry	2	0	0
Musculo-Skeletal			
Myalgia	4	2	1

^a Includes adverse events of bradykinesia, extrapyramidal disorder, and hypokinesia.

Dose Dependency of Adverse Events

Extrapyramidal Symptoms:

Two methods were used to measure extrapyramidal symptoms (EPS) in the 12-week, placebo-controlled trial comparing three doses of RISPERDAL[®] CONSTA[®] (25 mg, 50 mg, and 75 mg) with placebo, including: (1) the incidence of spontaneous reports of EPS symptoms; and (2) the change from baseline to endpoint on the total score (sum of the subscale scores for parkinsonism, dystonia, and dyskinesia) of the Extrapyramidal Symptom Rating Scale (ESRS).

As shown in Table 1, the overall incidence of EPS-related adverse events (akathisia, dystonia, parkinsonism, and tremor) in patients treated with 25 mg RISPERDAL[®] CONSTA[®] was comparable to that of patients treated with placebo; the incidence of EPS-related adverse events was higher in patients treated with 50 mg RISPERDAL[®] CONSTA[®].

The median change from baseline to endpoint in total ESRS score showed no worsening in patients treated with RISPERDAL[®] CONSTA[®] compared with patients treated with placebo: 0 (placebo group); -1 (25-mg group, significantly less than the placebo group); and 0 (50-mg group).

Vital Sign Changes:

RISPERDAL[®] is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS). In the placebo-controlled trial, orthostatic hypotension was observed in 2% of patients treated with 25 mg or 50 mg RISPERDAL[®] CONSTA[®] (see PRECAUTIONS).

Weight Changes:

In the 12-week, placebo-controlled trial, 9% of patients treated with RISPERDAL[®] CONSTA[®], compared with 6% of patients treated with placebo, experienced a weight gain of >7% of body weight at endpoint.

Laboratory Changes:

The percentage of patients treated with RISPERDAL[®] CONSTA[®] who experienced potentially important changes in routine serum chemistry, hematology, or urinalysis parameters was similar to or less than that of placebo patients. Additionally, no patients discontinued treatment due to changes in serum chemistry, hematology, or urinalysis parameters.

ECG Changes:

The electrocardiograms of 202 schizophrenic patients treated with 25 mg or 50 mg RISPERDAL[®] CONSTA[®] and 98 schizophrenic patients treated with placebo in a

12-week, double-blind, placebo-controlled trial were evaluated. Compared with placebo, there were no statistically significant differences in QTc intervals (using Fridericia's and linear correction factors) during treatment with RISPERDAL[®] CONSTA[®].

Between-group comparisons for pooled placebo-controlled trials with oral RISPERDAL[®] revealed no statistically significant differences between risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. When all oral RISPERDAL[®] doses were pooled from randomized controlled trials in several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenia trials, higher doses of oral risperidone (8-16 mg/day) were associated with a higher mean increase in heart rate compared to placebo (4-6 beats per minute).

Pain Assessment and Local Injection Site Reactions:

The mean intensity of injection pain reported by patients using a visual analog scale (0 = no pain to 100 = unbearably painful) decreased in all treatment groups from the first to the last injection (placebo: 16.7 to 12.6; 25 mg: 12.0 to 9.0; 50 mg: 18.2 to 11.8). After the sixth injection (Week 10), investigator ratings indicated that 1% of patients treated with 25 mg or 50 mg RISPERDAL[®] CONSTA[®] experienced redness, swelling, or induration at the injection site.

Other Events Observed During the Premarketing Evaluation of RISPERDAL[®] CONSTA[™]

During its premarketing assessment, RISPERDAL[®] CONSTA[®] was administered to 1499 patients in multiple-dose studies. The conditions and duration of exposure to RISPERDAL[®] CONSTA[®] varied greatly, and included (in overlapping categories) open-label and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term and long-term exposure studies. In all studies, untoward events associated with this exposure were obtained by spontaneous report and were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 1499 patients exposed to multiple doses of RISPERDAL[®] CONSTA[®] who experienced an event of the type cited on at least one occasion while receiving RISPERDAL[®] CONSTA[®]. All reported events are included

except those already listed in Table 1, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening. It is important to emphasize that, although the reported events occurred during treatment with RISPEDAL[®] CONSTA[®], they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from the placebo-controlled trial appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; and rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders

Frequent: anxiety, psychosis, depression, agitation, nervousness, paranoid reaction, delusion, apathy. *Infrequent:* anorexia, impaired concentration, impotence, emotional lability, manic reaction, decreased libido, increased appetite, amnesia, confusion, euphoria, depersonalization, paroniria, delirium, psychotic depression.

Central and Peripheral Nervous System Disorders

Frequent: hypertonia, dystonia. *Infrequent:* dyskinesia, vertigo, leg cramps, tardive dyskinesia^a, involuntary muscle contractions, paraesthesia, abnormal gait, bradykinesia, convulsions, hypokinesia, ataxia, fecal incontinence, oculogyric crisis, tetany, apraxia, dementia, migraine. *Rare:* neuroleptic malignant syndrome.

^a In the integrated database of multiple-dose studies (1499 patients with schizophrenia or schizoaffective disorder), 9 patients (0.6%) treated with RISPEDAL[®] CONSTA[®] (all dosages combined) experienced an adverse event of tardive dyskinesia.

Body as a Whole/General Disorders

Frequent: back pain, chest pain, asthenia. *Infrequent:* malaise, choking.

Gastrointestinal Disorders

Frequent: nausea, vomiting, abdominal pain. *Infrequent:* gastritis, gastroesophageal reflux, flatulence, hemorrhoids, melena, dysphagia, rectal hemorrhage, stomatitis, colitis, gastric ulcer, gingivitis, irritable bowel syndrome, ulcerative stomatitis.

Respiratory System Disorders

Frequent: dyspnea. *Infrequent:* pneumonia, stridor, hemoptysis. *Rare:* pulmonary edema.

Skin and Appendage Disorders

Frequent: rash. *Infrequent:* eczema, pruritus, erythematous rash, dermatitis, alopecia, seborrhea, photosensitivity reaction, increased sweating.

Metabolic and Nutritional Disorders

Infrequent: hyperuricemia, hyperglycemia, hyperlipemia, hypokalemia, glycosuria, hypercholesterolemia, obesity, dehydration, diabetes mellitus, hyponatremia.

Musculo-Skeletal System Disorders

Frequent: arthralgia, skeletal pain. *Infrequent:* torticollis, arthrosis, muscle weakness, tendinitis, arthritis, arthropathy.

Heart Rate and Rhythm Disorders

Frequent: tachycardia. *Infrequent:* bradycardia, AV block, palpitation, bundle branch block. *Rare:* T-wave inversion.

Cardiovascular Disorders

Frequent: hypotension. *Infrequent:* postural hypotension.

Urinary System Disorders

Frequent: urinary incontinence. *Infrequent:* hematuria, micturition frequency, renal pain, urinary retention.

Vision Disorders

Infrequent: conjunctivitis, eye pain, abnormal accommodation.

Reproductive Disorders, Female

Frequent: amenorrhea. *Infrequent:* nonpuerperal lactation, vaginitis, dysmenorrhea, breast pain, leukorrhea.

Resistance Mechanism Disorders

Infrequent: abscess.

Liver and Biliary System Disorders

Frequent: increased hepatic enzymes. *Infrequent:* hepatomegaly, increased SGPT. *Rare:* bilirubinemia, increased GGT, hepatitis, hepatocellular damage, jaundice, fatty liver, increased SGOT.

Reproductive Disorders, Male

Infrequent: ejaculation failure.

Application Site Disorders

Frequent: injection site pain. *Infrequent:* injection site reaction.

Hearing and Vestibular Disorders

Infrequent: earache, deafness, hearing decreased.

Red Blood Cell Disorders

Frequent: anemia.

White Cell and Resistance Disorders

Infrequent: lymphadenopathy, leucopenia, cervical lymphadenopathy.

Rare: granulocytopenia, leukocytosis, lymphopenia.

Endocrine Disorders

Infrequent: hyperprolactinemia, gynecomastia, hypothyroidism.

Platelet, Bleeding and Clotting Disorders

Infrequent: purpura, epistaxis. *Rare:* pulmonary embolism, hematoma, thrombocytopenia.

Myo-, Endo-, and Pericardial and Valve Disorders

Infrequent: myocardial ischemia, angina pectoris, myocardial infarction.

Vascular (Extracardiac) Disorders

Infrequent: phlebitis. *Rare:* intermittent claudication, flushing, thrombophlebitis.

Postintroduction Reports

Adverse events reported since market introduction which were temporally (but not necessarily causally) related to oral RISPERDAL[®] therapy include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, including cerebrovascular accident, hyperglycemia, diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving oral RISPERDAL[®]. A causal relationship with oral RISPERDAL[®] has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

RISPERDAL[®] CONSTA[™] (risperidone) is not a controlled substance.

Physical and Psychological Dependence

RISPERDAL[®] CONSTA[®] has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. Because RISPERDAL[®]

CONSTA[®] is to be administered by health care professionals, the potential for misuse or abuse by patients is low.

OVERDOSAGE

Human Experience

No cases of overdose were reported in premarketing studies with RISPERDAL[®] CONSTA[®] (risperidone). Because RISPERDAL[®] CONSTA[®] is to be administered by health care professionals, the potential for overdosage by patients is low.

In premarketing experience with oral RISPERDAL[®] (risperidone), there were eight reports of acute RISPERDAL[®] overdosage, with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure.

Postmarketing experience with oral RISPERDAL[®] includes reports of acute overdose, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia, hypotension, and extrapyramidal symptoms. Other adverse events reported since market introduction which were temporally (but not necessarily causally) related to oral RISPERDAL[®] overdose include torsades de pointes, prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

Management of Overdosage

In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of QT prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to oral RISPERDAL[®]. Therefore, appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate

measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

For patients who have never taken oral RISPARDAL[®], it is recommended to establish tolerability with oral RISPARDAL[®] prior to initiating treatment with RISPARDAL[®] CONSTA[®] (risperidone).

RISPARDAL[®] CONSTA[®] should be administered every 2 weeks by deep intramuscular (IM) gluteal injection. Each injection should be administered by a health care professional using the enclosed safety needle (see HOW SUPPLIED). Injections should alternate between the two buttocks. Do not administer intravenously.

The recommended dose is 25 mg IM every 2 weeks. Although dose response for effectiveness has not been established for RISPARDAL[®] CONSTA[®], some patients not responding to 25 mg may benefit from a higher dose of 37.5 mg or 50 mg. The maximum dose should not exceed 50 mg RISPARDAL[®] CONSTA[®] every 2 weeks. No additional benefit was observed with dosages greater than 50 mg RISPARDAL[®] CONSTA[®]; however, a higher incidence of adverse effects was observed.

Oral RISPARDAL[®] (or another antipsychotic medication) should be given with the first injection of RISPARDAL[®] CONSTA[®] and continued for 3 weeks (and then discontinued) to ensure that adequate therapeutic plasma concentrations are maintained prior to the main release phase of risperidone from the injection site (see CLINICAL PHARMACOLOGY).

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

Do not combine two different dosage strengths of RISPARDAL[®] CONSTA[®] in a single administration.

Pediatric Use

RISPARDAL[®] CONSTA[®] has not been studied in children younger than 18 years old.

Dosage in Special Populations

For elderly patients treated with RISPERDAL[®] CONSTA[®], the recommended dosage is 25 mg IM every 2 weeks. Oral RISPERDAL[®] (or another antipsychotic medication) should be given with the first injection of RISPERDAL[®] CONSTA[®] and should be continued for 3 weeks to ensure that adequate therapeutic plasma concentrations are maintained prior to the main release phase of risperidone from the injection site (see CLINICAL PHARMACOLOGY).

Patients with renal or hepatic impairment should be treated with titrated doses of oral RISPERDAL[®] prior to initiating treatment with RISPERDAL[®] CONSTA[®]. The recommended starting dose is 0.5 mg oral RISPERDAL[®] b.i.d. during the first week, which can be increased to 1 mg b.i.d. or 2 mg once daily during the second week. If a dose of at least 2 mg oral RISPERDAL[®] is well tolerated, an injection of 25 mg RISPERDAL[®] CONSTA[®] can be administered every 2 weeks. Oral supplementation should be continued for 3 weeks after the first injection until the main release of risperidone from the injection site has begun. In some patients, slower titration may be medically appropriate.

Patients with renal impairment may have less ability to eliminate risperidone than normal adults. Patients with impaired hepatic function may have an increase in the free fraction of the risperidone, possibly resulting in an enhanced effect (see CLINICAL PHARMACOLOGY). Elderly patients and patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk should be instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position). These patients should avoid sodium depletion or dehydration, and circumstances that accentuate hypotension (alcohol intake, high ambient temperature, etc.). Monitoring of orthostatic vital signs should be considered (see PRECAUTIONS).

Maintenance Therapy

Although no controlled studies have been conducted to answer the question of how long patients should be treated with RISPERDAL[®] CONSTA[®], oral risperidone has been shown to be effective in delaying time to relapse in longer-term use. It is recommended that responding patients be continued on treatment with RISPERDAL[®] CONSTA[®] at the lowest dose needed. Patients should be periodically reassessed to determine the need for continued treatment.

Reinitiation of Treatment in Patients Previously Discontinued

There are no data to specifically address reinitiation of treatment. When restarting patients who have had an interval off treatment with RISPERDAL[®] CONSTA[®], supplementation with oral RISPERDAL[®] (or another antipsychotic medication) should be administered.

Switching from Other Antipsychotics

There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to RISPERDAL[®] CONSTA[®], or concerning concomitant administration with other antipsychotics. Previous antipsychotics should be continued for 3 weeks after the first injection of RISPERDAL[®] CONSTA[®] to ensure that therapeutic concentrations are maintained until the main release phase of risperidone from the injection site has begun (see CLINICAL PHARMACOLOGY). For schizophrenic patients who have never taken oral RISPERDAL[®], it is recommended to establish tolerability with oral RISPERDAL[®] prior to initiating treatment with RISPERDAL[®] CONSTA[®]. As recommended with other antipsychotic medications, the need for continuing existing EPS medication should be re-evaluated periodically.

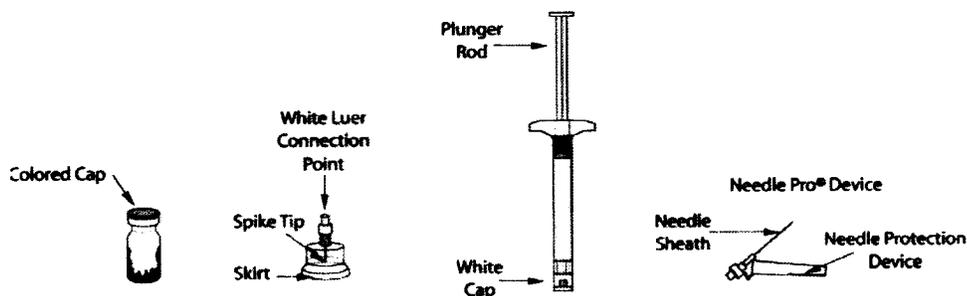
Co-Administration of RISPERDAL[®] CONSTA[®] with Certain Other Medications

Co-administration of carbamazepine and other enzyme inducers (e.g., phenytoin, rifampin, phenobarbital) with risperidone would be expected to cause decreases in the plasma concentrations of active moiety (the sum of risperidone and 9-hydroxyrisperidone), which could lead to decreased efficacy of risperidone treatment. The dose of risperidone needs to be titrated accordingly for patients receiving these enzyme inducers, especially during initiation or discontinuation of therapy with these inducers (see CLINICAL PHARMACOLOGY and PRECAUTIONS). At the initiation of therapy with carbamazepine or other known hepatic enzyme inducers, patients should be closely monitored during the first 4-8 weeks, since the dose of RISPERDAL[®] CONSTA[®] may need to be adjusted. A dose increase, or additional oral RISPERDAL[®], may need to be considered. On discontinuation of carbamazepine or other hepatic enzyme inducers, the dosage of RISPERDAL[®] CONSTA[®] should be re-evaluated and, if necessary, decreased. Patients may be placed on a lower dose of RISPERDAL[®] CONSTA[®] between 2 to 4 weeks before the planned discontinuation of carbamazepine therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone. For patients treated with the lowest available dose (25 mg) of RISPERDAL[®] CONSTA[®], it is recommended to continue treatment with the 25-mg dose unless

clinical judgment necessitates interruption of treatment with RISPERDAL[®] CONSTA[®].

Fluoxetine and paroxetine have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone an average of 13%. The dose of risperidone needs to be titrated accordingly when fluoxetine or paroxetine is co-administered. When either concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosage of RISPERDAL[®] CONSTA[®]. When initiation of fluoxetine or paroxetine is considered, patients may be placed on a lower dose of RISPERDAL[®] CONSTA[®] between 2 to 4 weeks before the planned start of fluoxetine or paroxetine therapy to adjust for the expected increase in plasma concentrations of risperidone. For patients treated with the lowest available dose (25 mg), it is recommended to continue treatment with the 25-mg dose unless clinical judgment necessitates interruption of treatment with RISPERDAL[®] CONSTA[®]. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied.

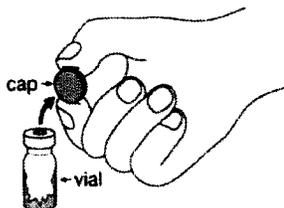
Instructions for Use



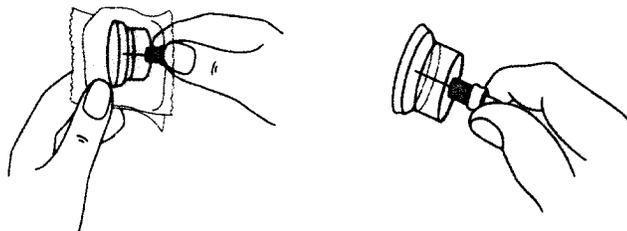
RISPERDAL[®] CONSTA[®] must be suspended **only** in the diluent supplied in the dose pack, and must be administered with the needle supplied in the dose pack. All components are required for administration. Do not substitute any components of the dose pack.

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

1. Flip off the plastic colored cap from the vial.



2. Peel back the blister pouch and remove the SmartSite[®] Needle-Free Vial Access Device by holding the white luer cap. Do **not** touch the spike tip of the access device at any time.



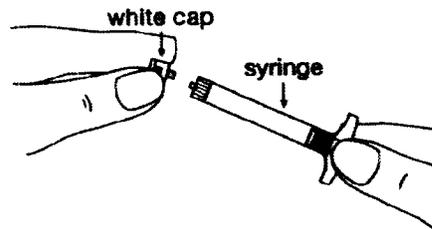
3. Press the spike tip of the SmartSite[®] Access Device through the vial's rubber stopper until the device clicks into place.



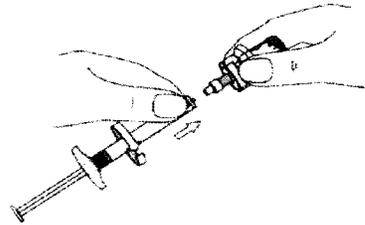
4. Swab the syringe connection point (blue circle) of the SmartSite[®] Access Device with preferred antiseptic prior to attaching the syringe to the SmartSite[®] Access Device.



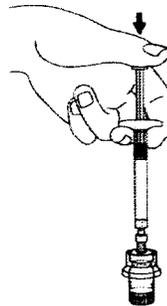
5. Twist off the white cap from the pre-filled syringe and remove together with the rubber tip cap inside.



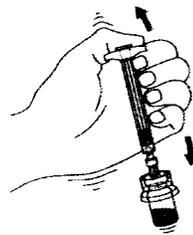
6. **Press** the syringe tip into the blue circle of the SmartSite[®] Access Device and **Twist** in a clockwise motion to ensure that the syringe is securely attached to the white luer cap of the access device. Keep the syringe and SmartSite[®] Access Device aligned, and hold the skirt of the access device during attachment to prevent spinning.



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

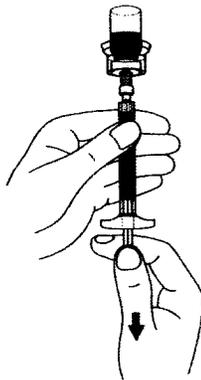


8. Shake the vial vigorously while holding the plunger rod down with the thumb for a minimum of 10 seconds to ensure a homogeneous suspension. When properly mixed, the suspension appears uniform, thick, and milky in color. The particles will be visible in liquid, but no dry particles remain.

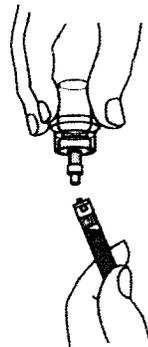


9. Do not store the vial after reconstitution or the suspension may settle. *If 2 minutes pass before injection, reconstitute by shaking vigorously.*

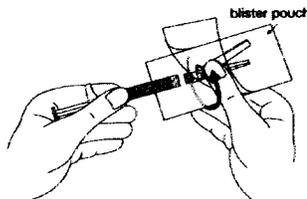
10. Invert the vial completely and slowly withdraw the suspension from the vial. Tear section of the vial label at the perforation and apply detached label to syringe for identification purposes.



11. Unscrew the syringe from the SmartSite[®] access device and discard both the vial and access device appropriately.



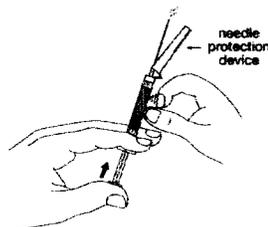
12. Peel the blister pouch of the Needle-Pro[®] device open halfway. Grasp sheath using the plastic peel pouch.



13. Attach the luer connection of the Needle-Pro[®] device to the syringe with an easy clockwise twisting motion. Seat the needle firmly on the Needle-Pro[®] device with a push and clockwise twist.

14. *If 2 minutes pass before injection, reconstitute by shaking vigorously.*

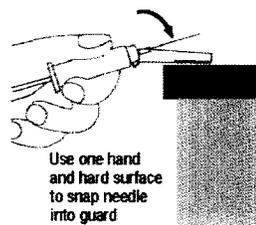
15. Pull sheath away from the needle. Do not twist sheath, as needle may be loosened from Needle-Pro[®] device. Tap the syringe gently to make any air bubbles rise to the top. De-aerate syringe by moving plunger rod carefully forward, with needle in an upward position. Inject entire contents intramuscularly (IM) into the upper-outer quadrant of the gluteal area within 2 minutes to avoid settling. **DO NOT ADMINISTER INTRAVENOUSLY.**



WARNING: To avoid a needle stick injury with a contaminated needle, do not:

- intentionally disengage the Needle-Pro[®] device
- attempt to straighten the needle or engage Needle-Pro[®] device if the needle is bent or damaged
- mishandle the needle protection device that could lead to protrusion of the needle from the needle protector sheath

16. After injection is complete, use only one hand and tabletop or other hard surface to snap needle into the orange safety guard before discarding. Discard needle appropriately.



Upon suspension in the diluent, it is recommended to use RISPERDAL[®] CONSTA[®] immediately. RISPERDAL[®] CONSTA[®] must be used within 6 hours of suspension. Resuspension of RISPERDAL[®] CONSTA[®] will be necessary prior to administration, as settling will occur over time once the product is in suspension. Keeping the vial upright, shake vigorously back and forth for as long as it takes to resuspend the microspheres. Once in suspension, the product should not be exposed to temperatures above 77°F (25°C).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

RISPERDAL[®] CONSTA[®] (risperidone) is available in dosage strengths of 25, 37.5, or 50 mg risperidone. It is provided as a dose pack, consisting of a vial containing the risperidone microspheres, a pre-filled syringe containing 2 mL of diluent for RISPERDAL[®] CONSTA[®], a SmartSite[®] Needle-Free Vial Access Device, and one Needle-Pro[®] safety needle for intramuscular injection (20 G TW needle with needle protection device).

25-mg vial/kit (NDC 50458-306-11): 25 mg of a white to off-white powder provided in a vial with a pink flip-off cap (NDC 50458-306-01).

37.5-mg vial/kit (NDC 50458-307-11): 37.5 mg of a white to off-white powder provided in a vial with a green flip-off cap (NDC 50458-307-01).

50-mg vial/kit (NDC 50458-308-11): 50 mg of a white to off-white powder provided in a vial with a blue flip-off cap (NDC 50458-308-01).

Storage and Handling

The entire dose pack should be stored in the refrigerator (36°-46°F; 2°-8°C) and protected from light.

If refrigeration is unavailable, RISPERDAL[®] CONSTA[®] can be stored at temperatures not exceeding 77°F (25°C) for no more than 7 days prior to administration. Do not expose unrefrigerated product to temperatures above 77°F (25°C).

Keep out of reach of children.

7519503
US Patent 4,804,663
Revised February 2005
©Janssen 2003

Risperidone is manufactured by:
Janssen Pharmaceutical Ltd.
Wallingstown, Little Island, County Cork, Ireland

Microspheres are manufactured by:
Alkermes Controlled Therapeutics II
Wilmington, Ohio

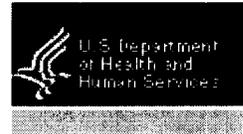
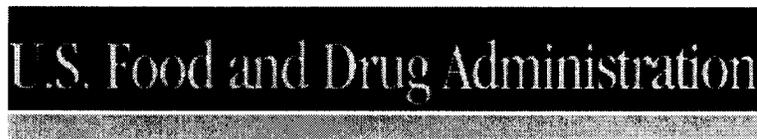
Diluent is manufactured by:
Vetter Pharma Fertigung GmbH & Co. KG
Ravensburg, Germany

RISPERDAL CONSTA[®] is distributed by:
Janssen Pharmaceutica Products, L.P.
Titusville, NJ 08560

RISPERDAL[®] tablets, RISPERDAL[®] M-TAB[®] Orally Disintegrating Tablets, and oral solution are distributed by:

Janssen Pharmaceutica Products, L.P.

Titusville, NJ 08560



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[Attachment 1](#) - Copy of Internet Orange Book Listing for ZPSYN (Piperacillin and Tazobactam)

[Attachment 2](#) - Copy of Wyeth's ZOSYN (Piperacillin and Tazobactam) Physician Insert

[Attachment 3](#) - Copy of Sandoz Proposed Physician Insert for Piperacillin and Tazobactam

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FDA/Dockets Management

Guidance for Industry

Labeling for Human Prescription Drug and Biological Products — Implementing the New Content and Format Requirements

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Janet Norden at 301-796-2270, or (CBER) Toni Stifano at 301-827-6190.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**January 2006
Labeling**





NDA 21-444

DISCIPLINE REVIEW LETTER

Janssen Research Foundation
Attention: Claude McGowan, Ph.D.
Associate Director, Regulatory Affairs
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

Dear Dr. McGowan:

Please refer to your November 16, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Risperdal (risperidone) Orally Disintegrating Tablets.

The Divisions of Drug Marketing, Advertising, and Communications (DDMAC) and Medication Errors and Technical Support (DMETS) have completed their reviews of your proposed proprietary name "Risperdal _____".

DDMAC has determined that the _____ modifier is not in compliance with 21 CFR 201.10(c)(3) which prohibits the employment of a fanciful proprietary name for a drug or ingredient in such a manner as to imply that the drug or ingredient has some unique effectiveness. _____ does not clearly describe that this dosage form is a quickly disintegrating tablet. Rather, _____ may imply efficacy claims of superiority. For example, this name suggests that the drug _____ your problem, or that it works _____ than other agents or Risperdal tablets.

We request that you amend your application with the removal of the proprietary name modifier, or with an alternative proprietary name modifier.

In the review of the draft blister label, draft carton and insert labeling, DMETS identified the following issues (note - all references in the following section to the modifier _____ are informational):

1) BLISTER LABEL

- a) The sponsor's name "JANSSEN" appears as large as the proprietary name. The proprietary name should have more prominence than the sponsor's name. Therefore, we recommend that the sponsor's name "JANSSEN" be decreased in size and prominence. In addition, we recommend that the proprietary name, established name, and strength appear above the sponsor's name.
- b) The established name should read as "risperidone orally disintegrating tablet" rather than "(risperidone) orally disintegrating tablets".