

Administrators Give Views of Chronic Pain Management

BY BETSY BATES
Los Angeles Bureau

PALM SPRINGS, CALIF. — A clear majority of administrators from managed care organizations believe pain management programs could save money for their organizations, but only a third have such programs in place, Dennis C. Turk, Ph.D., reported at the annual meeting of the American Academy of Pain Medicine.

Dr. Turk, professor of anesthesiology at

the University of Washington in Seattle, analyzed the data from a survey completed by 74 administrators from managed care organizations (MCOs) ranging in size from 2,200 to 25 million patients.

The administrators considered back pain, headache, and fibromyalgia the most difficult pain management problems. Almost as many administrators (18 of 74) thought overtreatment of pain was more common as thought undertreatment of pain was more common (21 of 74).

Nearly half said the costs of treating chronic pain exceeded the costs of treating patients with other chronic diseases. They tended to believe the cost of diagnostic tests, rather than the cost of pain medication, was an impediment to pain management. They believed that good evidence supported the efficacy of rehabilitation programs (60%), but not nerve blocks (23%) or surgery (9%).

The administrators strongly advocated urine screening to monitor patients pre-

scribed long-term opioids and the preferred use of sustained-release opioids for long-term prescriptions.

A definitive 84% of the administrators surveyed said pain management programs should emphasize self-management, but only 11% thought their organizations were doing a good job educating patients about the issue, Dr. Turk said.

Organon Pharmaceuticals USA Inc. and Ligand Pharmaceuticals Inc. sponsored the study. ■

Risperdal[®] CONSTA[®]

risperidone Long-Acting Injection

BEFORE PRESCRIBING, PLEASE CONSULT COMPLETE PRESCRIBING INFORMATION OF WHICH THE FOLLOWING IS A BRIEF SUMMARY.

INDICATIONS AND USAGE: RISPERDAL[®] CONSTA[®] (risperidone) is indicated for the treatment of schizophrenia.

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

WARNINGS - 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. 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. 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 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.

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[®]. 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 who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment.

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.

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.

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. 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. 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[®].

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 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.

Suicide The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy.

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 may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity may 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. Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment and 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).

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. Amtryptiline 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.

Valproate Repeated oral doses of risperidone (4 mg BID) did not affect the exposure (AUC) or peak 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 *in vitro* studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C3, 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 *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. 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 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 at doses 0.1 to 3 times the oral maximum recommended human dose. 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 peripost-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 peripost-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 agnathia 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 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 pathophysiologic 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.

ADVERSE REACTIONS

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 Commonly Observed Adverse Events in Controlled Clinical Trials

In the 12 week placebo-controlled trial, 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[®]: 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.

Dose Dependency of Adverse Events

Extrapyramidal Symptoms: 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[®].

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[®].

Pain assessment and local injection site reactions: The mean intensity of injection pain reported by patients using a visual analog scale decreased in all treatment groups from the first to the last injection. 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. The following reactions were reported: (Note: frequent adverse events are those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL[®] CONSTA[®], they were not necessarily caused by it.)

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, paranoia, delirium, psychotic depression.

Central and Peripheral Nervous System Disorders Frequent: hypertonía, dystonia. *Infrequent:* dyskinesia, vertigo, leg cramps, tardive dyskinesia[†], involuntary muscle contractions, paraesthesia, abnormal gait, bradykinesia, convulsions, hypokinesia, ataxia, fecal incontinence, oculogyric crisis, tetany, apraxia, dementia, migraine. *Rare:* neuroleptic malignant syndrome.

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 Frequent: 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** Frequent: conjunctivitis, eye pain, abnormal accommodation. **Reproductive Disorders, Female** Frequent: amenorrhea. *Infrequent:* nonpuerperal lactation, vaginitis, dysmenorrhea, breast pain, leukorrhea. **Resistance Mechanism Disorders** Frequent: 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** Frequent: ejaculation failure. **Application Site Disorders** Frequent: injection site pain.

Infrequent: injection site reaction. **Hearing and Vestibular Disorders** Frequent: earache, deafness, hearing decreased. **Red Blood Cell Disorders** Frequent: anemia. **White Cell and Resistance Disorders** Frequent: lymphadenopathy, leucopenia, cervical lymphadenopathy. *Rare:* granulocytopenia, leukocytosis, lymphopenia. **Endocrine Disorders** Frequent: hyperprolactinemia, gynecomastia, hypothyroidism. **Platelet, Bleeding and Clotting Disorders** Frequent: purpura, epistaxis. *Rare:* pulmonary embolism, hematoma, thrombocytopenia. **Myo-, Endo-, and Pericardial and Valve Disorders** Frequent: myocardial ischemia, angina pectoris, myocardial infarction.

Vascular (Extracardiac) Disorders Frequent: 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.

For more information on symptoms and treatment of overdosage, see full prescribing information.

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

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Titusville, NJ 08560