

Perceptions Differ on Roles of Dementia Patients

BY MARK S. LESNEY
Senior Editor

Persons suffering from dementia rate their distinct self-identity roles in the past and present differently from the way their family or staff caregivers rate those roles, according to Jiska Cohen-Mansfield, Ph.D.

Researchers studied 46 people attending six adult day care centers and 56 residents in two nursing homes in the Washington

metropolitan area. A previously developed self-identity in dementia questionnaire was used to interview the participants, their families, and staff caregivers, reported Dr. Cohen-Mansfield, research director of the Research Institute on Aging of the Hebrew Home of Greater Washington, Rockville, Md., and colleagues (Soc. Sci. Med. [Epub ahead of print] 2005. Article DOI number: doi:10.1016/j.socscimed.2005.06.031).

The four self-identity domains investi-

gated were professional, family/social, hobbies/leisure-time activities, and personal attributes/achievements/traits.

Of these self-identity categories, family roles ratings were the most likely to be maintained over time, with almost half of the participants (48%) identifying their parental role as the most important of these. In contrast, family members rated the spousal relationship as the most important (31%) with parental role a close second (29%).

The study showed a significant time effect, with a decline in the importance of role identity from past to present, and the family role being the most important throughout. The importance of professional identity declined most over time.

The greatest discrepancy between family and participant reports on professional roles involved the category of homemaker. Of the 24 participants categorized by the family as homemakers, only 21% (5) of those participants agreed. The differential



Brief Summary of Prescribing Information

INDICATIONS AND USAGE

ATROVENT HFA (ipratropium bromide HFA) Inhalation Aerosol is indicated as a bronchodilator for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema.

CONTRAINDICATIONS

ATROVENT HFA (ipratropium bromide HFA) Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to ipratropium bromide or other ATROVENT HFA Inhalation Aerosol components. ATROVENT HFA Inhalation Aerosol is also contraindicated in patients who are hypersensitive to atropine or its derivatives.

WARNINGS

ATROVENT HFA (ipratropium bromide HFA) Inhalation Aerosol is a bronchodilator for the maintenance treatment of bronchospasm associated with COPD and is not indicated for the initial treatment of acute episodes of bronchospasm where rescue therapy is required for rapid response.

Immediate hypersensitivity reactions may occur after administration of ipratropium bromide, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis and oropharyngeal edema.

Inhaled medicines, including ATROVENT HFA (ipratropium bromide HFA) Inhalation Aerosol, may cause paradoxical bronchospasm. If this occurs, treatment with ATROVENT HFA (ipratropium bromide HFA) Inhalation Aerosol should be stopped and other treatments considered.

PRECAUTIONS

General

ATROVENT HFA (ipratropium bromide HFA) Inhalation Aerosol should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy or bladder-neck obstruction.

Information for Patients

Appropriate and safe use of ATROVENT HFA Inhalation Aerosol includes providing the patient with the information listed below and an understanding of the way it should be administered (Please see complete Prescribing Information, including Patient's Instructions for Use, at http://www.bidocs.com/retent/Prescribing+Information/Pls/Atrovent+HFA/10003001_US_1.pdf?DMW_FORMAT=pdf or call 1-800-542-6257).

Patients should be advised that ATROVENT HFA (ipratropium bromide HFA) Inhalation Aerosol is a bronchodilator for the maintenance treatment of bronchospasm associated with COPD and is not indicated for the initial treatment of acute episodes of bronchospasm where rescue therapy is required for rapid response.

Patients should be cautioned to avoid spraying the aerosol into their eyes and be advised that this may result in precipitation or worsening of narrow-angle glaucoma, mydriasis, eye pain or discomfort, temporary blurring of vision, visual halos or colored images in association with red eyes from conjunctival and corneal congestion. Patients should also be advised that should any combination of these symptoms develop, they should consult their physician immediately.

The action of ATROVENT HFA Inhalation Aerosol should last 2-4 hours. Patients should be advised not to increase the dose or frequency of ATROVENT HFA Inhalation Aerosol without patients consulting their physician. Patients should also be advised to seek immediate medical attention if treatment with ATROVENT HFA Inhalation Aerosol becomes less effective for symptomatic relief, their symptoms become worse, and/or patients need to use the product more frequently than usual.

Patients should be advised on the use of ATROVENT HFA[®] Inhalation Aerosol in relation to other inhaled drugs. Patients should be reminded that ATROVENT HFA Inhalation Aerosol should be used consistently as prescribed throughout the course of therapy.

Patients should be advised that although the taste and inhalation sensation of ATROVENT HFA Inhalation Aerosol may be slightly different from that of the CFC (chlorofluorocarbon) formulation of ATROVENT Inhalation Aerosol, they are comparable in terms of safety and efficacy.

Drug Interactions

ATROVENT HFA Inhalation Aerosol has been used concomitantly with other drugs, including sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids, that may be used in the treatment of chronic obstructive pulmonary disease. With the exception of albuterol, there are no formal studies fully evaluating the interaction effects of ATROVENT and these drugs with respect to effectiveness.

Anticholinergic agents: Although ipratropium bromide is minimally absorbed into the systemic circulation, there is some potential for an additive interaction with concomitantly used anticholinergic medications. Caution is therefore advised in the co-administration of ATROVENT HFA Inhalation Aerosol with other anticholinergic-containing drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In two-year oral carcinogenicity studies in rats and mice ipratropium bromide at oral doses up to 6 mg/kg (approximately 240 and 120 times the maximum recommended daily inhalation dose in adults on a mg/m² basis) showed no carcinogenic activity. Results of various mutagenicity studies (Ames test, mouse dominant lethal test, mouse micronucleus test and chromosome aberration of bone marrow in Chinese hamsters) were negative.

Fertility of male or female rats at oral doses up to 50 mg/kg (approximately 2000 times the maximum recommended daily inhalation dose in adults on a mg/m² basis) was unaffected by ipratropium bromide administration. At an oral dose of 500 mg/kg (approximately 20,000 times the maximum recommended daily inhalation dose in adults on a mg/m² basis), ipratropium bromide produced a decrease in the conception rate.

Pregnancy

Teratogenic Effects, Pregnancy Category B

Oral reproduction studies were performed at doses of 10 mg/kg/day in mice, 1,000 mg/kg in rats and 125 mg/kg/day in rabbits. These doses correspond, in each species, respectively, to approximately 200, 40,000 and 10,000 times the maximum recommended daily inhalation dose in adults on a mg/m² basis. Inhalation reproduction studies were conducted in rats and rabbits at doses of 1.5 and 1.8 mg/kg (approximately 60 and 140 times the maximum recommended daily inhalation dose in adults on a mg/m² basis). These studies demonstrated no evidence of teratogenic effects as a result of ipratropium bromide. At oral doses of 90 mg/kg and above in rats (approximately 3600 times the maximum recommended daily inhalation dose in adults on a mg/m² basis) embryotoxicity was observed as increased resorption. This effect is not considered relevant to human use due to the large doses at which it was observed and the difference in route of administration. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ATROVENT HFA Inhalation Aerosol should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether the active component, ipratropium bromide, is excreted in human milk. Although lipid-insoluble quaternary cations pass into breast milk, it is unlikely that ipratropium bromide would reach the infant to an important extent, especially when taken by aerosol. However, because many drugs are excreted in human milk, caution should be exercised when ATROVENT HFA Inhalation Aerosol is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

Geriatric Use

In the pivotal 12-week study, both ATROVENT HFA Inhalation Aerosol and ATROVENT Inhalation Aerosol CFC formulations were equally effective in patients over 65 years of age and under 65 years of age.

Of the total number of subjects in clinical studies of ATROVENT HFA Inhalation Aerosol, 57% were ≥65 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

ADVERSE REACTIONS

The adverse reaction information concerning ATROVENT HFA (ipratropium bromide HFA) Inhalation Aerosol is derived from two 12-week, double-blind, parallel group studies and one open-label, parallel group study that compared ATROVENT HFA Inhalation Aerosol, ATROVENT Inhalation Aerosol CFC, and placebo (in one study only) in 1,010 COPD patients. The following table lists the incidence of adverse events that occurred at a rate of greater than or equal to 3% in any ipratropium bromide group. Overall, the incidence and nature of the adverse events reported for ATROVENT HFA Inhalation Aerosol, ATROVENT Inhalation Aerosol CFC, and placebo were comparable.

TABLE 1 Adverse Experiences Reported in ≥ 3% of Patients in any Ipratropium Bromide Group

	Placebo-controlled 12 week Study 244.1405 and Active-controlled 12 week Study 244.1408			Active-controlled 1-year Study 244.2453	
	Atrovent HFA (N=243) %	Atrovent CFC (N=183) %	Placebo (N=128) %	Atrovent HFA (N=305) %	Atrovent CFC (N=151) %
Total With Any Adverse Event	63	68	72	91	87
BODY AS A WHOLE - GENERAL DISORDERS					
back pain	2	3	2	7	3
headache	6	9	8	7	5
influenza-like symptoms	4	2	2	8	5
CENTR & PERIPH NERVOUS SYSTEM DISORDERS					
dizziness	3	3	2	3	1
GASTRO-INTESTINAL SYSTEM DISORDERS					
dyspepsia	1	3	1	5	3
mouth dry	4	2	2	2	3
nausea	4	1	2	4	4
RESPIRATORY SYSTEM DISORDERS					
bronchitis	10	11	6	23	19
COPD exacerbation	8	14	13	23	23
coughing	3	4	6	5	5
dyspnea	8	8	4	7	4
rhinitis	4	2	4	6	2
sinusitis	1	4	3	11	14
upper resp tract infection	9	10	16	34	34
URINARY SYSTEM DISORDERS					
urinary tract infection	2	3	1	10	8

In the one open label controlled study in 456 COPD patients, the overall incidence of adverse events was also similar between ATROVENT HFA Inhalation Aerosol and ATROVENT Inhalation Aerosol CFC formulations. Overall, in the above mentioned studies, 9.3% of the patients taking 42 mcg ATROVENT HFA Inhalation Aerosol and 8.7% of the patients taking 42 mcg ATROVENT Inhalation Aerosol CFC reported at least one adverse event that was considered by the investigator to be related to the study drug. The most common drug-related adverse events were dry mouth (1.6% of ATROVENT HFA Inhalation Aerosol and 0.9% of ATROVENT Inhalation Aerosol CFC patients), and taste perversion (bitter taste) (0.9% of ATROVENT HFA Inhalation Aerosol and 0.3% of ATROVENT Inhalation Aerosol CFC patients).

As an anticholinergic drug, cases of precipitation or worsening of narrow-angle glaucoma, mydriasis, acute eye pain, hypotension, urinary retention, tachycardia, constipation, bronchospasm, including paradoxical bronchospasm have been reported.

Allergic-type reactions such as skin rash, angioedema of tongue, lips and face, urticaria (including giant urticaria), laryngospasm and anaphylactic reaction have been reported (see **CONTRAINDICATIONS**).

Post-Marketing Experience

Post-marketing experience with ATROVENT Inhalation Aerosol CFC in a 5-year placebo-controlled study, found that hospitalizations for supraventricular tachycardia and atrial fibrillation occurred with an incidence rate of 0.5% in patients receiving ATROVENT Inhalation Aerosol CFC.

Allergic-type reactions such as skin rash, angioedema of tongue, lips and face, urticaria (including giant urticaria), laryngospasm and anaphylactic reactions have been reported, with positive challenge in some cases. Many of the patients had a history of allergies to other drugs and/or foods, including soybean.

Additionally, urinary retention, mydriasis, and bronchospasm, including paradoxical bronchospasm, have been reported during the post-marketing period with use of ATROVENT Inhalation Aerosol CFC.

OVERDOSAGE

Acute overdose by inhalation is unlikely since ipratropium bromide is not well absorbed systemically after inhalation or oral administration. Oral median lethal doses of ipratropium bromide were greater than 1000 mg/kg in mice (approximately 20,000 times the maximum recommended daily inhalation dose in adults on a mg/m² basis); 1,700 mg/kg in rats (approximately 68,000 times the maximum recommended daily inhalation dose in adults on a mg/m² basis); and 400 mg/kg in dogs (approximately 53,000 times the maximum recommended daily inhalation dose in adults on a mg/m² basis).

DOSE AND ADMINISTRATION

Patients should be instructed on the proper use of their inhaler (Please see complete Prescribing Information, including Patient's Instructions for Use, at http://www.bidocs.com/retent/Prescribing+Information/Pls/Atrovent+HFA/10003001_US_1.pdf?DMW_FORMAT=pdf or call 1-800-542-6257).

Patients should be advised that although ATROVENT HFA (ipratropium bromide HFA) Inhalation Aerosol may have a slightly different taste and inhalation sensation than that of an inhaler containing ATROVENT Inhalation Aerosol, they are comparable in terms of the safety and efficacy.

ATROVENT HFA Inhalation Aerosol is a solution aerosol that does not require shaking. However, as with any other metered dose inhaler, some coordination is required between actuating the canister and inhaling the medication. Patients should "prime" or actuate ATROVENT HFA Inhalation Aerosol before using for the first time by releasing 2 test sprays into the air away from the face. In cases where the inhaler has not been used for more than 3 days, prime the inhaler again by releasing 2 test sprays into the air away from the face. Patients should avoid spraying ATROVENT HFA Inhalation Aerosol in their eyes.

The usual starting dose of ATROVENT HFA Inhalation Aerosol is two inhalations four times a day. Patients may take additional inhalations as required; however, the total number of inhalations should not exceed 12 in 24 hours. Each actuation of ATROVENT HFA Inhalation Aerosol delivers 17 mcg of ipratropium bromide from the mouthpiece.

HOW SUPPLIED

ATROVENT HFA (ipratropium bromide HFA) Inhalation Aerosol is supplied in a 12.9 g pressurized stainless steel canister as a metered-dose inhaler with a white mouthpiece that has a clear, colorless sleeve and a green protective cap (NDC 0597-0087-17).

The ATROVENT HFA Inhalation Aerosol canister is to be used only with the accompanying ATROVENT HFA Inhalation Aerosol mouthpiece. This mouthpiece should not be used with other aerosol medications. Similarly, the canister should not be used with other mouthpieces. Each actuation of ATROVENT HFA Inhalation Aerosol delivers 21 mcg of ipratropium bromide from the valve and 17 mcg from the mouthpiece. Each 12.9 gram canister provides sufficient medication for 200 actuations. The canister should be discarded after the labeled number of actuations has been used. The amount of medication in each actuation cannot be assured after this point, even though the canister is not completely empty.

Store at 25°C (77°F). Excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. For optimal results, the canister should be at room temperature before use.

Patients should be reminded to read and follow the accompanying "Instructions for Use", which should be dispensed with the product.

Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw the inhaler into a fire or incinerator.

Warning: Keep out of children's reach. Avoid spraying in eyes.

Rx only

Manufactured for:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

By:
3M Pharmaceuticals
St. Paul, MN 55144 USA

Licensed from:
Boehringer Ingelheim International GmbH

© Copyright Boehringer Ingelheim International GmbH
2004. ALL RIGHTS RESERVED

Revised November 17, 2004

IT1902

10003001/US/1

U.S. Patent No. 6,739,333



AT-10149BS

was largely attributable to reports of family members who were children of the participants and described their mothers as homemakers, while the mothers described themselves as having other professions. More than a third (38%) of responses from staff members indicating ignorance of the participant's occupation were for those whose family members described them as homemakers, Dr. Cohen-Mansfield reported.

In addition, although no significant gender differences were seen in role importance as assigned by participants and staff caregivers for each role group over time, family members reported significantly higher importance ranking for professional identi-

ty for males than for females in the past as well as present. "Family members generally estimated the importance of role identities in the past to be higher, and that in the present as lower, than did the participants," Dr. Cohen-Mansfield reported.

"Our results show that while general trends of a decline in importance of role-identity domains are the same between family informants and participants, the absolute ratings were significantly influenced by [which group were] informants." Understanding the changing self-identities of these people with dementia is a crucial first step toward providing tailored care and enhancing their life experience. ■

Hypertension Control May Preserve Cognition in Some

BY MARK S. LESNEY
Senior Editor

Elderly patients with mild to moderate hypertension and lowered cognitive function show greater cognitive decline, compared with equivalent hypertensive individuals with high cognitive function, a posthoc analysis shows.

The first Study on Cognition and Prognosis in the Elderly (SCOPE) analysis showed inconclusive results in demonstrating that antihypertensive treatment, primarily with candesartan, may preserve cognitive function and reduce the incidence of dementia, according to Ingmar Skoog, M.D., of Sahlgrenska University Hospital, Göteborg, Sweden, and colleagues in the international SCOPE study group.

The post hoc analysis was performed to compare cognitive and cardiovascular outcomes between 2,070 patients with slightly lower baseline cognitive function (LCF) as defined by Mini-Mental State Examination (MMSE) scores of 24-28, and 2,867 patients with higher cognitive function (HCF), defined by MMSE scores of 29-30 (Am. J. Hypertens. 2005;18:1052-9).

Additionally, the analysis separately compared cognitive and cardiovascular

outcomes in the candesartan control groups for LCF and HCF patients.

Significant cognitive decline was nearly twice as common in patients with LCF (6.6%), compared with patients with HCF (3.6%).

Cognitive decline did not differ significantly between candesartan and control groups. (For ethical reasons in the SCOPE trial, control patients also were given off-label active hypertensive therapy when deemed necessary, primarily with hydrochlorothiazide, significantly lowering blood pressure in both treatment groups).

Dementia onset during the study was found to be over four times as common in patients with LCF (4.4%) as in patients with HCF (1.0%). Here, too, no difference was seen between the candesartan and control groups, Dr. Skoog and colleagues reported.

Contrary to perceived fears by many physicians that lowering blood pressure in the elderly would cause cognitive decline because of reduction in cerebral blood flow, cognitive function changed very little, even in patients with LCF, the authors reported. In addition, dementia incidence in the study was found to be in the lower range of expectation for this age group. Thus, there appeared to be no negative effect of blood pressure control, according to the report.

Such evidence, coupled with the observation that mild to moderate hypertension and slightly impaired cognitive function in the elderly at baseline were associated with increased risk of significant cognitive decline and dementia, indicate that effective antihypertensive therapy may reduce cognitive decline in these patients, Dr. Skoog and colleagues concluded. ■

SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder)

SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder)

For Oral Inhalation Only

Brief Summary of Prescribing Information INDICATIONS AND USAGE

SPIRIVA HandiHaler is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

CONTRAINDICATIONS

SPIRIVA HandiHaler is contraindicated in patients with a history of hypersensitivity to atropine or its derivatives, including ipratropium, or to any component of this product.

WARNINGS

SPIRIVA HandiHaler is intended as a once-daily maintenance treatment for COPD and is not indicated for the initial treatment of acute episodes of bronchospasm, i.e., rescue therapy.

Immediate hypersensitivity reactions, including angioedema, may occur after administration of SPIRIVA. If such a reaction occurs, therapy with SPIRIVA should be stopped at once and alternative treatments should be considered.

Inhaled medicines, including SPIRIVA, may cause paradoxical bronchospasm. If this occurs, treatment with SPIRIVA should be stopped and other treatments considered.

PRECAUTIONS

General

As an anticholinergic drug, SPIRIVA may potentially worsen symptoms and signs associated with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction and should be used with caution in patients with any of these conditions.

As a predominantly renally excreted drug, patients with moderate to severe renal impairment (creatinine clearance of ≤ 50 mL/min) treated with SPIRIVA should be monitored closely.

Information for Patients

It is important for patients to understand how to correctly administer SPIRIVA capsules using the HandiHaler inhalation device. SPIRIVA capsules should only be administered via the HandiHaler device and the HandiHaler device should not be used for administering other medications.

Capsules should always be stored in sealed blisters and only removed immediately before use. The blister strip should be carefully opened to expose only one capsule at a time. Open the blister foil as far as the STOP line to remove only one capsule at a time. The drug should be used immediately after the packaging over an individual capsule is opened, or else its effectiveness may be reduced. Capsules that are inadvertently exposed to air (i.e., not intended for immediate use) should be discarded.

Eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema may be signs of acute narrow-angle glaucoma. Should any of these signs and symptoms develop, consult a physician immediately. Miotic eye drops alone are not considered to be effective treatment.

Care must be taken not to allow the powder to enter into the eyes as this may cause blurring of vision and pupil dilation.

SPIRIVA HandiHaler is a once-daily maintenance bronchodilator and should not be used for immediate relief of breathing problems, i.e., as a rescue medication.

Drug Interactions

SPIRIVA has been used concomitantly with other drugs commonly used in COPD without increases in adverse drug reactions. These include sympathomimetic bronchodilators, methylxanthines, and oral and inhaled steroids. However, the co-administration of SPIRIVA with other anticholinergic-containing drugs (e.g., ipratropium) has not been studied and is therefore not recommended.

Drug/Laboratory Test Interactions

None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of tumorigenicity was observed in a 104-week inhalation study in rats at tiotropium doses up to 0.059 mg/kg/day, in an 83-week inhalation study in female mice at doses up to 0.145 mg/kg/day, and in a 101-week inhalation study in male mice at doses up to 0.002 mg/kg/day. These doses correspond to 25, 35, and 0.5 times the Recommended Human Daily Dose (RHDD) on a mg/m² basis, respectively. These dose multiples may be overestimated due to difficulties in measuring deposited doses in animal inhalation studies. Tiotropium bromide demonstrated no evidence of mutagenicity or clastogenicity in the following assays: the bacterial gene mutation assay, the V79 Chinese hamster cell mutagenesis assay, the chromosomal aberration assays in human lymphocytes *in vitro* and mouse micronucleus formation *in vivo*, and the unscheduled DNA synthesis in primary rat hepatocytes *in vitro* assay.

In rats, decreases in the number of corpora lutea and the percentage of implants were noted at inhalation tiotropium doses of 0.078 mg/kg/day or greater (approximately 35 times the RHDD on a mg/m² basis). No such effects were observed at 0.009 mg/kg/day (approximately 4 times the RHDD on a mg/m² basis). The fertility index, however, was not affected at inhalation doses up to 1.689 mg/kg/day (approximately 760 times the RHDD on a mg/m² basis). These dose multiples may be overestimated due to difficulties in measuring deposited doses in animal inhalation studies.

Pregnancy

Pregnancy Category C

No evidence of structural alterations was observed in rats and rabbits at inhalation tiotropium doses of up to 1.471 and 0.007 mg/kg/day, respectively. These doses correspond to approximately 660 and 6 times the recommended human daily dose (RHDD) on a mg/m² basis. However, in rats, fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation were observed at inhalation tiotropium doses of ≥ 0.078 mg/kg (approximately 35 times the RHDD on a mg/m² basis). In rabbits, an increase in post-implantation loss was observed at an inhalation dose of 0.4 mg/kg/day (approximately 360 times the RHDD on a mg/m² basis). Such effects were not observed at inhalation doses of 0.009 and up to 0.088 mg/kg/day in rats and rabbits, respectively. These doses correspond to approximately 4 and 80 times the RHDD on a mg/m² basis, respectively. These dose multiples may be overestimated due to difficulties in measuring deposited doses in animal inhalation studies.

There are no adequate and well-controlled studies in pregnant women. SPIRIVA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Labor and Delivery

The safety and effectiveness of SPIRIVA has not been studied during labor and delivery.

Nursing Mothers

Clinical data from nursing women exposed to tiotropium are not available. Based on lactating rodent studies, tiotropium is excreted into breast milk. It is not known whether tiotropium is excreted in human milk, but because many drugs are excreted in human milk and given these findings in rats, caution should be exercised if SPIRIVA is administered to a nursing woman.

Pediatric Use

SPIRIVA HandiHaler is approved for use in the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. This disease does not normally occur in children. The safety and effectiveness of SPIRIVA in pediatric patients have not been established.

Geriatric Use

Of the total number of patients who received SPIRIVA in the 1-year clinical trials, 426 were < 65 years, 375 were 65-74 years and 105 were ≥ 75 years of age. Within each age subgroup, there were no differences between the proportion of patients with adverse events in the SPIRIVA and the comparator groups for most events. Dry mouth increased with age in the SPIRIVA group (differences from placebo were 9.0%, 17.1%, and 16.2% in the aforementioned age subgroups). A higher frequency of constipation and urinary tract infections with increasing age was observed in the SPIRIVA group in the placebo-controlled studies. The differences from placebo for constipation were 0%, 1.8%, and 7.8% for each of the age groups. The differences from placebo for urinary tract infections were -0.6%, 4.6% and 4.5%. No overall differences in effectiveness were observed among these groups. Based on available data, no adjustment of SPIRIVA dosage in geriatric patients is warranted.

ADVERSE REACTIONS

Of the 2,663 patients in the four 1-year and two 6-month controlled clinical trials, 1,308 were treated with SPIRIVA at the recommended dose of 18 mcg once a day. Patients with narrow angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials.

The most commonly reported adverse drug reaction was dry mouth. Dry mouth was usually mild and often resolved during continued treatment. Other reactions reported in individual patients and consistent with possible anticholinergic effects included constipation, increased heart rate, blurred vision, glaucoma, urinary difficulty, and urinary retention.

Four multicenter, 1-year, controlled studies evaluated SPIRIVA in patients with COPD. Table 1 shows all adverse events that occurred with a frequency of $\geq 3\%$ in the SPIRIVA group in the 1-year placebo-controlled trials where the rates in the SPIRIVA group exceeded placebo by $\geq 1\%$. The frequency of corresponding events in the ipratropium-controlled trials is included for comparison.

Table 1: Adverse Experience Incidence (% Patients) in One-Year-COPD Clinical Trials

Body System (Event)	Placebo-Controlled Trials		Ipratropium-Controlled Trials	
	SPIRIVA (n=550)	Placebo (n=371)	SPIRIVA (n=356)	Ipratropium (n=179)
Body as a Whole				
Accidents	13	11	5	8
Chest Pain (non-specific)	7	5	5	2
Edema, Dependent	5	4	3	5
Gastrointestinal System Disorders				
Abdominal Pain	5	3	6	6
Constipation	4	2	1	1
Dry Mouth	16	3	12	6
Dyspepsia	6	5	1	1
Vomiting	4	2	1	2
Musculoskeletal System				
Myalgia	4	3	4	3
Resistance Mechanism Disorders				
Infection	4	3	1	3
Moniliasis	4	2	3	2
Respiratory System (upper)				
Epistaxis	4	2	1	1
Pharyngitis	9	7	7	3
Rhinitis	6	5	3	2
Sinusitis	11	9	3	2
Upper Respiratory Tract Infection	41	37	43	35
Skin and Appendage Disorders				
Rash	4	2	2	2
Urinary System				
Urinary Tract Infection	7	5	4	2

Arthritis, coughing, and influenza-like symptoms occurred at a rate of $\geq 3\%$ in the SPIRIVA treatment group, but were $< 1\%$ in excess of the placebo group.

Other events that occurred in the SPIRIVA group at a frequency of 1-3% in the placebo-controlled trials where the rates exceeded that in the placebo group include: *Body as a Whole*: allergic reaction, leg pain; *Central and Peripheral Nervous System*: dysphonia, paresthesia; *Gastrointestinal System Disorders*: gastrointestinal disorder not otherwise specified (NOS), gastroesophageal reflux, stomatitis (including ulcerative stomatitis); *Metabolic and Nutritional Disorders*: hypercholesterolemia, hyperglycemia; *Musculoskeletal System Disorders*: skeletal pain; *Cardiac Events*: angina pectoris (including aggravated angina pectoris); *Psychiatric Disorder*: depression; *Infections*: herpes zoster; *Respiratory System Disorder (Upper)*: laryngitis; *Vision Disorder*: cataract. In addition, among the adverse events observed in the clinical trials with an incidence of $< 1\%$ were atrial fibrillation, supraventricular tachycardia, angioedema, and urinary retention.

In the 1-year trials, the incidence of dry mouth, constipation, and urinary tract infection increased with age. Two multicenter, 6-month, controlled studies evaluated SPIRIVA in patients with COPD. The adverse events and the incidence rates were similar to those seen in the 1-year controlled trials.

In addition to adverse events identified during clinical trials, the following adverse reactions have been reported in the worldwide post-marketing experience: epistaxis, palpitations, pruritus, and urticaria.

DOSE AND ADMINISTRATION

The recommended dosage of SPIRIVA HandiHaler is the inhalation of the contents of one SPIRIVA capsule, once-daily, with the HandiHaler inhalation device.

No dosage adjustment is required for geriatric, hepatically-impaired, or renally-impaired patients. However, patients with moderate to severe renal impairment given SPIRIVA should be monitored closely. SPIRIVA capsules are for inhalation only and must not be swallowed.

HOW SUPPLIED

The following packages are available:

carton containing 6 SPIRIVA capsules (1 blister card) and 1 HandiHaler inhalation device (NDC 0597-0075-06)
carton containing 30 SPIRIVA capsules (5 blister cards) and 1 HandiHaler inhalation device (NDC 0597-0075-37)

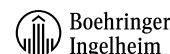
SV-B5 (09/04)

59873/US/2 September 2004

Rx only



SP183085BS



SV-9418BS