

## **Established Safety Profile of Spiriva Confirmed by 30 Rigorously Controlled Clinical Trials and the Landmark Trial, UPLIFT**

### **New Data from Landmark UPLIFT Trial Further Supports Spiriva's Safety Profile**

RIDGEFIELD, Conn. and NEW YORK, Sept. 23 /PRNewswire/ -- Boehringer Ingelheim and Pfizer Inc have released a new analysis of 30 rigorously controlled clinical trials, including UPLIFT<sup>®</sup>, confirming the long term safety profile of Spiriva<sup>®</sup> HandiHaler<sup>®</sup> (tiotropium bromide inhalation powder). The new and expanded safety data contradicts the conclusions about tiotropium in an article by Singh et al. published in the September 24<sup>th</sup> issue of the *Journal of the American Medical Association*.<sup>1</sup> Both companies considered it important to release these data to ensure doctors have the most comprehensive, up-to-date safety information on tiotropium in order to make the best treatment decisions for their patients.

Because COPD (Chronic Obstructive Pulmonary Disease) patients have in general a higher cardiovascular risk than the average population<sup>2</sup>, cardiovascular safety in a COPD medication is of critical importance. Therefore Boehringer Ingelheim has put special emphasis on the broad investigation of Spiriva including its cardiovascular safety.

The latest analysis of 30 placebo-controlled double-blind, randomized trials with data from 19,545 COPD patients (tiotropium 10,846, placebo 8,699) conducted by Boehringer Ingelheim demonstrated that there is no increased risk of death (all-cause) or death due to cardiovascular events in patients treated with Spiriva, specifically:

- No increased risk of total (all-cause) mortality (relative risk ratio for all cause mortality= 0.88, 95% CI=0.77, 0.999)
- No increased risk of mortality due to cardiac (relative risk ratio for mortality due to cardiac events= 0.77, CI = 0.55, 1.03) and vascular events (relative risk ratio for mortality due to vascular events= 0.44, 95% CI = 0.19, 1.02).
- No increased risk in stroke (relative risk ratio for stroke = 1.03, 95% CI = 0.79, 1.35), and
- No increased risk for myocardial infarction (relative risk ratio for myocardial infarction 0.78, 95% CI = 0.59, 1.02) associated with tiotropium.<sup>3</sup>

The UPLIFT results demonstrate that there is no increased risk of total mortality or cardiovascular mortality in COPD patients treated with Spiriva.

“We strongly disagree with the conclusion reached by Singh et al. We have disclosed to regulatory authorities worldwide this important information, which is part of a very robust analysis of all our double-blind, placebo-controlled, parallel group trials with a duration of at least 4 weeks. Our analysis, which includes data from the four-year UPLIFT trial, supports the safety profile of Spiriva,” commented Dr Andreas Barner, Vice Chairman of the Board of Managing Directors at Boehringer Ingelheim, responsible for Research, Development and Medicine. “Patients and physicians can be confident that Spiriva is a safe and effective medication. In clinical trials and since its introduction, we have collected extensive safety data adding up to an exposure of more than 10 million patient years.”

Peer-reviewed meta-analyses of aggregate published data like Singh et al have their appropriate place in scientific research. However, these analyses have well-recognized limitations, such as combining study summaries rather than analyzing individual patient data, or not correcting for patients who dropped out of trials early.

Most of the evidence in the analysis by Dr. Singh and colleagues is contributed by a single study, the Lung Health Study, involving a different anticholinergic medication, ipratropium. In this study, most of the cardiovascular deaths occurred among patients who were not using their medication. Other limitations include the inability to adjust for treatment duration and accounting for patients who discontinue the trial early, apparent double-counting of trials and combining placebo and active comparator drugs in the control group.

The integrated safety data presented today includes data from the UPLIFT trial, a study that includes mortality as a pre-specified endpoint. UPLIFT<sup>®</sup> (**U**nderstanding **P**otential **L**ong-term **I**mpacts on **F**unction with **T**iotropium), one of the largest COPD trials ever undertaken, involved 5,993 COPD patients from 37 countries around the globe over a four-year treatment period. Patient safety during the trial was closely followed by an independent Data Safety Monitoring Board.

The complete results of the UPLIFT trial will be presented on October 5th during the European Respiratory Society 2008 Annual Congress in Berlin.

### **About Spiriva<sup>®</sup> HandiHaler<sup>®</sup>**

Spiriva HandiHaler is a once-daily inhaled maintenance prescription treatment for breathing problems (airway narrowing) associated with chronic obstructive pulmonary disease (COPD). COPD includes both chronic bronchitis and emphysema.

Spiriva does not replace fast-acting inhalers for sudden symptoms.

Do not swallow the Spiriva capsule. Only use the HandiHaler device to take the Spiriva capsule. Do not use the HandiHaler to take any other medications.

Do not get Spiriva powder in your eyes.

The most common side effect with Spiriva is dry mouth. Others include constipation and problems passing urine. For a complete list of reported side effects, ask your doctor or pharmacist.

Tell your doctor about your medicines, including eye drops, and illnesses like glaucoma and urinary or prostate problems. These may worsen with Spiriva.

If you have vision changes, eye pain, your breathing suddenly worsens, you get hives, or your throat or tongue swells, stop taking Spiriva and contact your doctor.

Do not use Spiriva if you are allergic to atropine, ipratropium, tiotropium bromide, or lactose. A lactose allergy is not the same as lactose intolerance.

Read the step-by-step Patient's Instructions for Use for Spiriva before you take your medicine.

For full prescribing information, please visit [www.spiriva.com](http://www.spiriva.com).

**About Boehringer Ingelheim Pharmaceuticals, Inc.**

Boehringer Ingelheim Pharmaceuticals, Inc., based in Ridgefield, CT, is the largest U.S. subsidiary of Boehringer Ingelheim Corporation (Ridgefield, CT) and a member of the Boehringer Ingelheim group of companies.

The Boehringer Ingelheim group is one of the world's 20 leading pharmaceutical companies. Headquartered in Ingelheim, Germany, it operates globally with 135 affiliates in 47 countries and approximately 39,800 employees. Since it was founded in 1885, the family-owned company has been committed to researching, developing, manufacturing and marketing novel products of high therapeutic value for human and veterinary medicine.

In 2007, Boehringer Ingelheim posted net sales of US \$15.0 billion (10.9 billion euro) while spending approximately one-fifth of net sales in its largest business segment, Prescription Medicines, on research and development.

For more information, please visit <http://us.boehringer-ingelheim.com>.

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Founded in 1849, Pfizer is the world's largest research-based pharmaceutical company taking new approaches to better health. We discover, develop, manufacture and deliver quality, safe and effective prescription medicines to treat and help prevent disease for both people and animals. We also partner with healthcare providers, governments and local communities around the world to expand access to our medicines and to provide better quality health care and health system support. At Pfizer, more than 80,000 colleagues in more than 90 countries work every day to help people stay happier and healthier longer and to reduce the human and economic burden of disease worldwide.

**Contact:****Boehringer Ingelheim**

External Communications

Lara Crissey

Tel.: 203-798-4740

Email : [lara.crissey@boehringer-ingelheim.com](mailto:lara.crissey@boehringer-ingelheim.com)**Pfizer Inc**

Corporate Media Relations

Sally Beatty

Tel:212-733-5017

Email: [sally.beatty@pfizer.com](mailto:sally.beatty@pfizer.com)

Investor Relations

Jennifer Davis

Tel: 212-733-0717

Email: [jennifer.davis@pfizer.com](mailto:jennifer.davis@pfizer.com)**References**

<sup>1</sup>.Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease. A systematic review and meta-analysis. *JAMA*. 2008;300:1439-1450.

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<sup>2</sup> Huiart L, Ernst P, Suissa S. Cardiovascular morbidity and mortality in COPD. *Chest*.2005;128:2640-2646.

<sup>3</sup> Boehringer Ingelheim, Data on file.