Adding Inspra® (eplerenone) To Standard Therapy Reduces The Incidence Of New Onset Atrial Fibrillation/Flutter (AF/F) In Patients With Systolic Heart Failure, Sub-Analysis Shows

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Findings from the Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure (EMPHASIS-HF)

(BUSINESS WIRE)--Pfizer Inc. (NYSE: PFE) today announced results from a pre-specified sub-analysis1 of the EMPHASIS-HF trial2 which showed that Inspra® (eplerenone), added to standard recommended therapy, statistically significantly reduced the incidence of new onset atrial fibrillation or flutter (AF/F) in patients with systolic heart failure and mild symptoms, compared with placebo plus standard therapy. This analysis was a pre-specified secondary endpoint in the EMPHASIS-HF study, the results of which were presented to physicians attending the European Society of Cardiology Heart Failure Congress in Gothenburg, Sweden.

The EMPHASIS-HF trial enrolled 2,737 subjects with chronic systolic heart failure (NYHA class II) and mild symptoms. This sub-analysis looked at subjects without a history of AF/F based on the baseline ECG and physical examination (911 in the eplerenone group and 883 in the placebo group). New onset AF/F occurred in 25 (2.7%) patients in the eplerenone group versus 40 (4.5%) patients in the placebo group; hazard ratio (HR) 0.58 (95% CI 0.35-0.96), p=0.034.

The effect of eplerenone on the primary endpoint (CV mortality or hospitalization for heart failure) was similar among patients with or without AF/F at baseline (HR 0.60, 95% CI 0.46-0.79 vs. HR 0.70, 95% CI 0.57-0.85, p-value for interaction =0.41).

The EMPHASIS-HF trial showed a higher incidence of hyperkalemia (elevated potassium, defined as serum potassium level >5.5mmol/L.) among patients assigned to eplerenone compared to placebo (11.8% vs 7.2%, respectively; p<0.001). In contrast, the incidence of hypokalemia (low potassium, defined as serum potassium level <3.5mmol/L.) was lower in the eplerenone group compared to placebo (7.5% vs 11.0%, respectively; p=0.002).

Approximately 6.5 million people have chronic heart failure (CHF) in Europe3. Heart failure can lead to a reduction in the quality of life, frequent admissions to hospital and a greatly shortened life expectancy. AF affects between 10–26% of patients with mild to moderate CHF (NYHA functional class II and III) and between 30–50% patients with NYHA class IV4.

Professor Karl Swedberg, Department of Medicine, Sahlgrenska University Hospital, Gothenborg, Sweden, presenting the sub-analysis, commented: “Heart failure and atrial fibrillation often coincide in clinical practice, and they are known to worsen the overall prognosis of the patient, but not enough is known about optimal management of these complex conditions. Our findings, which suggest that aldosterone antagonism in heart failure might influence atrial fibrosis and remodeling, and therefore the risk of developing atrial fibrillation/flutter, should provide real encouragement for doctors and patients alike”.

Patients with chronic heart failure with mild symptoms (NYHA class II) and ejection fraction (EF) ≤35% were eligible for EMPHASIS-HF. In this sub-analysis, the history of AF/F at baseline was identified from the data collected from the following sections of the case report form: etiology of HF, cause or reason for prior CV hospitalization, significant medical conditions, medical history, and ECG reports.

Eplerenone is not authorised for use in the patient population studied in the EMPHASIS-HF trial or in patients with atrial fibrillation/flutter in any countries.

About the EMPHASIS-HF trial

EMPHASIS HF (A6141079) is a phase 3B, multinational (2,737 patients from 272 centres in 29 countries), randomized, double-blind placebo-controlled, parallel-group trial. It was conducted in patients with chronic systolic heart failure with mild symptoms (NYHA II) and

ejection fraction ≤30% or ≤35% if QRS duration >130msecs, which is a distinct population from the EPHESUS study5 population (patients with left ventricular dysfunction - LVEF ≤ 40 % - and clinical evidence of heart failure after recent myocardial infarction).

The primary objective of this trial was to evaluate the efficacy and safety of eplerenone plus standard heart failure (HF) therapy - including an angiotensin converting enzyme (ACE) inhibitor and/or an angiotensin receptor blocker (ARB), plus a beta–blocker – versus placebo plus standard HF therapy on the cumulative incidence of cardiovascular (CV) mortality and HF hospitalization (a composite primary endpoint). The mean follow-up time was 21.1 months.

Patients were randomized (1:1) to receive eplerenone 25 mg once daily (OD) or matching placebo. At four weeks, the dose of study drug could be increased to 50 mg OD (two 25mg tablets of eplerenone or two matching placebo tablets once daily) based on serum potassium level. The trial was designed to enroll 3,100 patients and to continue until a total of 813 adjudicated primary endpoint events were reported.

In May 2010, Pfizer announced that it would halt recruitment to the EMPHASIS-HF trial early on the recommendations of the trial’s independent Executive Steering Committee (ESC). The recommendations followed a second interim analysis by the independent Data Safety Monitoring Committee (DSMC) of the EMPHASIS-HF trial confirming the study has reached its primary efficacy endpoint early according to the protocol pre-defined stopping rules.

The results of the EMPHASIS study were published in 2010. The study was funded by Pfizer.

About Inspra®

Inspra® (eplerenone) is a steroid nucleus-based mineralcorticoid receptor (MR) antagonist with a higher degree of selectivity than spironolactone. Eplerenone is thought to be a more selective blocker at the mineralcorticoid receptor since there is evidence that some of the effects result from a blockade of cortisol stimulation of the MR-receptor.

Important Prescribing Information

In the United States, Inspra® (eplerenone) is indicated to improve survival of stable patients with left ventricular (LV) systolic dysfunction (ejection fraction less than or equal to 40%) and clinical evidence of congestive heart failure (CHF) after an acute myocardial infarction (MI). Eplerenone is also indicated for the treatment of hypertension. Eplerenone

may be used alone or in combination with other antihypertensive agents.

Eplerenone is contraindicated in all patients with serum potassium greater than 5.5 mEq/L at initiation, creatinine clearance less than or equal to 30 mL/min, or concomitant administration of strong CYP3A4 inhibitors. Eplerenone is also contraindicated for the treatment of hypertension in patients with type 2 diabetes with microalbuminuria, serum creatinine greater than 2.0 mg/dL in males or greater than 1.8 mg/dL in females, creatinine clearance less than 50 mL/min, or concomitant administration of potassium supplements or potassium sparing diuretics.

Serum potassium should be measured before initiating eplerenone therapy, within the first week, and at one month after the start of treatment or dose adjustment. Serum potassium should be assessed periodically thereafter, especially in patients at risk for the development of hyperkalemia such as elderly patients with renal insufficiency and patients with type 2 diabetes and microalbuminuria.

Most common adverse reactions (greater than 2% and more frequent than with placebo) in patients with CHF Post-MI: hyperkalemia and increased creatinine. Most common adverse reactions (greater than or equal to 2% and more frequent than with placebo) in hypertensive patients: dizziness, diarrhea, coughing, fatigue and flu-like symptoms.

In the EU, eplerenone is indicated to reduce the risk of cardiovascular mortality and morbidity in stable patients with left ventricular dysfunction (LVEF ≤40%) and clinical evidence of heart failure after recent myocardial infarction.

In Japan, eplerenone is approved for the treatment of hypertension.

For additional product information in the US, visit: \files\pressrelease_assets\pdf\USPI - Inspra - eplerenone - Tablets-.pdf

UK prescribing information is available at: http://www.medicines.org.uk/EMC/medicine/16746/SPC/Inspra+25mg+%26+50+mg+film-coated+tablets/

Other countries should refer to local prescribing information.

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This release contains forward-looking information about a potential additional indication for Inspra, including its potential benefits, that involves substantial risks and uncertainties. Such risks and uncertainties include, among other things, the uncertainties inherent in research and development; decisions by regulatory authorities regarding whether and when to approve any supplemental drug applications that have been or may be filed for this additional indication for Inspra as well as their decisions regarding labeling and other matters that could affect the availability or commercial potential of any such additional indication; and competitive developments.

A further list and description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2010 and in its reports on Form 10-Q and Form 8-K.

References:

1. Swedberg K, Zannad F, Krum H et al. Eplerenone reduces the incidence of new onset atrial fibrillation/flutter in patients with systolic heart failure [abstract]. Presented at ESC Heart Failure 2011, Gothenburg.

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4. Maisel W. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. The American Journal of Cardiology. 2003;91(suppl):2D-8D.

5. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. New England Journal of Medicine. 2003;348(14):1309-21.

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