AstraZeneca

news release

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FDA APPROVES ASTRAZENECA'S ATACAND® (CANDESARTAN CILEXETIL) FOR THE TREATMENT OF HEART FAILURE

AstraZeneca today announced that the US Food and Drug Administration (FDA) has approved its angiotensin receptor blocker (ARB) ATACAND® (candesartan cilexetil) for the treatment of heart failure (New York Heart Association Class II-IV and ejection fraction less than or equal to 40 percent) to reduce the risk of death from cardiovascular causes and reduce hospitalisations from heart failure. ATACAND is the first ARB in the US to receive an indication for reducing both cardiovascular mortality and hospitalisations for heart failure.

The US approval was primarily based on results from Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity Alternative Trial (CHARM-Alternative), which examined the effect of ATACAND (n= 1013) compared to placebo (n=1015) in 2028 heart failure patients who were intolerant to ACE inhibitors, but were receiving other standard heart failure therapy. In most cases, the starting dose of ATACAND was 4 mg once daily, which was doubled every two weeks up to the sixth week. Patients received the highest dose tolerated up to the target dose of 32 mg once daily. Patients were evaluated at 2, 4, and 6 weeks; at 6 months; and every 4 months after until the end of the trial (34 months on average). The primary endpoint was time to either cardiovascular mortality or hospitalisation for heart failure. The trial demonstrated that, in these CHF patients, the use of ATACAND resulted in a 23 percent (p less than 0.001) relative risk reduction in cardiovascular death or heart failure hospitalisation (406 events in the placebo arm compared to 334 events in the patients receiving ATACAND), with both components contributing to this effect.

This finding was supported by a second study of 2548 subjects (CHARM-Added) with New York Heart Association (NYHA) Class II-IV heart failure and ejection fraction less than or equal to 40 percent, in which subjects were already on ACE inhibitors. Together, in these studies, patients on ATACAND had a 15 percent lower risk of cardiovascular mortality (p=0.005). In these studies, symptoms of heart failure as assessed by NYHA functional class were also improved (p less than 0.001).

Heart failure, also called chronic heart failure or CHF, is a condition in which the heart is unable to pump blood adequately to the rest of the body. It is a serious, progressive, debilitating condition and frequently leads to a fatal outcome. Many heart failure patients have impaired left ventricular systolic function and this is the population that has been studied in most previous heart failure trials. In these patients, the heart's ability to function as a pump is compromised, as evidenced by a reduced ejection fraction, which

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is the percentage of blood ejected by the heart with each contraction. The normal heart ejects more than 50 percent of the blood in the left ventricle with each beat. Common causes of heart failure include coronary artery disease, heart attacks (or myocardial infarction), high blood pressure (or hypertension), and heart disease of unknown origin (or cardiomyopathy).

New York Heart Association (NYHA) Classification is a widely used and validated measure of symptomatic limitation in CHF. Class I: No limitation. Ordinary physical exercise does not cause fatigue, dyspnoea (breathlessness) or palpitations. Class II: Slight limitation of physical activity. Comfortable at rest but ordinary physical activity results in symptoms. Class III: Marked limitation of physical activity. Comfortable at rest but less than ordinary activity results in symptoms. Class IV: Unable to carry out any physical activity without discomfort. Symptoms present even at rest with increased discomfort with any physical activity.

The American Heart Association estimates that nearly 5 million Americans are currently living with heart failure, and more than half a million new cases are diagnosed each year.

The recommended initial dose of ATACAND for the treatment of heart failure is 4 mg once daily. The target dose is 32 mg once daily, which is achieved by doubling the dose at approximately two-week intervals, as tolerated by the patient.

In November 2004, AstraZeneca announced that the European Mutual Recognition Variation Procedure (MRP) evaluating the use of ATACAND for the treatment of patients with heart failure and impaired left ventricle systolic function had been completed. Worldwide sales of ATACAND totalled $879 million for 2004.

Candesartan Cilexetil is marketed by AstraZeneca under trademark ATACAND®. ATACAND® is manufactured under agreement from Takeda Pharmaceutical Company Limited.

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