

Sildenafil

Sildenafil was the first commercially available phosphodiesterase V inhibitor as well as the first phosphodiesterase V inhibitor approved for the treatment of pulmonary artery hypertension. Phosphodiesterase V is a naturally occurring compound located throughout the body whose purpose is to terminate signaling from cyclic GMP, the second messenger for the signaling molecule, nitric oxide. It has been long known that patients with pulmonary artery hypertension have lower levels of both NO and cyclic GMP, signaling molecules that promote relaxation of blood vessels, inhibit the “stickiness” of the inner lining of the pulmonary arteries, and may inhibit other signaling processes within the pulmonary artery cells to counteract the blood vessel narrowing and abnormal cell growth seen in pulmonary artery hypertension. As is the case with many pulmonary artery hypertension drugs, it appears that the benefit of early administration is related to the vasorelaxant properties of the drug, while the chronic response comes through biological modification of the abnormal cellular processes active in pulmonary artery hypertension.

Sildenafil, marketed as Revatio, has FDA approval in a dosage of 20mgs to be taken three times per day. Drug tolerance has been high, while side-effects have generally been low and manageable through dose reduction or accommodation. There has been some controversy over the drug dosing. The qualifying trial for FDA approval did not show a statistically significant advantage to higher dosages, however, a careful review of the data suggests that there was high variability in dose response. Thus there may be a subset of patients who respond to higher dosages that was not discovered because of the small size of the study.

Currently sildenafil is being tested in multi-drug studies to see if combination therapy provides further improvement in patient outcomes. Preliminary data from small, non-randomized studies, mostly unpublished, suggests this may be the case, however, final acceptance of this hypothesis awaits confirmatory data from the randomized trials.

