

they would at first appear<sup>10-12</sup>. This should not hinder development of ways and means in fast track surgery because a reduction in morbidity and early return to work adds to cost benefits.

The basic concept of fast track surgery, which could be expressed as multimodal control of perioperative pathophysiology, seems to be a highly promising approach to improving surgical outcome. The principles and techniques embodied in this approach should eventually be integrated into the care of all surgical patients as they lead to shorter hospital stay, early return to work and less postoperative pain and morbidity for most, if not all, surgical procedures.

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### Drug Profile

### Darusentan : A promising drug for resistant hypertension

**Introduction:** Resistant hypertension is defined as inability to reduce blood pressure to less than 14/90 mm Hg using an adequate and appropriate triple-drug regimen, including an oral diuretic, with all three drugs near the maximum recommended dose<sup>1</sup> about 10% to 30% of hypertension patient for the remain of developing cardiovascular and renal complications.

**Mechanism of Action:** Endothelin (ET) is a small peptide hormone that is believed to play a critical role in the control of blood flow and cell growth. Elevated endothelin blood levels are associated with several cardiovascular disease conditions, including pulmonary arterial hypertension (PAH), chronic kidney disease, hypertension, acute myocardial infarction, chronic heart failure and stroke<sup>2</sup>. Endothelin 1 (ET-1), which consists of 21 amino acid residues is the predominant isoform of the endothelin peptide family, which also includes ET-2 and ET-3<sup>3</sup>. It exerts various biological effects, including vasoconstriction and the stimulation of cell proliferation in tissues both within and outside cardiovascular system. ET receptors have been divided into two different subtypes, ETa (ET-1 selective) and ETb (nonselective for the isopeptides)<sup>4</sup>. ETA receptors are distributed predominantly in vascular smooth muscle, cardiac myocytes and intestine, whereas ETB receptors are found on endothelial cells, cerebral cortex, kidney and trachea. The binding of endothelin to ETA receptors located on smooth muscle cells causes vasoconstriction. However, the binding of endothelin to ETB receptors located on the vascular endothelium causes vasodilation through the production of nitric oxide and prostacyclin. In addition, ETB receptors in the lung are a major pathway for the clearance of ET-1 from plasma<sup>5</sup>. The activity of the ETB receptor is thought to be counter-regulatory, protecting against excessive vasoconstriction. Hence, selective ETA receptor antagonists can counteract negative effects of endothelin by preventing vasoconstriction and cell proliferation, while preserving the beneficial effects mediated through ETB receptor (Blocking the Beast while Leaving the Beauty Untouched) Dr. experimental stands the drug has shown benefit in lung to oxide. Darusentan is a member of a class of therapeutic agents known as endothelin receptor antagonists (ERA) that is selective for the ETA receptor and is being developed as an oral therapy for the treatment of uncontrolled hypertension based on the evidence that it significantly reduces both systolic and diastolic blood pressure in patients who have failed to achieve optimal blood pressure even with multiple drugs.

Darusentan acts through a different mechanism than existing anti-hypertensive therapies. It is an ERA that is selective for the ETA receptor and can block the negative effects of endothelin by preventing vasoconstriction and cell proliferation, while preserving the beneficial effects associated with ETB receptor stimulation.

**Pharmacokinetic parameters:** the affinity of darusentan for ETA receptors is about 130 times than that for ETB receptors. The compound demonstrates high potency, high oral bioavailability and has a long half-life (16-18 hrs) that is suitable for once daily dosing<sup>5</sup>. In addition, the compound does not induce or inhibit the Cytochrome P450 metabolic pathway.

**Adverse effects:** Darusentan is well tolerated and exhibits favorable safety profile. In the trials with darusentan, headache was the most commonly reported adverse event, with no relevant difference among placebo and active treatment groups. Other frequent adverse events include flushing and peripheral edema were dose-dependent. Whereas, previous clinical trials with other ERAs in patients with hypertension demonstrated dose-related hepatotoxicity requiring withdrawal of therapy for safety reasons, there were no treatment-related elevations in liver enzymes with darusentan. **Clinical Trials:** Earlier studies with darusentan in patients with Chronic heart failure did not show significant improvement in clinical outcome<sup>6</sup>. Subsequently, trials in patients with uncontrolled hypertension or resistant hypertension were undertaken.

**Preclinical trial :** In a rat model of genetic hypertension, animals from the salt-sensitive (SBH/y) and salt-resistant strains (SBN/y) were either salt-loaded with deoxycorticosterone acetate (DOCA) and salt or fed a normal diet. Salt-loading in SBH/y increased systolic blood pressure by 75 mm Hg and urinary albumin excretion 23-fold (P<0.0001). However when darusentan was administered in additional salt-loaded groups it attenuated the rise of systolic blood pressure (50%) and urinary albumin excretion (63%, P<0.01, respectively)<sup>7</sup>. Clinical Trials: In 2000, Hy-

pertension Endothelin Antagonist Treatment (HEAT) study which was a randomized, double-blind, placebo-controlled, dose-ranging trial evaluated the safety and efficacy of darusentan in 392 patients with moderate essential hypertension (Stage-II). The result of this study demonstrated that darusentan produced statistically significant reductions in diastolic and systolic blood pressures in a dose-dependent manner and was well tolerated<sup>5</sup>. In July 2004, a Phase 2b randomized, double-blind, placebo-controlled clinical trial was undertaken to evaluate the safety and efficacy of darusentan in patients with resistant hypertension, patients with systolic blood pressure greater than or equal to 140 mmHg despite treatment with full doses of three anti-hypertensive medications, one of which was a diuretic were enrolled in the study. A total of 115 patients were randomized to darusentan or placebo at approximately 30 investigative sites in the United States. Patients underwent forced titration every two weeks through 10,50,100 and 150 mg of darusentan or placebo until the target dose of 300 mg once daily was achieved. The treatment period was ten weeks followed by a two week drug withdrawal period. The trial results demonstrated that 300 mg of darusentan dosed once daily provided statistically significant, placebo-corrected reductions of 11.6 mmHg in systolic blood pressure and 5.8 mmHg in diastolic blood pressure. Based on encouraging results of Phase 2 trials, company has initiated Phase 3 clinical trial in June 2006 and is presently recruiting patients for this trial. This trial is entitled DORADO – Fixed Doses of Darusentan as Compared to Placebo in Resistant hypertension. It is a randomized, double-blind, placebo-controlled, multi center, parallel group study to evaluate the efficacy and safety of fixed doses of darusentan subjects with resistant systolic hypertension receiving combination therapy with four or more antihypertensive drugs, including a diuretic. Indication & dosage: Darusentan is indicated in resistant hypertension and has shown efficacy at dose of 300mg daily Through trials with darusentan were undertaken as potential therapy for congestive heart failure receptor blockers which have an associated risk of hepatotoxicity, darusentan is well tolerated with no such risk. Conclusion: ET antagonists are promising new agents in the treatment of cardiovascular diseases. Darusentan could be the first of a new class of agents for treating resistant hypertension. Although it is primarily being investigated as antihypertensive drug but various preclinical studies with darusentan in experimental models of acute lung injury have also shown promising results comparable to inhaled Nitric oxide (iNO) by improving gas exchange and preventing an increase in mean pulmonary artery pressure<sup>8</sup>. More information about darusentan is available on websites

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