

Drug-Antihypertensive Interactions

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Study Design

- Tolerability of 5 mg Uprima™ versus placebo
 - ACE inhibitors
 - beta blockers
 - diuretics
 - calcium channel blockers
 - alpha₁ blockers
 - short-acting nitrates
 - long-acting nitrates

Study Design

- 24 males per group on at least 4 weeks of single-agent antihypertensive therapy
- Double-blind, crossover design (24 hour washout)
- Patients on a stable antihypertensive regimen were randomized to receive:
 - Uprima™ 5 mg → Placebo
 - Placebo → Uprima™ 5 mg

Study Design

- Blood pressure and pulse (standing and supine)
 - 30 and 15 minutes prior to dosing
 - 5, 10, 15, 20, 30, 40, 50 minutes, 1, 1.5 and 2 hours post-dosing
- Adverse events, ECG and Holter monitoring
- No pharmacokinetic sampling

Study Results: Mean BP

- Non-nitrate groups demonstrated no significant effects on mean BP changes
- Short-acting nitrate group demonstrated no significant effects on mean BP changes
- Long-acting nitrates showed minimal effects on mean BP changes

Analysis per Patient

- Adverse events
 - significant
 - N/V/diaph/hypot/sync/palpitations
 - not significant
 - HA/URI/fever/SOB/tinnitus/rash/asthenia
- BP results
 - absolute SBP < 85 or DBP < 45
 - fall in SBP by 30 mm Hg
 - fall in DBP by 20 mm Hg

Analysis per Patient

- n = 162 enrolled
- n = 26 with adverse events of concern
 - n = 24 with both AE and BP findings
 - n = 2 with AE alone

Non-Nitrate Therapies Results per Patient

	n	Placebo	Uprima™
ACE inhibitors	25	1	2
Beta blockers	26	1	3
Diuretics	21	0	2
Calcium blockers	26	0	1
Alpha blockers	24	0	3
Total	122	2 (1.6 %)	11 (9.0 %)

Non-nitrate Therapies Results per Patient

- One syncopal event
 - beta blocker group
 - baseline BP 105/75 fell to 71/30 approximately 20 minutes after Uprima™ dosing (associated with dizziness, nausea, diaphoresis)
 - placed supine, given IV fluids, hospitalized for 24 hours

Non-nitrate Therapies Summary Comments

- Adverse events of concern were noted in 1.6% of subjects taking placebo vs. 9% of subjects taking Uprima™
- One serious adverse event
 - syncopal event in a beta blocker subject taking Uprima™
- Patients did not tolerate Uprima™ as well as placebo

Nitrate Therapies Results per Patient

	n	Placebo	Uprima™
Short-acting nitrates	20	0	6
Long-acting nitrates	20	2	5
Total	40	2 (5.0 %)	11 (28.0 %)

Nitrate Therapies Summary Comments

- Adverse events of concern occurred in 5% of patients taking placebo vs. 28% of subjects taking Uprima™
- Patients did not tolerate Uprima™ as well as placebo

FDA Summary of Concerns

Selective Patient Population Organic ED Excluded

- Relevance to Efficacy
 - Uprima™ could work better in patients with organic ED
 - Uprima™ may not work as well in patients with organic ED
- Relevance to Safety
 - in patients with organic ED, Uprima™ may pose more serious safety concerns

Diabetic Patients with Organic ED 4 mg Uprima™

- 25% successful attempts vs. 15% with placebo
- 4% rate of hypotension and syncope

Uprima™ 2 mg

- Efficacy Concerns
 - overall success rates of 44 to 47% versus placebo responses of 32 to 38%
 - few patients (~ 10%) remain on a 2 mg dose long-term when given the option to titrate upward

Uprima™ 4 mg

- Safety Concerns
 - nausea, dizziness, sweating, somnolence, and vomiting
 - 3.3 % rate of syncope and hypotension
 - narrow margin of safety (based on data from patients dosed with 5 or 6 mg)

Uprima™ 2 mg → 4 mg

- One study
 - placebo, 5 mg, 6 mg, and 2 mg → 6 mg
- Efficacy
 - 48% successful attempts with 2 mg → 4 mg vs 35% with placebo
- Safety
 - 5.4 % rate of hypotension and syncope with 2 mg → 6 mg

Uprima™
Interactions with Other Drugs

- Alcohol interaction
 - noted with the equivalent of approximately 2 oz. of vodka
- Possible nitrate interaction
 - manifested by increased reporting of adverse events of nausea, vomiting, diaphoresis, dizziness, and hypotension

Questions for the Committee

**Questions for the Committee
Points to Consider**

- Selective population studied
- Clinical relevance of efficacy results
- Safety concerns
 - adverse events (hypotension and syncope)
 - alcohol interaction
 - PK variability
 - antihypertensive interaction
- Use in real life

Questions for the Committee

1. Does the patient population studied support the proposed indication “for the treatment of erectile dysfunction”?
 - a. If yes, please elaborate.
 - b. If no, please describe your concerns.

Questions for the Committee

2. Do the data presented support an acceptable risk:benefit profile for the 2 mg dose of Uprima™?
 - a. If yes, please elaborate.
 - b. If no, please describe your concerns, including additional studies that might address these concerns.

Questions for the Committee

3. Do the data presented support an acceptable risk:benefit profile for the 4 mg dose of Uprima™?
 - a. If yes, please elaborate.
 - b. If no, please describe your concerns, including additional studies that might address these concerns.