

Advisory Committee Presentation
on
Uprima™ (apomorphine)

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Overview of Presentation

- FDA presentations
- Erectile Dysfunction (ED)
 - etiologies
 - history of treatment
- Points to consider

FDA Presentations

- "Pharmacokinetics and Drug-Alcohol Interactions"
 - Venkateswar Jarugula, Ph.D.
- "Clinical Safety and Efficacy"
 - Mark Hirsch, M.D.
- Drug-Antihypertensive Interactions"
 - Marianne Mann, M.D.

Erectile Dysfunction (ED)

- Etiologies
 - Psychogenic vs. Organic
 - Nocturnal Penile Tumescence (NPT)
 - most Uprima™ ED patients had normal NPT
- History of treatment

**Points to Consider:
Select Patient Population**

- ED patients with "no major organic component"
- Study inclusion criteria
 - NPT must have demonstrated erection
 - must have had one erection within previous 3 months
 - must have had up to 50% successes during baseline period

**Points to Consider:
Interaction with Alcohol**

- Apomorphine used as a "behavior altering agent" in alcoholics most likely due to its emetic properties
- Patients were cautioned to limit alcohol intake "to a **minimum**" for six hours prior to dosing
- Alcohol/Uprima™ drug interaction studies were performed

**Points to Consider:
Real-Life Simulation?**

- Clinical trials may underestimate real-life risk:
 - 1 month in duration
 - 1st dose and/or dose increase was administered in the office
 - food intake restricted within 1 hour of dosing
 - alcohol intake was restricted
 - "healthier" patients

**Points to Consider:
Doses To Be Discussed**

- 2 mg
- 3 mg (no studies)
- 4 mg
- 5 and 6 mg (dropped by sponsor)

**Points to Consider:
Efficacy**

- Statistical significance vs. clinical significance
- Clinical relevance of effect size
- Patient acceptance
 - 2 mg: patients opt for a higher dose
 - higher doses: patients discontinue treatment
- Results in organic ED patients

**Points to Consider:
Adverse Event Profile**

- Definition of serious adverse events was changed in mid-development of drug
 - more inclusive definition used for the first 20% of patients studied
 - any untoward medical occurrence that results in death, is life threatening, requires hospitalization or prolongation of hospitalization, results in persistent disability/incapacity ...OR events that require intervention to prevent impairment or damage
 - less inclusive definition used for the remaining 80% of patients studied

**Point to Consider:
Adverse Event Profile**

- Hypotension in the NDA:
 - generally not included as SAE
 - many not included in main body of study report
 - many found in appendices
- Hypotension in the sponsor's briefing document
 - only 2/140 included as SAEs (n = 3035)