Sodium oxybate did not impair fertility in rats at doses up to 1000 mg/kg (approximately equal to the maximum recommended human daily dose on a mg/m^2 basis).

Pregnancy

Pregnancy Category B: Reproduction studies conducted in pregnant rats at doses up to 1000 mg/kg (approximately equal to the maximum recommended human daily dose on a mg/m^2 basis) and in pregnant rabbits at doses up to 1200 mg/kg (approximately 3 times the maximum recommended human daily dose on a mg/m^2 basis) revealed no evidence of teratogenicity. In a study in which rats were given sodium oxybate from day 6 of gestation through day 21 post-partum, slight decreases in pup and maternal weight gains were seen at 1000 mg/kg; there were no drug effects on other developmental parameters. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

Sodium oxybate has not been studied in labor or delivery. In obstetric anesthesia using an injectable formulation of sodium oxybate newborns had stable cardiovascular and respiratory measures but were very sleepy, causing a slight decrease in Apgar scores. There was a fall in the rate of uterine contractions 20 minutes after injection. Placental transfer is rapid, but umbilical vein levels of sodium oxybate were no more than 25% of the maternal concentration. No sodium oxybate was detected in the infant's blood 30 minutes after delivery. Elimination curves of sodium oxybate between a 2-day old infant and a 15-year old patient were similar. Subsequent effects of sodium oxybate on later growth, development and maturation in humans are unknown.

Nursing Mothers

It is not known whether sodium oxybate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sodium oxybate is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in patients under 16 years of age have not been established.

Race and Gender Effects

effects on safety or efficacy. More than 90% of the subjects in clinical trials were Caucasian.

The database was 58% female.

The overall percentage of patients with at least one adverse event was slightly higher in women (80%) than in men (69%). The incidence of serious adverse events and discontinuations due to adverse events were similar in both men and women.

ADVERSE REACTIONS

A total of 448 narcoleptic patients were exposed to sodium oxybate in clinical trials. The most commonly observed adverse events associated with the use of sodium oxybate were:

Headache (25%), nausea (21%), dizziness (17%), pain (16%), somnolence (13%), pharyngitis (11%), infection (10%), viral infection (10%), flu syndrome (9%), accidental injury (9%), diarrhea (8%), urinary incontinence (8%), vomiting (8%), rhinitis (8%), asthenia (8%), sinusitis (7%), nervousness (7%), back pain (7%), confusion (7%), sleepwalking (7%), depression (6%), dyspepsia (6%), abdominal pain (6%), abnormal dreams (6%), insomnia (5%).

2 deaths occurred these clinical trials, both from drug overdoses. Both these deaths resulted from the ingestion of multiple drugs, including sodium oxybate in one patient

In these clinical trials, 13% of patients discontinued because of adverse events. The most frequent reasons for discontinuation (> 1%) were nausea (2%) and headache (1.3%)

Approximately 6 % of patients receiving sodium oxybate in 3 controlled clinical trials (n=147) withdrew due to an adverse event, compared to 1% receiving placebo (n=79).

Incidence in Controlled Clinical Trials

Most Commonly Reported Adverse Events in Controlled Clinical Trials

The most commonly reported adverse events associated with the use of sodium oxybate and occurring with at least 5% greater frequency than seen in placebo-treated patients were dizziness (23%), headache (20%), nausea (16%), pain (12%), sleep disorder (9%), confusion (7%), infection (7%), vomiting (6%) and urinary incontinence (5%). These incidences are based on combined data from Trial 1 and two smaller randomized, double-blind, placebo-controlled, cross-over trials (n=181).

Trial 1, [redacted] used 3 fixed doses of sodium oxybate (3g, 6g, and 9g). In that trial dizziness, nausea, urinary incontinence, and vomiting were more common at higher doses, with the majority of events occurring in the 6g and 9g dose groups.

Adverse Events With an Incidence of > 1% in Trial 1

Table lists the incidence of treatment emergent adverse events in Trial 1. Events have been included for which there are at least 2 episodes in the considered drug group and for which the incidence in at least one dosage group is greater on drug than placebo.

The prescriber should be aware that data provided below cannot be used to predict the incidence of adverse experiences during the course of usual medical practice where patient characteristics and other factors may differ from those occurring during clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescribing physician with some basis for

estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Table —

Incidence (%) of Treatment-Emergent Adverse Events in Trial 1

	Sodium Oxybate Dose			
Body System Preferred Term	Placebo (n=34)	3g (n=34)	6g (n=33)	9g (n=35)
Body as a Whole				
Asthenia	1 (3%)	0 (0%)	2 (6%)	0 (0%)
Flu Syndrome	0 (0%)	1 (3%)	0 (0%)	2 (6%)
Headache	7 (21%)	3 (9%)	5 (15%)	11 (31%)
Infection	1 (3%)	3 (9%)	5 (15%)	0 (0%)
Infection Viral	1 (3%)	1 (3%)	3 (9%)	0 (0%)
Pain	2 (6%)	3 (9%)	4 (12%)	7 (20%)
Digestive System				
Diarrhea	0 (0%)	0 (0%)	2 (6%)	2 (6%)
Dyspepsia	2 (6%)	0 (0%)	3 (9%)	2 (6%)
Nausea	2 (6%)	2 (6%)	5 (15%)	12 (34%)
Nausea and Vomiting	0 (0%)	0 (0%)	2 (6%)	2 (6%)
Vomiting	0 (0%)	0 (0%)	2 (6%)	4 (11%)
Musculoskeletal System				
Myasthenia	0 (0%)	2 (6%)	1 (3%)	0 (0%)
Nervous System				
Amnesia	0 (0%)	1 (3%)	0 (0%)	2 (6%)
Anxiety	1 (3%)	1 (3%)	0 (0%)	2 (6%)
Confusion	1 (3%)	3 (9%)	1 (3%)	5(14%)
Dizziness	2(6%)	8(24%)	10(30%)	12(34%)
Dream Abnormal	0 (0%)	0 (0%)	3 (9%)	1 (3%)
Hypertension	1 (3%)	0 (0%)	2 (6%)	0 (0%)
Hypesthesia	0 (0%)	2 (6%)	0 (0%)	0 (0%)
Sleep Disorder	1 (3%)	2 (6%)	4 (12%)	5(14%)

Somnolence	4 (12%)	5 (15%)	4 (12%)	5(14%)
Thinking Abnormal	0 (0%)	1 (3%)	0 (0%)	2 (6%)
Skin				
Increased sweating	0 (0%)	1 (3%)	1 (3%)	4(11%)
Special Senses				
Amblyopia	1 (3%)	2 (6%)	0 (0%)	0 (0%)
Tinnitus	0 (0%)	2 (6%)	0 (0%)	0 (0%)
Urogenital System				
Dysmenorrhea	1 (3%)	1 (3%)	0 (0%)	2 (6%)
Incontinence Urine	0 (0%)	0 (0%)	2 (6%)	5(14%)

Other Adverse Events Observed During All Clinical Trials

[redacted] To establish the rate of adverse events, data from all subjects receiving any dose of sodium oxybate were pooled. All adverse events reported by at least two people are included except for those already listed elsewhere in the labeling, terms too general to be informative, or events unlikely to be drug-induced. Events are classified by body system and listed under the following definitions: **frequent** adverse events (those occurring in at least 1/100 people); **infrequent** events (those occurring in 1/100 – 1/1000 people). These events are not necessarily related to sodium oxybate treatment.

Body As A Whole

Frequent: Allergic reaction, chills, [redacted] **Infrequent:** Abdomen enlarged, [redacted] hangover effect, [redacted], neck rigidity.

Cardiovascular system

[redacted] **Infrequent:** [redacted] syncope,

Digestive system

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