## TOT Complication Rate Similar, Problems Different

BY DAMIAN MCNAMARA

Miami Bureau

CHAMPIONSGATE, FLA. — Transobturator tape procedures are as likely to result in complications as retropubic tape procedures, but the complications are different, according to Austrian registry data presented at the annual meeting of the Society of Gynecologic Surgeons.

In 2003, transobturator tape became available for correction of stress urinary incontinence in Austria. In 2004, researchers established a registry to track complications and outcomes. They compared performance against retropubic tape data collected in a previous registry.

"Of the intraoperative problems reported to us, increased bleeding was the most common," said Dr. Karl Tamussino, attending obstetrician and gynecologist at the Medical University of Graz (Aus-

Increased bleeding was reported with

3.5% of the 2,436 operations performed at 47 centers.

The surgeons in Austria used a variety of transobturator tape products, including the TVT-Obturator (Gynecare), Monarc (AMS), and Obtape (Mentor-Porges). A meeting attendee asked if there were any significant differences among products. "Bleeding was pretty much the same," Dr. Tamussino replied.

Centers were asked to voluntarily complete a one-page, 15-item questionnaire with each procedure. "The registry is very simple. That is the key to amassing numbers," said Dr. Tamussino, who presented the findings on behalf of the Austrian Urogynecology Working Group. Disclosures for the working group researchers include AMS, Contura, Lilly/Boehringer, and Gynecare.

Other intraoperative complications included 11 bladder perforations, 10 vaginal perforations, and 2 urethral perforations. "Bladder and urethral perforations were more common with systems inserted from the outside," Dr. Tamussino said at the meeting, which was jointly sponsored by the American College of Surgeons.

A total of 51 patients had a tape-related reoperation. Voiding dysfunction was the most common reason; the tape was loos-

Vaginal erosions, abscesses, and pain may be more common with transobturator tape procedures than with retropubic tape procedures.

ened or cut for 27 patients. An inability to void completely postoperatively seems to be very similar to what is seen with conven-TVT tional [tension-free vaginal tape],' Dr. Tamussino

said. Vaginal tape erosions in nine patients required reoperations, as did a hematoma in one patient at 14 days postoperatively. In addition, seven patients experienced erosions and/or abscesses. Of these, four occurred with Obtape, which is no longer available in Austria, Dr. Tamussino said. The others occurred with the Monarc. TVT-Obturator, and intravaginal sling-

plasty systems. "What we did not expect is these can occur months later," he said.

A meeting attendee asked why erosion and abscesses were reported together. "There were 0.4% erosions alone, and we will separate these out in the [future] randomized trial," Dr. Tamussino said.

Another unexpected postoperative complication was groin pain, with about a 1% incidence, Dr. Tamussino said.

'Unfortunately, we were not expecting the pain issue. We did not have this on the sheet, so we are probably underreporting."

Vaginal erosions, abscesses, and pain may be more common with transobturator than retropubic tape procedures, the authors concluded. "Complications seem more related to the tape materials and not

the technique," Dr. Tamussino said. These are very important complication data on a very large number of procedures," said study discussant Dr. R. Edward Varner of the department of obstetrics and gynecology at the University of Alabama, Birmingham. "Transobturator tapes seem to be relatively safe, especially in experienced hands.'

The registry was voluntary, a potential limitation, Dr. Tamussino said. "We just invited people to participate, we did not motivate them." Dr. Varner agreed that the "reporting of data relies on patients with varying amounts of compulsive-

## ORozerem.

Brief Summary of Prescribing Information

**ROZEREM™** 

(ramelteon) Tablets
INDICATIONS AND USAGE
ROZEREM is indicated for the treatment of insomnia characterized by
difficulty with sleep onset.

CONTRAINDICATIONS
ROZEREM is contraindicated in patients with a hypersensitivity to ramelteon or any components of the ROZEREM formulation.

or any components of the nozeroem formations.

WARNINGS

Since sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insommia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after a reasonable period of treatment may indicate the presence of a primary psychiatric and/or medical liness that should be evaluated. Worsening of insomnia, or the emergence of new cognitive or behavioral abnormalities, may be the result of an unrecognized underlying psychiatric or physical disorder and requires further evaluation of the patient. As with other hypnotics, exacerbation of insomnia and emergence of cognitive and behavioral abnormalities were seen with ROZEREM during the clinical development program.

ROZEREM should not be used by patients with severe hepatic impairment. Trainies were seen wan rozzerew during the calification even primer programs. ROZEREM should not be used by patients with severe hepatic impairm ROZEREM should not be used in combination with fluvoxamine (see PRECAUTIONS: Drug Interactions).

A variety of cognitive and behavior changes have been reported to occur in association with the use of hypnotics. In primarily depressed patients, worsening of depression, including suicidal ideation, has been reported in association with the use of hypnotics.

ents should avoid engaging in hazardous activities that require concentration in as operating a motor vehicle or heavy machinery) after taking ROZEREM. After taking ROZEREM, patients should confine their activities to those necessary to prepare for bed.

General

ROZEREM has not been studied in subjects with severe sleep apnea or severe COPD and is not recommended for use in those populations.

Patients should be advised to exercise caution if they consume alcohol in combination with ROZEREM.

Information for Patients
Patients should be advised to take ROZEREM within 30 minutes prior to going to bed and should confine their activities to those necessary to prepare for bed Patients should be advised to avoid engaging in hazardous activities (such as operating a motor vehicle or heavy machinery) after taking ROZEREM. ents should be advised that they should not take ROZEREM with or nediately after a high-fat meal.

Patients should be advised to consult their health care provider if they experience worseling of insomnia or any new behavioral signs or symptoms of concern.

Patients should consult their health care provider if they experience one of the following: cessation of menses or galactorrhea in females, decreased libido, or problems with fertility.

boratory Tests standard monitoring is required.

and testosterone levels should be considered as appropriate.

Drug Interactions

ROZEREM has a highly variable intersubject pharmacokinetic profile (approximately 100% coefficient of variation in C<sub>max</sub> and AUC). As noted above, CYP1A2 is the major isozyme involved in the metabolism of ROZEREM, the CYP2C subfamily and CYP3A4 isozymes are also involved to a minor degree

CYP2C subfamily and CYP3A4 isozymes are also involved to a minor degree. 
Effects of Other Drugs on ROZEREM Metabolism 
Fluvoxamine (strong CYP1A2 inhibitor): When fluvoxamine 100 mg twice 
dally was administered for 3 days prior to single-dose co-administration of 
ROZEREM 16 mg and fluvoxamine, the AUC<sub>pin</sub> for ramelteon increased 
approximately 190-fold, and the C<sub>max</sub> increased approximately 70-fold, 
compared to ROZEREM administered alone. ROZEREM should not be used 
in combination with fluvoxamine (see WARNINGS). Other less potent CYP1A2 
inhibitors have not been adequately studied. ROZEREM should be administered with caution to patients taking less strong CYP1A2 inhibitors. 
Rifampin (strong CYP enzyme inducer): Administration of rifampin 600 mg 
once daily for 11 days resulted in a mean decrease of approximately 80% 
(40% to 90%) in total exposure to ramelteon and metabolite M-II, (both 
AUC<sub>punt</sub> and C<sub>may</sub> after a single 32 mg dose of ROZEREM. Efficacy may be 
reduced when ROZEREM is used in combination with strong CYP enzyme 
inducers such as rifampin. reduced when nozarian is seen in the state of the inducers such as rifampin. Inducers such as rifampin. Ketoconazole (strong CYP3A4 inhibitor): The AUC<sub>0-inf</sub> and C<sub>max</sub> of ramelteon state of the stat

Kebconazole (strong CYP3A4 inhibitor): The AUC<sub>0-inf</sub> and  $C_{\rm max}$  of ramelteon increased by approximately 84% and 36%, respectively, when a single 16 mg dose of R0ZEREM was administered on the fourth day of ketoconazole 200 mg twice daily administration, compared to administration of R0ZEREM adnoe. Similar increases were seen in M-I pharmacokinetic variables. R0ZEREM should be administered with caution in subjects taking strong CYP3A4 inhibitors such as ketoconazole. Fluconazole (strong CYP2O3 inhibitor): The total and peak systemic exposure (AUC<sub>0-inf</sub> and  $C_{\rm max}$ ) of ramelteon after a single 16 mg dose of R0ZEREM was increased by approximately 150% when administered with fluconazole. Similar increases were also seen in M-II exposure. R0ZEREM should be administered with caution in subjects taking strong CYP2C9 inhibitors such as fluconazole.

as fluconazole. Interaction studies of concomitant administration of ROZEREM with fluoxetine (CYP2D6 inhibitor), omeprazole (CYP1A2 inducer/CYP2C19 inhibitor), theophylline (CYP1A2 substrate), and dextromethorphan (CYP2D6 substrate) did not produce clinically meaningful changes in either peak or total exposures to ramelteon or the M-II metabolite.

exposures to traineteori of the "in-linetatomics" Effects of ROZEREM on Metabolism of Other Drugs Concomitant administration of ROZEREM with omeprazole (CYP2C19 substrate), dextromethorphan (CYP2D6 substrate), midazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate), dipoxin (ip-glycoprotein substrat and warfarin (CYP2C9 [S]/CYP1A2 [R] substrate) did not produce clinically meaningful changes in peak and total exposures to these drugs.

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Effect of Alcohol on Rozerem 
Alcohol: With single-dose, daytime co-administration of ROZEREM 32 mg and 
alcohol (0.6 g/kg), there were no clinically meaningful or statistically significant 
effects on peak or total exposure to ROZEREM. However, an additive effect was 
seen on some measures of psychomotor performance (i.e., the Digit Symbol 
Substitution Test, the Psychomotor Vigilance Task Test, and a Visual Analog 
Scale of Sedation) at some post-dose time points. No additive effect was seen 
on the Delayed Word Recognition Test. Because alcohol by itself impairs 
performance, and the intended effect of ROZEREM is to promote sleep, 
patients should be cautioned not to consume alcohol when using ROZEREM.

Drug/Laboratory Test Interactions
ROZEREM is not known to interfere with commonly used clinical laboratory
tests. In addition, in vitro data indicate that ramelteon does not cause
false-positive results for benzodiazepines, opiates, barbiturates, cocaine,
cannabinoids, or amphetamines in two standard urine drug screening

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis, Mutagenesis, and Impairment of Fertility Carcinogenesis
In a two-year carcinogenicity study, B6C3F, mice were administered ramelteen at doses of 0, 30, 100, 300, or 1000 mg/kg/day by oral gavage. Male mice exhibited a dose-related increase in the incidence of hepatic tumors at dose levels ≥ 100 mg/kg/day including hepatic adenoma, hepatic carcinoma, and hepatoblastoma. Female mice developed a dose-related increase in the incidence of hepatic adenomas at dose levels ≥ 300 mg/kg/day dose level. The no-effect level for hepatic tumors in male mice was 30 mg/kg/day fl03-times and 3-times the therapeutic exposure to ramelteen and the active metabolite M-II, respectively, at the maximum recommended human dose [MRHID] based on a rare under the concentration-time curve [AUC] companison). The no-effect level for hepatic tumors in female mice was 100 mg/kg/day (827-times and 12-times the therapeutic exposure to ramelteen and M-III, respectively, at the MRHID based on AUC).

the MRHD based on AUC).

In a two-year carcinogenicity study conducted in the Sprague-Dawley rat, male and female rats were administered ramelteon at doses of 0,15,60,250 or 1000 mg/kg/day by oral gavage. Male rats exhibited a dose-related increase in the incidence of hepatic adenoma and benign Leydig cell tumors of the testis at dose levels ≥ 250 mg/kg/day and hepatic carcinoma at the 1000 mg/kg/day dose level. Female rats exhibited a dose-related increase in the incidence of hepatic adenoma at dose levels ≥ 60 mg/kg/day and hepatic carcinoma at the 1000 mg/kg/day dose level. The no-effect level for hepatic tumors and benign Leydig cell tumors in male rats was 60 mg/kg/day (1,429-times and 12-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC). The no-effect level for hepatic tumors in female rats was 15 mg/kg/day (472-times and 16-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

the MRHD based on AUC).

The development of hepatic tumors in rodents following chronic treatment with non-genotoxic compounds may be secondary to microsomal enzym induction, a mechanism for tumor generation not thought to occur in human Leydig cell tumor development following treatment with non-genotoxic compounds in rodents has been linked to reductions in circulating testosterone levels with compensatory increases in luteinizing hormone release, which is a known proliferative stimulus to Leydig cells in the rat testis. Rat Leydig cells are more sensitive to the stimulatory effects of luteinizing hormone than human Leydig cells. In mechanistic studies conducted in the rat, daily ramelteon administration at 250 and 1000 mg/kg/day for 4 weeks was associated with a reduction in plasma testosterone levels. In the same study, luteinizing hormone levels were elevated over a 24-hour period after the last ramelteon treatment; howeve the durability of this luteinizing hormone finding and its support for the proposed mechanistic explanation was not clearly established.

Although the rodent tumors observed following ramelteon treatment occurred at plasma levels of ramelteon and M-II in excess of mean clinical plasma concentrations at the MRHD, the relevance of both rodent hepatic tumors and benign rat Leydig cell tumors to humans is not known.

Mutagenesis
Ramelteon was not genotoxic in the following: in vitro bacterial reverse mutation (Ames) assay; in vitro mammalian cell gene mutation assay using the mouse lymphoma TK+f\* cell line; in vivo/in vitro unscheduled DNA synthesis assay in rat hepatocytes; and in in vivo micronucleus assays conducted in mouse and raf. Ramelteon was positive in the chromosomal aberration assay in Chinese hamster lung cells in the presence of S9 metabolic activation.

Separate studies indicated that the concentration of the M-II metabolite formed by the rat liver S9 fraction used in the in vitro genetic toxicology studies described above, exceeded the concentration of ramelteon; therefore, the genotoxic potential of the M-II metabolite was also assessed in these studies.

therefore, the genotoxic potential of the M-11 metabodies was assessed in these studies.

Impairment of Fertility
Ramelteon was administered to male and female Sprague-Dawley rats in an initial fertility and early embryonic development study at dose levels of 6, 60, or 600 mg/kg/day. No effects on male or female mating or fertility were observed with a ramelteon dose up to 600 mg/kg/day (786-times higher than the MRHD on a mg/m² basis). Irregular estrus cycles, reduction in the number of implants, and reduction in the number of inversive were noted with dosing females at ≥ 60 mg/kg/day (79-times higher than the MRHD on a mg/m² basis). A reduction in the number of corpora lutea occurred at the 600 mg/kg/day dose level. Administration of ramelteon up to 600 mg/kg/day to male rats for 7 weeks had no effect on sperm quality and when the treated male rats twere mated with untreated female rats there was no effect on implants or embryos. In a repeat of this study using oral administration of ramelteon at 20, 60 or 200 mg/kg/day for the same study duration, females demonstrated irregular estrus cycles with doses ≥ 60 mg/kg/day, but remales cemonstrated irregular estrus cycles with doses ≥ 60 mg/kg/day, but offects were seen on implantation or embryo viability. The no-effect dose for fertility endpoints was 20 mg/kg/day in females (26-times the MRHD) on a mg/m² basis) and 600 mg/kg/day in males (786-times higher than the MRHD on a mg/m² basis) when considering all studies.

Pregnancy: Pregnancy Category C

controlled studies in pregnant women. Hameleton should be used curing pregnancy only if the potential benefit justifies the potential risk to the fetus. The effects of ramelteon on embryo-fetal development were assessed in both the rat and rabbit. Pregnant rats were administered ramelteon by oral gavage at doses of 0, 10, 40, 150, or 600 mg/kg/day during gestation days 6-17, which is the period of organogenesis in this species. Evidence of maternal toxicity and fetal teratogenicity was observed at doses greater than or equal to 150 mg/kg/day. Maternal toxicity was chiefly characterized by decreased body weight and, at 600 mg/kg/day, atxia and decreased spontaneous movement. At maternally toxic doses (150 mg/kg/day of a consisting of diaphragmatic hernia and minor anatomical variations of the skeleton (irregularly shaped scapula). At 600 mg/kg/day, rations in fetal body weights and malformations including cysts on the external genitalia were additionally observed. The no-effect level for teratogenicity in this study was 40 mg/kg/day (1,892-times and 45-times higher than the therapeutic exposure to ramelteon and the active metabolite M-II, respectively, at the MRHD based on an area under the concentration-time curve [AUC] companison). Pregnant rabbits were administered ramelteon by oral gavage at doses of 0, 12, 60, or 300 mg/kg/day during gestation days 6-18, which is the period of organogenesis in this species. Although maternal toxicity was apparent with a ramelteon dose of 300 mg/kg/day, no evidence of fetal effects or teratogenicity was sporarent with a ramelteon dose of 300 mg/kg/day, foe vidence of fetal effects or teratogenicity was sporarent with a ramelteon dose of 300 mg/kg/day, no evidence of fetal effects or teratogenicity was sporarent with a ramelteon dose of 300 mg/kg/day, no evidence of fetal effects or teratogenicity was therefore, 300 mg/kg/day (1,862-times and 99-times higher than the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

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Takeda studied by administration of ramelteon to the prepnant rat by oral gavage at doses of 0, 30, 100, or 300 mg/kg/day from day 6 of gestation through parturition to postnatal (lactation) day 21, at which time offspring were weaned. Maternal toxicity was noted at doses of 100 mg/kg/day or greater and consisted of reduced body weight upin and increased adrenal gland weight. Reduced body weight uping the post-weaning period was also noticed in the offspring of the groups given 100 mg/kg/day and higher. Offspring in the 300 mg/kg/day group demonstrated physical and developmental delays including delayed eruption of the lower incisors, a delayed acquisition of the righting reflex, and an afteration of emotional response. These delays are often observed in the presence of reduced offspring body weight but may still be indicative of developmental delay, an apparent decrease in the viability of offspring in the 300 mg/kg/day group was likely due to altered maternal behavior and function observed at this dose level. Offspring of the 300 mg/kg/day group also showed evidence of diaphragmatic hernia, a finding observed in the embryo-fetal development study previously described. There were no effects on the reproductive capacity of offspring and the resulting progeny were not different from those of vehicle-treated offspring. The no-effect level for pre- and post-natal development in this study was 30 mg/kg/day (39-times higher than the MRHD on a mg/m² basis).

Labor and Delivery
The potential effects of ROZEREM on the duration of labor and/or delivery,
for either the mother or the fetus, have not been studied. ROZEREM has
no established use in labor and delivery.

Nursing Mothers
Ramelteon is secreted into the milk of lactating rats. It is not known whether this drug is excreted in human milk. No clinical studies in nursing mothers have been performed. The use of ROZEREM in nursing mothers is not recommended.

Geriatric Use used safety in pre-possession and personnel of the Geriatric Use. A total of 654 subjects in double-blind, placebo-controlled, efficacy trials who received ROZEREM were at least 65 years of age; of these, 199 were 75 years of age or older. No overall differences in safety or efficacy were observed between elderly and younger adult subjects.

ADVERSE REACTIONS

Inducing 346 exposed for 6 montes or longer, and 47.3 subjects for one year.

Adverse Reactions Resulting in Discontinuation of Treatment
Six percent of the 3594 individual subjects exposed to ROZEREM in clinical
studies discontinued treatment owing to an adverse event, compared with
2% of the 1370 subjects receiving placebo. The most frequent adverse
events leading to discontinuation in subjects receiving ROZEREM were
somnolence (0.8%), dizziness (0.5%), nausea (0.3%), fatigue (0.3%),
headache (0.3%), and insomnia (0.3%).

ROZEREM Most Commonly Observed Adverse Events in Phase 1-3 trials The incidence of adverse events during the Phase 1 through 3 trials (% placebo, n=1370', % rameliteon [8 mg], n=1250) were: headache NOS (7%, 7%), somolence (3%, 5%), taigue (2%, 4%), dizziness (3%, 5%), nausea (2%, 3%), insomnia exacerbated (2%, 3%), insomnia exacerbated (2%, 3%), mayigia (1%, 2%), depression (1%, 2%), dysgeusia (1%, 2%), arthralgia (1%, 2%), influenza (0, 1%), blood cortisol decreased (0, 1%).

(0, 1%), blood cortisol decreased (0, 1%). Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of other drugs, and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates. DRUG ABUSE AND DEPENDENCE ROZEREM is not a controlled substance.

Animal Data: Ramelteon did not produce any signals from animal behaviora studies indicating that the drug produces rewarding effects. Monkeys did not self-administer ramelteon and the drug did not induce a conditioned place preference in rats. There was no generalization between ramelteon and midazolam. Ramelteon did not affect rotorod performance, an indicator of disruption of motor function, and it did not potentiate the ability of diazepam to interfere with rotorod performance.

Signs and Symptoms
No cases of ROZEREM overdose have been reported during clinical development.

Recommended Treatment
General symptomatic and supportive measures should be used, along with
immediate gastric lavage where appropriate. Intravenous fluids should be
administered as needed. As in all cases of drug overdose, respiration, pulse,
blood pressure, and other appropriate vital signs should be monitored, and
general supportive measures employed.

Hemodialysis does not effectively reduce exposure to ROZEREM. Therefore, the use of dialysis in the treatment of overdosage is not appropriate.

Poison Control Center
As with the management of all overdosage, the possibility of multiple drug
ingestion should be considered. The physician may contact a poison control
center for current information on the management of overdosage.

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References: 1. Rozerem package insert, Takeda Pharmaceuticals America, Inc. 2. Johnson MW, Suess PE, Griffiths RR. Ramelteon: a novel hypnotic lacking abuse liability and sedative adverse effects. Arch Gen Psychiatry, 2006;63:1149-1157.