# Figure Family Structure Into BRCA Screening

BY BRUCE JANCIN

Denver Bureau

SAN ANTONIO — Consider lowering the threshold for BRCA mutation testing in patients with early-onset breast cancer who have fewer than two first- or seconddegree female relatives older than age 45, Dr. Jeffrey N. Weitzel advised at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

Patients with this sort of family situa-

tion, which he terms a "limited family structure," were 3.5-fold more likely to carry a deleterious BRCA mutation than were early-onset breast cancer patients with an adequate family structure, in his observational study.

Current guidelines agree that testing is not appropriate for women without breast cancer in the general population. But the guidelines are less clear regarding what to do about women who develop breast cancer at a young age in the absence of a family history of breast or ovarian cancer. Consideration of family structure provides a quick, useful aid in this decision making, according to Dr. Weitzel, director of the department of clinical cancer genetics and the cancer screening and prevention program at City of Hope National Medical Center, Duarte, Calif.

He reported on 1,097 women who underwent BRCA mutation testing in the center's clinic for genetic cancer risk assessment. Of these women, 210 had breast

(Takeda)

cancer prior to age 50 and no family history of breast or ovarian cancer in first- or second-degree relatives. Half of these 210 women had a limited family structure.

A BRCA mutation was found in 17.3% of the women with early-onset breast cancer and a limited family structure, and in 5.7% of those with early-onset disease and an adequate family structure.

Family structure as a predictive factor for BRCA mutation had a sensitivity of 75% and a specificity of 54%. Family structure's positive predictive value of 18% and negative predictive value of 91% were superior to the commonly used models for estimating the probability that a woman has a BRCA mutation, Dr. Weitzel said.

### ORozerem...

### ROZEREM™

INDICATIONS AND USAGE
RO7EREM is indicated for the treatment of insomnia characterized by diffi

### CONTRAINDICATIONS

or any components of the MUZENEM NUMBERS.

WARNINGS
Since sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The fallure of insomnia to remit after a reasonable period of treatment may indicate the presence of a primary psychiatric and/or medical illness 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 ornoram.

ROZEREM should not be used by patients with severe hepatic impairment

ROZEREM should not be used by patients with severe neparic impairment. ROZEREM should not be used in combination with fluvoxamine (see PRE-CAUTIONS: 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.

After taking ROZEREM, patients should confine their activities to those neces sary to prepare for bed.

### PRECAUTIONS

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.

Combination with NUZEREN.

Was in Adolescents and Children

ROZEREM has been associated with an effect on reproductive hormones in

adults, e.g. decreased testosterone levels and increased profactin levels. It is

not known what effect chronic or even chronic intermittent use of ROZEREM

may have on the reproductive axis in developing humans (see Pediatric Use)

nation for Patients
ts should be advised to take ROZEREM within 30 minutes prior to
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.

Patients should be advised that they should not take ROZEREM with or immediately after a high fat meal.

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

### **Laboratory Tests**No standard monitoring is required.

For patients presenting with unexplained amenorrhea, galactorrhea, decreased libido, or problems with fertility, assessment of prolactin levels and testosterone levels should be considered as appropriate.

Drug Interactions
ROCEREM has a highly variable inter-subject pharmacokinetic profile
(approximately 100% coefficient of variation in C.,... and AUC). As noted
above, CVP1A2 is the major isozyme involved in the metabolism of
ROZEREM, the CVP2C subhamily and CVP9A4 isozymes are also involved

ROZEREM; the CYP2C subfamily and CYP3A4 isozymes are also involved to a minor depree.

Effects of Other Drugs on ROZEREM Metabolism Fluvoxamine (strong CYP1A2 inhibitor): When fluvoxamine (strong CYP1A2 inhibitor): When fluvoxamine 100 mg twice daily was administered for 3 days prior to single-dose co-administration of ROZEREM 16 mg and fluvoxamine, the AUC<sub>pell</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) and C<sub>max</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.

moucers such as rifampin. Ketoconazole (strong CYP3A4 inhibitor): The AUC<sub>olet</sub> and  $C_{\rm mix}$  of ramelteon increased by approximately 84% and 36%, respectively, when a single 16 mg dose of ROZEREM was administered on the fourth day of ketoconazole 200 mg twice daily administration, compared to administration of ROZEREM alone. Similar increases were seen in M-II pharmacokinetic variables. ROZEREM should be administration of the CEPEMS hould be administration of ROZEREM should be administration as the CYP3A4 inhibitors such as ketoconazole.

fluconazole. teraction studies of concomitant administration of ROZEREM with fluoxe-teraction studies of concomitant administration of ROZEREM with fluoxe-eophylline (CYP1A2 substrate), and dextromethorphan (CYP2D6 substrate) of not produce chinically meaningful changes in either peak or total expo-ures to ramelteon or the M-II metabolite.

sures to rametreon or time M-II metabolite. Effects of ROZEREM on Metabolism of Other Drugs Concomitant administration of ROZEREM with omeprazole (CYP2C19 strate), dextromethorphan (CYP2D6 substrate), midazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate), digoxin (p-glycoprotien strate), and warrarin (CYP2C3 SIJ/CYP1A2 [R] substrate) did not prod clinically meaningful changes in peak and total exposures to these dru

ect of Alcohol on Rozerem ohol: With single-dose, daytime co-administration of ROZEREM 32 mg I alcohol (0.6 g/kg), there were no clinically meaningful or statistically s

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### inogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Carcinogenesis
In a two-year carcinogenicity study, B6C3F, mice were administered ramelteor
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 and hepatic
carcinoma at the 1000 mg/kg/day dose level. The no-effect level for hepatic
tumors in male mice was 30 mg/kg/day (103-times and 3-times the therapeutic exposure to ramelleon and the active metabolite M-II, respectively, at the
maximum recommended human dose [MRHD] based on an are-underhecurve [AUC] comparison). The no-effect level for hepatic tumors in female
mice was 100 mg/kg/day etc. "times and 12-times the therapeutic exposure
to ramelleon and M-II, respectively, at 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 car olg avage. Male rats schibited a dose-related
increase in the incidence of hepatic adenoma and benign Leydig cell tumors
of the testis at dose levels ≥ 550 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 in female rats was 15 mg/kg/day (1472-times and 15-times the
therapeutic exposure to ramelteon and M-II,
respectively, at the MRHD based on AUC). The o-effect level for hepatic
tumors in female rats was 15 mg/kg/day (1472-times and 16-times the
therapeutic exposure to ramelteon and M-II, respectively, at the MRHD
based on AUC).

Interapeutic exposure to rameteon and M-II, respectively, at the MHHU based on AUC.

The development of hepatic tumors in rodents following chronic treatment with non-genotoxic compounds may be secondary to microsomal enzyme induction, a mechanism for tumor generation not thought to occur in humans. Leydig cell tumor development following treatment with non-genotoxic compounds in rodents has been linked to reductions in circulati testosterone levels with compensatory increases in lutenizing hormone relaase, which is a known proliferative stimulus to Leydig cells in the rat testis. Rat Leydig cells are more sensitive to the stimulatory effects of futenizing hormone than human Leydig cells. In mechanistic studies conducted in the rat, daily ramelteon administration at 250 and 1000 mg/kg/d for 4 weeks was associated with a reduction in plasma testosterone levels in the same study, lutenizing hormone levels were elevated over a 24 hou period after the last ramelteon treatment; however, the durability of this lutenizing 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

Mutagenesis'

Ramelteon was not genotoxic in the following: in vitro bacterial reverse muton (Ames) assay, in vitro mammalian cell gene mutation assay using the mouse lymphoma TK<sup>+/-</sup> cell line; in vivo/in vitro unscheduled DNA synthes assay in rat hepatocytes; and in in vivo micronucleus assay conducted in mouse and rat. Ramelteon was positive in the chromosomal abertation ass 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 ramelten; therefor the genotoxic potential of the M-II metabolite was also assessed in these studies.

the genotoxic potential of the M-II metabolite was also assessed in these studies. 
Impairment of Fartility
Rametleon 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. Defeates on male or female mating of refullity were observed with a ramelleon dose up to 600 mg/kg/day of refulling were observed with a ramelleon dose up to 600 mg/kg/day of refulling were observed with a ramelleon dose up to 600 mg/kg/day of refulling were observed with a ramelleon dose up to 600 mg/kg/day of refulling were observed with a ramelleon dose up to 600 mg/kg/day (78-times higher than the MRHD on a mg/m² basis). I reduction in the number of itive embryos were noted with dosing females at 2.6 60 mg/kg/day (78-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 rameleon up to 600 mg/kg/day dose level. Administration of rameleon at 20.6 or 200 mg/kg/day for male rats vere mated with untreated female rats there was no effect on implants or embryos. In a repeat of this study using oral administration of rameleon at 20.6 or 200 mg/kg/day for male rats were mated with untreated female rats there was no effect on implants or embryos. In a repeat of this study using oral administration of ramelton at 20.6 or 200 mg/kg/day in males (786-times the MRHD on a mg/m² basis) when considering all studies.

Pregnancy: Pregnancy Category C.

Ramelteon has been shown to be a developmental teratogen in the rat when given in doses 197 times higher than the maximum recommended human dose [MRHD] on a mg/m² basis. She necessary of the maximum encommended human dose [MRHD] on a mg/m² basis. There are no adequate and well-controlled studies in pregnant women. Ramelteon should be used during pregnancy only if the potential benefit justifies the potential risk to the fests.

The effects of ramelteon on embryo-fetal development were assessed in both the rat a

RAM-00238

higher than the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

The effects of ramelteon on pre- and post-natal development in the rat were studied by administration of ramelteon to the pregnant rat by oral gavage at doses of 0, 30, 100, or 300 m/g/dgday from day 6 of gestation through narburition 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 during 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 inclosors, a delayed acquisition of the righting reflex, and an alteration of emotional responses. 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 also showed evidence of diaphragmatic hermia, 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 postnatal 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

Amelteon is secreted into the milk of lactating rats. It is not known whether

ursing Mothers amelteon is secreted into the milk of lactating rats. It is not known wi is drug is excreted in human milk. No clinical studies in nursing mot ave been performed. The use of ROZEREM in nursing mothers is not commanded.

may be used sately in pre-puessent and puessent patients.

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

one year.

Adverse Reactions Resulting in Discontinuation of Treatment
Five 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 even
leading to discontinuation in subjects receiving ROZEREM were somnolence
(0.8%), dizziness (0.5%), nausea (0.3%), tatigue (0.3%), headache (0.3%),
and insomnia (0.3%).

(U.X%), Ouzziness (0.5%), nausea (0.3%), fatigue (0.3%), headache (0.3%), and insomnia (0.3%), and insomnia (0.3%).

ROZEREM Most Commonly Observed Adverse Events in Phass 1-3 trials The incidence of adverse events during the Phase 1 through 3 trials (% placebo, n=1370, % ramelteon [8 mg], n=1250) were: headache NOS (7%, 7%), somnolence (3%, 5%), latigue (2%, 4%), düzziness (3%, 5%), naussea (2%, 3%), insomnia evacerbated (2%, 3%), upre respiratory fractinfection NOS (2%, 2%), organism (3%, 2%), adminism (3%, 2%), digermea NOS (2%, 2%), myadija (1%, 2%), depression (1%, 2%), dispuesia (1%, 2%), affritaglia (1%, 2%), service (1%), and (1%)

nan Data: See the CLINICAL TRIALS section, Studies Pertinent to ety Concerns for Sleep-Promoting Agents in the Complete Prescrib

Information.

Animal Data. Ramelteon did not produce any signals from animal behavioral 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.

OVERDOSAGE
Signs and Symptoms
No cases of ROZEREM overdose have been reported during clinical develop

ment.

ROZEREM was administered in single doses up to 160 mg in an abuse liability rail. No safety or tolerability concerns were seen.

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.

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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## **Breast Cancer Prognosis Tied** Tightly to Genes

SAN ANTONIO — Breast cancer prognosis appears to have a strong and previously unrecognized inherited component, Dr. Mikael Hartman said at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

His study of 2,787 mother-daughter and 831 sister pairs with breast cancer showed that 5-year breast cancer-specific mortality was 60%-80% greater among first-degree relatives of a woman who died of the disease within 5 years of diagnosis than in those whose affected mother or sister had a good prognosis.

Information about the outcome of breast cancer among affected first-degree relatives may be relevant for optimal clinical management of women with newly diagnosed breast cancer," said Dr. Hartman of the Karolinska Institute, Stockholm.

Among the 831 pairs of sisters, each with breast cancer, 5-year breast cancer-specific survival was 88% if the older affected sister was alive within 5 years of diagnosis, but only 70% if she was not.

After adjusting for potential confounders, including age at cancer diagnosis, treatment era, nulliparity or age at first live birth, and socioeconomic status, the risk of dying because of breast cancer within 5 years after diagnosis was 80% greater in women whose sister died of breast cancer less than 5 years following her diagnosis than in those whose sister had a good-prognosis form of the disease as defined in a multivariate model.

Similarly, the adjusted risk of breast cancer-specific mortality was 60% higher in the daughters of mothers with a poorprognosis form of breast cancer, compared with mothers with a good prognosis, he continued. Concordance with regard to prognosis was strongest among mother-daughter pairs in whom the mother was diagnosed before age 40.

The determinants of this newly recognized inherited component of breast cancer prognosis are likely to turn out to be genetic, Dr. Hartman said.

-Bruce Jancin