

# VTE Rates With Oral, Transdermal Estrogens

VITALS

**Major Finding:** There were 0.40 events per 100 person-years in transdermal estrogen users and 0.56 events per 100 person-years in oral estrogen users ( $P = .006$ ).

**Data Source:** Observational data from 50,000 women in the Thomas Reuters MarketScan database.

**Disclosures:** The study was sponsored by Novartis; several of the coinvestigators are employed by Novartis.

BY HEIDI SPLETE

FROM THE ANNUAL MEETING OF THE NORTH AMERICAN MENOPAUSE SOCIETY

NATIONAL HARBOR, MD. – Women who used transdermal estrogen had a 30% lower risk of venous thromboembolism than did patients who used oral estrogen, based on data collected from more

than 50,000 women, said Eric Beresford, Pharm.D., of Novartis.

The observation is limited, however, by the lack of data on specific estrogen doses in the oral estrogen users. Further, the data were not adjusted for the participants' weights or BMIs.

Transdermal estrogen has the potential to reduce VTE risk by delivering unmetabolized estradiol

directly to the bloodstream, he said.

In a retrospective, matched-cohort study, Dr. Beresford and colleagues compared VTE incidence for up to 90 days in 27,018 women who began taking oral estrogen only, and in 27,018 who began using an estradiol transdermal system (ETS) between January 2002 and October 2009. The data were collected from the Thomson Reuters MarketScan database of health insurance claims.

The mean age of the women was 49 years, and 22% of them had menopausal or postmenopausal disorders.

Overall, 115 women (0.40 events per 100 person-years) in the ETS group developed VTE, compared with 164 women (0.56 events per 100 person-years) in the oral estrogen group; this difference was statistically significant ( $P = .006$ ).

The incidence of hospitalization-related VTE events was significantly lower in the ETS group, compared with the oral estrogen group (24 vs. 44, respectively). The number of events per 100 person-years was 0.08 and 0.15, respectively.

VTE was defined as at least one diagnosis code for deep vein thrombosis or pulmonary embolism. Women with a prior VTE diagnosis were excluded from the study.

When shown on a Kaplan-Meier curve, the rates of VTE in the ETS group at 6, 12, and 24 months after the start of therapy were 0.24%, 0.42%, and 0.68%, respectively. The rates of VTE in the oral estrogen group were 0.31%, 0.59%, and 1.13%, respectively.

The differences between the two groups were statistically significant ( $P = .006$ ).

The differences in VTE rates between the two groups were significant with ETS doses of either 0.075 mg/day or 0.1 mg/day, Dr. Beresford noted. The women in the oral estrogen hormone therapy group were taking a variety of brands of oral estrogen replacements in various dosages; the study was not designed to compare ETS with specific oral estrogen doses, he added.

The most common concomitant medications were antihypertensives, which were taken by 11% of the women in each group. The most common risk factor for VTE was surgical resection of abdominal or pelvic cancer (24%) and other major surgery (17%).

The findings were limited by the lack of information about the participants' weight or body mass index, which can affect the risk of thrombotic events, and by the observational nature of the study, Dr. Beresford said.

However, the results suggest that "women receiving ETS have a significantly lower incidence of VTE and hospitalization-related VTE than [do] women receiving oral estrogen-only hormone therapy," he said.

More research is needed to assess transdermal estrogen as an option for women at increased risk for VTE. ■

**Makena**<sup>TM</sup>  
hydroxyprogesterone  
caproate injection

## BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please consult full prescribing information.

### INDICATIONS AND USAGE

Makena is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. The effectiveness of Makena is based on improvement in the proportion of women who delivered <37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity.

**Limitation of use:** While there are many risk factors for preterm birth, safety and efficacy of Makena has been demonstrated only in women with a prior spontaneous singleton preterm birth. It is not intended for use in women with multiple gestations or other risk factors for preterm birth.

### CONTRAINDICATIONS

Do not use Makena in women with any of the following conditions:

- Current or history of thrombosis or thromboembolic disorders
- Known or suspected breast cancer, other hormone-sensitive cancer, or history of these conditions
- Undiagnosed abnormal vaginal bleeding unrelated to pregnancy
- Cholestatic jaundice of pregnancy
- Liver tumors, benign or malignant, or active liver disease
- Uncontrolled hypertension

### WARNINGS AND PRECAUTIONS

#### Thromboembolic Disorders

Discontinue Makena if an arterial or deep venous thrombotic or thromboembolic event occurs.

#### Allergic Reactions

Allergic reactions, including urticaria, pruritus and angioedema, have been reported with use of Makena or with other products containing castor oil. Consider discontinuing the drug if such reactions occur.

#### Decrease in Glucose Tolerance

A decrease in glucose tolerance has been observed in some patients on progestin treatment. The mechanism of this decrease is not known. Carefully monitor prediabetic and diabetic women while they are receiving Makena.

#### Fluid Retention

Because progestational drugs may cause some degree of fluid retention, carefully monitor women with conditions that might be influenced by this effect (e.g., preeclampsia, epilepsy, migraine, asthma, cardiac or renal dysfunction).

#### Depression

Monitor women who have a history of clinical depression and discontinue Makena if clinical depression recurs.

#### Jaundice

Carefully monitor women who develop jaundice while receiving Makena and consider whether the benefit of use warrants continuation.

#### Hypertension

Carefully monitor women who develop hypertension while receiving Makena and consider whether the benefit of use warrants continuation.

### ADVERSE REACTIONS

For the most serious adverse reactions to the use of progestins, see *Warnings and Precautions*.

#### Clinical Trials Experience

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 the rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In a vehicle (placebo)-controlled clinical trial of 463 pregnant women at risk for spontaneous preterm delivery based on obstetrical history, 310 received 250 mg of Makena and 153 received a vehicle formulation containing no drug by a weekly intramuscular injection beginning at 16 to 20 weeks of gestation and continuing until 37 weeks of gestation or delivery, whichever occurred first. [See *Clinical Studies*.]

Certain pregnancy-related fetal and maternal complications or events were numerically increased in the Makena-treated subjects as compared to control subjects, including miscarriage and stillbirth, admission for preterm labor, preeclampsia or gestational hypertension, gestational diabetes, and oligohydramnios (Tables 1 and 2).

**Table 1 Selected Fetal Complications**

Pregnancy Complication	Makena n/N	Control n/N
Miscarriage (<20 weeks) <sup>1</sup>	5/209	0/107
Stillbirth (≥20 weeks) <sup>2</sup>	6/305	2/153

<sup>1</sup>N = Total number of subjects enrolled prior to 20 weeks 0 days

<sup>2</sup>N = Total number of subjects at risk ≥20 weeks

**Table 2 Selected Maternal Complications**

Pregnancy Complication	Makena N=310 %	Control N=153 %
Admission for preterm labor <sup>1</sup>	16.0	13.8
Preeclampsia or gestational hypertension	8.8	4.6
Gestational diabetes	5.6	4.6
Oligohydramnios	3.6	1.3

<sup>1</sup>Other than delivery admission.

#### Common Adverse Reactions:

The most common adverse reaction was injection site pain, which was reported after at least one injection by 34.8% of the Makena group and 32.7% of the control group. Table 3 lists adverse reactions that occurred in ≥2% of subjects and at a higher rate in the Makena group than in the control group.

**Table 3 Adverse Reactions Occurring in ≥2% of Makena-Treated Subjects and at a Higher Rate than Control Subjects**

Preferred Term	Makena N=310 %	Control N=153 %
Injection site pain	34.8	32.7
Injection site swelling	17.1	7.8
Urticaria	12.3	11.1
Pruritus	7.7	5.9
Injection site pruritus	5.8	3.3
Nausea	5.8	4.6
Injection site nodule	4.5	2.0
Diarrhea	2.3	0.7

In the clinical trial, 2.2% of subjects receiving Makena were reported as discontinuing therapy due to adverse reactions compared to 2.6% of control subjects. The most common adverse reactions that led to discontinuation in both groups were urticaria and injection site pain/swelling (1% each).

Pulmonary embolus in one subject and injection site cellulitis in another subject were reported as serious adverse reactions in Makena-treated subjects.

#### DRUG INTERACTIONS

No drug-drug interaction studies were conducted with Makena.

#### Drugs Metabolized by CYP1A2, CYP2A6 and CYP2B6

The metabolism of drugs metabolized by CYP1A2 (such as theophylline, tizidine, clozapine), CYP2A6 (such as acetaminophen, halothane, nicotine) and CYP2B6 (such as efavirenz, bupropion, methadone) may be increased during treatment with Makena [See *Clinical Pharmacology*].

#### USE IN SPECIFIC POPULATIONS

##### Pregnancy

**Pregnancy Category B:** There are no adequate and well-controlled studies of Makena use in women during the first trimester of pregnancy. Data from a vehicle (placebo)-controlled clinical trial of 310 pregnant women who received Makena at weekly doses of 250 mg by intramuscular injection in their second and third trimesters, as well as long-term (2-5 years) follow-up safety data on 194 of their infants, did not demonstrate any teratogenic risks to infants from in utero exposure to Makena.

Reproduction studies have been performed in mice and rats at doses up to 95 and 5, respectively, times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Makena.

Makena administration produced embryolethality in rhesus monkeys but not in cynomolgus monkeys exposed to 1 and 10 times the human dose equivalent every 7 days between days 20 and 146 of gestation. There were no teratogenic effects in either species.

##### Labor and Delivery

Makena is not intended for use to stop active preterm labor. The effect of Makena in active labor is unknown.

##### Nursing Mothers

Discontinue Makena at 37 weeks of gestation or upon delivery. Detectable amounts of progestins have been identified in the milk of mothers receiving progestin treatment. Many studies have found no adverse effects of progestins on breastfeeding performance, or on the health, growth, or development of the infant.

##### Pediatric Use

Makena is not indicated for use in children. Safety and effectiveness in pediatric patients less than 16 years of age have not been established. A small number of women under age 18 years were studied; safety and efficacy are expected to be the same in women aged 16 years and above as for users 18 years and older. [See *Clinical Studies*.]

Marketed by: Ther-Rx Corporation St. Louis, MO 63044