

# Essure Approved With Two Ablation Techniques

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SAN FRANCISCO — The Essure sterilization procedure can be used in combination with two methods of endometrial ablation, according to studies presented at the annual meeting of the American Association of Gynecologic Laparoscopists.

The Essure procedure may be performed immediately before or immedi-

ately after using the ThermaChoice uterine balloon ablation system. It also can be done immediately after—but not immediately before—using the NovaSure radiofrequency ablation system, investigators reported.

The Food and Drug Administration approved the use of the Essure system with ThermaChoice ablation in July 2004. The agency has not approved the use of Essure with NovaSure, and a spokesperson for Conceptus Inc., which distributes Essure,

told this newspaper that the company has no plans to apply for such approval. “The majority of women who undergo endometrial ablation are in their reproductive years, so many of them request Essure sterilization to control fertility after or during endometrial ablation,” Rafael F. Valle, M.D., a consultant for Conceptus, reported.

“Because these two methods utilize the same approach, the transvaginal approach, they can be performed concomi-

tantly,” said Dr. Valle of Northwestern University, Chicago. In his study, 40 women who were about to undergo hysterectomy for benign uterine bleeding consented to ThermaChoice endometrial ablation before or after placement of the Essure microinserts. Their average age was 43 years.

The microinserts were placed before ablation in 24 of the women, and in 16 of these women the combined procedure was successful. In the other eight, gross uterine pathology prevented proper placement of the microinserts.

A total of 16 women underwent ablation before placement of the Essure microinserts, and placement was successful in eight of those cases. The failures were caused by unsuspected pathology and debris remaining in the cornual regions after the ablation, which made it difficult to

visualize the tubal ostia.

The combined procedure took an average of 25.7 minutes, including taking a second look by hysteroscopy.

The FDA requested a study on the temperature increase in the serosa during the combined procedure.

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Dr. Valle recruited nine additional women for this study: Seven underwent Essure insertion before ablation, and two underwent Essure insertion alone as controls. Each woman had eight thermocouples inserted via laparotomy before the procedure began.

The average maximum temperature in this subserosal space was 37.1° C, ranging from 34.7° C to 38.9° C. Tissue damage occurs only at temperatures above 45° C. Furthermore, no tissue damage could be seen either on gross or histologic examination.

Although the FDA required the investigators to perform the Essure procedure both before and after ThermaChoice ablation, in practice, “It doesn’t make sense to do the endometrial ablation first,” Dr. Valle said.

When ablation was performed first, “there was a lot of tissue that sometimes even occluded the tubal os, and we had to remove it with forceps before we found the opening.”

Placing the Essure microinserts before ablation is not an option when NovaSure radiofrequency ablation is used, said Robert Sabbah, M.D., of Sacré-Couer Hospital in Montreal.

“We don’t feel that using an electrical current with a metal tail in the cavity would be safe,” he said. “Therefore, we think the only way to go about doing it if you want to combine both procedures is to start first with endometrial ablation and follow later by the installation of the Essure.”

Dr. Sabbah stated that he had no relevant conflicts of interest. ■

before use of such preparations with AVALIDE (irbesartan-hydrochlorothiazide) Tablets.

**Non-steroidal Anti-inflammatory Drugs** — In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when AVALIDE and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

**Carcinogenesis, Mutagenesis, Impairment Of Fertility**

**Irbesartan-Hydrochlorothiazide**

No carcinogenicity studies have been conducted with the irbesartan-hydrochlorothiazide combination. Irbesartan-hydrochlorothiazide was not mutagenic in standard *in vitro* tests (Ames microbial test and Chinese hamster mammalian-cell forward gene-mutation assay). Irbesartan-hydrochlorothiazide was negative in tests for induction of chromosomal aberrations (*in vitro*-human lymphocyte assay; *in vivo*-mouse micronucleus study).

The combination of irbesartan and hydrochlorothiazide has not been evaluated in definitive studies of fertility.

**Irbesartan**

No evidence of carcinogenicity was observed when irbesartan was administered at doses of up to 500/1000 mg/kg/day (males/females, respectively) in rats and 1000 mg/kg/day in mice for up to two years. For male and female rats, 500 mg/kg/day provided an average systemic exposure to irbesartan (AUC<sub>0-24hours</sub>, bound plus unbound) about 3 and 11 times, respectively, the average systemic exposure in humans receiving the maximum recommended dose (MRD) of 300 mg irbesartan/day, whereas 1000 mg/kg/day (administered to females only) provided an average systemic exposure about 21 times that reported for humans at the MRD. For male and female mice, 1000 mg/kg/day provided an exposure to irbesartan about 3 and 5 times, respectively, the human exposure at 300 mg/day.

Irbesartan was not mutagenic in a battery of *in vitro* tests (Ames microbial test, rat hepatocyte DNA repair test, V79 mammalian-cell forward gene-mutation assay). Irbesartan was negative in several tests for induction of chromosomal aberrations (*in vitro*-human lymphocyte assay; *in vivo*-mouse micronucleus study).

Irbesartan had no adverse effects on fertility or mating of male or female rats at oral doses of 650 mg/kg/day, the highest dose providing a systemic exposure to irbesartan (AUC<sub>0-24hours</sub>, bound plus unbound) about 5 times that found in humans receiving the maximum recommended dose of 300 mg/day.

**Hydrochlorothiazide**

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 µg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation.

**Pregnancy**

**Pregnancy Categories C (first trimester) and D (second and third trimesters)**  
(See WARNINGS: Fetal/Neonatal Morbidity and Mortality.)

**Nursing Mothers**

It is not known whether irbesartan is excreted in human milk, but irbesartan or some metabolite of irbesartan is secreted at low concentration in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use**

Clinical studies of AVALIDE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

**ADVERSE REACTIONS**

**Irbesartan-hydrochlorothiazide**

AVALIDE (irbesartan-hydrochlorothiazide) Tablets has been evaluated for safety in 898 patients treated for essential hypertension. In clinical trials with AVALIDE, no adverse experiences peculiar to this combination drug product have been observed. Adverse experiences have been limited to those that were reported previously with irbesartan and/or hydrochlorothiazide (HCTZ). The overall incidence of adverse experiences reported with the combination was comparable to placebo. In general, treatment with AVALIDE was well tolerated. For the most part, adverse experiences have been mild and transient in nature and have not required discontinuation of therapy. In controlled clinical trials, discontinuation of AVALIDE therapy due to clinical adverse experiences was required in only 3.6%. This incidence was significantly less (p=0.023) than the 6.8% of patients treated with placebo who discontinued therapy.

In these double-blind controlled clinical trials, the following adverse experiences reported with AVALIDE occurred in B1% of patients, and more often on the irbesartan-hydrochlorothiazide combination than on placebo, regardless of drug relationship:

	Irbesartan/HCTZ (n=898) (%)	Placebo (n=236) (%)	Irbesartan (n=400) (%)	HCTZ (n=380) (%)
<b>Body as a Whole</b>				
Chest Pain	2	1	2	2
Fatigue	7	3	4	3
Influenza	3	1	2	2
<b>Cardiovascular</b>				
Edema	3	3	2	2
Tachycardia	1	0	1	1
<b>Gastrointestinal</b>				
Abdominal Pain	2	1	2	2
Dyspepsia/heartburn	2	1	0	2
Nausea/vomiting	3	0	2	0
<b>Immunology</b>				
Allergy	1	0	1	1

(continued)

	Irbesartan/HCTZ (n=898) (%)	Placebo (n=236) (%)	Irbesartan (n=400) (%)	HCTZ (n=380) (%)
<b>Musculoskeletal</b>				
Musculoskeletal Pain	7	5	6	10
<b>Nervous System</b>				
Dizziness	8	4	6	5
Dizziness Orthostatic	1	0	1	1
<b>Renal/Genitourinary</b>				
Abnormality Urination	2	1	1	2

The following adverse events were also reported at a rate of 1% or greater, but were as, or more, common in the placebo group: headache, sinus abnormality, cough, URI, pharyngitis, diarrhea, rhinitis, urinary tract infection, rash, anxiety/nervousness, and muscle cramp.

Adverse events occurred at about the same rates in men and women, older and younger patients, and black and non-black patients.

**Irbesartan**

Other adverse experiences that have been reported with irbesartan, without regard to causality are listed below:

**Body as a Whole:** fever, chills, orthostatic effects, facial edema, upper extremity edema  
**Cardiovascular:** flushing, hypertension, cardiac murmur, myocardial infarction, angina pectoris, hypotension, syncope, arrhythmic/conduction disorder, cardio-respiratory arrest, heart failure, hyper-tensive crisis

**Dermatologic:** pruritus, dermatitis, ecchymosis, erythema face, urticaria  
**Endocrine/Metabolic/Electrolyte Imbalances:** sexual dysfunction, libido change, gout

**Gastrointestinal:** diarrhea, constipation, gastroenteritis, flatulence, abdominal distention  
**Musculoskeletal/Connective Tissue:** musculoskeletal trauma, extremity swelling, muscle cramp, arthritis, muscle ache, musculoskeletal chest pain, joint stiffness, bursitis, muscle weakness

**Nervous System:** anxiety/nervousness, sleep disturbance, numbness, somnolence, vertigo, emotional disturbance, depression, paresthesia, tremor, transient ischemic attack, cerebrovascular accident  
**Renal/Genitourinary:** prostate disorder

**Respiratory:** cough, upper respiratory infection, epistaxis, tracheobronchitis, congestion, pulmonary congestion, dyspnea, wheezing  
**Special Senses:** vision disturbance, hearing abnormality, ear infection, ear pain, conjunctivitis

**Hydrochlorothiazide**

Other adverse experiences that have been reported with hydrochlorothiazide, without regard to causality, are listed below:

**Body as a Whole:** weakness  
**Digestive:** pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation

**Hematologic:** aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia  
**Hypersensitivity:** purpura, photosensitivity, urticaria, necrotizing angitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions

**Metabolic:** hyperglycemia, glycosuria, hyperuricemia  
**Musculoskeletal:** muscle spasm

**Nervous System/Psychiatric:** restlessness  
**Renal:** renal failure, renal dysfunction, interstitial nephritis

**Skin:** erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis

**Special Senses:** transient blurred vision, xanthopsia

**Post-Marketing Experience**

The following have been very rarely reported in post-marketing experience: urticaria; angioedema (involving swelling of the face, lips, pharynx, and/or tongue). Hyperkalemia has been rarely reported.

Very rare cases of jaundice have been reported with irbesartan.

**Laboratory Test Findings**

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of AVALIDE (irbesartan-hydrochlorothiazide) Tablets.

**Creatinine, Blood Urea Nitrogen:** Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in 2.3 and 1.1 percent, respectively, of patients with essential hypertension treated with AVALIDE alone. No patient discontinued taking AVALIDE due to increased BUN. One patient discontinued taking AVALIDE due to a minor increase in serum creatinine.

**Hemoglobin:** Mean decreases of approximately 0.2 g/dL occurred in patients treated with AVALIDE alone, but were rarely of clinical importance. This compared to a mean of 0.4 g/dL in patients receiving placebo. No patients were discontinued due to anemia.

**Liver Function Tests:** Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with AVALIDE alone, one patient was discontinued due to elevated liver enzymes.

**Serum Electrolytes:** (See PRECAUTIONS.)

**OVERDOSAGE**

**Irbesartan**

No data are available in regard to overdosage in humans. However, daily doses of 900 mg for 8 weeks were well-tolerated. The most likely manifestations of overdosage are expected to be hypotension and tachycardia; bradycardia might also occur from overdose. Irbesartan is not removed by hemodialysis.

**Hydrochlorothiazide**

The most common signs and symptoms of overdose observed in humans are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

To obtain up-to-date information about the treatment of overdosage, a good resource is a certified Regional Poison-Control Center. Telephone numbers of certified poison-control centers are listed in the Physicians' Desk Reference (PDR). In managing overdose, consider the possibilities of multiple-drug interactions, drug-drug interactions, and unusual drug kinetics in the patient.

**Consult package insert before prescribing AVALIDE (irbesartan-hydrochlorothiazide) Tablets.**

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