

# 3-D Fetal Ultrasound Can Help With Counseling

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KAILUA KONA, HAWAII — Three-dimensional ultrasound is less helpful for diagnosing fetal abnormalities than for counseling patients, Dr. Dolores H. Pretorius said at a conference on obstetrics, gynecology, perinatal medicine, neonatology, and the law.

Always performed as an adjunct to two-dimensional prenatal ultrasound,

never as a replacement for it, 3-D ultrasound can help visualize and evaluate certain fetal abnormalities, give clinicians more confidence about what they're identifying, and help explain the problem to patients, she said.

Rarely does 3-D ultrasound identify additional abnormalities, said Dr. Pretorius, professor of radiology and director of imaging at the University of California, San Diego.

The most helpful medical use of 3-D ul-

trasound may be for imaging facial anomalies, especially small cleft lips and cleft palates that are difficult to see with 2-D ultrasound, according to a 2005 consensus panel convened by the American Institute of Ultrasound in Medicine.

Because 3-D ultrasound can provide consistent symmetrical views, unlike 2-D ultrasound, it may help diagnose micrognathia (small chin), but further research is needed to confirm that, she said at the conference, which was sponsored by

Boston University. It also may be helpful for imaging brain and spinal anomalies, identifying sutures on the fetal skull, and for research studies of cardiac anomalies, the consensus panel suggested.

Anomalies of the ear or the extremities can be seen with 3-D ultrasound. A diagnosis of club feet by 3-D ultrasound is false 12%-22% of the time, however, so patients must be warned of the false-positive rate, she cautioned. "We've had patients terminate the pregnancy for club feet and then have normal feet at autopsy."

Referrals to check for central nervous system anomalies include cases of craniosynostosis or of mild ventriculomegaly, to look for the corpus callosum. A 3-D ultrasound of a neural tube defect can lo-

calize the level of the defect. "Most of the time this does not impact patient care" except when surgical treatment is planned, she said. Scoliosis is much more apparent on 3-D than on 2-D ultrasound to the parents and clinicians.

**Show parents a 3-D image of a fetal movement disorder, however, 'and all of a sudden the light bulb goes off in their head and they can understand it.'**

Trying to get parents to understand a fetal movement disorder can be difficult with just a 2-D image of an outstretched arm. Show them a 3-D image, however, "and all of a sudden the light bulb goes off in their head and they can understand it. Sometimes for patients the visual appearance of these can be very helpful," Dr. Pretorius said.

Parents love to see 3-D images of the fetal face, which has led some nonmedical businesses to offer controversial "entertainment" 3-D ultrasound services in shopping malls and elsewhere. "I've already seen several lawsuits coming through related to 3-D ultrasounds that missed anomalies. The key question is, did the patient know that this was for entertainment, not diagnosis?" said Dr. Pretorius, who has studied 3-D ultrasound for 17 years.

A 3-D exam can be a frustrating experience for sonographers. Even experts only manage to image the face in 80% of midtrimester fetuses and 50% of third-trimester fetuses. The fetus must be in the right position without anything obscuring the face, and with plenty of amniotic fluid around it. The results are affected by gestational age and other factors.

At the start of a 3-D exam, "there's no predicting whether I'm going to make a good picture or not. If the parents don't get a good picture, they think that I'm not a good doctor," Dr. Pretorius said.

As 3-D ultrasound gets used more and more, clinicians must become familiar with a slew of new imaging artifacts. To the untrained eye, a 3-D ultrasound may seem to show a fetus with a single nostril, or a black eye. Motion artifacts can simulate a cleft lip. Rendering artifacts can look like terrible ventriculomegaly. What seems to be a missing arm bone may be a shadow artifact. ■

## Sanctura® (trospium chloride) 20-mg Tablets

**Brief Summary:** please see package insert for full prescribing information.

### INDICATIONS AND USAGE

Sanctura is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.

### CONTRAINDICATIONS

Sanctura is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions. Sanctura is also contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

### PRECAUTIONS

#### General

**Risk of Urinary Retention:** Sanctura should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention.

**Decreased Gastrointestinal Motility:** Sanctura should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention (See CONTRAINDICATIONS). Sanctura, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis, intestinal atony and myasthenia gravis.

**Controlled Narrow-angle Glaucoma:** In patients being treated for narrow-angle glaucoma, Sanctura should only be used if the potential benefits outweigh the risks and in that circumstance only with careful monitoring.

**Patients with Renal Insufficiency:** Dose modification is recommended in patients with severe renal insufficiency (Cl<sub>cr</sub> < 30 mL/min). In such patients, Sanctura should be administered as 20 mg once a day at bedtime (See DOSAGE AND ADMINISTRATION).

**Patients with Hepatic Impairment:** Caution should be used when administering Sanctura in patients with moderate or severe hepatic dysfunction (See full prescribing information).

#### Information for Patients

Patients should be informed that anticholinergic agents, such as Sanctura, may produce clinically significant adverse effects related to anticholinergic pharmacological activity. For example, heat prostration (fever and heat stroke due to decreased sweating) can occur when anticholinergics such as Sanctura are used in a hot environment. Because anticholinergics such as Sanctura may also produce dizziness or blurred vision, patients should be advised to exercise caution. Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents.

Sanctura should be taken 1 hour prior to meals or on an empty stomach. If a dose is skipped, patients are advised to take their next dose 1 hour prior to their next meal.

#### Drug Interactions

The concomitant use of Sanctura with other anticholinergic agents that produce dry mouth, constipation, and other anticholinergic pharmacological effects may increase the frequency and/or severity of such effects. Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility.

**Drugs Eliminated by Active Tubular Secretion:** Although studies to assess drug-drug interactions with Sanctura have not been conducted, Sanctura has the potential for pharmacokinetic interactions with other drugs that are eliminated by active tubular secretion (eg digoxin, procainamide, pancuronium, morphine, vancomycin, metformin and tenofovir). Coadministration of Sanctura with drugs that are eliminated by active renal tubular secretion may increase the serum concentration of Sanctura and/or the coadministered drug due to competition for this elimination pathway. Careful patient monitoring is recommended in patients receiving such drugs (See full prescribing information).

#### Drug-Laboratory-Test Interactions

Interactions between Sanctura and laboratory tests have not been studied.

#### Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with trospium chloride were conducted in mice and rats. A 78-week carcinogenicity study in mice and a 104-week carcinogenicity study in rats were conducted at doses of 2, 20, and 200 mg/kg/day. No evidence of a carcinogenic effect was found in either mice or rats. The 200 mg/kg/day dose in the mouse and rat represents approximately 25 and 60 times, respectively, the human dose based on body surface area. At 200 mg/kg/day in the mouse and rat after 4 weeks the AUC was 34 and 753 ng•h/mL, respectively. The exposure in the rat is 8.6-fold higher than the AUC following 40 mg daily exposure in healthy young or elderly subjects (88 ng•h/mL).

Trospium chloride was not mutagenic in tests for detection of gene mutations in bacteria (Ames test) and mammalian cells (L5178Y mouse lymphoma and CHO cells) or in vivo in the rat micronucleus test.

No evidence of impaired fertility was observed in rats administered doses up to 200 mg/kg/day (about 10 multiples of the expected clinical exposure via AUC).

#### Pregnancy: Teratogenic Effects

**Pregnancy Category C:** Trospium chloride has been shown to cause maternal toxicity in rats and a decrease in fetal survival in rats administered approximately 10 times the expected clinical exposure (AUC). The no effect levels for maternal and fetal toxicity were approximately equivalent to the expected clinical exposure in rats, and about 5-6 times the expected clinical exposure in rabbits. No malformations or developmental delays were observed. There are no adequate and well controlled studies in pregnant women. Sanctura should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

#### Nursing Mothers

Trospium chloride (2 mg/kg PO and 50 µg/kg IV) was excreted, to a limited extent (< 1%), into the milk of lactating rats. The activity observed in the milk was primarily from the parent compound. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Sanctura is administered to a nursing woman. Sanctura should be used during lactation only if the potential benefit justifies the potential risk to the newborn.

#### Pediatric Use

The safety and effectiveness of Sanctura in pediatric patients have not been established.

#### Geriatric Use

Of the 591 patients with overactive bladder who received treatment with Sanctura in the two U.S., placebo-controlled, efficacy and safety studies, 249 patients (42%) were 65 years of age and older. Eighty-eight Sanctura-treated patients (15%) were ≥ 75 years of age.

In these 2 studies, the incidence of commonly reported anticholinergic adverse events in patients treated with Sanctura (including dry mouth, constipation, dyspepsia, UTI, and urinary retention) was higher in patients 75 years of age and older as compared to younger patients. This effect may be related to an enhanced sensitivity to anticholinergic agents in this patient population (See full prescribing information). Therefore, based upon tolerability, the dose frequency of Sanctura may be reduced to 20 mg once daily in patients 75 years of age and older.

#### ADVERSE REACTIONS

The safety of Sanctura was evaluated in Phase 2 and 3 controlled clinical trials in a total of 2975 patients, who were treated with Sanctura (N=1673), placebo (N=1056) or active control medications (N=246). Of this total, 1181 patients participated in two, twelve-week, Phase 3, U.S., efficacy and safety studies and a 9-month open-label extension. Of this total, 591 patients received Sanctura 20 mg twice daily. In all controlled trials combined, 232 and 208 patients received treatment with Sanctura for at least 24 and 52 weeks, respectively. In all placebo-controlled trials combined, the incidence of serious adverse events was 2.9% among patients receiving Sanctura 20 mg bid and 1.5% among patients receiving placebo. Of these, 0.2% and 0.3% were judged to be at least possibly related to treatment with Sanctura or placebo, respectively, by the investigator.

Table 1 lists treatment emergent adverse events from the combined 12-week U.S. safety and efficacy trials that were judged to be at least possibly related to treatment with Sanctura by the investigator, were reported by at least 1% of patients, and were reported more frequently in the Sanctura group than in the placebo group.

The 2 most common adverse events reported by patients receiving Sanctura 20 mg bid were dry mouth and constipation. The single most frequently reported adverse event for Sanctura, dry mouth, occurred in 20.1% of Sanctura treated patients and 5.8% of patients receiving placebo. In the two Phase 3 U.S. studies, dry mouth led to discontinuation in 1.9% of patients treated with Sanctura 20 mg bid. For the patients who reported dry mouth, most had their first occurrence of the event within the first month of treatment.

**Table 1. Incidence (%) of adverse events judged at least possibly related to treatment with Sanctura, reported in ≥ 1% of all patients treated with Sanctura and more frequent with Sanctura (20 mg bid) than placebo in Studies 1 and 2 combined.**

Adverse Event	Placebo (N=590)	Sanctura 20 mg bid (N=591)
<b>Gastrointestinal disorders</b>		
Dry mouth	34 (5.8)	119 (20.1)
Constipation	27 (4.6)	57 (9.6)
Abdominal pain upper	7 (1.2)	9 (1.5)
Constipation aggravated	5 (0.8)	8 (1.4)
Dyspepsia	2 (0.3)	7 (1.2)
Flatulence	5 (0.8)	7 (1.2)
<b>Nervous system disorders</b>		
Headache	12 (2.0)	25 (4.2)
<b>General Disorders</b>		
Fatigue	8 (1.4)	11 (1.9)
<b>Renal and Urinary Disorders</b>		
Urinary retention	2 (0.3)	7 (1.2)
<b>Eye Disorders</b>		
Dry eyes NOS	2 (0.3)	7 (1.2)

Abbreviations: bid=twice daily, NOS=not otherwise specified.

Other adverse events from the Phase 3, U.S., placebo-controlled trials judged possibly related to treatment with Sanctura by the investigator, occurring in ≥ 0.5% of Sanctura-treated patients, and more common with Sanctura than placebo are: tachycardia NOS, vision blurred, abdominal distension, vomiting NOS, dysgeusia, dry throat, and dry skin. During controlled clinical studies, one event of angioneurotic edema was reported.

#### Postmarketing Surveillance

Additional spontaneous adverse events, regardless of relationship to drug, reported from marketing experience with trospium chloride include: gastritis, palpitations, supraventricular tachycardia, chest pain, Stevens-Johnson syndrome, anaphylactic reaction, syncope, rhabdomyolysis, vision abnormal, hallucinations and delirium, and "hypertensive crisis".

#### OVERDOSAGE

##### Management of Overdosage

Overdosage with Sanctura may result in severe anticholinergic effects. Treatment should be provided according to symptoms and supportive. In the event of overdosage, ECG monitoring is recommended.

#### DOSAGE AND ADMINISTRATION

The recommended dose is 20 mg twice daily. Sanctura should be dosed at least one hour before meals or given on an empty stomach.

Dosage modification is recommended in the following patient populations:

For patients with severe renal impairment (Cl<sub>cr</sub> < 30 mL/min), the recommended dose is 20 mg once daily at bedtime (See PRECAUTIONS: General).

In geriatric patients ≥ 75 years of age, dose may be titrated down to 20 mg once daily based upon tolerability (See PRECAUTIONS: Geriatric Use).

#### Rx only

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