

Kaposi's Seen in HIV Patients on Antiretrovirals

BY TIMOTHY F. KIRN
Sacramento Bureau

SAN FRANCISCO — Some HIV-infected patients who are well managed on highly active antiretroviral therapy are developing Kaposi's sarcoma, Dr. Toby A. Maurer said at a meeting on HIV management sponsored by the University of California, San Francisco.

In this trend, which has been identified in San Francisco by Dr. Maurer and her as-

sociates, patients often have CD4 counts of 300 and even 600 cells/mL and low viral loads. Yet they have the telltale purple blotches of Kaposi's, said Dr. Maurer, chief of dermatology at San Francisco General Hospital.

"These patients are very perplexing to us clinically," she said, explaining that these are not flares of Kaposi's, which can sometimes happen at the start of highly active antiretroviral therapy (HAART). Rather, these are occurrences in patients who are

fairly well maintained on the therapy.

The question is whether these patients have developed abnormal T-cell function over time on HAART, despite high CD4 cell counts, thus causing the loss of immunologic control of their Kaposi's sarcoma; or whether their systemic disease was not detected and treated.

"Clinically we are trying to decide what to do with these patients because antiretrovirals don't seem to do it," Dr. Maurer said. "And, [the patients] are not sick

enough nor do they have evidence of systemic KS to warrant chemotherapy."

Although she said there is still no good, reliable method of detecting Kaposi's that has spread and is systemic, Dr. Maurer offered a suggestion to those checking Kaposi's lesions on the legs: Look for edema in the appendage because that is a sign of systemic disease. Systemic disease has a high mortality rate, about 25%, and those patients need more than just antiretroviral treatment.

Dermatologists who have seen this phenomenon of patients on HAART who have had a recurrence of Kaposi's sarcoma may contact Dr. Maurer at maurert@derm.ucsf.edu. ■

Gonorrheal Testing of Anus, Throat Urged

SAN FRANCISCO — As the incidence of gonorrhea continues to increase, physicians need to be doing more testing for the venereal disease in the anus and the throat, particularly in gay men, said Dr. Gail Bolan, chief of the sexually transmitted diseases control branch for California.

Gonorrhea incidence in the United States as a whole and in California specifically had been declining for 3 decades before starting to climb in about the year 2000, Dr. Bolan said at a meeting on HIV management sponsored by the University of California, San Francisco.

A recent study in San Francisco of men who have sex with men reported that if only urine and urethral screening were performed in those men, about 65% of gonorrhea cases would be missed, she noted.

The study found that 85% of the rectal infections were asymptomatic, indicating the possibility that these infections may be an important factor fueling the incidence increase (Clin. Infect. Dis. 2005;41:67-74).

In addition, the study also reported that 53% of chlamydial infections were at nonurethral sites.

Partly because of these concerns, the Centers for Disease Control and Prevention recently updated its sexually transmitted diseases guidelines to include what to ask when taking a sexual history to screen for disease.

The new guidelines suggest that the sexual history taking must include specific questions regarding what is known as the "5 P's": partners, pregnancy protection, protection from sexually transmitted diseases, practices, and past history of sexually transmitted diseases. "You need to do appropriate sexual history, identify sites of exposure, and then, depending on those sites, do appropriate testing," she said.

Dr. Bolan also said that fluoroquinolone-resistant gonorrhea continues to be a problem. The CDC guidelines recommend that fluoroquinolones not be used in men who have sex with men or in areas where fluoroquinolone resistance is high.

—Timothy F. Kirn

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 (CLcr < 30mL/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 CLINICAL PHARMACOLOGY: Pharmacokinetics in Special Populations).

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 demonstrated in a drug-drug interaction study not to affect the pharmacokinetics of digoxin, Sanctura has the potential for pharmacokinetic interactions with other drugs that are eliminated by active tubular secretion (e.g. procainamide, pancuronium, morphine, vancomycin, metformin and tenofovir). Coadministration of Sanctura with these drugs 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 CLINICAL PHARMACOLOGY: Excretion, and CLINICAL PHARMACOLOGY: Drug-Drug Interactions).

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 CLINICAL PHARMACOLOGY: Pharmacokinetics in Special Populations and DOSAGE AND ADMINISTRATION). 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, 12-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 two 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)
Gastrointestinal disorders		
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)
Nervous system disorders		
Headache	12 (2.0)	25 (4.2)
General Disorders		
Fatigue	8 (1.4)	11 (1.9)
Renal and Urinary Disorders		
Urinary retention	2 (0.3)	7 (1.2)
Eye Disorders		
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: Gastrointestinal – gastritis; Cardiovascular – palpitations, supraventricular tachycardia, chest pain, syncope, "hypertensive crisis"; Immunological – Stevens-Johnson syndrome, anaphylactic reaction; Nervous System – vision abnormal, hallucinations and delirium; Musculoskeletal – rhabdomyolysis; General – rash.

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.

A 7-month-old baby experienced tachycardia and mydriasis after administration of a single dose of trospium 10 mg given by a sibling. The baby's weight was reported as 5 kg. Following admission into the hospital and about 1 hour after ingestion of the trospium, medicinal charcoal was administered for detoxification. While hospitalized, the baby experienced mydriasis and tachycardia up to 230 bpm. Therapeutic intervention was not deemed necessary. The baby was discharged as completely recovered the following day.

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 (CLcr < 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

Manufactured for: Esprit Pharmaceuticals East Brunswick, NJ 08816 USA and
Manufactured by: Madaus GmbH Troisdorf, Germany

Indevus Pharmaceuticals, Inc. Lexington, MA 02421 USA

Address Medical Inquiries to: 866-230-0375
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