

Inspector General Faults Specialty Hospitals' EDs

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Physician-owned specialty hospitals are largely unprepared to handle emergencies and should be more closely tracked by the government to ensure that they comply with Medicare rules, according to a report from the Inspector General of the Department of Health and Human Services.

The IG's office reviewed written policies

for managing medical emergencies, staffing schedules, and staffing policies for 8 days at 109 physician-owned facilities that were identified from a list provided by the Centers for Medicare and Medicaid Services. There are an unknown number of physician-owned specialty hospitals, according to the IG, which is urging the CMS to begin compiling a list.

Of the 109 hospitals surveyed, 66 were surgical, 23 were orthopedic, and 20 were cardiac hospitals. Eighteen of the cardiac

hospitals had an emergency department; only 11 of the 23 orthopedic hospitals and 31 of the surgical hospitals had an ED. Thirty-three of the 109 hospitals were in Texas, 15 were in Louisiana, 9 in Oklahoma, 9 in Kansas, and 8 in South Dakota. The rest were spread across other states.

While half of the physician-owned hospitals surveyed had an emergency department, more than half of those EDs only had a single bed. Only 45% of the EDs had a physician on site at all times.

Ninety-three percent of the hospitals met Medicare staffing requirements: having a registered nurse on duty at all times, and a physician on call at all times. But seven hospitals did not have an RN on duty, and one hospital did not have a physician on call or on duty on at least 1 of the 8 days reviewed.

Two-thirds of the hospitals told staff to call 911 in case of emergency.

While transferring a patient with an emergent problem to another hospital's ED is acceptable, it might be a violation of Medicare conditions of participation if a hospital uses 911 to obtain medical assistance to stabilize a patient, according to the IG. Thirty-seven of the 109 hospitals (34%) engaged in that practice, the IG reported.

A hospital also is not in compliance if it uses 911 as a substitute for providing services required by the conditions of Medicare participation, noted the IG.

Almost 25% of the hospitals did not address in written policies the "appraisal of emergencies, initial treatment of emergencies, or referral and transfer of patients," according to the report.

The IG urged the CMS to enforce Medicare staffing requirements. Hospitals should also have information in their written policies on how to manage a medical emergency, such as how to use emergency response equipment or how to follow life-saving protocols, said the IG.

The CMS issued a written response to the IG that was included in the report. The agency said it agreed with the IG's recommendations and that it would examine current compliance through its routine hospital surveys. As many as 42% of the 109 hospitals would not have been subject to CMS oversight, however, according to the IG. Those facilities were instead accredited by the Joint Commission or the American Osteopathic Association.

Finally, the CMS said it would use its existing authority to require hospitals to have written policies and procedures on managing emergencies, but that it would also consider whether regulatory changes are needed to establish specific requirements for equipment and staff qualifications.

The report was requested by the Senate Finance Committee, whose leaders—Sen. Chuck Grassley (R-Iowa) and Sen. Max Baucus (D-Mont.)—have a history of seeking restrictions on physician-owned specialty hospitals, and have successfully implemented moratoriums on new facilities.

These senators will likely introduce a new proposal to rein in specialty hospitals this spring, Molly Sandvig, executive director of Physician Hospitals of America, said in an interview.

Ms. Sandvig said that her organization—which represents 108 physician-owned facilities—believed that all hospitals should meet Medicare conditions of participation. However, not every hospital should have an emergency department, she said.

And while transfers may be acceptable, "No hospital should use 911 as a substitute for providing proper care to patients," said Ms. Sandvig. That practice, however, is very limited, she said, alleging that the IG had misrepresented facilities' policies and practices.

actos
pioglitazone HCl



adequate contraception in premenopausal women should be recommended. This possible effect has not been investigated in clinical studies so the frequency of this occurrence is not known.

Drug Interactions

In vivo drug-drug interaction studies have suggested that pioglitazone may be a weak inducer of CYP 450 isoform 3A4 substrate.

An enzyme inhibitor of CYP2C8 (such as gemfibrozil) may significantly increase the AUC of pioglitazone and an enzyme inducer of CYP2C8 (such as rifampin) may significantly decrease the AUC of pioglitazone. Therefore, if an inhibitor or inducer of CYP2C8 is started or stopped during treatment with pioglitazone, changes in diabetes treatment may be needed based on clinical response.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A two-year carcinogenicity study was conducted in male and female rats at oral doses up to 63 mg/kg (approximately 14 times the maximum recommended human oral dose of 45 mg based on mg/m²). Drug-induced tumors were not observed in any organ except for the urinary bladder. Benign and/or malignant transitional cell neoplasms were observed in male rats at 4 mg/kg/day and above (approximately equal to the maximum recommended human oral dose based on mg/m²). A two-year carcinogenicity study was conducted in male and female mice at oral doses up to 100 mg/kg/day (approximately 11 times the maximum recommended human oral dose based on mg/m²). No drug-induced tumors were observed in any organ.

During prospective evaluation of urinary cytology involving more than 1800 patients receiving ACTOS in clinical trials up to one year in duration, no new cases of bladder tumors were identified. In two 3-year studies in which pioglitazone was compared to placebo or glyburide, there were 16/3656 (0.44%) reports of bladder cancer in patients taking pioglitazone compared to 5/3679 (0.14%) in patients not taking pioglitazone. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were six (0.16%) cases on pioglitazone and two (0.05%) on placebo.

Pioglitazone HCl was not mutagenic in a battery of genetic toxicology studies, including the Ames bacterial assay, a mammalian cell forward gene mutation assay (CHO/HPRT and ASS2/XPR1), an *in vitro* cytogenetics assay using CHL cells, an unscheduled DNA synthesis assay, and an *in vivo* micronucleus assay.

No adverse effects upon fertility were observed in male and female rats at oral doses up to 40 mg/kg pioglitazone HCl daily prior to and throughout mating and gestation (approximately 9 times the maximum recommended human oral dose based on mg/m²).

Animal Toxicology

Heart enlargement has been observed in mice (100 mg/kg), rats (4 mg/kg and above) and dogs (3 mg/kg) treated orally with pioglitazone HCl (approximately 11, 1, and 2 times the maximum recommended human oral dose for mice, rats, and dogs, respectively, based on mg/m²). In a one-year rat study, drug-related early death due to apparent heart dysfunction occurred at an oral dose of 160 mg/kg/day (approximately 35 times the maximum recommended human oral dose based on mg/m²). Heart enlargement was seen in a 13-week study in monkeys at oral doses of 8.9 mg/kg and above (approximately 4 times the maximum recommended human oral dose based on mg/m²), but not in a 52-week study at oral doses up to 32 mg/kg (approximately 13 times the maximum recommended human oral dose based on mg/m²).

Pregnancy

Pregnancy Category C. Pioglitazone was not teratogenic in rats at oral doses up to 80 mg/kg or in rabbits given up to 160 mg/kg during organogenesis (approximately 17 and 40 times the maximum recommended human oral dose based on mg/m², respectively). Delayed parturition and embryotoxicity (as evidenced by increased postimplantation losses, delayed development and reduced fetal weights) were observed in rats at oral doses of 40 mg/kg/day and above (approximately 10 times the maximum recommended human oral dose based on mg/m²). No functional or behavioral toxicity was observed in offspring of rats. In rabbits, embryotoxicity was observed at an oral dose of 160 mg/kg (approximately 40 times the maximum recommended human oral dose based on mg/m²). Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats at oral doses of 10 mg/kg and above during late gestation and lactation periods (approximately 2 times the maximum recommended human oral dose based on mg/m²).

There are no adequate and well-controlled studies in pregnant women. ACTOS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies, as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers

Pioglitazone is secreted in the milk of lactating rats. It is not known whether ACTOS is secreted in human milk. Because many drugs are excreted in human milk, ACTOS should not be administered to a breastfeeding woman.

Pediatric Use

Safety and effectiveness of ACTOS in pediatric patients have not been established.

Elderly Use

Approximately 500 patients in placebo-controlled clinical trials of ACTOS were 65 and over. No significant differences in effectiveness and safety were observed between these patients and younger patients.

ADVERSE REACTIONS

Over 8500 patients with type 2 diabetes have been treated with ACTOS in randomized, double-blind, controlled clinical trials. This includes 2605 high-risk patients with type 2 diabetes treated with ACTOS from the PROactive clinical trial. Over 6000 patients have been treated for 6 months or longer, and over 4500 patients for one year or longer. Over 3000 patients have received ACTOS for at least 2 years.

The overall incidence and types of adverse events reported in placebo-controlled clinical trials of ACTOS monotherapy at doses of 7.5 mg, 15 mg, 30 mg, or 45 mg once daily are shown in Table 2.

Table 2 Placebo-Controlled Clinical Studies of ACTOS Monotherapy: Adverse Events Reported at a Frequency \geq 5% of Patients Treated with ACTOS

(% of Patients)	Placebo		ACTOS	
	N=259	N=606	N=2605	N=2605
Upper Respiratory Tract Infection	8.5	13.2	8.5	13.2
Headache	6.9	9.1	6.9	9.1
Sinusitis	4.6	6.3	4.6	6.3
Myalgia	2.7	5.4	2.7	5.4
Tooth Disorder	2.3	5.3	2.3	5.3
Diabetes Mellitus Aggravated	8.1	5.1	8.1	5.1
Pharyngitis	0.8	5.1	0.8	5.1

For most clinical adverse events the incidence was similar for groups treated with ACTOS monotherapy and those treated in combination with sulfonylureas, metformin, and insulin. There was an increase in the occurrence of edema in the patients treated with ACTOS and insulin compared to insulin alone.

In a 16-week, placebo-controlled ACTOS plus insulin trial (n=379), 10 patients treated with ACTOS plus insulin developed dyspnea and also, at some point during their therapy, developed either weight change or edema. Seven of these 10 patients received diuretics to treat these symptoms. This was not reported in the insulin plus placebo group.

The incidence of withdrawals from placebo-controlled clinical trials due to an adverse event other than hyperglycemia was similar for patients treated with placebo (2.8%) or ACTOS (3.3%).

In controlled combination therapy studies with either a sulfonylurea or insulin, mild to moderate hypoglycemia, which appears to be dose related, was reported (see **PRECAUTIONS, General, Hypoglycemia**).

In U.S. double-blind studies, anemia was reported in \leq 2% of patients treated with ACTOS plus sulfonylurea, metformin or insulin (see **PRECAUTIONS, General, Hematologic**).

In monotherapy studies, edema was reported for 4.8% (with doses from 7.5 mg to 45 mg) of patients treated with ACTOS versus 1.2% of placebo-treated patients. In combination therapy studies, edema was reported for

7.2% of patients treated with ACTOS and sulfonylureas compared to 2.1% of patients on sulfonylureas alone. In combination therapy studies with metformin, edema was reported in 6.0% of patients on combination therapy compared to 2.5% of patients on metformin alone. In combination therapy studies with insulin, edema was reported in 15.3% of patients on combination therapy compared to 7.0% of patients on insulin alone. Most of these events were considered mild or moderate in intensity (see **PRECAUTIONS, General, Edema**).

In one 16-week clinical trial of insulin plus ACTOS combination therapy, more patients developed congestive heart failure on combination therapy (1.1%) compared to none on insulin alone (see **WARNINGS, Cardiac Failure and Other Cardiac Effects**).

Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive)

In PROactive, 5238 patients with type 2 diabetes and a prior history of macrovascular disease were treated with ACTOS (n=2605), force-titrated up to 45 mg daily or placebo (n=2633) in addition to standard of care. Almost all subjects (95%) were receiving cardiovascular medications (beta blockers, ACE inhibitors, ARBs, calcium channel blockers, nitrates, diuretics, aspirin, statins, fibrates). Patients had a mean age of 61.8 years, mean duration of diabetes 9.5 years, and mean HbA_{1c} 8.1%. Average duration of follow-up was 34.5 months. The primary objective of this trial was to examine the effect of ACTOS on mortality and macrovascular morbidity in patients with type 2 diabetes mellitus who were at high risk for macrovascular events. The primary efficacy variable was the time to the first occurrence of any event in the cardiovascular composite endpoint (see **Table 3** below). Although there was no statistically significant difference between ACTOS and placebo for the 3-year incidence of a first event within this composite, there was no increase in mortality or in total macrovascular events with ACTOS.

Table 3

Number of First and Total Events for Each Component within the Cardiovascular Composite Endpoint	Placebo N=2633		ACTOS N=2605	
	First Events (N)	Total Events (N)	First Events (N)	Total Events (N)
Cardiovascular Events				
Any event	572	900	514	803
All-cause mortality	122	186	110	177
Non-fatal MI	118	157	105	131
Stroke	96	119	76	92
ACS	63	78	42	65
Cardiac intervention	101	240	101	195
Major leg amputation	15	28	9	28
Leg revascularization	57	92	71	115

Postmarketing reports of new onset or worsening diabetic macular edema with decreased visual acuity have also been received (see **PRECAUTIONS, General, Macular Edema**).

Laboratory Abnormalities

Hematologic: ACTOS may cause decreases in hemoglobin and hematocrit. The fall in hemoglobin and hematocrit with ACTOS appears to be dose related. Across all clinical studies, mean hemoglobin values declined by 2% to 4% in patients treated with ACTOS. These changes generally occurred within the first 4 to 12 weeks of therapy and remained relatively stable thereafter. These changes may be related to increased plasma volume associated with ACTOS therapy and have rarely been associated with any significant hematologic clinical effects. **Serum Transaminase Levels:** During all clinical studies in the U.S., 14 of 4780 (0.30%) patients treated with ACTOS had ALT values \geq 3 times the upper limit of normal during treatment. All patients with follow-up values had reversible elevations in ALT. In the population of patients treated with ACTOS, mean values for bilirubin, AST, ALT, alkaline phosphatase, and GGT were decreased at the final visit compared with baseline. Fewer than 0.9% of patients treated with ACTOS were withdrawn from clinical trials in the U.S. due to abnormal liver function tests.

In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure (see **PRECAUTIONS, General, Hepatic Effects**).

CPK Levels: During required laboratory testing in clinical trials, sporadic, transient elevations in creatine phosphokinase levels (CPK) were observed. An isolated elevation to greater than 10 times the upper limit of normal was noted in 9 patients (values of 2150 to 11400 IU/L). Six of these patients continued to receive ACTOS, two patients had completed receiving study medication at the time of the elevated value and one patient discontinued study medication due to the elevation. These elevations resolved without any apparent clinical sequelae. The relationship of these events to ACTOS therapy is unknown.

OVERDOSAGE

During controlled clinical trials, one case of overdose with ACTOS was reported. A male patient took 120 mg per day for four days, then 180 mg per day for seven days. The patient denied any clinical symptoms during this period.

In the event of overdose, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

Rx only

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