

# POLICY & PRACTICE

## Bill Halts 4.4% Cut

Congress' long-awaited passage of the budget reconciliation package (also called the Deficit Reduction Act) put a freeze on a 4.4% cut Medicare physicians experienced in the month of January. While the congressional action stopped any further reductions to payments, it did not increase Medicare physician pay for 2006. The Centers for Medicare and Medicaid Services will reimburse physicians retroactively for the reductions experienced in January, and has instructed its contractors to automatically reprocess claims. But work on this issue is far from over, Dr. J. Edward Hill, president of the American Medical Association, said in a statement. "With 6 years of cuts still scheduled to come as practice costs continue to rise, we fear more physicians will make difficult practice decisions about treating Medicare patients. ... We must build on the momentum and awareness raised in 2005 to make 2006 the year Congress permanently repeals the broken Medicare physician payment formula."

## Junk Food Lawsuit

Consumer groups and parents are suing Nickelodeon (Viacom International Inc.) and the Kellogg Co. in an attempt to stop them from marketing junk food to children. The announcement follows an Institute of Medicine report that found food advertising aimed at children encourages them to request high-calorie, low-nutrient foods. "Nickelodeon and Kellogg engage in business practices that literally sicken our children," said Michael Jacobson, executive director of the Center for Science in the Public Interest, one of the plaintiffs. "It's a multimedia brainwashing and reeducation campaign and a disease-promoting one at that." Other plaintiffs in the suit include the Campaign for a Commercial-Free Childhood and parents Sherri Carlson of Wakefield, Mass., and Andrew Leong of Brookline, Mass. Because of the pending litigation, Kellogg is not commenting, said Jill Saletta, Kellogg's director of communications.

## 2007 Medicare Formulary Guidance

In February, the U.S. Pharmacopeia released its final model guidelines for use in developing Medicare prescription drug formularies in 2007. The model guidelines are used by the Centers for Medicare and Medicaid Services to evaluate the formularies created by private drug plans that participate in the Medicare Part D program. There are fewer unique categories and classes in the 2007 document—133, compared with 146 in 2006. In addition, the number of formulary key drug types, which are used by CMS to test the comprehensiveness of the formulary, has increased from 118 to 141. The U.S. Pharmacopeia model guidelines are available online at [www.usp.org/healthcareInfo](http://www.usp.org/healthcareInfo).

## ADA Announces Policy Agenda

Increasing the budget for diabetes research and making stem cell research easier to perform are two of the major public policy priorities for the American Diabetes Association this year. "Policymakers will hear from our army of volunteers and grassroots advocates about the urgent

need for Congress and the [Bush] Administration to set a new course for diabetes policy," Dr. Robert A. Rizza, president for medicine and science at the ADA, said in a statement. Specific priorities include increasing the budget for the Centers for Disease Control and Prevention's division of diabetes translation by \$20.8 million, increasing the budget for research at the National Institute of Diabetes and Digestive and Kidney Diseases by \$92 million, and getting Congress to pass the Stem Cell Research Enhancement Act of 2005 (S. 471/H.R. 810), which would greatly in-

crease the number of stem cells available for use in research.

## Hospital Ethnicity Data

Most hospitals collect data about the race, ethnicity, and language preference of their patients, but few are using the data to improve health care quality, according to a study conducted by the National Public Health and Hospital Institute. Researchers surveyed 500 acute care hospitals and found that half collect information on patients' language, more than three-fourths collect information on patients' race, and half collect information on ethnicity and language preference. Of the hospitals that

did not collect this information, more than half said they did not see the need to. "We are encouraged to know that so many hospitals already have quality data that enable them to develop and monitor interventions to eliminate racial and ethnic disparities in health care," said Marsha Regenstein, Ph.D., the study's lead author and director of NPHHI. "Our challenge now is to work with hospital staff to make sure they recognize the importance of this quality data and that they put the data to use immediately." The study was supported by the Robert Wood Johnson Foundation.

—Joyce Frieden



### Brief Summary of Prescribing Information 05-1113

**ACTOS®** (pioglitazone hydrochloride) Tablets

#### INDICATIONS AND USAGE

ACTOS is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. ACTOS is indicated for monotherapy. ACTOS is also indicated for use in combination with a sulfonylurea, metformin, or insulin when diet and exercise plus the single agent does not result in adequate glycemic control.

Management of type 2 diabetes should also include nutritional counseling, weight reduction as needed, and exercise. These efforts are important not only in the primary treatment of type 2 diabetes, but also to maintain the efficacy of drug therapy.

#### CONTRAINDICATIONS

ACTOS is contraindicated in patients with known hypersensitivity to this product or any of its components.

#### WARNINGS

##### Cardiac Failure and Other Cardiac Effects

ACTOS, like other thiazolidinediones (TZDs), can cause fluid retention when used alone or in combination with other antidiabetic agents, including insulin. Fluid retention may lead to or exacerbate heart failure. Patients should be observed for symptoms of heart failure (see Information for Patients). ACTOS should be discontinued if any deterioration in cardiac status occurs. Patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during pre-approval clinical trials; ACTOS is not recommended in these patients (see PRECAUTIONS, Cardiovascular).

In one 16-week US double-blind, placebo-controlled clinical trial involving 566 patients with type 2 diabetes, ACTOS at doses of 15 mg and 30 mg in combination with insulin was compared to insulin therapy alone. This trial included patients with long-standing diabetes and a high prevalence of pre-existing medical conditions as follows: arterial hypertension (57.2%), peripheral neuropathy (22.6%), coronary heart disease (19.6%), retinopathy (13.1%), myocardial infarction (MI) (8.8%), vascular disease (6.4%), angina pectoris (4.4%), stroke and/or transient ischemic attack (4.1%), and congestive heart failure (CHF) (2.3%). In this study, 2191 patients receiving 15 mg ACTOS plus insulin (1.1%) and 2188 patients receiving 30 mg ACTOS plus insulin (1.1%) developed CHF compared with 0/187 patients receiving insulin therapy alone. All 4 of these patients had previous histories of cardiovascular conditions including coronary artery disease, previous CABG procedures, and MI. In a 24-week dose-controlled study in which ACTOS was co-administered with insulin, 0.3% of patients (1/345) on 30 mg and 0.9% (3/345) of patients on 45 mg reported CHF as a serious adverse event.

In type 2 diabetes and congestive heart failure (systolic dysfunction): In a 24-week post-marketing safety study comparing ACTOS (n=262) to glyburide (n=256) in uncontrolled diabetic patients (mean glycosylated hemoglobin, [A1c] 8.8% at baseline) with NYHA Class II and III heart failure and ejection fraction (EF) less than 40% (mean EF 30% at baseline), overnight hospitalization for CHF was reported in 9.9% of patients on ACTOS vs 4.7% of patients on glyburide with a treatment difference observed from 6 weeks. This adverse event associated with ACTOS was more marked in patients using insulin at baseline and in patients ≥64 years old. No difference in cardiovascular mortality between the treatment groups was seen.

ACTOS should be initiated at the lowest approved dose if it is prescribed for patients with type 2 diabetes and systolic heart failure (NYHA Class II). If subsequent dose escalation is necessary, the dose should be increased gradually only after several months of treatment with careful monitoring for weight gain, edema, or signs of CHF exacerbation.

#### Drug-Drug Interactions

The following drugs were studied in healthy volunteers with a co-administration of ACTOS 45 mg once daily:

**Oral Contraceptives:** Co-administration of ACTOS and an oral contraceptive (1 mg norethindrone plus 0.035 mg ethinyl estradiol once daily) for 21 days, resulted in 11% and 11-14% decreases in ethinyl estradiol AUC<sub>(0-24h)</sub> and C<sub>max</sub>, respectively. There were no significant changes in norethindrone AUC<sub>(0-24h)</sub> and C<sub>max</sub>. In view of the high variability of ethinyl estradiol pharmacokinetics, the clinical significance of this finding is unknown.

**Midazolam:** Administration of ACTOS for 15 days followed by a single 7.5 mg dose of midazolam syrup resulted in a 26% reduction in midazolam C<sub>max</sub> and AUC.

**Nifedipine ER:** Co-administration of ACTOS for 7 days with 30 mg nifedipine ER administered orally once daily for 4 days to male and female volunteers resulted in least square mean (90% CI) values for unchanged nifedipine of 0.83 (0.73 - 0.95) for C<sub>max</sub> and 0.89 (0.80 - 0.96) for AUC. In view of the high variability of nifedipine pharmacokinetics, the clinical significance of this finding is unknown.

**Ketconazole:** Co-administration of ACTOS for 7 days with ketconazole 200 mg administered twice daily resulted in least square mean (90% CI) values for unchanged pioglitazone of 1.14(1.06 - 1.23) for C<sub>max</sub>, 1.34(1.26 - 1.41) for AUC and 1.87(1.71 - 2.04) for C<sub>min</sub>.

**Atorvastatin Calcium:** Co-administration of ACTOS for 7 days with atorvastatin calcium (LIPITOR®) 80 mg once daily resulted in least square mean (90% CI) values for unchanged pioglitazone of 0.69 (0.57 - 0.85) for C<sub>max</sub>, 0.76 (0.65 - 0.88) for AUC and 0.96 (0.87 - 1.05) for C<sub>min</sub>. For unchanged atorvastatin the least square mean (90% CI) values were 0.77 (0.66 - 0.90) for C<sub>max</sub>, 0.86 (0.78 - 0.94) for AUC and 0.92 (0.82 - 1.02) for C<sub>min</sub>.

In other drug-drug interaction studies, pioglitazone had no significant effect on the pharmacokinetics of fexofenadine HCl, glipizide, digoxin, warfarin, metformin, ranitidine HCl or theophylline.

**Cytochrome P450 (CYP450):** See PRECAUTIONS

#### PRECAUTIONS

##### General

ACTOS exerts its antihyperglycemic effect only in the presence of insulin. Therefore, ACTOS should not be used in patients with type 1 diabetes or in patients with diabetic ketoacidosis. **Hypoglycemia:** Patients receiving ACTOS with insulin or oral hypoglycemic agents may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary. **Cardiovascular:** In US placebo-controlled clinical trials that excluded patients with NYHA Class III and IV cardiac status, the incidence of serious cardiac adverse events related to volume expansion was not increased in patients treated with ACTOS as monotherapy or in combination with sulfonylureas or metformin vs placebo-treated patients. In insulin combination studies, a small number of patients with a history of previously existing cardiac disease developed CHF when treated with ACTOS in combination with insulin (see WARNINGS). Patients with NYHA Class III and IV cardiac status were not studied in these ACTOS clinical trials. ACTOS is not indicated in patients with NYHA Class III or IV cardiac status.

In postmarketing experience with ACTOS, cases of CHF have been reported in patients both with and without previously known heart disease.

**Edema:** ACTOS should be used with caution in patients with edema. In all US clinical trials, edema was reported more frequently in patients treated with ACTOS than with placebo and appears to be dose related (see ADVERSE REACTIONS). In postmarketing experience, initiation or worsening of edema has been reported.

**Weight Gain:** Dose related weight gain was seen with ACTOS alone and in combination with other hypoglycemic agents (Table 1). The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Table 1 Weight Changes (kg) from Baseline during Double-Blind Clinical Trials with ACTOS

		Control Group (Placebo)				ACTOS 15 mg				ACTOS 30 mg				ACTOS 45 mg			
		Median (25 <sup>th</sup> /75 <sup>th</sup> percentile)	n	Median (25 <sup>th</sup> /75 <sup>th</sup> percentile)	n	Median (25 <sup>th</sup> /75 <sup>th</sup> percentile)	n	Median (25 <sup>th</sup> /75 <sup>th</sup> percentile)	n	Median (25 <sup>th</sup> /75 <sup>th</sup> percentile)	n	Median (25 <sup>th</sup> /75 <sup>th</sup> percentile)	n	Median (25 <sup>th</sup> /75 <sup>th</sup> percentile)	n		
Monotherapy		-1.4 (-2.7/0.0)	n=256	0.9 (-0.5/3.4)	n=79	1.0 (-0.9/3.4)	n=188	2.6 (0.2/5.4)	n=79								
	Sulfonylurea	-0.5 (-1.8/0.7)	n=187	2.0 (0.2/3.2)	n=183	3.1 (1.1/5.4)	n=528	4.1 (1.8/7.3)	n=333								
Combination Therapy	Metformin	-1.4 (-3.2/0.3)	n=160	N/A		0.9 (-0.3/3.2)	n=567	1.8 (-0.9/5.0)	n=407								
	Insulin	0.2 (-1.4/1.4)	n=182	2.3 (0.5/4.3)	n=190	3.3 (0.9/6.3)	n=522	4.1 (1.4/6.8)	n=338								

Note: Trial durations of 16 to 26 weeks

**Ovulation:** Therapy with ACTOS, like other TZDs, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking ACTOS. Adequate contraception in premenopausal women should be recommended. This possible effect has not been investigated in clinical studies, therefore the frequency is not known.

**Hematologic:** ACTOS may cause decreases in hemoglobin and hematocrit. Across all clinical studies, mean hemoglobin values declined by 2%-4% in patients treated with ACTOS. These changes primarily occurred within the first 4-12 weeks of therapy and remained relatively constant thereafter. These changes may be related to increased plasma volume and have rarely been associated with any significant hematologic clinical effects (see ADVERSE REACTIONS, Laboratory Abnormalities).

**Hepatic Effects:** In pre-approval clinical studies worldwide, >4500 subjects were treated with ACTOS. In US clinical studies, >4700 patients with type 2 diabetes have received ACTOS. There was no evidence of drug-induced hepatotoxicity or elevation of alanine aminotransferase (ALT) levels in the clinical studies.

During pre-approval placebo-controlled clinical trials in the US, a total of 4/1526 (0.26%) patients treated with ACTOS and 2/793 (0.25%) placebo-treated patients had ALT values ≥3X the upper limit of normal (ULN). The ALT elevations in patients treated with ACTOS were reversible and not clearly related to ACTOS therapy.

In postmarketing experience with ACTOS, reports of hepatitis and hepatic enzyme elevations to ≥5X ULN have been received. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established.

Pioglitazone is structurally related to troglitazone, a TZD no longer marketed in the US that was associated with idiosyncratic hepatotoxicity and cases of liver failure, liver transplants and death during postmarketing use. In pre-approval controlled clinical trials in patients with type 2 diabetes, troglitazone was more frequently associated with clinically significant elevations of hepatic enzymes (ALT >3X ULN) vs placebo, and cases of reversible jaundice were reported.

Pending the availability of the results of additional large, long-term controlled clinical trials and additional postmarketing safety data, it is recommended that patients treated with ACTOS undergo periodic monitoring of liver enzymes.

Serum ALT levels should be evaluated prior to the initiation of ACTOS therapy in all patients and periodically thereafter per the clinical judgment of the health professional. Liver function tests should also be obtained for patients if symptoms suggestive of hepatic dysfunction occur, eg, nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine. The decision whether to continue ACTOS therapy should be guided by clinical judgment pending laboratory evaluations. If jaundice is observed, ACTOS should be discontinued.

ACTOS therapy should not be initiated if the patient exhibits clinical signs of active liver disease or the ALT levels exceed 2.5X ULN. Patients with mildly elevated liver enzymes (ALT levels at 1 - 2.5X ULN) at baseline or any time during ACTOS therapy should be evaluated to determine the cause of the liver enzyme elevation. Initiation or continuation of ACTOS therapy in patients with mildly elevated liver enzymes should proceed with caution and include appropriate clinical follow-up, which may include more frequent liver enzyme monitoring. If serum transaminase levels are increased (ALT >2.5X ULN), liver function tests should be evaluated more frequently until the levels return to normal or pretreatment values. If ALT levels exceed 3X ULN, the test should be repeated as soon as possible. If ALT levels remain >3X ULN or the patient is jaundiced, ACTOS therapy should be discontinued.

No data are available to evaluate the safety of ACTOS in patients who experienced liver abnormalities, hepatic dysfunction, or jaundice while on troglitazone. ACTOS should not be used in patients who experienced jaundice while taking troglitazone.

#### Laboratory Tests

Fasting plasma glucose (FPG) and A1c measurements should be performed periodically to monitor glycemic control and the therapeutic response to ACTOS.

Liver enzyme monitoring is recommended prior to initiation of therapy with ACTOS in all patients and periodically thereafter per the clinical judgment of the health professional (see PRECAUTIONS, General, Hepatic Effects and ADVERSE REACTIONS, Serum Transaminase Elevations).

#### Information for Patients

It is important to instruct patients to adhere to dietary instructions and to have blood glucose and A1c tested regularly. During periods of stress, eg, fever, trauma, infection, or surgery, medication requirements may change and patients should be reminded to seek medical advice promptly.

Patients who experience a rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on ACTOS should immediately report these symptoms to their physician.

Patients should be told that blood tests for liver function will be performed prior to the start of therapy and periodically thereafter per the clinical judgment of the health professional. Patients should be told to seek immediate medical advice for unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine.

Patients should be told to take ACTOS once daily. ACTOS can be taken with or without meals. If a dose is missed on one day, the dose should not be doubled the following day.

When using combination therapy with insulin or oral hypoglycemic agents, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to it should be explained to patients and their family members.

Therapy with ACTOS, like other TZDs, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking ACTOS. Adequate contraception in premenopausal women should be recommended. This possible effect has not been investigated in clinical studies so the frequency of this effect is not known.

#### Drug Interactions

In vivo drug-drug interaction studies have suggested that pioglitazone may be a weak inducer of CYP450 isozyme 3A4 substrate (see Drug-Drug Interactions).

#### Carcinogenesis, Mutagenesis, Impairment of Fertility

A 2-year carcinogenicity study was conducted in rats at oral doses ≤63 mg/kg (approximately 14 times) (x) the maximum recommended human oral dose of 45 mg based on mg/m<sup>2</sup>). 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 (approximately equal to the maximum recommended human oral dose based on mg/m<sup>2</sup>). A 2-year carcinogenicity study was conducted in male and female mice at oral doses ≤100 mg/kg/day (approximately 11x the maximum recommended human oral dose based on mg/m<sup>2</sup>). No drug-induced tumors were observed in any organ. Urinary tract tumors have been reported in rodents taking experimental drugs with dual PPARα/γ activity; however, ACTOS is a selective agonist for PPARγ. During prospective evaluation of urinary cytology involving >1800 patients receiving ACTOS up to 1-year in clinical trials, no new cases of bladder tumors were identified. Abnormal urinary cytology results indicating possible malignancy were observed in both patients treated with ACTOS (0.72%) and patients treated with placebo (0.8%).

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/Xprt), an in vitro cytogenetics assay using CHL cells, an unscheduled DNA synthesis assay, and an in vivo micronucleus assay. No adverse effects on fertility were observed in male and female rats at oral doses ≤40 mg/kg daily prior to and throughout mating and gestation (approximately 9x the maximum recommended human oral dose based on mg/m<sup>2</sup>).

#### Animal Toxicology

Heart enlargement has been observed in mice (100 mg/kg), rats (≥4 mg/kg) and dogs (3 mg/kg) treated orally with pioglitazone HCl (approximately 11x, 1x, and 2x the maximum recommended human oral dose based on mg/m<sup>2</sup>, respectively). Delayed parturition and embryotoxicity were observed in rats at oral doses ≥40 mg/kg/day (approximately 10x the maximum recommended human oral dose based on mg/m<sup>2</sup>). 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 40x the maximum recommended human oral dose based on mg/m<sup>2</sup>). Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats at oral doses ≥10 mg/kg during late gestation and lactation periods (approximately 2x the maximum recommended human oral dose based on mg/m<sup>2</sup>).

There are no adequate, 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 and 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 unknown whether ACTOS is secreted in human milk. Because many drugs are excreted in human milk, ACTOS should not be given 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 years. No significant differences in effectiveness and safety were observed between them and younger patients.

#### ADVERSE REACTIONS

In worldwide clinical trials, >5900 patients with type 2 diabetes have been treated with ACTOS. In US clinical trials, >4700 patients have received ACTOS. >3300 patients have been treated ≥6 months and >450 patients for 1-year or longer.

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 ≥5% of Patients Treated with ACTOS

	(% of Patients)	
	Placebo N=259	ACTOS N=606
Upper respiratory tract infection	8.5	13.2
Headache	6.9	9.1
Sinusitis	4.6	6.3
Myalgia	2.7	5.4
Tooth disorder	2.3	5.3
Diabetes mellitus aggravated	8.1	5.1
Pharyngitis	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 vs insulin alone.

In a 16-week, placebo-controlled ACTOS plus insulin trial (n=379), 10 patients treated with ACTOS plus insulin developed dyspnea and, at some point during their therapy, developed either weight change or edema; of these 10 patients, 7 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/moderate hypoglycemia, which appears to be dose related, was reported (see PRECAUTIONS, General, Hypoglycemia).

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

In monotherapy studies, edema was reported for 4.8% of patients treated with ACTOS vs 1.2% of placebo-treated patients. In combination therapy studies, edema was reported for 7.2% of patients treated with ACTOS and sulfonylureas vs 2.1% of patients on sulfonylureas alone. In combination therapy studies with metformin, edema was reported in 6.0% of patients on combination therapy vs 2.5% of patients on metformin alone. In combination therapy studies with insulin, edema was reported in 15.3% of patients on combination therapy vs 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, CHF developed in 1.1% of patients on combination therapy vs 0% of patients receiving insulin alone (see WARNINGS, Cardiac Failure and Other Cardiac Effects).

#### 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%-4% in patients treated with ACTOS. These changes generally occurred within the first 4-12 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 US clinical studies, 14/4780 (0.30%) patients treated with ACTOS had ALT values ≥3X ULN 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. Less than 0.9% of patients treated with ACTOS were withdrawn from US clinical trials 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, 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 >10X ULN was noted in 9 patients (values of 2150-11400 IU/L). Of these patients, 6 continued to receive ACTOS, 2 had completed receiving study medication at the time of the elevated value and 1 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, 1 case of overdose with ACTOS was reported. A male patient took 120 mg per day for 4 days, then 180 mg per day for 7 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

Manufactured by: Takeda Pharmaceutical Company Limited, Osaka, Japan

Marketed by: Takeda Pharmaceuticals America, Inc., 475 Half Day Road, Lincolnshire, IL 60069

and Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46225

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For more detailed information, see Complete Prescribing Information P101-0049-2

**References:** 1. Data on file, Takeda Pharmaceuticals North America, Inc. 2. ACTOS package insert, Takeda Pharmaceuticals America, Inc. 3. American Diabetes Association. Dyslipidemia management in adults with diabetes. Diabetes Care. 2004;27(suppl 1):S68-S71. 4. American Diabetes Association. Standards of medical care in diabetes—2006. Diabetes Care. 2006;29(suppl 1):S4-S42. 5. Charbonnel B, Scherhauer G, Brunnhuber P et al. Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliziclide or metformin in patients with type 2 diabetes. Diabetologia. 2005;48:1093-1104. 6. Tan MH, Baksi A, Kralovich B, et al. for the GLAD Study Group. Comparison of pioglitazone and gliziclide in sustaining glycemic control over 2 years in patients with type 2 diabetes. Diabetes Care. 2005;28:544-550. 7. Aronoff S, Rosenblatt S, Braitwaite S, Egan JW, Mathisen AL, Schneider RL, and the Pioglitazone 001 Study Group. Pioglitazone hydrochloride monotherapy improves