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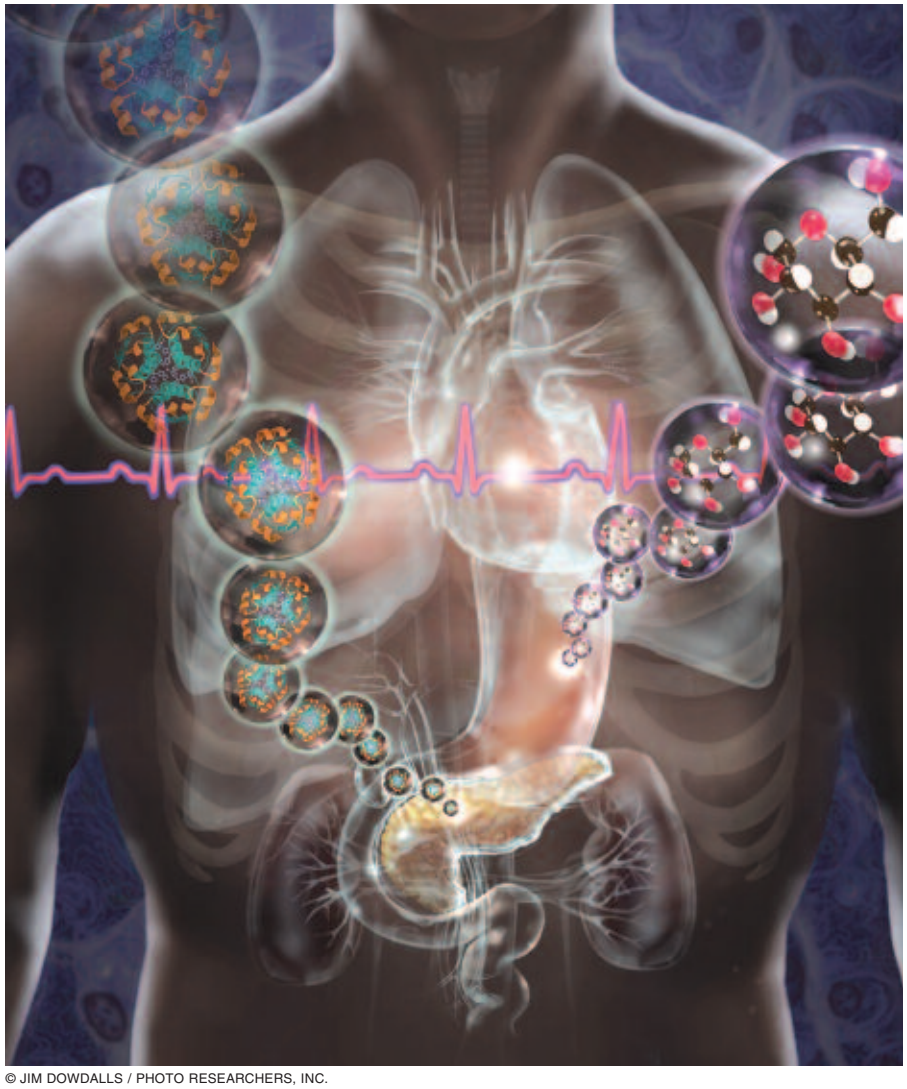
PRODUCT INFORMATION GUIDE



ACTOS® (pioglitazone HCl) in the Management of Type 2 Diabetes

SPECIAL ADVERTISING SECTION

This Product Information Guide is supported by a grant from Takeda.

PHG0801

ACTOS (pioglitazone HCl) in the Management of Type 2 Diabetes

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

Diabetes is a chronic disease in which blood glucose levels are too high (hyperglycemia).[1] Normally, glucose obtained by the digestion of foods is regulated in the bloodstream by the hormone insulin. This ensures that the correct amount of glucose is provided to the cells of the body to be used as a source of energy. Diabetes disrupts this process.[2]

Diabetes is distinguished as three types. In type 1, the pancreas experiences an autoimmune attack by the body and becomes incapable of producing insulin. An individual with type 1 diabetes must be prescribed insulin in order to survive. In type 2, diabetes may arise when excess body weight and physical inactivity cause insufficient insulin to be produced or when insulin cannot be used effectively by the body to control blood glucose levels. Another type, known as gestational diabetes, may occur in pregnant women and resolves when a pregnancy has concluded. However, this can increase the risk of developing chronic diabetes later in life.[3]

Elevated blood glucose can provoke frequent urination and cause dehydration, which increases thirst and water consumption, and also affects protein, fat, and carbohydrate metabolism. Insulin is an anabolic hormone, namely, one that encourages the storage of fat and protein. Relative or absolute insulin deficiency eventually causes weight loss despite an increase in appetite. Some people with untreated diabetes also complain of fatigue, nausea, and vomiting and are susceptible to the development of bladder, skin, and vaginal infections.[4]

Untreated diabetes causes damage to small blood vessels (microvascular disease) and damage to large blood vessels (macrovascular disease). Uncontrolled diabetes can lead to serious damage to the nerves and eyes. It can cause hardening of the arteries (atherosclerosis), which causes heart disease and strokes.[5] Diabetes may eventually necessitate the amputation of limbs.[6] Grossly elevated glucose levels can lead to coma and death.[7]

Prevalence

Diabetes is one of the primary causes of death and disability in the U.S. In 2005, 20.8 million adults and children in the U.S. were estimated to have diabetes. Of these, 6.2 million remain undiagnosed.[8]

There are notable demographic differences for diabetes occurrence in the U.S. For adults 20 years or older, non-Hispanic blacks are 1.8 times more likely to develop diabetes as non-Hispanic whites. Mexican-Americans, the largest Hispanic subgroup, are 1.7 times more likely to develop diabetes as non-Hispanic whites.

Type 2 diabetes typically occurs in individuals over 20 years old and the incidence increases with age. However, clinical reports and regional data suggest that type 2 diabetes is being diagnosed more frequently in children and adolescents, particularly in American Indians, African-Americans, and Latino-Americans.[9]

Contributing Factors

The degree of obesity and type 2 diabetes are causally linked. Excessive body fat has a number of harmful consequences for an individual's health. Increased weight can lead to insulin resistance, which places a greater demand on the pancreas. This stress on the pancreas may then develop into type 2 diabetes. This is true for adults and children.

In the U.S., up to 45% of children with newly diagnosed diabetes are diagnosed with type 2 diabetes, and most are obese.[10]

Diagnostic Assessment

Early assessment and immediate treatment is important. For individuals aged 45 years and older, diabetes testing should

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be considered. For those 45 or older with a Body Mass Index (BMI) indicating possible obesity, testing is highly recommended. For those younger than 45 that are overweight, and have one or more of the risk factors listed below, testing is also recommended. A Fasting Plasma Glucose (FPG) or an Oral Glucose Tolerance Test (OGTT) should be requested from a physician.

Risk Factors:

- Aged 45 or older.
- Overweight or obese.
- A parent, brother, or sister has diabetes.
- Family background is African-American, American Indian, Asian-American, Pacific Islander, or Hispanic-American/Latino.
- Had gestational diabetes or gave birth to at least one baby weighing more than nine pounds.
- Blood pressure is 140/90 or higher, or is diagnosed with high blood pressure.
- Cholesterol levels are not normal.
- Exercises fewer than three times a week.

Based on test results, a physician will recognize normal or pathologically high glucose levels. If blood glucose is higher than normal but lower than the typical diabetes range (prediabetes), it is recommended that blood glucose be checked again in one to two years.[11]

When to Seek Treatment

Following diagnosis, it may be advisable for treatment to start immediately. The goal in treatment is to minimize blood glucose elevations without creating abnormally low levels of blood glucose. Following a healthful diet is crucial for controlling blood glucose. The American Diabetes Association (ADA) provides guidelines for a diet that is balanced and nutritious, containing a wide variety of foods. The key factors are achieving weight control by reducing calories, reducing the intake of dietary fat (specifically saturated fat), and following individualized guidelines for carbohydrate intake based on the type of diabetes diagnosed in order to control blood glucose levels. Total daily calories are divided into three meals. The ADA has also recently removed the complete ban on simple sugars, which are now allowed in small amounts with a complex meal.

Depending on blood glucose levels, a physician may simply recommend weight loss and a modified diet and exercise regimen to delay or prevent the onset of diabetes and its complications. Losing weight and exercising are very important, as they increase the body's responsiveness to insulin, helping to control blood glucose elevations.

Insulin must be used to treat type 1 diabetes along with exercise and diet. Type 2 diabetes is first treated with the aforementioned weight reduction, diet, and exercise regimens. When these measures are not sufficient to control elevated blood glucose, oral medications are employed. Insulin is considered in type 2 diabetes only when other medications are not effective on their own.[12]

Treatments for Type 2 Diabetes

Medications known as DPP-IV inhibitors work by decreasing the breakdown of the incretin hormone that stimulates insulin secretion in the body, thus increasing the body's ability to produce insulin.[13]

Metformin, a member of the biguanide class of drugs, available for many years in Europe and Canada, and FDA approved for use in the U.S. since 1994, is effective in reducing glucose production by the liver. It may be used by itself or with other medications, but it is not indicated for those with kidney impairment and should be employed with caution for those with liver disease.[14]

Sulfonylureas are insulin stimulators and work by increasing the release of insulin from the pancreas. These drugs are effective in lowering blood glucose rapidly, but can cause hypoglycemia and should be avoided by patients allergic to sulfa drugs.[15]

Meglitinides raise insulin levels rapidly by enhancing insulin release from the pancreas over a short period of time when the blood glucose level is high, so that the risk of hypoglycemia is reduced. Their activity mimics insulin release when food is eaten by a person without diabetes. However, certain drugs may increase or decrease the effect of these medications.[16]

About ACTOS (pioglitazone HCl)

ACTOS, approved by the FDA in July of 1999, is a thiazolidinedione or TZD, an oral diabetes medication that makes the cells in the body more sensitive to insulin. When cells are more sensitive to insulin, glucose in the blood moves more easily into the cells of the body where it is needed, rather than remaining in the bloodstream where it can rise to dangerous levels.

ACTOS is a once-a-day prescription medication for type 2 diabetes that, along with healthful eating and physical activity, helps control blood glucose levels. ACTOS can be used by itself or in combination with metformin, insulin, or sulfonylureas when healthful eating and physical activity do not control blood glucose levels alone. The once-a-day medication regimen is convenient and can be taken at any time of the day, with or without food. Though not intended to treat lipid disorders, ACTOS does offer additional lipid improvements as it may improve HDL (good) cholesterol and lower triglyceride levels, but with no con-

sistent change in LDL or total cholesterol.

ACTOS has not been associated with stomach upset when used alone, an important factor for treatment adherence. Taken alone, ACTOS does not cause hypoglycemia (low blood glucose levels). ACTOS often begins working immediately, although it may take several weeks to achieve its full effect.

ACTOS can be used alone or in combination with certain other diabetes medicines and is available in three different dose levels. It is also available in combination tablets: ACTO*plus* met® combines ACTOS and metformin in one tablet. *duet*act® combines ACTOS and glimepiride in one tablet.[17]

As with any prescription medication, once started, it is important to adhere to the medication regimen as advised by a physician. The ADA advises that controlling blood glucose prevents short-term and long-term complications of diabetes from developing.[18]

Pharmacokinetic Profile

Serum concentrations of total pioglitazone (pioglitazone plus active metabolites) remain elevated 24 hours after once daily dosing. Steady-state serum concentrations of both pioglitazone and total pioglitazone are achieved within 7 days. At steady-state, two of the pharmacologically active metabolites of pioglitazone, Metabolites III (M-III) and IV (M-IV), reach serum concentrations equal to or greater than pioglitazone. In both healthy volunteers and patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the peak total pioglitazone serum concentrations and 20% to 25% of the total area under the serum concentration-time curve (AUC).

Maximum serum concentration (C_{max}), AUC, and trough serum concentrations (C_{min}) for both pioglitazone and total pioglitazone increase proportionally at doses of 15 mg and 30 mg per day.

Efficacy in Clinical Trials

Monotherapy: ACTOS was studied in three randomized, double-blind, placebo-controlled trials in the U.S. to evaluate the use of ACTOS as monotherapy in patients with type 2 diabetes. These studies examined ACTOS at doses up to 45 mg or placebo once daily in 865 patients.

In a 26-week study, treatment with 15 mg, 30 mg, and 45 mg of ACTOS produced statistically significant improvements in HbA1c and fasting plasma glucose (FPG) at endpoint compared to placebo.

In a 24-week study, 260 patients with type 2 diabetes were randomized to one of two forced-titration ACTOS treatment groups or a mock titration placebo group. Treatment with ACTOS, as described, produced statistically significant improvements in HbA1c and FPG at endpoint compared to placebo.

In a 16-week study, 197 patients with type 2 diabetes were randomized to treatment with 30 mg of ACTOS or placebo once daily. Treatment with 30 mg of ACTOS produced statistically significant improvements in HbA1c and FPG at endpoint compared to placebo.

Combination Therapy: Clinical studies were conducted with ACTOS in combination with sulfonylurea, metformin, and insulin. Three 16-week, randomized, double-blind, placebo-controlled clinical studies and three 24-week, randomized, double-blind, dose-controlled clinical studies evaluated the effects of ACTOS on glycemic control in patients with type 2 diabetes who were inadequately controlled (HbA1c; 8%) despite current therapy with a sulfonylurea, metformin, or insulin. Previous diabetes treatment may have been monotherapy or combination therapy. The therapeutic effect of ACTOS in combination with sulfonylurea, metformin, or insulin was observed in patients regardless of the dosage of the accompanying medication.

Other Clinical Benefits: Patients with lipid abnormalities were included in clinical trials with ACTOS. Overall, patients treated with ACTOS had mean decreases in triglycerides, mean increases in HDL cholesterol, and no consistent mean changes in LDL and total cholesterol. In a 26-week, placebo-controlled, dose-ranging study, mean triglyceride levels decreased in the 15-mg, 30-mg, and 45-mg ACTOS dose groups compared to a mean increase in the placebo group. Mean HDL levels increased to a greater extent in patients treated with ACTOS than in the placebo-treated patients.

Summary: ACTOS is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes, also called non–insulin-dependent diabetes mellitus (NIDDM). 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 do not result in adequate glycemic control.[19]

Safety Advisory

BOXED WARNING: CONGESTIVE HEART FAILURE

Thiazolidinediones (TZDs), including ACTOS, cause or exacerbate congestive heart failure (CHF) in some patients. After initiation of ACTOS and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive rapid weight gain, dyspnea, and/or edema). If these signs and

symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of ACTOS must be considered.

ACTOS is not recommended in patients with symptomatic heart failure. Initiation of ACTOS in patients with established NYHA Class III or IV heart failure is contraindicated.

Cardiac Considerations: Like other TZDs, ACTOS can cause fluid retention when used alone or in combination with other antidiabetic agents, including insulin. Fluid retention may lead to or exacerbate CHF. ACTOS should be used with caution in patients at risk for heart failure. Patients should be monitored for symptoms of heart failure or other adverse events related to fluid retention. In clinical trials, a small number of patients with a history of previously existing cardiac disease were reported to develop CHF when treated with ACTOS in combination with insulin. Reports of CHF have been received in postmarketing experience in patients with and without previously known heart disease.

Hepatic Safety: Reports of hepatitis and of hepatic enzyme elevations to three or more times the upper limit of normal (ULN) have been received in postmarketing experience with pioglitazone. Very rarely, these reports have involved hepatic failure with or without fatal outcome, although causality has not been established. Liver enzymes, including serum ALT, should be evaluated in all patients at initiation of therapy with ACTOS, and periodically thereafter per the clinical judgment of the health care professional. If ALT >2.5X ULN at baseline or if the patient exhibits clinical evidence of active liver disease, do not initiate therapy with ACTOS.

Other Considerations: ACTOS may also be associated with hypoglycemia, edema, anemia, weight gain, and/or ovulation in premenopausal, anovulatory women. Adequate contraception should be recommended for premenopausal women. Macular edema has been reported in some diabetic patients receiving TZD therapy, although a causal relationship is unknown. Persons with diabetes should have routine eye exams and be instructed to immediately report any visual changes to their health care provider. An increased incidence of bone fracture was noted in female patients taking ACTOS. The risk of fracture should be considered in the care of patients treated with ACTOS, particularly females, and attention should be given to assessing and maintaining bone health according to current standards of care.

Well-Tolerated Therapy: In U.S. placebo-controlled ACTOS monotherapy clinical trials, the most common adverse events (≥5%) were upper respiratory tract infection, headache, sinusitis, myalgia, tooth disorder, aggravated diabetes mellitus, and pharyngitis.

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 approved for use as monotherapy and in combination with sulfonylureas, metformin, or insulin when diet and exercise plus the single agent do not result in adequate glycemic control. ACTOS should not be used in patients with type 1 diabetes. Management of type 2 diabetes should also include nutritional counseling, weight reduction as needed, and exercise.

The major metabolic defects in type 2 diabetes are increased peripheral insulin resistance in muscle and fat, decreased pancreatic insulin secretion, and increased hepatic glucose output. Dyslipidemia in insulin resistance is represented by hypertriglyceridemia, decreased HDL levels, and increased small dense LDL particles. Renal and gastrointestinal function are also clinical considerations when prescribing an oral agent for type 2 diabetes.[20]

Conclusion

Diabetes and its complications are major causes of illness and mortality in the U.S.[21] It is estimated that the number of individuals in the U.S. diagnosed with diabetes will increase by 165% by 2050, based on prevalence estimates from 2000.[22]

However, numerous treatments exist. Along with diet modifications and exercise, individuals may be able to prevent or manage the complications of type 2 diabetes, including cardiovascular disease.[23] Cardiovascular disease is the most frequent cause of illness and death for patients with type 2 diabetes. In the PROactive study, there was no increase in mortality or total macrovascular events with ACTOS compared to standard of care in high-risk patients. The percentage of patients who had an event of serious heart failure was higher for patients treated with ACTOS plus standard of care than for patients treated with standard of care. The incidence of death subsequent to a report of serious heart failure was 1.5% in patients treated with ACTOS plus standard of care and 1.4% in patients treated with standard of care.[24]

Pharmacists have a unique opportunity to educate the public about diabetes testing, lifestyle modifications to prevent diabetes and its complications, well-tolerated and reliable treatment options, and the importance of adhering to a medication regimen that controls the disease.u

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COUNSELING CORNER

The following series of questions and answers serves as a patient education aid to assist health care professionals in counseling patients who may be prescribed ACTOS (pioglitazone HCl).

Q. What is type 2 diabetes?
A. Type 2 diabetes (formerly called non–insulin-dependent diabetes mellitus or adult-onset diabetes) occurs when the body does not produce enough insulin or cannot properly use the insulin it makes to control blood sugar. Insulin allows sugar to enter the cells of your body. Once inside the cells, sugar is used as a source of energy. If your body is resistant to the effects of insulin (a condition known as insulin resistance), and if it cannot make enough insulin to overcome that resistance, sugar builds up in the blood (hyperglycemia).

Q. Why is it important to control type 2 diabetes?
A. It is important to control type 2 diabetes because the buildup of sugar in the blood, if not controlled, can lead to serious medical problems such as kidney damage, amputation, heart disease, and blindness.

Q. How can ACTOS help treat type 2 diabetes?
A. ACTOS, along with healthful eating and physical activity, works by treating type 2 diabetes by addressing insulin resistance, a condition of type 2 diabetes. ACTOS helps your body use insulin more effectively by making your cells more sensitive to insulin. That is why it is called an insulin sensitizer. It does not cause your body to produce more insulin; instead, it helps your body respond better to insulin.

Q. What should I discuss with my health professional before taking ACTOS?
A. ACTOS is not for everyone. You should talk to

your health professional if you have a history of congestive heart failure, liver problems, or swelling (edema), or if you are pregnant, intend to become pregnant, or are breast-feeding. ACTOS can cause fluid retention or swelling, which may lead to or worsen heart failure. It is also important to tell your health professional if you are taking other prescription medications or over-the-counter products.

Q. How should I take ACTOS?
A. ACTOS only needs to be taken once a day. Food does not change how ACTOS works, so you can take it with or without meals. To help you remember to take ACTOS, it is a good idea to take it at the same time every day.

Q. How soon will ACTOS begin to work?
A. Your blood sugar levels may be significantly reduced in as quickly as 2 weeks, though the full effect of ACTOS may take several more weeks to be seen. If you do not respond adequately to your starting dose of ACTOS, your health professional may increase your daily dose to improve your blood sugar control.

Q. Can I take ACTOS with other diabetes medications?
A. Only your health professional can determine which medications are best for your type 2 diabetes. If healthful eating, physical activity, and a single drug are not enough to control your diabetes, ACTOS can be taken in combination with certain other medicines (sulfonylureas, metformin, or insulin). Because ACTOS works differently than any of these drugs, combining ACTOS with another diabetes medication can provide additional improvements in your blood sugar levels.

ACTOS is not likely to cause low blood sugar when taken alone, because it does not cause your body to produce more insulin. However, people taking ACTOS with sulfonylureas or insulin may be at increased risk for low blood sugar, and an adjustment in the dose of sulfonylureas or insulin may be needed.

Q. Do I still need to test my blood sugar while using ACTOS?
A. Yes. You should test your blood sugar as often as your health professional recommends.

Q. Can ACTOS increase my risk for pregnancy?
A. If you are a premenopausal woman who is not ovulating, you should know that ACTOS might increase your risk of pregnancy by causing you to ovulate. Therefore, you may need to consider birth control options. However, women using oral contraceptives should talk with their health professionals, as they may be at increased risk for pregnancy if appropriate contraceptive methods or adjustments are not used.u

PATIENT INFORMATION AID: TYPE 2 DIABETES

Diabetes is a disease where the body is no longer able to regulate blood sugar properly. This condition is called "hyperglycemia."

There are three kinds of diabetes. In type 1, the pancreas becomes incapable of naturally producing insulin and insulin must be prescribed. In type 2, excess body weight and physical inactivity cause too little insulin to be produced or insulin that is produced cannot be used effectively by the body. A third type, known as "gestational diabetes," may develop when a woman is pregnant, but ends after pregnancy. However, the woman may then develop chronic diabetes later in life.

Elevated blood sugar is dangerous. It can cause frequent urination, dehydration, and increased thirst and water consumption. Insulin deficiency eventually causes weight loss even as appetite increases. Some people with untreated diabetes experience fatigue, nausea, and vomiting and may be susceptible to the development of bladder, skin, and vaginal infections.

Untreated diabetes causes damage to small blood vessels known as "microvascular disease" and damage to large blood vessels called "macrovascular disease." Uncontrolled diabetes can lead to serious damage to the nerves and eyes, amputations, and hardening of the arteries (atherosclerosis), which causes heart disease and strokes. Very high blood sugar levels can lead to coma and death.

Diagnosis

Diabetes testing should be considered for individuals aged 45 years and older and is recommended for those over 45 who are overweight. For those younger than 45 and overweight, with one or more of the risk factors listed, testing is also recommended. A Fasting Plasma Glucose (FPG) or an Oral Glucose Tolerance Test (OGTT) should be requested from your doctor.

PATIENT INFORMATION AID: TYPE 2 DIABETES

Risk Factors:

- *I am 45 or older.*
- *I am overweight or obese.*
- *I have a parent, brother, or sister with diabetes.*
- *My family background is African-American, American Indian, Asian-American, Pacific Islander, or Hispanic-American/Latino.*
- *I had gestational diabetes, or gave birth to at least one baby weighing more than nine pounds.*
- *My blood pressure is 140/90 or higher, or I have been diagnosed with high blood pressure.*
- *My cholesterol levels are not normal.*
- *I exercise fewer than three times a week.*

Blood sugar higher than normal but lower than the typical diabetes range is called "pre-diabetes" and should be checked again in one to two years in order to prevent the development of diabetes.

Treatment

A doctor may recommend weight loss, an exercise regimen, and a modified diet to minimize blood sugar elevations without creating abnormally low levels of blood sugar in order to prevent, delay, or manage the onset of diabetes. Weight loss and exercise increase the body's sensitivity to insulin, which helps to control high blood sugar levels. The American Diabetes Association (ADA) provides guidelines for a balanced diet that is nutritious and low in fat, cholesterol, and simple sugars.

Insulin must be used to treat type 1 diabetes along with exercise and a diabetic diet. Type 2 diabetes is first treated with weight reduction, a diabetic diet, and exercise. When these measures do not succeed alone, oral medications are used. Insulin is considered in type 2 diabetes only when other medications are not completely effective on their own.

Medication Therapy

One class of medications reduces blood sugar levels by preventing the absorption of carbohydrates from the intestine. Others work to decrease blood sugar levels by limiting glucose production by the liver. Some are prescribed with insulin to better control blood sugar levels rather than using insulin alone. Another class of medications stimulates the body to increase its production of insulin in order to normalize blood sugar levels.

ACTOS is a once-a-day prescription medication that increases the sensitivity of the body's cells to its own naturally produced insulin, that, along with healthful eating and physical activity, helps to control blood sugar levels. It can be used by itself or in combination with other diabetes medications. ACTOS also offers additional benefits as it may improve HDL (good) cholesterol and lower triglyceride levels. When used alone, ACTOS does not cause an upset stomach and does not cause hypoglycemia (low blood sugar levels). Your doctor can advise you if ACTOS is the right medication for you.

If you do need any kind of medication to control diabetes, it is very important to take it regularly and tell your doctor if you have any side effects, rather than stopping the medication on your own.u

IMPORTANT SAFETY INFORMATION FOR PATIENTS

The prescription medication ACTOS is used along with diet and exercise to lower blood sugar (glucose) in adults with type 2 diabetes. ACTOS is taken once daily either alone or in combination with insulin, sulfonylureas, or metformin.

ACTOS is not for everyone. Certain patients with heart failure should not start taking ACTOS. ACTOS can cause or worsen congestive heart failure. Talk to your doctor immediately if you experience rapid weight gain, fluid retention, or shortness of breath.

Do not take ACTOS if you have active liver disease. Your doctor should perform a blood test to check for liver problems before you start ACTOS and periodically thereafter. Talk to your doctor immediately if you experience nausea, vomiting, stomach pain, tiredness, loss of appetite, dark urine, or yellowing of the skin. If you are of childbearing age, talk to your doctor before taking ACTOS, as it could increase your chance of becoming pregnant. Some people taking ACTOS may experience flulike symptoms, mild-to-moderate swelling of legs and ankles, and anemia. Some people, particularly women, are at higher risk of having bone fractures while taking ACTOS. When taking ACTOS with insulin or sulfonylureas, you may be at risk for low blood sugar. Patients with diabetes should have regular eye exams. If you experience vision problems, consult your doctor immediately. Very rarely, some patients have experienced visual changes while taking ACTOS.u

ACTOS®
(pioglitazone hydrochloride) Tablets

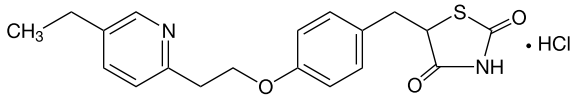
WARNING: CONGESTIVE HEART FAILURE

- Thiazolidinediones, including ACTOS, cause or exacerbate congestive heart failure in some patients (see **WARNINGS**). After initiation of ACTOS, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to the current standards of care. Furthermore, discontinuation or dose reduction of ACTOS must be considered.
- ACTOS is not recommended in patients with symptomatic heart failure. Initiation of ACTOS in patients with established NYHA Class III or IV heart failure is contraindicated (see **CONTRAINDICATIONS** and **WARNINGS**).

DESCRIPTION

ACTOS (pioglitazone hydrochloride) is an oral antidiabetic agent that acts primarily by decreasing insulin resistance. ACTOS is used in the management of type 2 diabetes mellitus (also known as non-insulin-dependent diabetes mellitus [NIDDM] or adult-onset diabetes). Pharmacological studies indicate that ACTOS improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. ACTOS improves glycemic control while reducing circulating insulin levels.

Pioglitazone [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-] thiazolidinedione monohydrochloride belongs to a different chemical class and has a different pharmacological action than the sulfonylureas, metformin, or the α-glucosidase inhibitors. The molecule contains one asymmetric carbon, and the compound is synthesized and used as the racemic mixture. The two enantiomers of pioglitazone interconvert *in vivo*. No differences were found in the pharmacologic activity between the two enantiomers. The structural formula is as shown:



Pioglitazone hydrochloride is an odorless white crystalline powder that has a molecular formula of $C_{19}H_{20}N_2O_3S$•HCl and a molecular weight of 392.90 daltons. It is soluble in *N,N*-dimethylformamide, slightly soluble in anhydrous ethanol, very slightly soluble in acetone and acetonitrile, practically insoluble in water, and insoluble in ether.

ACTOS is available as a tablet for oral administration containing 15 mg, 30 mg, or 45 mg of pioglitazone (as the base) formulated with the following excipients: lactose monohydrate NF, hydroxypropylcellulose NF, carboxymethylcellulose calcium NF, and magnesium stearate NF.

CLINICAL PHARMACOLOGY

Mechanism of Action

ACTOS is a thiazolidinedione antidiabetic agent that depends on the presence of insulin for its mechanism of action. ACTOS decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Unlike sulfonylureas, pioglitazone is not an insulin secretagogue. Pioglitazone is a potent agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism.

In animal models of diabetes, pioglitazone reduces the hyperglycemia, hyperinsulinemia, and hypertriglyceridemia characteristic of insulin-resistant states such as type 2 diabetes. The metabolic changes produced by pioglitazone result in increased responsiveness of insulin-dependent tissues and are observed in numerous animal models of insulin resistance.

Since pioglitazone enhances the effects of circulating insulin (by decreasing insulin resistance), it does not lower blood glucose in animal models that lack endogenous insulin.

Pharmacokinetics and Drug Metabolism

Serum concentrations of total pioglitazone (pioglitazone plus active metabolites) remain elevated 24 hours after once daily dosing. Steady-state serum concentrations of both pioglitazone and total pioglitazone are achieved within 7 days. At steady-state, two of the pharmacologically active metabolites of pioglitazone, Metabolites III (M-III) and IV (M-IV), reach serum concentrations equal to or greater than pioglitazone. In both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the peak total pioglitazone serum concentrations and 20% to 25% of the total area under the serum concentration-time curve (AUC).

Maximum serum concentration (C_{max}), AUC, and trough serum concentrations (C_{min}) for both pioglitazone and total pioglitazone increase proportionally at doses of 15 mg and 30 mg per day. There is a slightly less than proportional increase for pioglitazone and total pioglitazone at a dose of 60 mg per day.

Absorption: Following oral administration, in the fasting state, pioglitazone is first measurable in serum within 30 minutes, with peak concentrations observed within 2 hours. Food slightly delays the time to peak serum concentration to 3 to 4 hours, but does not alter the extent of absorption.

Distribution: The mean apparent volume of distribution (Vd/F) of pioglitazone following single-dose administration is 0.63 ± 0.41 (mean ± SD) L/kg of body weight. Pioglitazone is extensively protein bound (> 99%) in human serum, principally to serum albumin. Pioglitazone also binds to other serum proteins, but with lower affinity. Metabolites M-III and M-IV also are extensively bound (> 98%) to serum albumin.

Metabolism: Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-II and M-IV (hydroxy derivatives of pioglitazone) and M-III (keto derivative of pioglitazone) are pharmacologically active in animal models of type 2 diabetes. In addition to pioglitazone, M-III and M-IV are the principal drug-related species found in human serum following multiple dosing. At steady-state, in both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the total peak serum concentrations and 20% to 25% of the total AUC.

In vitro data demonstrate that multiple CYP isoforms are involved in the metabolism of pioglitazone. The cytochrome P450 isoforms involved are CYP2C8 and, to a lesser degree, CYP3A4 with additional contributions from a variety of other isoforms including the mainly extrahepatic CYP1A1. *In vivo* studies of pioglitazone in combination with P450 inhibitors and substrates have been performed (see **Drug Interactions**). Urinary 6β-hydroxycortisol/cortisol ratios measured in patients treated with ACTOS showed that pioglitazone is not a strong CYP3A4 enzyme inducer.

Excretion and Elimination: Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible, and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces.

The mean serum half-life of pioglitazone and total pioglitazone ranges from 3 to 7 hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be 5 to 7 L/hr.

Special Populations

Renal Insufficiency: The serum elimination half-life of pioglitazone, M-III, and M-IV remains unchanged in patients with moderate (creatinine clearance 30 to 60 mL/min) to severe (creatinine clearance < 30 mL/min) renal impairment when compared to normal subjects. No dose adjustment in patients with renal dysfunction is recommended (see **DOSAGE AND ADMINISTRATION**).

Hepatic Insufficiency: Compared with normal controls, subjects with impaired hepatic function (Child-Pugh Grade B/C) have an approximate 45% reduction in pioglitazone and total pioglitazone mean peak concentrations but no change in the mean AUC values.

ACTOS therapy should not be initiated if the patient exhibits clinical evidence of active liver disease or serum transaminase levels (ALT) exceed 2.5 times the upper limit of normal (see **PRECAUTIONS**, Hepatic Effects).

Elderly: In healthy elderly subjects, peak serum concentrations of pioglitazone and total pioglitazone are not significantly different, but AUC values are slightly higher and the terminal half-life values slightly longer than for younger subjects. These changes were not of a magnitude that would be considered clinically relevant.

Pediatrics: Pharmacokinetic data in the pediatric population are not available.

Gender: The mean C_{max} and AUC values were increased 20% to 60% in females. As monotherapy and in combination with sulfonylurea, metformin, or insulin, ACTOS improved glycemic control in both males and females. In controlled clinical trials, hemoglobin A_{1c} (HbA_{1c}) decreases from baseline were generally greater for females than for males (average mean difference in HbA_{1c} 0.5%). Since therapy should be individualized for each patient to achieve glycemic control, no dose adjustment is recommended based on gender alone.

Ethnicity: Pharmacokinetic data among various ethnic groups are not available.

Drug-Drug Interactions

The following drugs were studied in healthy volunteers with a co-administration of ACTOS 45 mg once daily. Listed below are the results:

Oral Contraceptives: Co-administration of ACTOS (45 mg once daily) and an oral contraceptive (1 mg norethindrone plus 0.035 mg ethinyl estradiol once daily) for 21 days, resulted in 11% and 11-14% decrease in ethinyl estradiol AUC (0-24h) and C_{max} respectively. There were no significant changes in norethindrone AUC (0-24h) and C_{max}. In view of the high variability of ethinyl estradiol pharmacokinetics, the clinical significance of this finding is unknown.

Fexofenadine HCl: Co-administration of ACTOS for 7 days with 60 mg fexofenadine administered orally twice daily resulted in no significant effect on pioglitazone pharmacokinetics. ACTOS had no significant effect on fexofenadine pharmacokinetics.

Glipizide: Co-administration of ACTOS and 5 mg glipizide administered orally once daily for 7 days did not alter the steady-state pharmacokinetics of glipizide.

Digoxin: Co-administration of ACTOS with 0.25 mg digoxin administered orally once daily for 7 days did not alter the steady-state pharmacokinetics of digoxin.

Warfarin: Co-administration of ACTOS for 7 days with warfarin did not alter the steady-state pharmacokinetics of warfarin. ACTOS has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

Metformin: Co-administration of a single dose of metformin (1000 mg) and ACTOS after 7 days of ACTOS did not alter the pharmacokinetics of the single dose of metformin.

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_{max} and AUC.

Ranitidine HCl: Co-administration of ACTOS for 7 days with ranitidine administered orally twice daily for either 4 or 7 days resulted in no significant effect on pioglitazone pharmacokinetics. ACTOS showed no significant effect on ranitidine pharmacokinetics.

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_{max} and 0.88 (0.80 - 0.96) for AUC. In view of the high variability of nifedipine pharmacokinetics, the clinical significance of this finding is unknown.

Ketoconazole: Co-administration of ACTOS for 7 days with ketoconazole 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_{max}, 1.34 (1.26 - 1.41) for AUC and 1.87 (1.71 - 2.04) for C_{min}.

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_{max}, 0.76 (0.65 - 0.88) for AUC and 0.96 (0.87 - 1.05) for C_{min}. For unchanged atorvastatin the least square mean (90% CI) values were 0.77 (0.66 - 0.90) for C_{max}, 0.86 (0.78 - 0.94) for AUC and 0.92 (0.82 - 1.02) for C_{min}.

Theophylline: Co-administration of ACTOS for 7 days with theophylline 400 mg administered twice daily resulted in no change in the pharmacokinetics of either drug.

Cytochrome P450: See **PRECAUTIONS**

Gemfibrozil: Concomitant administration of gemfibrozil (oral 600 mg twice daily), an inhibitor of CYP2C8, with pioglitazone (oral 30 mg) in 10 healthy volunteers pre-treated for 2 days prior with gemfibrozil (oral 600 mg twice daily) resulted in pioglitazone exposure (AUC_{0-24}) being 226% of the pioglitazone exposure in the absence of gemfibrozil (see **PRECAUTIONS**).[1]

Rifampin: Concomitant administration of rifampin (oral 600 mg once daily), an inducer of CYP2C8 with pioglitazone (oral 30 mg) in 10 healthy volunteers pre-treated for 5 days prior with rifampin (oral 600 mg once daily) resulted in a decrease in the AUC of pioglitazone by 54% (see **PRECAUTIONS**).[2]

Pharmacodynamics and Clinical Effects

Clinical studies demonstrate that ACTOS improves insulin sensitivity in insulin-resistant patients. ACTOS enhances cellular responsiveness to insulin, increases insulin-dependent glucose disposal, improves hepatic sensitivity to insulin, and improves dysfunctional glucose homeostasis. In patients with type 2 diabetes, the decreased insulin resistance produced by ACTOS results in lower plasma glucose concentrations, lower plasma insulin levels, and lower HbA_{1c} values. Based on results from an open-label extension study, the glucose lowering effects of ACTOS appear to persist for at least one year. In controlled clinical trials, ACTOS in combination with sulfonylurea, metformin, or insulin had an additive effect on glycemic control.

Patients with lipid abnormalities were included in clinical trials with ACTOS. Overall, patients treated with ACTOS had mean decreases in triglycerides, mean increases in HDL cholesterol, and no consistent mean changes in LDL and total cholesterol.

In a 26-week, placebo-controlled, dose-ranging study, mean triglyceride levels decreased in the 15 mg, 30 mg, and 45 mg ACTOS dose groups compared to a mean increase in the placebo group. Mean HDL levels increased to a greater extent in patients treated with ACTOS than in the placebo-treated patients. There were no consistent differences for LDL and total cholesterol in patients treated with ACTOS compared to placebo (**Table 1**).

Table 1 Lipids in a 26-Week Placebo-Controlled Monotherapy Dose-Ranging Study

	Placebo	ACTOS 15 mg Once Daily	ACTOS 30 mg Once Daily	ACTOS 45 mg Once Daily
Triglycerides (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	262.8	283.8	261.1	259.7
Percent change from baseline (mean)	4.8%	-9.0%	-9.6%	-9.3%
HDL Cholesterol (mg/dL)	N=79	N=79	N=83	N=77
Baseline (mean)	41.7	40.4	40.8	40.7
Percent change from baseline (mean)	8.1%	14.1%	12.2%	19.1%
LDL Cholesterol (mg/dL)	N=65	N=63	N=74	N=62
Baseline (mean)	138.8	131.9	135.6	126.8
Percent change from baseline (mean)	4.8%	7.2%	5.2%	6.0%
Total Cholesterol (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	224.6	220.0	222.7	213.7
Percent change from baseline (mean)	4.4%	4.6%	3.3%	6.4%

In the two other monotherapy studies (24 weeks and 16 weeks) and in combination therapy studies with sulfonylurea (24 weeks and 16 weeks) and metformin (24 weeks and 16 weeks), the results were generally consistent with the data above. In placebo-controlled trials, the placebo-corrected mean changes from baseline decreased 5% to 26% for triglycerides and increased 6% to 13% for HDL in patients treated with ACTOS. A similar pattern of results was seen in 24-week combination therapy studies of ACTOS with sulfonylurea or metformin.

In a combination therapy study with insulin (16 weeks), the placebo-corrected mean percent change from baseline in triglyceride values for patients treated with ACTOS was also decreased. A placebo-corrected mean change from baseline in LDL cholesterol of 7% was observed for the 15 mg dose group. Similar results to those noted above for HDL and total cholesterol were observed. A similar pattern of results was seen in a 24-week combination therapy study with ACTOS with insulin.

Clinical Studies

Monotherapy

In the U.S., three randomized, double-blind, placebo-controlled trials with durations from 16 to 26 weeks were conducted to evaluate the use of ACTOS as monotherapy in patients with type 2 diabetes. These studies examined ACTOS at doses up to 45 mg or placebo once daily in 865 patients.

In a 26-week, dose-ranging study, 408 patients with type 2 diabetes were randomized to receive 7.5 mg, 15 mg, 30 mg, or 45 mg of ACTOS, or placebo once daily. Therapy with any previous antidiabetic agent was discontinued 8 weeks prior to the double-blind period. Treatment with 15 mg, 30 mg, and 45 mg of ACTOS produced statistically significant improvements in HbA_{1c} and fasting plasma glucose (FPG) at endpoint compared to placebo (**Figure 1, Table 2**).

Figure 1 shows the time course for changes in FPG and HbA_{1c} for the entire study population in this 26-week study.

Figure 1 Mean Change from Baseline for FPG and HbA_{1c} in a 26-Week Placebo-Controlled Dose-Ranging Study

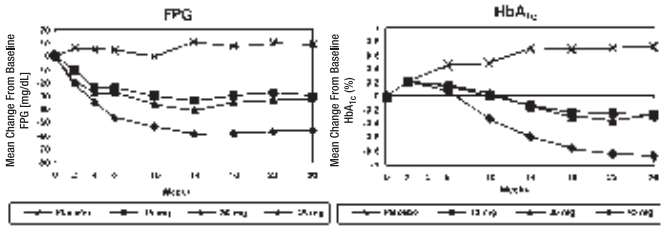


Table 2 shows HbA_{1c} and FPG values for the entire study population.

Table 2 Glycemic Parameters in a 26-Week Placebo-Controlled Dose-Ranging Study

	Placebo	ACTOS 15 mg Once Daily	ACTOS 30 mg Once Daily	ACTOS 45 mg Once Daily
Total Population				
HbA_{1c} (%)	N=79	N=79	N=85	N=76
Baseline (mean)	10.4	10.2	10.2	10.3
Change from baseline (adjusted mean+)	0.7	-0.3	-0.3	-0.9
Difference from placebo (adjusted mean+)		-1.0*	-1.0*	-1.6*
FPG (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	268	267	269	276
Change from baseline (adjusted mean+)	9	-30	-32	-56
Difference from placebo (adjusted mean+)		-39*	-41*	-65*

+ Adjusted for baseline, pooled center, and pooled center by treatment interaction
* $p \leq 0.050$ vs. placebo

The study population included patients not previously treated with antidiabetic medication (naïve; 31%) and patients who were receiving antidiabetic medication at the time of study enrollment (previously treated; 69%). The data for the naïve and previously-treated patient subsets are shown in Table 3. All patients entered an 8 week washout/run-in period prior to double-blind treatment. This run-in period was associated with little change in HbA_{1c} and FPG values from screening to baseline for the naïve patients; however, for the previously-treated group, washout from previous antidiabetic medication resulted in deterioration of glycemic control and increases in HbA_{1c} and FPG. Although most patients in the previously-treated group had a decrease from baseline in HbA_{1c} and FPG with ACTOS, in many cases the values did not return to screening levels by the end of the study. The study design did not permit the evaluation of patients who switched directly to ACTOS from another antidiabetic agent.

Table 3 Glycemic Parameters in a 26-Week Placebo-Controlled Dose-Ranging Study

	Placebo	ACTOS 15 mg Once Daily	ACTOS 30 mg Once Daily	ACTOS 45 mg Once Daily
Naïve to Therapy				
HbA_{1c} (%)	N=25	N=26	N=26	N=21
Screening (mean)	9.3	10.0	9.5	9.8
Baseline (mean)	9.0	9.9	9.3	10.0
Change from baseline (adjusted mean*)	0.6	-0.8	-0.6	-1.9
Difference from placebo (adjusted mean*)		-1.4	-1.3	-2.6
FPG (mg/dL)	N=25	N=26	N=26	N=21
Screening (mean)	223	245	239	239
Baseline (mean)	229	251	225	235
Change from baseline (adjusted mean*)	16	-37	-41	-64
Difference from placebo (adjusted mean*)		-52	-56	-80
Previously Treated				
HbA_{1c} (%)	N=54	N=53	N=59	N=55
Screening (mean)	9.3	9.0	9.1	9.0
Baseline (mean)	10.9	10.4	10.4	10.6
Change from baseline (adjusted mean*)	0.8	-0.1	-0.0	-0.6
Difference from placebo (adjusted mean*)		-1.0	-0.9	-1.4
FPG (mg/dL)	N=54	N=53	N=58	N=56
Screening (mean)	222	209	230	215
Baseline (mean)	285	275	286	292
Change from baseline (adjusted mean*)	4	-32	-27	-55
Difference from placebo (adjusted mean*)		-36	-31	-59

* Adjusted for baseline and pooled center

In a 24-week, placebo-controlled study, 260 patients with type 2 diabetes were randomized to one of two forced-titration ACTOS treatment groups or a mock titration placebo group. Therapy with any previous antidiabetic agent was discontinued 6 weeks prior to the double-blind period. In one ACTOS treatment group, patients received an initial dose of 7.5 mg once daily. After four weeks, the dose was increased to 15 mg once daily and after another four weeks, the dose was increased to 30 mg once daily for the remainder of the study (16 weeks). In the second ACTOS treatment group, patients received an initial dose of 15 mg once daily and were titrated to 30 mg once daily and 45 mg once daily in a similar manner. Treatment with ACTOS, as described, produced statistically significant improvements in HbA_{1c} and FPG at endpoint compared to placebo (**Table 4**).

Table 4 Glycemic Parameters in a 24-Week Placebo-Controlled Forced-Titration Study

	Placebo	ACTOS 30 mg+ Once Daily	ACTOS 45 mg+ Once Daily
Total Population			
HbA_{1c} (%)	N=83	N=85	N=85
Baseline (mean)	10.8	10.3	10.8
Change from baseline (adjusted mean++)	0.9	-0.6	-0.6
Difference from placebo (adjusted mean++)		-1.5*	-1.5*
FPG (mg/dL)	N=78	N=82	N=85
Baseline (mean)	279	268	281
Change from baseline (adjusted mean++)	18	-44	-50
Difference from placebo (adjusted mean++)		-62*	-68*

+ Final dose in forced titration
++ Adjusted for baseline, pooled center, and pooled center by treatment interaction
* $p \leq 0.050$ vs. placebo

For patients who had not been previously treated with antidiabetic medication (24%), mean values at screening were 10.1% for HbA_{1c} and 238 mg/dL for FPG. At baseline, mean HbA_{1c} was 10.2% and mean FPG was 243 mg/dL. Compared with placebo, treatment with ACTOS titrated to a final dose of 30 mg and 45 mg resulted in reductions from baseline in mean HbA_{1C} of 2.3% and 2.6% and mean FPG of 63 mg/dL and 95 mg/dL, respectively. For patients who had been previously treated with antidiabetic medication (76%), this medication was discontinued at screening. Mean values at screening were 9.4% for HbA_{1c} and 216 mg/dL for FPG. At baseline, mean HbA_{1c} was 10.7% and mean FPG was 290 mg/dL. Compared with placebo, treatment with ACTOS titrated to a final dose of 30 mg and 45 mg resulted in reductions from baseline in mean HbA_{1c} of 1.3% and 1.4% and mean FPG of 55 mg/dL and 60 mg/dL, respectively. For many previously-treated patients, HbA_{1c} and FPG had not returned to screening levels by the end of the study.

In a 16-week study, 197 patients with type 2 diabetes were randomized to treatment with 30 mg of ACTOS or placebo once daily. Therapy with any previous antidiabetic agent was discontinued 6 weeks prior to the double-blind period. Treatment with 30 mg of ACTOS produced statistically significant improvements in HbA_{1c} and FPG at endpoint compared to placebo (**Table 5**).

Table 5 Glycemic Parameters in a 16-Week Placebo-Controlled Study

	Placebo	ACTOS 30 mg Once Daily
Total Population		
HbA_{1c} (%)	N=93	N=100
Baseline (mean)	10.3	10.5
Change from baseline (adjusted mean+)	0.8	-0.6
Difference from placebo (adjusted mean+)		-1.4*
FPG (mg/dL)	N=91	N=99
Baseline (mean)	270	273
Change from baseline (adjusted mean+)	8	-50
Difference from placebo (adjusted mean+)		-58*

+ Adjusted for baseline, pooled center, and pooled center by treatment interaction
* $p \leq 0.050$ vs. placebo

For patients who had not been previously treated with antidiabetic medication (40%), mean values at screening were 10.3% for HbA_{1c} and 240 mg/dL for FPG. At baseline, mean HbA_{1c} was 10.4% and mean FPG was 254 mg/dL. Compared with placebo, treatment with ACTOS 30 mg resulted in reductions from baseline in mean HbA_{1c} of 1.0% and mean FPG of 62 mg/dL. For patients who had been previously treated with antidiabetic medication (60%), this medication was discontinued at screening. Mean values at screening were 9.4% for HbA_{1c} and 216 mg/dL for FPG. At baseline, mean HbA_{1c} was 10.6% and mean FPG was 287 mg/dL. Compared with placebo, treatment with ACTOS 30 mg resulted in reductions from baseline in mean HbA_{1c} of 1.3% and mean FPG of 46 mg/dL. For many previously-treated patients, HbA_{1c} and FPG had not returned to screening levels by the end of the study.

Combination Therapy

Three 16-week, randomized, double-blind, placebo-controlled clinical studies and three 24-week, randomized, double-blind, dose-controlled clinical studies were conducted to evaluate the effects of ACTOS on glycemic control in patients with type 2 diabetes who were inadequately controlled ($HbA_{1c} \geq 8\%$) despite current therapy with a sulfonylurea, metformin, or insulin. Previous diabetes treatment may have been monotherapy or combination therapy.

ACTOS Plus Sulfonylurea Studies

Two clinical studies were conducted with ACTOS in combination with a sulfonylurea. Both studies included patients with type 2 diabetes on a sulfonylurea, either alone or in combination with another antidiabetic agent. All other antidiabetic agents were withdrawn prior to starting study treatment. In the first study, 560 patients were randomized to receive 15 mg or 30 mg of ACTOS or placebo once daily for 16 weeks in addition to their current sulfonylurea regimen. When compared to placebo at Week 16, the addition of ACTOS to the sulfonylurea significantly reduced the mean HbA_{1c} by 0.9% and 1.3% and mean FPG by 39 mg/dL and 58 mg/dL for the 15 mg and 30 mg doses, respectively.

In the second study, 702 patients were randomized to receive 30 mg or 45 mg of ACTOS once daily for 24 weeks in addition to their current sulfonylurea regimen. The mean reductions from baseline at Week 24 in HbA_{1c} were 1.55% and 1.67% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 51.5 mg/dL and 56.1 mg/dL.

The therapeutic effect of ACTOS in combination with sulfonylurea was observed in patients regardless of whether the patients were receiving low, medium, or high doses of sulfonylurea.

ACTOS Plus Metformin Studies

Two clinical studies were conducted with ACTOS in combination with metformin. Both studies included patients with type 2 diabetes on metformin, either alone or in combination with another antidiabetic agent. All other antidiabetic agents were withdrawn prior to starting study treatment. In the first study, 328 patients were randomized to receive either 30 mg of ACTOS or placebo once daily for 16 weeks in addition to their current metformin regimen. When compared to placebo at Week 16, the addition of ACTOS to metformin significantly reduced the mean HbA_{1c} by 0.8% and decreased the mean FPG by 38 mg/dL.

In the second study, 827 patients were randomized to receive either 30 mg or 45 mg of ACTOS once daily for 24 weeks in addition to their current metformin regimen. The mean reductions from baseline at Week 24 in HbA_{1c} were 0.80% and 1.01% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 38.2 mg/dL and 50.7 mg/dL.

The therapeutic effect of ACTOS in combination with metformin was observed in patients regardless of whether the patients were receiving lower or higher doses of metformin.

ACTOS Plus Insulin Studies

Two clinical studies were conducted with ACTOS in combination with insulin. Both studies included patients with type 2 diabetes on insulin, either alone or in combination with another antidiabetic agent. All other antidiabetic agents were withdrawn prior to starting study treatment. In the first study, 566 patients receiving a median of 60.5 units per day of insulin were randomized to receive either 15 mg or 30 mg of ACTOS or placebo once daily for 16 weeks in addition to their insulin regimen. When compared to placebo at Week 16, the addition of ACTOS to insulin significantly reduced both HbA_{1c} by 0.7% and 1.0% and FPG by 35 mg/dL and 49 mg/dL for the 15 mg and 30 mg dose, respectively.

In the second study, 690 patients receiving a median of 60.0 units per day of insulin received either 30 mg or 45 mg of ACTOS once daily for 24 weeks in addition to their current insulin regimen. The mean reductions from baseline at Week 24 in HbA_{1c} were 1.17% and 1.46% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 31.9 mg/dL and 45.8 mg/dL. Improved glycemic control was accompanied by mean decreases from baseline in insulin dose requirements of 6.0% and 9.4% per day for the 30 mg and 45 mg dose, respectively.

The therapeutic effect of ACTOS in combination with insulin was observed in patients regardless of whether the patients were receiving lower or higher doses of insulin.

INDICATIONS AND USAGE

ACTOS is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes (non-insulin-dependent diabetes mellitus, NIDDM). 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 do 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

Initiation of ACTOS in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated (see **BOXED WARNING**).

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, 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 signs and symptoms of heart failure. If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of ACTOS must be considered (see **BOXED WARNING**). Patients with NYHA Class III and IV cardiac status were not studied during pre-approval clinical trials and ACTOS is not recommended in these patients (see **BOXED WARNING** and **CONTRAINDICATIONS**).

In one 16-week, U.S. 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 (8.8%), vascular disease (6.4%), angina pectoris (4.4%), stroke and/or transient ischemic attack (4.1%), and congestive heart failure (2.3%).

In this study, two of the 191 patients receiving 15 mg ACTOS plus insulin (1.1%) and two of the 188 patients receiving 30 mg ACTOS plus insulin (1.1%) developed congestive heart failure compared with none of the 187 patients on insulin therapy alone. All four of these patients had previous histories of cardiovascular conditions including coronary artery disease, previous CABG procedures, and myocardial infarction. In a 24-week, dose-controlled study in which ACTOS was coadministered 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.

Analysis of data from these studies did not identify specific factors that predict increased risk of congestive heart failure on combination therapy with insulin.

In type 2 diabetes and congestive heart failure (systolic dysfunction)

A 24-week post-marketing safety study was performed to compare ACTOS (n=262) to glyburide (n=256) in uncontrolled diabetic patients (mean HbA_{1c} 8.8% at baseline) with NYHA Class II and III heart failure and ejection fraction less than 40% (mean EF 30% at baseline). Over the course of the study, overnight hospitalization for congestive heart failure was reported in 9.9% of patients on ACTOS compared to 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 over 64 years of age. No difference in cardiovascular mortality between the treatment groups was observed.

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 and symptoms of CHF exacerbation.

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 once daily, or placebo (n=2633) (see **ADVERSE REACTIONS**). The percentage of patients who had an event of serious heart failure was higher for patients treated with ACTOS (5.7%, n=149) than for patients treated with placebo (4.1%, n=108). The incidence of death subsequent to a report of serious heart failure was 1.5% (n=40) in patients treated with ACTOS and 1.4% (n=37) in placebo-treated patients. In patients treated with an insulin-containing regimen at baseline, the incidence of serious heart failure was 6.3% (n=54/864) with ACTOS and 5.2% (n=47/896) with placebo. For those patients treated with a sulfonylurea-containing regimen at baseline, the incidence of serious heart failure was 5.8% (n=94/1624) with ACTOS and 4.4% (n=71/1626) with placebo.

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 for the treatment of diabetic ketoacidosis.

Hypoglycemia: Patients receiving ACTOS in combination 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 U.S. placebo-controlled clinical trials that excluded patients with New York Heart Association (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 congestive heart failure 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 congestive heart failure 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 U.S. clinical trials, edema was reported more frequently in patients treated with ACTOS than in placebo-treated patients and appears to be dose related (see **ADVERSE REACTIONS**). In postmarketing experience, reports of initiation or worsening of edema have been received. Since thiazolidinediones, including ACTOS, can cause fluid retention, which can exacerbate or lead to congestive heart failure, ACTOS should be used with caution in patients at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure (see **BOXED WARNING**, **WARNINGS**, and **PRECAUTIONS**, **Information for Patients**).

Weight Gain: Dose related weight gain was seen with ACTOS alone and in combination with other hypoglycemic agents (**Table 6**). The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Table 6 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^{th} / 75^{th} percentile)	Median (25^{th} / 75^{th} percentile)	Median (25^{th} / 75^{th} percentile)	Median (25^{th} / 75^{th} percentile)
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
Combination Therapy	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
	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 thiazolidinediones, 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. Thus, 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.

Hematologic: ACTOS may cause decreases in hemoglobin and hematocrit. Across all clinical studies, mean hemoglobin values declined by 2% to 4% in patients treated with ACTOS. These changes primarily occurred within the first 4 to 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, over 4500 subjects were treated with ACTOS. In U.S. clinical studies, over 4700 patients with type 2 diabetes received ACTOS. There was no evidence of drug-induced hepatotoxicity or elevation of ALT levels in the clinical studies.

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

In postmarketing experience with ACTOS, reports of hepatitis and of hepatic enzyme elevations to 3 or more times the upper limit of normal have been received. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established.

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

Therapy with ACTOS should not be initiated if the patient exhibits clinical evidence of active liver disease or the ALT levels exceed 2.5 times the upper limit of normal. Patients with mildly elevated liver enzymes (ALT levels at 1 to 2.5 times the upper limit of normal) at baseline or any time during therapy with ACTOS should be evaluated to determine the cause of the liver enzyme elevation. Initiation or continuation of therapy with ACTOS 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 > 2.5 times the upper limit of normal), liver function tests should be evaluated more frequently until the levels return to normal or pretreatment values. If ALT levels exceed 3 times the upper limit of normal, the test should be repeated as soon as possible. If ALT levels remain > 3 times the upper limit of normal or if the patient is jaundiced, ACTOS therapy should be discontinued.

Macular Edema: Macular edema has been reported in post-marketing experience in diabetic patients who were taking pioglitazone or another thiazolidinedione. Some patients presented with blurred vision or decreased visual acuity, but some patients appear to have been diagnosed on routine ophthalmologic examination. Some patients had peripheral edema at the time macular edema was diagnosed. Some patients had improvement in their macular edema after discontinuation of their thiazolidinedione. It is unknown whether or not there is a causal relationship between pioglitazone and macular edema. Patients with diabetes should have regular eye examinations by an ophthalmologist, per the Standards of Care of the American Diabetes Association. Additionally, any diabetic who reports any kind of visual symptom should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings (see **ADVERSE REACTIONS**).

Fractures: In a randomized trial (PROactive) in patients with type 2 diabetes (mean duration of diabetes 9.5 years), an increased incidence of bone fracture was noted in female patients taking pioglitazone. During a mean follow-up of 34.5 months, the incidence of bone fracture in females was 5.1% (44/870) for pioglitazone versus 2.5% (23/905) for placebo. This difference was noted after the first year of treatment and remained during the course of the study. The majority of fractures observed in female patients were nonvertebral fractures including lower limb and distal upper limb. No increase in fracture rates was observed in men treated with pioglitazone 1.7% (30/1735) versus placebo 2.1% (37/1728). The risk of fracture should be considered in the care of patients, especially female patients, treated with pioglitazone and attention should be given to assessing and maintaining bone health according to current standards of care.

Laboratory Tests

FPG and HbA_{1c} 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 care professional (see **PRECAUTIONS**, **General**, Hepatic Effects and **ADVERSE REACTIONS**, **Serum Transaminase Levels**).

Information for Patients

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

Patients who experience an unusually 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 care 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 its development should be explained to patients and their family members.

Therapy with ACTOS, like other thiazolidinediones, 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. Thus, 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 (see **CLINICAL PHARMACOLOGY, Metabolism** and **Drug-Drug Interactions**).

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 (see **CLINICAL PHARMACOLOGY**, **Drug-Drug Interactions**).

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/m^2). 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/m^2). 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/m^2). 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 AS52/XPRT), 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/m^2).

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/m^2). 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/m^2). 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/m^2), 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/m^2).

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/m^2, 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/m^2). 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/m^2). 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/m^2).

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 7.

Table 7 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 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 and **DOSAGE and ADMINISTRATION**, **Combination Therapy**).

In U.S. 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% (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 8** 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 8

Number of First and Total Events for Each Component within the Cardiovascular Composite Endpoint

	Placebo N=2633		ACTOS N=2605	
Cardiovascular Events	First Events (N)	Total Events (N)	First Events (N)	Total Events (N)
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 ≥ 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 overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

DOSAGE AND ADMINISTRATION

ACTOS should be taken once daily without regard to meals.

The management of antidiabetic therapy should be individualized. Ideally, the response to therapy should be evaluated using HbA_{1c} which is a better indicator of long-term glycemic control than FPG alone. HbA_{1c} reflects glycemia over the past two to three months. In clinical use, it is recommended that patients be treated with ACTOS for a period of time adequate to evaluate change in HbA_{1c} (three months) unless glycemic control deteriorates. After initiation of ACTOS or with dose increase, patients should be carefully monitored for adverse events related to fluid retention (see **BOXED WARNING** and **WARNINGS**).

Monotherapy

ACTOS monotherapy in patients not adequately controlled with diet and exercise may be initiated at 15 mg or 30 mg once daily. For patients who respond inadequately to the initial dose of ACTOS, the dose can be increased in increments up to 45 mg once daily. For patients not responding adequately to monotherapy, combination therapy should be considered.

Combination Therapy

Sulfonylureas: ACTOS in combination with a sulfonylurea may be initiated at 15 mg or 30 mg once daily. The current sulfonylurea dose can be continued upon initiation of ACTOS therapy. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased.

Metformin: ACTOS in combination with metformin may be initiated at 15 mg or 30 mg once daily. The current metformin dose can be continued upon initiation of ACTOS therapy. It is unlikely that the dose of metformin will require adjustment due to hypoglycemia during combination therapy with ACTOS.

Insulin: ACTOS in combination with insulin may be initiated at 15 mg or 30 mg once daily. The current insulin dose can be continued upon initiation of ACTOS therapy. In patients receiving ACTOS and insulin, the insulin dose can be decreased by 10% to 25% if the patient reports hypoglycemia or if plasma glucose concentrations decrease to less than 100 mg/dL. Further adjustments should be individualized based on glucose-lowering response.

Maximum Recommended Dose

The dose of ACTOS should not exceed 45 mg once daily in monotherapy or in combination with sulfonylurea, metformin, or insulin.

Dose adjustment in patients with renal insufficiency is not recommended (see **CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism).**

Therapy with ACTOS should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT greater than 2.5 times the upper limit of normal) at start of therapy (see **PRECAUTIONS, General**, Hepatic Effects and **CLINICAL PHARMACOLOGY**, **Special Populations**, Hepatic Insufficiency). Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with ACTOS and periodically thereafter (see **PRECAUTIONS**, **General**, Hepatic Effects).

There are no data on the use of ACTOS in patients under 18 years of age; therefore, use of ACTOS in pediatric patients is not recommended.

No data are available on the use of ACTOS in combination with another thiazolidinedione.

HOW SUPPLIED

ACTOS is available in 15 mg, 30 mg, and 45 mg tablets as follows:

15 mg Tablet: white to off-white, round, convex, non-scored tablet with "ACTOS" on one side, and "15" on the other, available in:
NDC 64764-151-04 Bottles of 30
NDC 64764-151-05 Bottles of 90
NDC 64764-151-06 Bottles of 500

30 mg Tablet: white to off-white, round, flat, non-scored tablet with "ACTOS" on one side, and "30" on the other, available in:
NDC 64764-301-14 Bottles of 30
NDC 64764-301-15 Bottles of 90
NDC 64764-301-16 Bottles of 500

45 mg Tablet: white to off-white, round, flat, non-scored tablet with "ACTOS" on one side, and "45" on the other, available in:
NDC 64764-451-24 Bottles of 30
NDC 64764-451-25 Bottles of 90
NDC 64764-451-26 Bottles of 500

STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed, and protect from moisture and humidity.

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