Cardiovascular Disease and Diabetes

A Science Writer's Guide

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1. Introduction

What is "CardioDiabetes"?

In recent years, scientists and physicians are recognizing a growing convergence of two epidemic diseases – cardiovascular disease and diabetes. CardioDiabetes is a term increasingly being used to refer to this convergence. According to the AHA/ADA Consensus Statement, diabetes is an independent risk factor for cardiovascular disease. In fact, some experts are of the opinion that "diabetes *is* a cardiovascular disease."

Consider the facts:

- Cardiovascular disease is the leading cause of premature death among people with diabetes.
- Adults with diabetes are two to four times more likely to have heart disease or suffer a stroke than people without diabetes.
- A diagnosis of diabetes as an adult presents the same risk as already having one heart attack.

This convergence of heart disease and type 2 diabetes, "CardioDiabetes," represents a much wider spectrum of diabetes and heart disease than you may have realized exists.

The Progression of Cardiovascular Disease in Persons With Type 2 Diabetes

"CardioDiabetes" doesn't start when a heart attack or stroke occurs. Rather, it begins many years earlier.

First, the initial hidden phase – **subclinical heart disease with concomitant type 2 diabetes** – is only now being more fully diagnosed and recognized. By definition, subclinical is a period before the appearance of symptoms typical of a disease. Subclinical diabetic heart disease may include problems such as abnormalities at the cellular level of the heart, and is of growing concern to specialists who treat patients with type 2 diabetes.

Second, there are the **clinical manifestations of cardiovascular disease in people with type 2 diabetes**, who are at risk for a variety of factors. These include high blood pressure and lipid disorders, such as diabetic dyslipidemia (low levels of HDL-C and high levels of triglycerides).

Cardiovascular disease (CVD) is the leading cause of diabetes-related death. At least 65 percent of deaths among people with diabetes are due to heart disease and stroke.

This guide, which was developed by Takeda Pharmaceutical Company Limited, provides the latest insights on why "CardioDiabetes" happens, how it is different from CVD in people without diabetes, and what can be done to help prevent the convergence of these two diseases.

2. About Cardiovascular Disease (CVD)

What is the magnitude of the CVD problem worldwide?

- According to World Health Organization (WHO) estimates, nearly 17 million people around the globe die of cardiovascular diseases each year. This is about one-third of all deaths globally.
- By 2020, heart disease and stroke will become the leading cause of both death and disability worldwide, with the number of fatalities projected to increase to more than 20 million a year and to more than 24 million a year by 2030.
- CVD is the leading cause of death in the European Union (EU), accounting for over 1.5 million deaths each year. Nearly half of all deaths in the EU are from CVD.

The two major types of diabetic vascular disease complications are:

- *Microvascular complications*, which affect small blood vessels such as those found in the eyes and kidneys.
- *Macrovascular complications*, which affect large blood vessels such as those in the heart, leading to heart attack and/or stroke.

Some alarming international statistics associated with CVD:

- About 15-37 percent of the global adult population has high blood pressure. In those older than age 60, as many as one-half in some populations have high blood pressure.
- According to WHO, in 2002 there were 7.22 million deaths from coronary heart disease (CHD) globally.
- Each year 15 million people suffer strokes and 5 million are left permanently disabled.
- In developing countries, congestive heart failure (CHF) is the most common cause for hospital admission among older people, and is an emerging epidemic.

According to the National Heart, Lung, and Blood Institute's 44-year Framingham Heart Study, the average annual rates of first major cardiovascular events rises from seven per 1,000 men at ages 35-44 to 68 per 1,000 at ages 85-94. Similar rates for women tend to occur about 10 years later than men. According to the American Heart Association, women with diabetes seem to lose most of their inherent protection against developing cardiovascular disease later than men. People with diabetes who develop CVD have a worse prognosis for survival than do people without diabetes who develop CVD.

Cardiovascular Disease Risk Factors

Pivotal to the development of CVD are risk factors such as hypertension, obesity and diabetes. According to the National Heart, Lung and Blood Institute, in the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults from 2002, **diabetes "substantially increases risk for all forms of CVD."**

According to the American Heart Association, among adults age 18 and older, 27.9 percent had two or more risk factors for CVD in 1999. The most common combination was high blood pressure and high cholesterol. Among those with *three* risk factors, the most common combination added obesity to the two above. Among those with *four* risk factors, about 40 percent had the combination of high blood pressure, high cholesterol, obesity and diabetes. These combinations were also the most common at younger ages.

3. About Type 2 Diabetes

There are two main types of diabetes. Type 1 diabetes is a disorder in which the body does not sufficiently produce and efficiently use insulin, so insulin shots are needed to help the body use glucose from meals. Type 2 diabetes is a disorder involving the body's inability to use its own insulin, which affects most of the 194 million people in the adult population who have diabetes. When we talk about "CardioDiabetes," we are largely talking about people with type 2 diabetes, its precursor pre-diabetes, and/or the subclinical stages that precede it.

Type 2 diabetes involves insulin resistance – the body's inability to effectively *use* its own insulin.

In contrast to people with type 1 diabetes who don't produce enough insulin, those with type 2 diabetes generally produce more insulin but their bodies don't use it properly. Type 2 diabetes usually occurs in those over 45 and overweight, but with the growing epidemic of obesity in young people, it increasingly afflicts overweight children and teens.

Prevalence

- There are currently more than 194 million people with diabetes worldwide. If nothing is done to slow the epidemic, the number will exceed 333 million by 2025.
- Type 2 diabetes constitutes about 85 to 95 percent of all diabetes cases in developed countries and accounts for an even higher percentage in developing countries.
- Diabetes is the fourth main cause of death in most developed countries.
- The populations of most countries are aging. Diabetes is particularly common in aging populations and is increasing in proportion to the number of people living longer.

Pre-diabetes is a condition in which "the level of glucose in the blood becomes higher than normal, although not high enough to be diagnosed with diabetes," according to the International Diabetes Federation. The medical terms for pre-diabetes are impaired fasting glucose (IFG) or impaired glucose tolerance (IGT).

When a physician recognizes pre-diabetes, aggressive treatment of CVD risk factors may be appropriate because pre-diabetes is a risk factor for future diabetes and CVD.

Symptoms

The most common symptoms of diabetes are:

- polyuria – frequent urination
- polydipsia – excessive thirst
- unexplained weight loss
- polyphagia – excessive hunger
- blurred vision
- irritability

Diagnosis

Diabetes may be diagnosed by a doctor based on the patient's report of symptoms plus the results of a "casual" blood glucose test, which is one done any time of day, without regard to the time since the person's last meal. Or the diagnosis may be made without regard to symptoms if it is a "fasting" blood glucose test, which is one done after no food intake for at least eight hours. Or the diagnosis may be made after a more complex blood glucose test called a two-hour oral glucose tolerance test.

Controlling Blood Glucose Levels

Glycemic control is fundamental to the management of diabetes. Several long-term prospective randomized clinical trials, such as the Diabetes Control and Complications Trial (DCCT) and the U.K. Prospective Diabetes Study (UKPDS), have shown that improved glycemic control is associated with sustained decreased rates of retinopathy, nephropathy and neuropathy. In these trials, treatment regimens that reduced average A1C to ~7 percent (~1 percent above the upper limits of normal) were associated with fewer of these long-term microvascular complications.

Glucose Control – Just the First Step

Normalizing blood glucose levels is the essential first step, but it's just the beginning. Glucose is not the only thing people with diabetes and their doctors have to worry about.

According to Eugene Barrett, M.D., Ph.D., former president of the American Diabetes Association, "Diabetes management requires equal attention to control of blood glucose, cholesterol, blood pressure and other cardiovascular risk factors."

Because comprehensive treatment of diabetes requires more than just glucose control, most people with diabetes may require more than one doctor. It's a team effort. That's why, in addition to a primary care physician, people with diabetes often also may consult with an endocrinologist, cardiologist, neurologist, ophthalmologist, nephrologist, foot specialist, registered dietitian for medical nutrition therapy, physical therapist, mental health professional or behavioral therapist, and/or diabetes educator.

4. "CardioDiabetes"

Overview

Why is lifespan more seriously curtailed in those with diabetes than in those without? Although there has been a reduction in the incidence of heart attacks, strokes and CVD death among people with diabetes over the past 50 years, the absolute risk of such events is still twice as great in those with diabetes compared to the general population, according to a survey of the Framingham Heart Study population.

Based on an exhaustive survey of clinical data, the most recent guidelines issued by the National Cholesterol Education Program (NCEP) concluded, "Because of growing evidence that many people with diabetes carry a risk for CHD similar to that of people with established CHD, diabetes should be put in a separate category of higher risk." **In other words, even if people with diabetes don't already have clinical evidence of coronary heart disease, their risk of a heart attack is that of someone who already has been diagnosed with coronary heart disease.** Why?

Because "atherosclerotic lesions occur at an earlier age and with greater severity in people with diabetes." Why?

We don't know all the answers, not even most of them. However, three key areas now getting attention with further research and consideration for potential treatment are subclinical diabetic heart disease, diabetic dyslipidemia and insulin resistance.

Subclinical Diabetic Heart Disease

Subclinical heart disease is damage to the heart that is detectable only with sophisticated diagnostic techniques. Patients with subclinical heart disease are associated with a significant risk of coronary heart disease.

In fact, the increased risk of total mortality is 2.9 times greater for men and 1.7 times greater for women. Therefore, subclinical heart disease is an important determinant of clinical cardiovascular disease among people with diabetes.

A diagnosis of subclinical heart disease is especially difficult in people with diabetes. As an example, while chest pain (angina) is typically the painful symptom of insufficient blood flow to the heart (myocardial ischemia) that sends people to their doctor, this sign is often *not* reliable. This delayed recognition of coronary heart disease undoubtedly worsens the prognosis for survival in many patients with type 2 diabetes.

One reason for this is that patients with both diabetes and coronary heart disease have an enhanced myocardial dysfunction that leads to heart failure. While heart failure becomes evident as it progresses, diabetes patients usually have it before it can be easily diagnosed. Such subclinical dysfunction of the left ventricle (the chamber of the heart pumping oxygen-rich blood to arteries) may be detected using diagnostic tools such as echocardiography that may not be routinely used by office-based physicians. In fact, a clinical study has shown that significant subclinical dysfunction of the left ventrical was present in 27 percent of 219 unselected type 2 diabetes patients given stress echocardiography and that the extent of this silent disease was independently associated with hemoglobin A1C levels.

Diabetic Dyslipidemia

Dyslipidemia (irregularity of the lipid profile) occurs both in people with and without diabetes. The specific abnormalities in the lipoprotein pattern characteristic of diabetic dyslipidemia appear to add excess risk for people with diabetes. That diabetic dyslipidemia pattern is:

- Elevated triglycerides
- Reduced levels of HDL-C
- Normal *or* elevated levels of total cholesterol and LDL-C
- A shift toward smaller and denser LDL-C particles

These lipid abnormalities, usually in the presence of normal LDL-C, confer a CVD risk equal to or exceeding that of a high-risk LDL-C cholesterol level of 150-220 mg/dL. Thus, while therapy to lower LDL-C is essential if it is elevated, strategies are also essential to modify the other abnormalities of the dyslipidemia, according to the National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III) and the American Diabetes Association.

Insulin Resistance, PPARs and Diabetes

As we have discussed, people with type 2 diabetes have insulin resistance – an inability to efficiently use their own insulin. Such resistance is present years before the onset of diabetes, but people are able to maintain normal glucose levels by increasing their insulin production to compensate for the decrease in insulin action. However, in susceptible individuals, progressive insulin resistance with concomitant failure of the beta cells to maintain high enough insulin secretion eventually leads to diabetes. The cause of the susceptibility to insulin resistance is likely genetic.

PPAR (peroxisome proliferator-activated receptor) agonists are drugs that play a critical role in the regulation of numerous processes in the body, many of which relate to energy metabolism.

In diabetes, actions of PPARs that relate to glucose metabolism, fat oxidation and fat cell differentiation are of importance. Currently, medications affecting two classes of these receptors are available: fibrates that are PPAR alpha agonists, which have been used for several decades; and thiazolidinediones (also called glitazones or TZDs) that are PPAR gamma agonists, which are newer drugs used to treat insulin resistance and type 2 diabetes. PPAR gamma receptors have been found in several tissues, including the heart, specifically in the coronary artery. While conventional agents used in the treatment of diabetes lower glucose levels, they don't appreciably attenuate CVD. Through sustained metabolic effects that reduce hyperglycemia and help address diabetic dyslipidemia, these new agents may represent a turning point in the therapeutic approach to the treatment of diabetes and its complications. Because the predominant effect of PPAR gamma is to enhance the action of insulin, a medication such as pioglitazone that induces PPAR gamma will be beneficial in insulin resistance therapy.

5. Prevention of "CardioDiabetes"

Can CVD risk – and mortality – be reduced even if you have type 2 diabetes? Yes – and new approaches are coming down the pike, as you will soon read.

We have seen that diabetic heart disease does not begin at the first symptoms of pain – or even when first detected in the typical screening – and that it progresses faster in people with diabetes than in the general population. We have seen that aggressively treating diabetes and the associated risk factors affects mortality. What else can be done to forestall end events? How can we do better?

People should be checked for diabetes every three years if they are over the age of 45, according to the American Diabetes Association. Testing should be considered at a younger age or be done more frequently in those who are overweight and have additional risk factors, such as a first-degree relative with diabetes, or signs of insulin resistance.

When and how should a doctor look for early signs of heart disease in patients with diabetes? In order to reduce mortality, the search should begin earlier when pre-diabetes is suspected or other risk factors, such as obesity, elevated blood pressure, insulin resistance and elevated blood lipids, are evident.

According to ATP III, a diabetes patient should become concerned about CVD immediately upon diagnosis.

In addition to glucose control, comprehensive care to reduce CVD risk factors may include lifestyle modification, such as nutrition therapy (reducing the intake of saturated fats), increased physical activity, weight reduction and therapeutic options for LDL-C lowering. If lifestyle modification does not achieve target goals, medication should be considered.

6. Integrated "CardioDiabetes" Treatment

Lifestyle changes and medications are used to treat "CardioDiabetes." Here's what's happening now.

Lifestyle – The Clinical Trial Results for Glucose Control and Lipid Control

The Finnish Diabetes Prevention Study (DPS) was one of the first controlled, randomized clinical trials to show that type 2 diabetes can be prevented with lifestyle modification.

A group of 522 middle-aged, overweight patients with impaired glucose tolerance were randomized to either an intervention or control group. Those in the intervention group received individualized dietary counseling and were offered circuit-type resistance training. Their goals were to reduce body weight and dietary and saturated fat, and increase their physical activity and dietary fiber. After three years, the risk of diabetes was reduced by 58 percent in the lifestyle intervention group compared with the control group. These results have been reproduced by the Diabetes Prevention Program in the U.S., in which the lifestyle intervention achieved a similar 58 percent risk reduction, which was superior to the metformin treatment.

In a follow-up to the famous Ornish Lifestyle Heart Trial, the first randomized clinical trial to demonstrate regression of coronary atherosclerosis through a program of nutrition, exercise and stress management, the program was extended for five years.

The experimental group patients maintained comprehensive lifestyle changes (10 percent fat, whole foods, vegetarian diet, aerobic exercise, stress management training, smoking cessation, and group psychological support) for five years while control group patients made more moderate changes. "More regression of atherosclerosis occurred after five years than after one year in the experimental group. In contrast, atherosclerosis continued to progress, and more than twice as many cardiac events occurred in patients in the control group." While this was not specifically a study of people with diabetes, it is instructive that despite the benefits they saw through participation in the first year, only 20 of 28 patients maintained the original intensive lifestyle changes.

Oral Drugs Treating Aspects of "CardioDiabetes"

The Diabetes Aspect

Current oral drugs used for reducing blood glucose levels include:

- Those that increase the body's own insulin secretion, such as the sulfonylureas, other secretagogues and insulin itself
- Those that directly decrease hepatic glucose production, such as biguanides (metformin)
- Those that decrease insulin resistance or improve insulin's effectiveness, such as thiazolidinediones (TZDs), including pioglitazone and rosiglitazone
- Those that reduce the rate of glucose absorption, the alpha-glucosidase inhibitors, such as acarbose

If a patient does not respond to one drug, another is tried or added. One study showed, "After three years, 50 percent of patients need a second drug; after nine years, the proportion increases to 75 percent."

Although currently there is no unified therapy for the treatment of diabetic dyslipidemia, there are medications that are prescribed individually or in combination for certain elements of dyslipidemia, depending on the patient's lipid problems and comorbidities.

The Cardiovascular Aspect

Current oral drugs used for reducing lipid levels include:

- Those that reduce LDL-C and triglycerides and increase HDL-C like the statins, including atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin
- Those that just reduce LDL-C such as the bile acid-binding resins, including cholestyramine, colesevelam, and colestipol
- Those that increase HDL-C and reduce LDL-C and triglycerides such as niacin, that is, vitamin B-3 or nicotinic acid
- Those that reduce triglycerides and increase HDL-C such as fibrates, including fenofibrate and gemfibrozil
- Combination products that reduce LDL-C and triglycerides, and moderately increase HDL-C, such as the cholesterol absorption inhibitor ezetimibe with the statin simvastatin

Again, as with treatment of diabetes, when patients don't respond adequately to single drug therapy for their lipid problems, a second drug may be considered to further correct the dyslipidemia.

In addition, depending on the patient's CVD status, other medications may be prescribed:

- Blood pressure medication, such as beta blockers or angiotensin-converting enzyme (ACE) inhibitors
- Antiplatelet agents or anticoagulants, such as aspirin or warfarin
- ACE inhibitors and beta blockers for post-heart attack patients
- ACE inhibitors for patients with nephropathy

7. The Future – Better Treatment and Prevention of "CardioDiabetes"

As discussed, doctors continue to try to recognize "CardioDiabetes" ever earlier in its course. Can treating diabetic dyslipidemia or inflammation, as evidenced by CRP, alter the course of "CardioDiabetes"? Only time will tell.

The clinical data currently available suggest aggressive multi-factorial intervention may help to reduce cardiovascular morbidity and mortality among people with type 2 diabetes.

And major clinical studies are ongoing to find an answer:

COMPLEMENT: This is a multi-center, open-label study that compares the lipid-lowering effects of pioglitazone and another TZD, rosiglitazone, in patients taking statins. Patients were first given rosiglitazone for at least 90 days, followed by 17 weeks on pioglizatone. The findings have been evaluated to determine the change in triglyceride levels, as well as other lipids and CVD markers.

In addition, selected studies exploring other new frontiers of "CardioDiabetes" include:

PROactive: An ongoing double-blind, multi-center, clinical trial in Europe (**PRO**spective Pioglit**A**zone **C**linical **Tr**I**a**l In Macro**V**ascular **E**vents) is studying mortality and macrovascular morbidity associated with CVD progression in high-risk patients with type 2 diabetes. The study has randomized patients to pioglitazone or placebo (in addition to their existing diabetes and cardiovascular therapies) in more than 5,200 patients who have experienced one or more cardiovascular events such as a heart attack, coronary artery bypass surgery or stroke. They will be followed until the occurrence of a new CVD event or death, and duration of that time is estimated at four years.

CHICAGO: An ongoing double-blind, multi-center clinical trial is evaluating **C**arotid Intima-Media T**HIC**kness in **A**therosclerosis using Pio**G**litaz**O**ne. It is comparing the effects of either pioglitazone or glimepiride, in addition to existing diabetes and cardiovascular therapies, in 400 patients with type 2 diabetes. The rate of progression of carotid (neck) artery atherosclerosis and of coronary artery calcium deposition will be evaluated at baseline and after 18 months of therapy with either drug, with noninvasive electron beam tomography.

PERISCOPE: The **P**ioglitazone **E**ffect on **R**egression of **I**ntravascular **S**onographic **C**oronary **O**bstruction **P**rospective **E**valuation complements the CHICAGO study, in that it is an 18-month study that looks inside an artery in the heart with intravascular ultrasound to determine whether pioglitazone or glimepiride therapy alters the course of coronary atherosclerosis. This double-blind, multi-center trial is evaluating 600 patients.

The results of these and other studies will help determine the future of therapy for "CardioDiabetes."

Please see important product information on page 15.

Important Information about ACTOS® (pioglitazone HCl)

ACTOS is not for everyone. ACTOS can cause fluid retention that may lead to or worsen heart failure, so tell your doctor if you have a history of these conditions. Talk to your doctor immediately if you experience rapid weight gain, fluid retention, or shortness of breath while taking ACTOS. If you have moderate to severe heart failure, ACTOS is not recommended. Your doctor should perform a blood test to check for liver problems before you start ACTOS and periodically thereafter. Do not take ACTOS if you have active liver disease. 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 flu-like symptoms, mild to moderate swelling of legs and ankles, and anemia. When taking ACTOS with insulin or sulfonylureas, you may be at risk for low blood glucose.

Management of type 2 diabetes requires nutritional counseling, weight reduction as needed, and exercise. When diet and exercise are not enough, ACTOS may be used alone or in combination with sulfonylureas, metformin or insulin to improve blood glucose control. ACTOS should not be used in the treatment of type 1 diabetes.

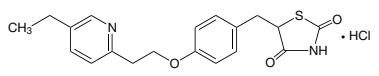
Please see accompanying complete prescribing information.

ACTOS®
(pioglitazone hydrochloride) Tablets

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 and highly selective 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**.

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 (see 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

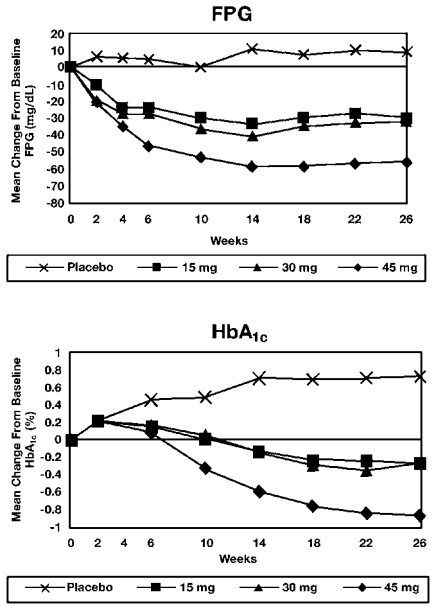


Table 2 shows HbA_{1c} and FPG values for the entire study population.

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 ≤ 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 (see 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 (see 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 does not result in adequate glycemic control.

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

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

WARNINGS
Cardiac Failure and Other Cardiac Effects
ACTOS, like other thiazolidinediones, 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 (see Information for Patients). ACTOS should be discontinued if any deterioration in cardiac status occurs. Patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during pre-approval clinical trials; ACTOS is not recommended in these patients (see PRECAUTIONS, Cardiovascular).

In one 16-week 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.

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.

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 (25th/75th percentile)	Median (25th/75th percentile)	Median (25th/75th percentile)	Median (25th/75th 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.

Pioglitazone is structurally related to troglitazone, a thiazolidinedione no longer marketed in the United States, which was associated with idiosyncratic hepatotoxicity and cases of liver failure, liver transplants and death during postmarketing clinical use. In pre-approval controlled clinical trials in patients with type 2 diabetes, troglitazone was more frequently associated with clinically significant elevations of hepatic enzymes (ALT > 3 times the upper limit of normal) compared to placebo, and cases of reversible jaundice were reported.

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

Serum ALT (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.

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

Laboratory Tests
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).

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. Urinary tract tumors have been reported in rodents taking experimental drugs with dual PPAR α/γ activity; however, ACTOS is a selective agonist for PPARγ.

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. Occasionally, abnormal urinary cytology results indicating possible malignancy were observed in both patients treated with ACTOS (0.72%) and patients treated with placebo (0.88%).

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 breast-feeding 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

In worldwide clinical trials, over 5900 patients with type 2 diabetes have been treated with ACTOS. In U.S. clinical trials, over 4700 patients have received ACTOS, over 3300 patients have been treated for 6 months or longer, and over 450 patients for one year or longer.

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

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, 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.

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.

Rx only

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