DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Eileen T. Valenta
Manager, Regulatory Affairs Promotion, Surveillance & Communications
Takeda Pharmaceuticals North America, Inc.
475 Half Day Road, Suite 500
Lincolnshire, IL 60069

RE: **NDA 21-073**
Actos (pioglitazone hydrochloride) Tablets
MACMIS 10933

Dear Ms. Valenta:

This letter concerns promotional materials disseminated by Takeda Pharmaceuticals America, Inc. (Takeda). As part of its routine monitoring program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed promotional materials for Actos (pioglitazone hydrochloride) Tablets and has concluded that these materials are in violation of the Federal Food, Drug, and Cosmetic Act and its implementing regulations. Specifically, DDMAC has identified two Sales Aids for Actos (SS01-0013-1; SS01-0028-1), distributed in the promotional exhibit hall at the 2002 American Pharmaceutical Association (APhA) Annual Meeting and Exposition on March 16 – 19. The Sales Aids are misleading in that they omit safety information critical to appropriate use of the drug and promote effects on outcome that have not been demonstrated. Our specific objections follow:

Background

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."

As you know, since February 2000, the Actos approved product labeling (PI) was revised twice. In May 2001, the PI was revised to include important new risk information

regarding serious adverse hepatic events associated with Actos. Specifically, the May 2001 revision added the following information, "In postmarketing experience with ACTOS, reports of hepatitis and 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." In January 2002, the PI was again revised, this time to include important information regarding cardiac safety concerns with Actos. Specifically, a new Warnings section was added to address concerns about fluid retention, which may contribute to heart failure, with particular concern when Actos is used in combination with insulin. In addition, the Precautions and Adverse Reactions sections were revised with respect to cardiac effects of Actos monotherapy and combination therapy, weight gain, and edema. In a letter dated January 18, 2002, DDMAC informed Takeda that all promotional materials should be revised to include the new risk information no later than February 7, 2002.

Omission of Important Safety Information

Your sales representatives at the APhA meeting on March 16 – 19, 2002, distributed the Sales Aids listed above. These Sales Aids are misleading in that they fail to present any of the important risk information from the changes to the PI. Specifically, these materials make no reference to the following new information from the PI:

Cardiovascular:

WARNINGS

"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. Actos should be discontinued if any deterioration in cardiac status occurs."

PRECAUTIONS

"In postmarketing experience with Actos, cases of congestive heart failure have been reported in patients both with and without previously known heart disease."

"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."

Edema

PRECAUTIONS

"In all U.S. clinical trials, edema was reported more frequently in patients treated with Actos than in placebo-treated patients. In postmarketing experience, reports of initiation or worsening of edema have been received."

ADVERSE REACTIONS
"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."

Hepatic Effects

PRECAUTIONS
"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."

Moreover, these materials were distributed with outdated PIs (dated February 2000) that do not include any of the new risk information.

Promotion of Effects on Outcome That Have Not Been Demonstrated

- **Actos helps the body stand strong against the challenges of insulin resistance**
- **Left untreated, the insulin-resistant patient may face serious consequences**
- **As glucose intolerance from insulin resistance progresses, the metabolic risk factors for cardiovascular disease continuously increase**
- **Insulin resistance with associated hyperglycemia and dyslipidemia in type 2 diabetes can lead to micro- and macrovascular complications**
- **In addition, hyperinsulinemia is linked to elevated triglyceride and low HDL-C levels, which individually are major risk factors for CHD**

These claims are misleading because they fail to distinguish between a mechanism you hope will prove to be of value in type 2 diabetes (beyond simply helping to control blood sugar and HbA1c, which Actos does do) and evidence of such value. Absent data demonstrating these outcomes, the suggestion that Actos can help prevent micro- and macrovascular complications of diabetes, including cardiovascular disease, is misleading. The PI states "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)." FDA is not aware of any data to suggest that Actos has a favorable effect on any complications of type 2 diabetes.

Requested Action

Takeda should immediately cease distribution and publication of these Sales Aids, and all other promotional materials for Actos that omit important safety information and that contain the same or similar claims or presentations. Please submit a written response to DDMAC, on or before November 21, 2002, describing your intent and plans to comply with the above. In its letter to DDMAC, Takeda should include a list of all promotional materials that were discontinued, and the discontinuation date.

If you have any questions, please contact me by telephone at (301) 827-2831, by facsimile at (301) 594-6771, or write to me at the Division of Drug Marketing, Advertising, and Communications, HFD-42; Room 8B-45; 5600 Fishers Lane; Rockville, MD 20857. DDMAC reminds Takeda that only written communications are considered official. In all future correspondence regarding this matter, please refer to MACMIS # 10933 and NDA 21-073.

Sincerely,

{See appended electronic signature page}

Marci C. Kiester, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Marci C. Kiester
11/7/02 09:29:01 AM

When choosing therapy for a broad spectrum of patients...

ACTOS QD delivers a strong performance

- Effectively reduces insulin resistance.[7]
- Significantly improves glycemic control.[7]
- Provides unique lipid effects, significantly improving mean triglyceride and mean HDL-C levels, with no consistent mean changes in LDL-C and total-C levels.[10]
- Convenient QD dosing, alone and in combination with sulfonylureas, metformin, or insulin; available in 15-, 30-, and 45-mg tablets.[7]

serum albumin. Pioglitazone also binds to other serum proteins, but with lower affinity. Meta
extensively bound (> 98%) to serum albumin.

Metabolism: Pioglitazone is extensively metabolized by hydroxylation and oxidation; the me
glucuronide or sulfate conjugates. Metabolites M-II and M-IV (hydroxy derivatives of pioglit
tive of pioglitazone) are pharmacologically active in animal models of type 2 diabetes. In add
M-IV are the principal drug-related species found in human serum following multiple dosing.
volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% t
concentrations and 20% to 25% of the total AUC.

Pioglitazone incubated with expressed human P450 or human liver microsomes results i
a much lesser degree, M-II. The major cytochrome P450 isoforms involved in the hepatic r
CYP2C8 and CYP3A4 with contributions from a variety of other isoforms including the
Ketoconazole inhibited up to 85% of hepatic pioglitazone metabolism in vitro at a concentrati
Pioglitazone did not inhibit P450 activity when incubated with human P450 liver microsome
not been performed to investigate any induction of CYP3A4 by pioglitazone.

Excretion and Elimination: Following oral administration, approximately 15% to 30% of the
in the urine. Renal elimination of pioglitazone is negligible, and the drug is excreted prim
conjugates. It is presumed that most of the oral dose is excreted into the bile either unchang
inated in the feces.

The mean serum half-life of pioglitazone and total pioglitazone ranges from 3 to 7 hour
tively. 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 remai
moderate (creatinine clearance 30 to 60 mL/min) to severe (creatinine clearance < 30 mL
compared to normal subjects. No dose adjustment in patients with renal dysfunction is rec
ADMINISTRATION).

Hepatic Insufficiency: Compared with normal controls, subjects with impaired hepatic fun
have an approximate 45% reduction in pioglitazone and total pioglitazone mean peak concen
mean AUC values.

ACTOS® is a registered trademark of Takeda Chemical Industries, Ltd. and used under license by Takeda Pharmaceuticals North America, Inc. and Eli Lilly and Company.

Please see attached complete Prescribing Information.

Always QD Power

actos®

pioglitazone HCl

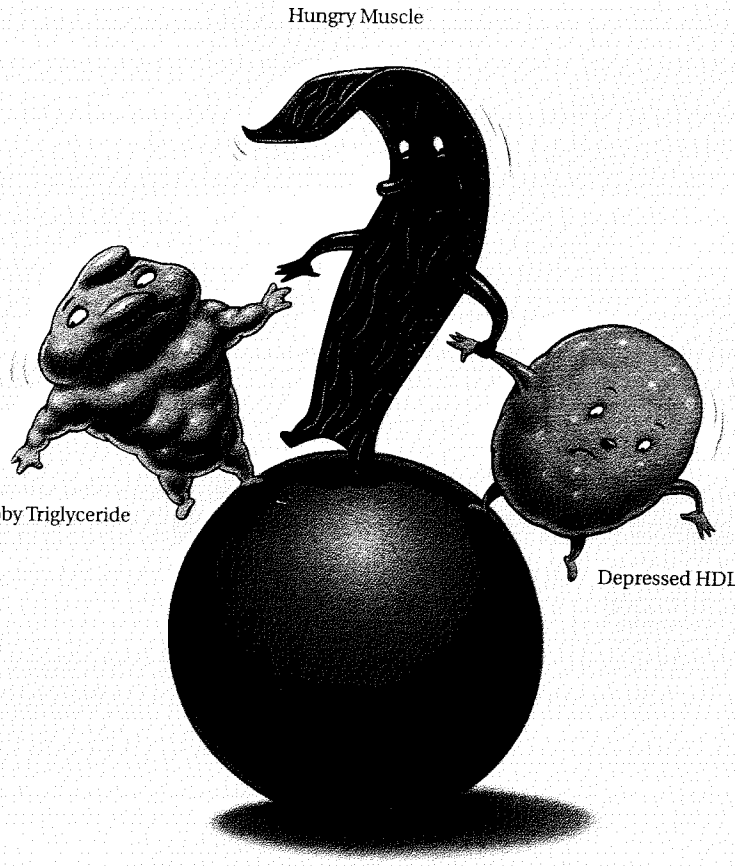
For performance that benefits the body

Diabetes Lilly

ADVANCING CARE TOGETHER™

 SS01-0013-1 AC20443 4/01 Printed in U.S.A.

Because insulin resistance throws the body off balance



#1 Prescribed TZD by Endocrinologists since February 18, 2000!*

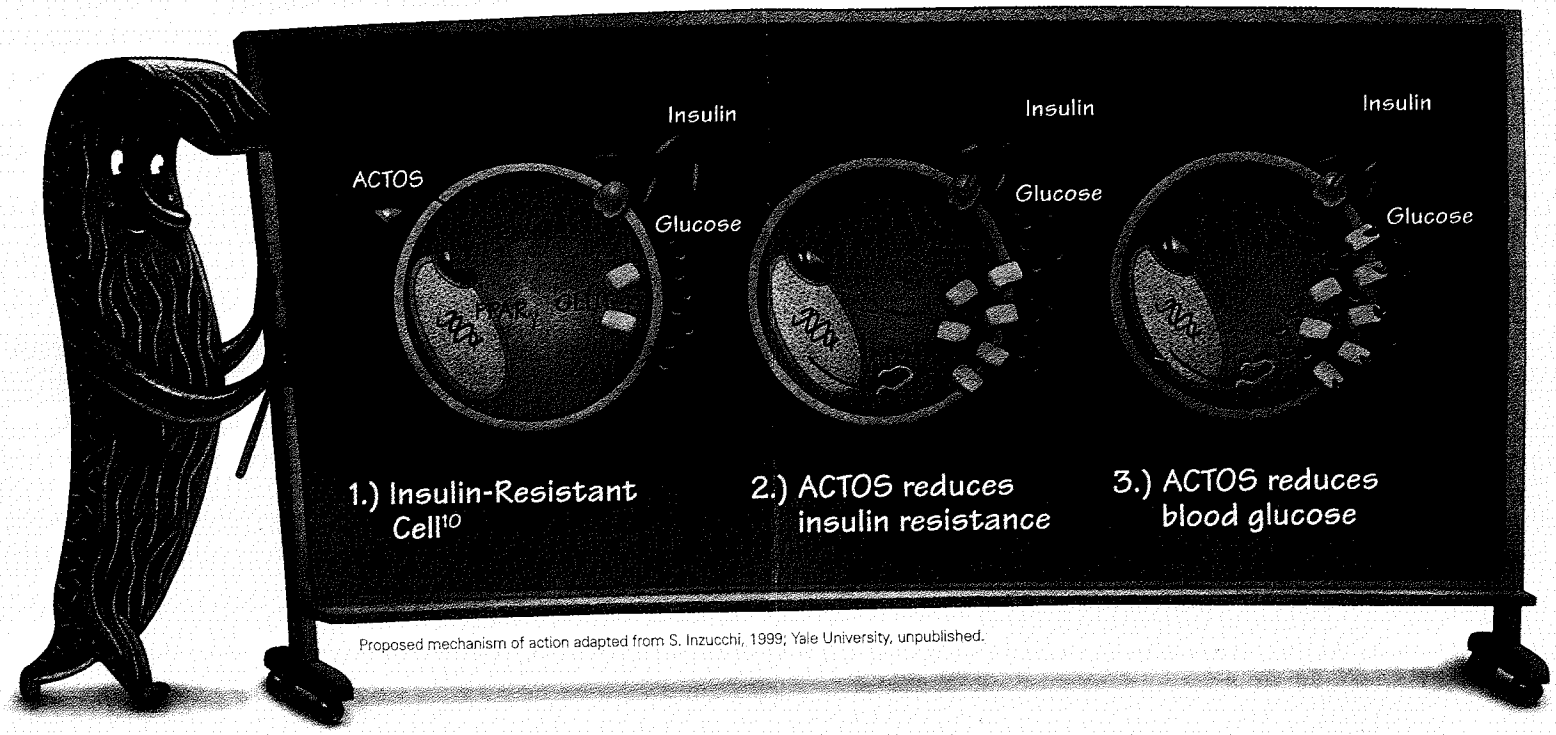
*IMS Health. NPA™ by Specialty, March 16, 2001.

ACTOS QD confronts the challenges of insulin resistance

Effectively acts on peripheral cells

- ACTOS activates PPARγ, a nuclear receptor shown to play a role in regulating insulin resistance in peripheral cells.[8,9]
- Sulfonylureas and metformin have not been shown to activate PPARγ.[8,9]

ACTOS increases insulin action on peripheral cells to increase glucose signaling and uptake, improving glycemic control and positively impacting patient lipid profiles.[7]



Proposed mechanism of action adapted from S. Inzucchi, 1999; Yale University, unpublished.

Effectively reduces insulin resistance

- Data show that treatment with ACTOS QD significantly decreased insulin resistance in peripheral cells vs placebo based on HOMA calculations.*[10,11]
- ACTOS QD was also associated with increased beta-cell response compared to placebo based on HOMA calculations.*[10,11]

Effectively reduces fasting insulin

- In monotherapy, ACTOS 30 or 45 mg QD produced significant mean reductions in fasting insulin levels.[12]

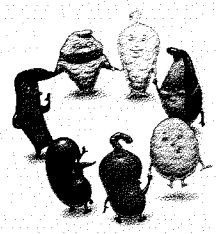
Effectively reduces blood glucose

- ACTOS decreases insulin resistance in the periphery and the liver, resulting in increased peripheral glucose uptake and decreased hepatic glucose output.[7]
- In patients unable to control their diabetes with diet and exercise, ACTOS QD reduces HbA_{1c}.[10]

Addressing tolerability and safety

- In US placebo-controlled clinical trials with ACTOS including over 4,500 patients, there was no evidence of drug-induced hepatotoxicity or serum transaminase (ALT) elevations.[7]
- Because ACTOS is a member of the thiazolidinedione (TZD) class, periodic monitoring of liver enzymes is recommended at baseline, every 2 months for the first year, and periodically thereafter.[7]
- If ALT >2.5X ULN at baseline or if the patient exhibits clinical evidence of active liver disease, do not initiate therapy with ACTOS (please see attached complete Prescribing Information for liver monitoring recommendations).[7]
- The majority of side effects reported during clinical trials were mild. Those most commonly reported included symptoms of upper respiratory tract infection, headache, sinusitis, muscle pain, tooth disorder, aggravated diabetes mellitus, and sore throat. As observed with other members of this class of drugs, weight gain has been noted. Additionally, mild to moderate edema and anemia have been reported in patients taking ACTOS. ACTOS should be used with caution in patients with edema. ACTOS has not been tested in patients with NYHA Class III and IV cardiac status; therefore, ACTOS is not indicated in these patients. Patients receiving ACTOS in combination with insulin or a sulfonylurea may be at risk for hypoglycemia, and a reduction in the dose of insulin or sulfonylurea may be necessary. Therapy with ACTOS, like other TZDs, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking ACTOS, and adequate contraception should be recommended. Administration of oral contraceptives has not been fully evaluated in patients being treated with ACTOS. Therefore, additional caution regarding contraception should be exercised.[7]
- As an adjunct to diet and exercise, ACTOS may be used as monotherapy to lower blood glucose, and in combination with sulfonylureas, metformin, or insulin when diet plus the single agent does not result in adequate glycemic control. ACTOS should not be used in type 1 diabetes or for the treatment of diabetic ketoacidosis. Management of type 2 diabetes should also include nutritional counseling, weight reduction as needed, and exercise.[7]

References: 1. Haffner SM. Insulin sensitivity in subjects with type 2 diabetes. *Diabetes Care.* 1999;22:562-568. **2.** American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care.* 2000;24(suppl 1):S33-S43. **3.** DeFronzo RA. The triumvirate: β-cell, muscle, liver—a collusion responsible for NIDDM. *Diabetes.* 1988;37:667-687. **4.** Goke B. Type 2 diabetes: are current oral treatment options sufficient? *Exp Clin Endocrinol Diabetes.* 2000;108(suppl 2):S243-S249. **5.** Inzucchi SE, Maggs DG, Spollett GR, et al. Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. *N Engl J Med.* 1998;338:867-872. **6.** Stumvoll M, Nurjhan N, Perriello G, et al. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. *N Engl J Med.* 1995;333:550-554. **7.** ACTOS package insert, Takeda Pharmaceuticals America, Inc. **8.** Lehmann JM, Moore LB, Smith-Oliver TA, et al. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). *J Biol Chem.* 1995;270:12953-12956. **9.** Lenhard JM, Kliewer SA, Paulik MA, et al. Effects of troglitazone and metformin on glucose and lipid metabolism: alterations of two distinct molecular pathways. *Biochem Pharmacol.* 1997;54:801-808. **10.** Data on file, Takeda Pharmaceuticals North America, Inc. **11.** Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia.* 1985;28:412-419. **12.** Aronoff S, Rosenblatt S, Braithwaite S, et al. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. The Pioglitazone 001 Study Group. *Diabetes Care.* 2000;23:1605-1611.



Always QD Power

actos®

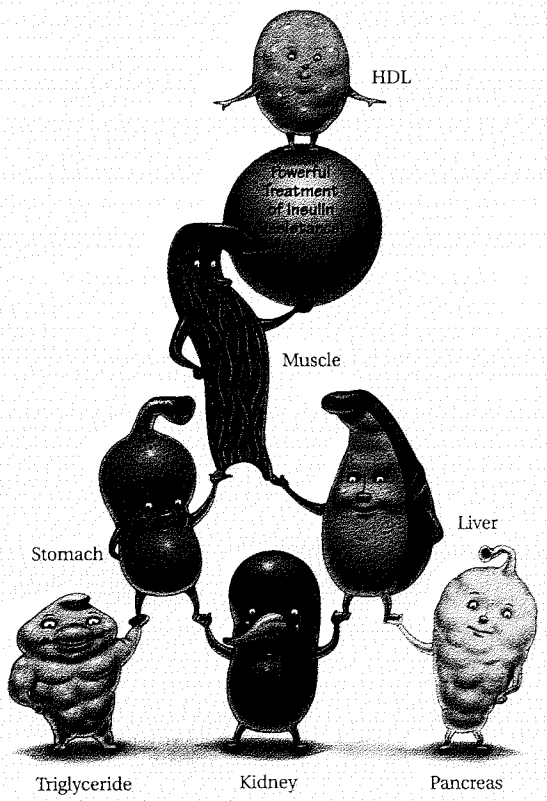
pioglitazone HCl

For performance that benefits the body

*Homeostasis Model Assessment (HOMA) calculations of study 001 data.

Please see attached complete Prescribing Information.

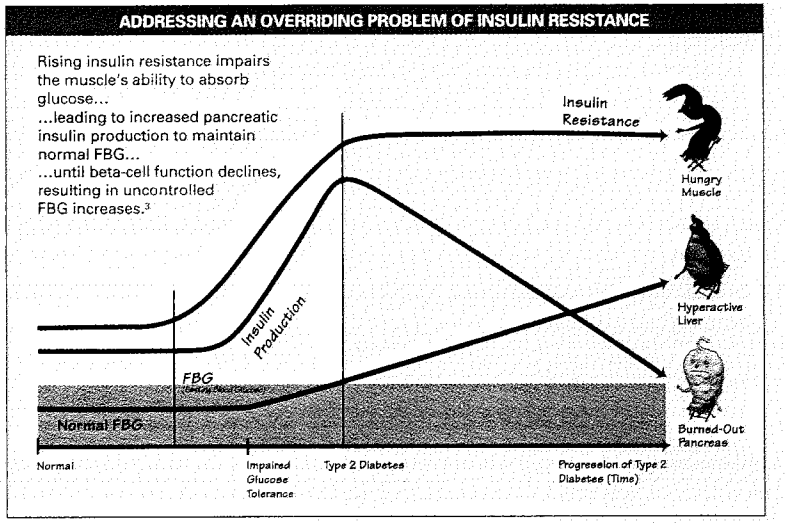
ACTOS helps the body stand strong against the challenges of insulin resistance



The major metabolic defects in type 2 diabetes are 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.[1] Clinical considerations regarding renal and gastrointestinal function are also common concerns when prescribing an oral agent for type 2 diabetes.[2] Management of type 2 diabetes should also include nutritional counseling, weight reduction as needed, and exercise.

The continuing problem of insulin resistance in type 2 diabetes

In a recent study, 92% of patients with type 2 diabetes demonstrated insulin resistance.[1]



Adapted from Type 2 Diabetes BASICS, ©2000 International Diabetes Center, Minneapolis, MN.

Primary effects of traditional oral antidiabetic agents

- Sulfonylureas increase insulin secretion.[4]
- Metformin primarily decreases hepatic glucose production, according to articles published in the *New England Journal of Medicine*.[5,6]

ACTOS decreases insulin resistance

- ACTOS reduces insulin resistance, resulting in increased glucose uptake, decreased hepatic glucose output, and decreased fasting insulin.[7]

Please see attached complete Prescribing Information.

Always QD Power

actos®

pioglitazone HCl

For performance that benefits the body

When choosing therapy for a broad spectrum of patients...

ACTOS QD delivers a strong performance

- Effectively reduces insulin resistance.[10]
- Significantly improves glycemic control.[10]
- Provides unique lipid effects, significantly improving mean triglyceride and mean HDL-C levels, with no consistent mean changes in LDL-C and total-C levels.[14]
- Convenient QD dosing, alone and in combination with sulfonylureas, metformin, or insulin; available in 15-, 30-, and 45-mg tablets.[10]

Please see attached complete Prescribing Information.

Always QD Power

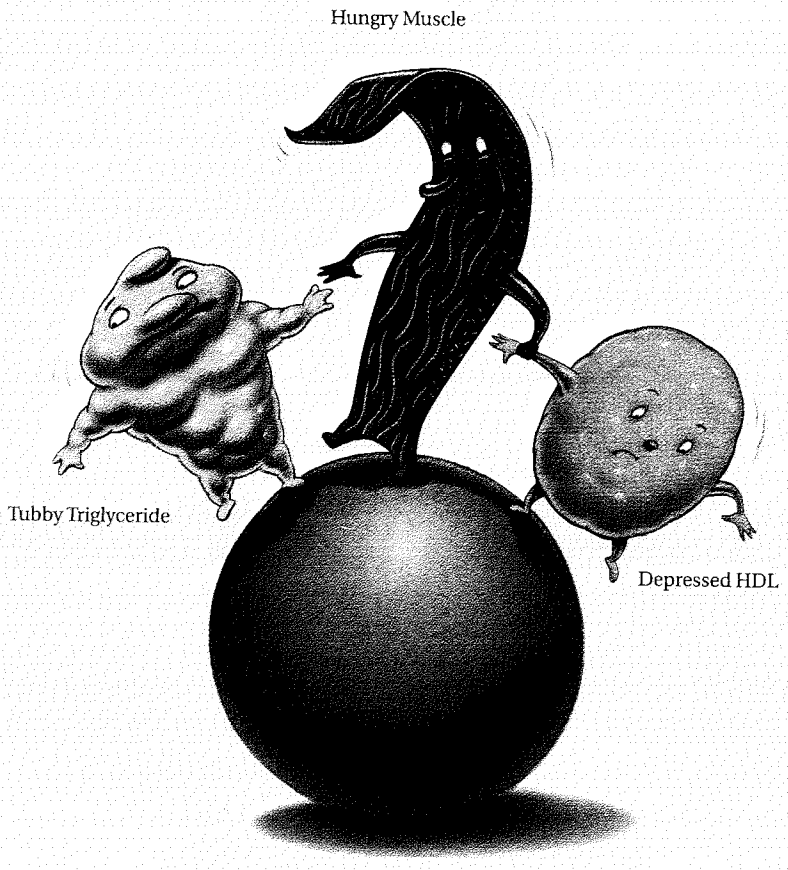
actos®

pioglitazone HCl

For performance that benefits the body

SS01-0028-1 AC20911 4/01 Printed in U.S.A.

Because insulin resistance throws the body off balance

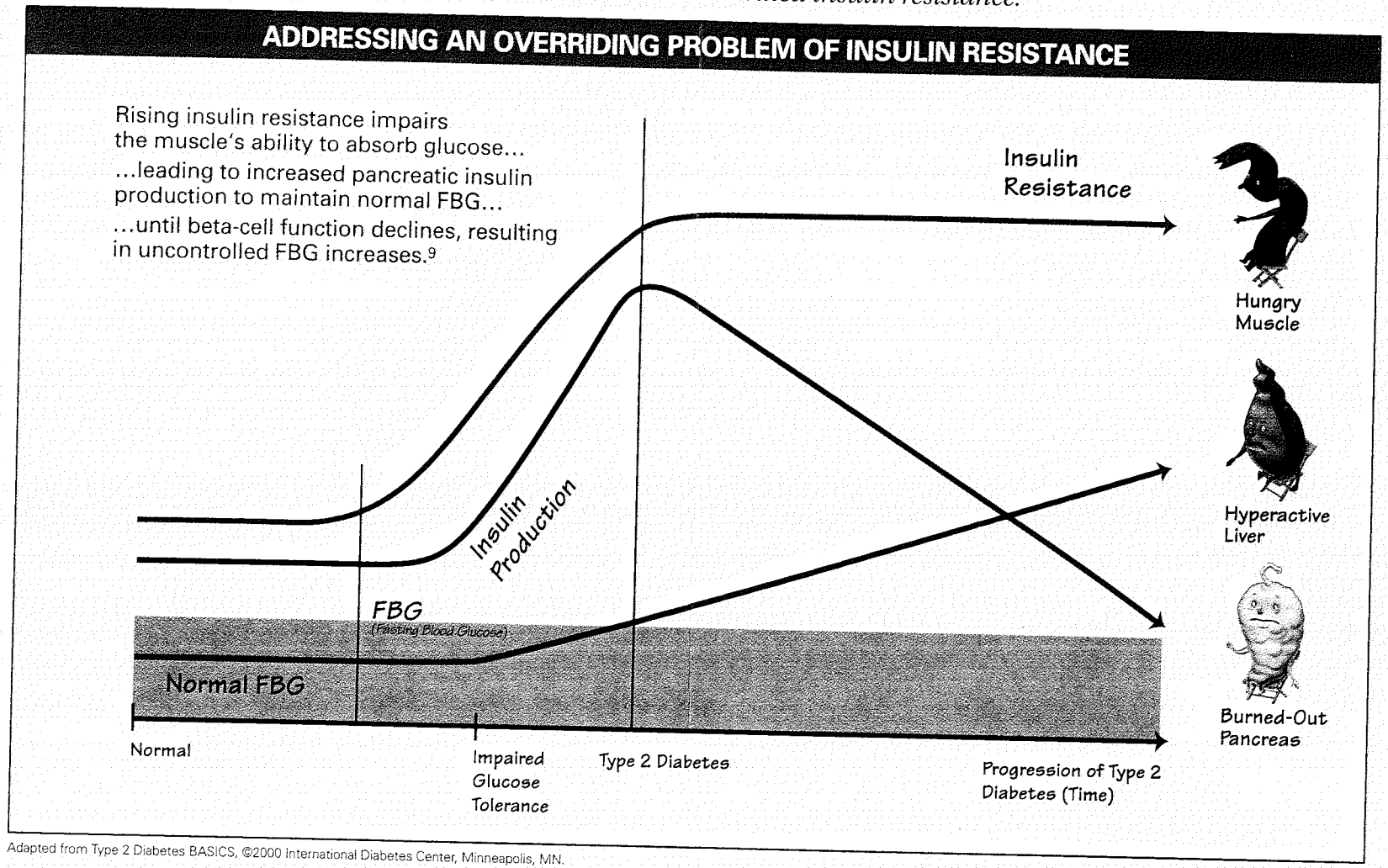


#1 Prescribed TZD by Endocrinologists since February 18, 2000!*

*IMS Health. NPA™ by Specialty, April 13, 2001.

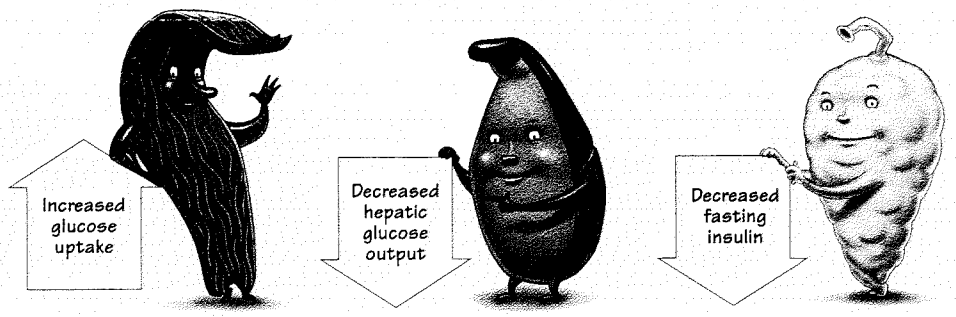
ACTOS QD confronts the challenges of insulin resistance in type 2 diabetes

In a recent study, 92% of patients with type 2 diabetes demonstrated insulin resistance.[1]



Adapted from Type 2 Diabetes BASICS, ©2000 International Diabetes Center, Minneapolis, MN.

ACTOS decreases insulin resistance, resulting in:[10]



Primary effects of traditional oral antidiabetic agents

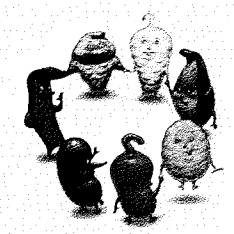
- Sulfonylureas increase insulin secretion.[11]
- Metformin primarily decreases hepatic glucose production, according to articles published in the *New England Journal of Medicine*.[12,13]

Addressing tolerability and safety

- In US placebo-controlled clinical trials with ACTOS including over 4,500 patients, there was no evidence of drug-induced hepatotoxicity or serum transaminase (ALT) elevations.[10]
- Because ACTOS is a member of the thiazolidinedione (TZD) class, periodic monitoring of liver enzymes is recommended at baseline, every 2 months for the first year, and periodically thereafter.[10]
- If ALT >2.5X ULN at baseline or if the patient exhibits clinical evidence of active liver disease, do not initiate therapy with ACTOS (please see attached complete Prescribing Information for liver monitoring recommendations).[10]
- The majority of side effects reported during clinical trials were mild. Those most commonly reported included symptoms of upper respiratory tract infection, headache, sinusitis, muscle pain, tooth disorder, aggravated diabetes mellitus, and sore throat. As observed with other members of this class of drugs, weight gain has been noted. Additionally, mild to moderate edema and anemia have been reported in patients taking ACTOS. ACTOS should be used with caution in patients with edema. ACTOS has not been tested in patients with NYHA Class III and IV cardiac status; therefore, ACTOS is not indicated in these patients. Patients receiving ACTOS in combination with insulin or a sulfonylurea may be at risk for hypoglycemia, and a reduction in the dose of insulin or sulfonylurea may be necessary. Therapy with ACTOS, like other TZDs, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking ACTOS, and adequate contraception should be recommended. Administration of oral contraceptives has not been fully evaluated in patients being treated with ACTOS. Therefore, additional caution regarding contraception should be exercised.[10]
- As an adjunct to diet and exercise, ACTOS may be used as monotherapy to lower blood glucose, and in combination with sulfonylureas, metformin, or insulin when diet plus the single agent does not result in adequate glycemic control. ACTOS should not be used in type 1 diabetes or for the treatment of diabetic ketoacidosis. Management of type 2 diabetes should also include nutritional counseling, weight reduction as needed, and exercise.[10]

References: **1.** Haffner SM. Insulin sensitivity in subjects with type 2 diabetes. *Diabetes Care.* 1999;22:562-568. **2.** American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care.* 2001;24(suppl 1):S33-S43. **3.** American Diabetes Association. Consensus development conference on insulin resistance. *Diabetes Care.* 1998;21:310-314. **4.** Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care.* 2001;24(suppl 1):S5-S20. **5.** DeFronzo RA. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidaemia and atherosclerosis. *Neth J Med.* 1997;50:191-197. **6.** American Diabetes Association. Management of dyslipidemia in adults with diabetes. *Diabetes Care.* 2001;24(suppl 1):S58-S61. **7.** American Diabetes Association. Nutrition recommendations and principles for people with diabetes mellitus. *Diabetes Care.* 2001;24(suppl 1):S44-S47. **8.** Meigs JB, Nathan DM, Wilson PWF, et al. Metabolic risk factors worsen continuously across the spectrum of nondiabetic glucose tolerance: The Framingham Offspring Study. *Ann Intern Med.* 1998;128:524-533. **9.** DeFronzo RA. The triumvirate: ß-cell, muscle, liver—a collusion responsible for NIDDM. *Diabetes.* 1988;37:667-687. **10.** ACTOS package insert, Takeda Pharmaceuticals America, Inc. **11.** Goke B. Type 2 diabetes: are current oral treatment options sufficient? *Exp Clin Endocrinol Diabetes.* 2000;108(suppl 2):S243-S249. **12.** Inzucchi SE, Maggs DG, Spollett GR, et al. Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. *N Engl J Med.* 1998;338:867-872. **13.** Stumvoll M, Nurjhan N, Perriello G, et al. Metabolic effects of metformin in non-insulin dependent diabetes mellitus. *N Engl J Med.* 1995;333:A9. **14.** Data on file, Takeda Pharmaceuticals North America, Inc.

Please see attached complete Prescribing Information.



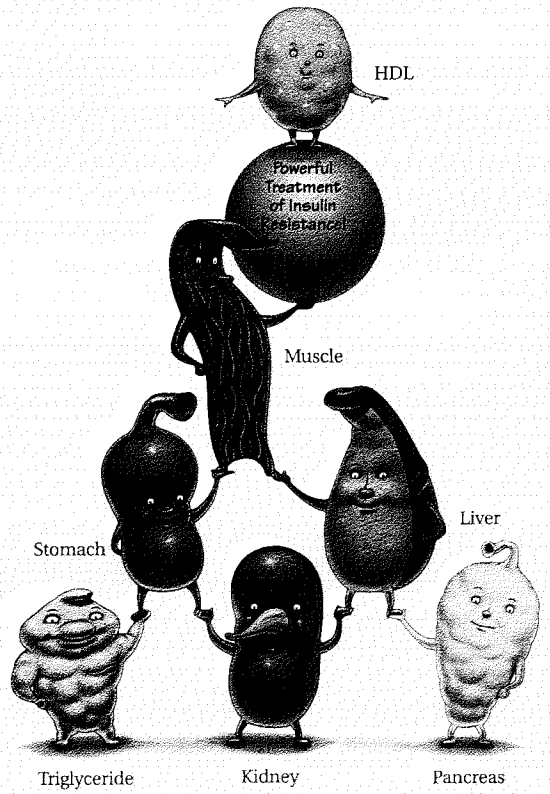
Always QD Power

actos®

pioglitazone HCl

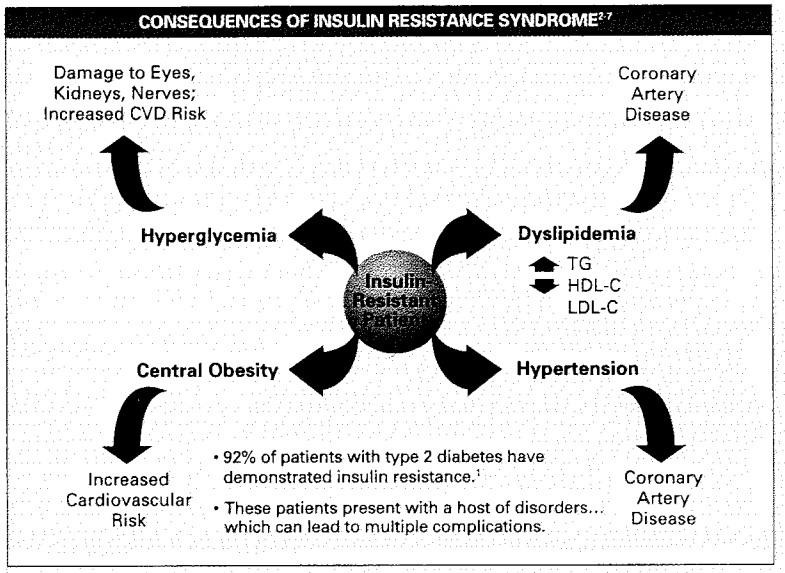
For performance that benefits the body

ACTOS helps the body stand strong against the challenges of insulin resistance



The major metabolic defects in type 2 diabetes are 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.[1] Clinical considerations regarding renal and gastrointestinal function are also common concerns when prescribing an oral agent for type 2 diabetes.[2] Management of type 2 diabetes should also include nutritional counseling, weight reduction as needed, and exercise.

Left untreated, the insulin-resistant patient may face serious consequences



- As glucose intolerance from insulin resistance progresses, the metabolic risk factors for cardiovascular disease continuously increase.[8]
- Insulin resistance with associated hyperglycemia and dyslipidemia in type 2 diabetes can lead to micro- and macrovascular complications.[5]
- In addition, hyperinsulinemia is linked to elevated triglyceride and low HDL-C levels, which individually are major risk factors for coronary heart disease.[5]

Please see attached complete Prescribing Information.

Always QD Power
actos®
pioglitazone HCl
For performance that benefits the body