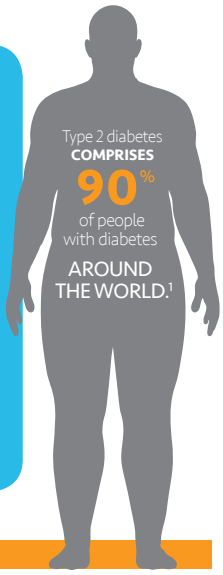
PIOGLITAZONE BACKGROUNDER

For Media Inquiries Contact: Elissa Johnsen (elissa.johnsen@takeda.com or +1-224-554-3185)

Takeda stands firmly behind the substantial data confirming a positive benefit-to-risk profile for pioglitazone, which includes more than 14 years of clinical and patient experience with the product.

As a company, Takeda has conducted and supported clinical research, including randomized controlled trials, as well as prospective and retrospective observational studies in order to advance knowledge in the medical community around diabetes, the mechanism of metabolic diseases, and around pioglitazone.



1982
Pioglitazone was discovered.

1984

1986

1988

1990

1992

1994

1996

1998

1999
Pioglitazone was first approved in the United States.

2000
Pioglitazone was approved in the European Union.

2001

2002

Pioglitazone Use and In-Depth Scientific Rigor: A Closer Look

Two large long-term observational studies found no significant increase in the risk of bladder cancer in diabetic patients taking pioglitazone.[2,3] However, other short-term studies have suggested the possibility of a small increased risk of bladder cancer.[4,5] As a small risk can never be fully excluded, physicians are informed not to initiate pioglitazone in patients with active bladder cancer and to use caution in patients with a history of bladder cancer.

The final data from a large prospective 10-year observational cohort study conducted in the United States found **no significant increase in the risk** of bladder cancer in diabetic patients ever exposed to pioglitazone, compared to those never exposed to pioglitazone (hazard ratio [HR] =1.06 [95% confidence interval [CI] 0.89 – 1.26]).[2]

The *Pan European Multi-Database Bladder Cancer Risk Characterization Study*, a large, multi-database retrospective cohort study, conducted in four European countries, with up to 10 years of follow up, **found no association** of bladder cancer in diabetic patients ever exposed to pioglitazone, compared to those never exposed to pioglitazone (HR 0.99, [95% CI 0.75 - 1.30]).[3]

Additionally, both studies found no association between the risk of bladder cancer and:[2,3]

- **Duration of pioglitazone use**
- **Increased cumulative dose of pioglitazone**

Data from both studies has been submitted to the U.S. Food & Drug Administration (FDA) and European Medicines Agencies (EMA) for potential label updates.

Understanding Observational Studies and Randomized Controlled Trials

Observational studies reflect the patient population in a practice setting and can study long-term safety outcome data in larger populations over broader timeframes compared to randomized controlled trials , which can provide high quality evidence when investigating the beneficial effects of treatment in a selected population.

PAUL DOLIN, M.D., HEAD OF PHARMACOEPIDEMIOLOGY, TAKEDA PHARMACEUTICALS

The Differences Between Randomized Controlled Trials and Observational Studies Include:

RANDOMIZED CONTROLLED TRIALS

- Well-defined homogenous population[6]
- Intensive clinical support and short term follow-up[7]
- Primary outcomes determined in advance of data collection[8]
- Prospective data collection
- Limitations include short-term follow-up, modest sample size and outcomes are difficult to generalize for a more general population[6]

OBSERVATIONAL STUDIES

- Large, heterogeneous populations that reflect typical cases seen by physicians in their clinics[6]
- Treatments prescribed based on real world, standard clinical care[7]
- Opportunity for long-term follow-up[8]
- Prospective or retrospective data collection
- Limitations include possible under-reporting or incorrect coding, available data limited to variables in the data source, and no randomization[6]

Bladder Cancer in the General Population

Bladder cancer is the 9TH MOST COMMON CANCER IN THE WORLD[9]

About **330,000** diagnosed with new bladder cancer in 2012[9]

99,000

Some risk factors can make a person more likely to develop bladder cancer.[10]

TOBACCO SMOKING
Smoking is the most known risk factor for bladder cancer.[10]

CHEMICALS
Occupational exposure to specfic chemicals considered as the second most important risk factor for bladder cancer.[10]

ETHNICITY
Ethnicity impacts the incidence of bladder cancer: Caucasians are at much higher risk (in some instances over double the risk) than other ethnicities.[10]

2004

JANUARY 2003 — FDA

Based on discussions with the U.S. Food and Drug Administration (FDA), Takeda agreed to support a 10-year observational cohort study for pioglitazone. Began study in January.

2006

2008

2010

5 YRS — 2011

Takeda announced the 5-year interim data of the observational cohort study for pioglitazone.[11]

2012 — STUDY BEGAN — 2012

The *Pan European Multi-Database Bladder Cancer Risk Characterization Study* began in Europe.

2014

10 YRS — AUGUST 2014

Takeda announced the completion of the 10-year observational cohort study for pioglitazone.

2015

JULY 2015

Takeda announced the completion of the *Pan European Multi-Database Bladder Cancer Risk Characterization Study.*

Important Safety Information

CONTRAINDICATIONS

Initiation of ACTOS is contraindicated in patients with NYHA Class III or IV heart failure.
ACTOS is contraindicated in patients with known hypersensitivity to pioglitazone or any of its excipients so as to avoid inducing a potentially serious hypersensitivity reaction.

WARNINGS AND PRECAUTIONS

Fluid retention and cardiac failure: Thiazolidinediones, including ACTOS, can cause dose-dependent fluid retention, which may exacerbate or precipitate heart failure. After initiation of ACTOS, and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., excessive, rapid weight gain, dyspnea, and/or edema). If heart failure develops, discontinuation of ACTOS must be considered. ACTOS should be used with caution in patients with cardiac dysfunction whose physical activity is markedly limited. Combination use with insulin may increase risk.

Hepatic effects: Post-marketing reports of hepatitis and hepatic dysfunction have been received. Very rarely these reports have involved hepatic failure, with and without a fatal outcome, although causality has not been established. Obtain liver tests before starting ACTOS and periodically thereafter.

Pioglitazone therapy should not be initiated in patients with increased liver enzyme levels (ALT> 2.5x upper limit of normal) or with any other evidence of liver disease. Existing pioglitazone therapy should be discontinued if ALT levels are persistently higher than 3x the upper limit of normal, and symptoms suggesting hepatic dysfunction should cause the liver enzymes to be checked. Pending the results of laboratory investigations, the decision as to whether pioglitazone therapy should continue must be based on clinical judgment; in the presence of jaundice, drug therapy should be discontinued.

Weight gain: Weight gain was observed in clinical trials and has been seen in post-marketing experience with pioglitazone, so patient weight should be closely monitored.

Fractures: An increased incidence of bone fracture has been noted in female patients.

Bladder cancer: Some data suggest there may be an increased risk of bladder cancer in ACTOS users and also that the risk increases with duration of use. Do not use ACTOS in patients with active bladder cancer. Use caution when using in patients with a prior history of bladder cancer. Tell patients to promptly report any sign of hematuria or other symptoms such as dysuria or urinary urgency as these may be due to bladder cancer.

Hypoglycemia: When ACTOS is used with insulin, a sulfonylurea or other oral hypoglycemic agents, hypoglycemia may occur.

Ovulation: Ovulation in premenopausal anovulatory women or women with polycystic ovarian syndrome may occur with ACTOS.

Macular edema: Post-marketing reports of new-onset or worsening diabetic macular edema with decreased visual acuity have been reported with thiazolidinediones, including pioglitazone. Physicians should consider the possibility of macular edema if a patient reports decreased visual activity.

Drug interactions: Use of ACTOS with CYP2C8 inducers or strong inhibitors may require dose adjustment.

Please refer to the Summary of Product Characteristics (SmPC) for ACTOS before prescribing.

ACTOS should be used according to the indication, posology and method of administration described in the product information.

References

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