DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021073/S-043, 044
NDA 021842/S-014, 015
NDA 022024/S-008, 007
NDA 021925/S-010, 011

SUPPLEMENT APPROVALS

Takeda Global Research & Development Center, Inc.
Attention: Jessie Y. Lee, Ph.D.
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Dr. Lee:

Please refer to your Supplemental New Drug Applications (sNDAs) dated July 7, 2011, received July 8, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for:

- ACTOS (pioglitazone hydrochloride) Tablets (sNDA 21-073/S-043),
- ACTOPLUS MET (pioglitazone hydrochloride and metformin hydrochloride) fixed-dose combination Tablets (sNDA 21-842/S-014),
- ACTOPLUS MET XR (pioglitazone hydrochloride and metformin hydrochloride extended-release) fixed-dose combination Tablets (sNDA 22-024/S-008), and
- DUETACT (pioglitazone hydrochloride and glimepiride) fixed-dose combination Tablets (sNDA 21-925/S-010).

Please also refer to your sNDAs dated and received July 8, 2011 for ACTOS (sNDA 21-073/S-044), ACTOPLUS MET (sNDA 21-842/S-015), ACTOPLUS MET XR (sNDA 22-024/S-007), and DUETACT (sNDA 21-925/S-011).

We acknowledge receipt of your amendments dated August 1 and 3, 2011, for ACTOS, ACTOPLUS MET, ACTOPLUS MET XR, and DUETACT, and your risk evaluation and mitigation strategy (REMS) assessments submitted on March 7, 2011, for ACTOS and DUETACT, and on November 4, 2010, for ACTOPLUS MET and ACTOPLUS MET XR.

We also refer to our letter dated June 9, 2011, notifying you of new safety information that we believe should be included in the labeling for ACTOS, ACTOPLUS MET, ACTOPLUS MET XR, and DUETACT under Section 505(o)(4) of the FDCA, notifying you that you must submit a proposed REMS modification under Section 505-1, and notifying you of a requirement for a postmarketing study under Section 505(o)(3). The new safety information pertains to a dose- and duration-dependent increase in the risk of bladder cancer in subjects exposed to pioglitazone hydrochloride compared to subjects never exposed to pioglitazone hydrochloride.

Supplemental new drug applications (sNDA 21-073/S-044, sNDA 21-842/S-015, sNDA 22-024/S-007, and sNDA 21-925/S-011) provide for revisions to the labeling for ACTOS, ACTOPLUS MET, ACTOPLUS MET XR, and DUETACT, respectively. The agreed upon changes to the language included in our June 9, 2011, letter are as follows (additions are noted by underline and deletions are noted by ~~strikethrough)~~.

For ACTOS:

On the Highlights page, under **WARNINGS AND PRECAUTIONS**:

Bladder cancer: Preclinical and clinical trial data, and results from an observational study suggest an increased risk of bladder cancer in pioglitazone users. The observational data ~~indicate~~ further suggest that the risk increases with duration of use. Do not use in patients with active bladder cancer. Use caution when using in patients with a prior history of bladder cancer (5.5)

In the Full Prescribing Information, under **WARNINGS AND PRECAUTIONS, 5.5 Urinary Bladder Tumors:**

A five-year interim report of an ongoing 10-year observational cohort study found a nonsignificant increase in the risk for bladder cancer in subjects ever exposed to ACTOS, compared to subjects never exposed to ACTOS (HR 1.2 [95% CI 0.9 – 1.5]). Compared to never exposure, a duration of ACTOS therapy longer than 12 months was associated with an ~~40%~~ increase in risk (HR 1.4 [95% CI 0.9 – 2.1]), which reached statistical significance after more than 24 months of ACTOS use (HR 1.4 [95% CI 1.03 – 2.0]). Interim results from this study suggested that taking ACTOS ~~A duration of therapy~~ longer than 12 months increased the relative risk of developing bladder cancer in any given year by 40% which equates to an absolute increase of 3 cases in 10,000 (from approximately 7 in 10,000 [without ACTOS] to approximately 10 in 10,000 [with ACTOS]) ~~was associated with 27.5 excess cases of bladder cancer per 100,000 person-years of follow-up, compared to never use of ACTOS~~.

In the Full Prescribing Information, under **PATIENT COUNSELING INFORMATION, Instructions:**

Tell patients to promptly report any sign~~s~~ of macroscopic hematuria or other symptoms ~~of blood in the urine,~~ such as dysuria or urinary urgency that develop or increase during treatment ~~urinary urgency, pain on urination, back or abdominal pain~~ as these may be due to bladder cancer.

To the Medication Guide, under "**What are the possible side effects of ACTOS? ACTOS may cause serious side effects including":**

- **bladder cancer.** There may be an increased chance of having bladder cancer when you take ACTOS. You should not take ACTOS if you are receiving treatment for bladder cancer. Tell your doctor right away if you have any of the following symptoms of bladder cancer:
  - ~~you see~~ blood or a red color in your urine.
  - ~~you have~~ an increased ~~urgent~~ need to urinate ~~or pain while urinating~~
  - ~~you have pain in your back or lower abdomen~~
  - pain while you urinate

For ACTOPLUS MET:

Under **PRECAUTIONS, General:** ***Pioglitazone hydrochloride:***

A five-year interim report of an ongoing 10-year observational cohort study found a nonsignificant increase in the risk for bladder cancer in subjects ever exposed to ACTOS, compared to subjects never exposed to ACTOS (HR 1.2 [95% CI 0.9 – 1.5]). Compared to never exposure, a duration of ACTOS therapy longer than 12 months was associated with an ~~40%~~ increase in risk (HR 1.4 [95% CI 0.9 – 2.1]), which reached statistical significance after more than 24 months of ACTOS use (HR 1.4 [95% CI 1.03 – 2.0]). Interim results from this study suggested that taking ACTOS ~~A duration of therapy~~ longer than 12 months increased the relative risk of developing bladder cancer in any given year by 40% which equates to an absolute increase of 3 cases in 10,000 (from approximately 7 in 10,000 [without ACTOS] to approximately 10 in 10,000 [with ACTOS]) ~~was associated with 27.5 excess cases of bladder cancer per 100,000 person-years of follow-up, compared to never use of ACTOS~~.

Under **Information for Patients:**

Patients should be told to promptly report any sign~~s~~ of macroscopic hematuria or other symptoms such as dysuria or urinary urgency that develop or increase during treatment ~~of blood in the urine, urinary urgency, pain on urination, back or abdominal pain~~ as these may be due to bladder cancer.

To the Medication Guide, under "**What are the possible side effects of ACTOPLUS MET? ACTOPLUS MET may cause serious side effects including":**

- **Bladder cancer.** There may be an increased chance of having bladder cancer when you take ACTOPLUS MET. You should not take ACTOPLUS MET if you are receiving treatment for bladder cancer. Tell your doctor right away if you have any of the following symptoms of bladder cancer:
  - ~~you see~~ blood or a red color in your urine.
  - ~~you have~~ an increased ~~urgent~~ need to urinate ~~or pain while urinating~~
  - ~~you have pain in your back or lower abdomen~~
  - pain while you urinate

~~In studies of pioglitazone (one of the medicines in ACTOPLUS MET), bladder cancer occurred in a few more people who were taking pioglitazone than in people who were taking other diabetes medicines. There were too few cases to know if the bladder cancer was related to pioglitazone.~~

For ACTOPLUS MET XR:

Under **PRECAUTIONS, General:** ***Pioglitazone:***

A five-year interim report of an ongoing 10-year observational cohort study found a non-significant increase in the risk for bladder cancer in subjects ever exposed to ACTOS, compared to subjects never exposed to ACTOS (HR 1.2 [95% CI 0.9 – 1.5]). Compared to never exposure, a duration of ACTOS therapy longer than 12 months was associated with an ~~40%~~ increase in risk (HR 1.4 [95% CI 0.9 – 2.1]), which reached statistical significance after more than 24 months of ACTOS use (HR 1.4 [95% CI 1.03 – 2.0]). Interim results from this study suggested that taking ACTOS ~~A duration of therapy~~ longer than 12 months increased the relative risk of developing bladder cancer in any given year by 40% which equates to an absolute increase of 3 cases in 10,000 (from approximately 7 in 10,000 [without ACTOS] to approximately 10 in 10,000 [with ACTOS]) ~~was associated with 27.5 excess cases of bladder cancer per 100,000 person-years of follow-up, compared to never use of ACTOS~~.

Under **Information for Patients:**

Patients should be told to promptly report any sign~~s~~ of macroscopic hematuria or other symptoms such as dysuria or urinary urgency that develop or increase during treatment ~~of blood in the urine, urinary urgency, pain on urination, back or abdominal pain~~ as these may be due to bladder cancer.

To the Medication Guide, under "**What are the possible side effects of ACTOPLUS MET XR? ACTOPLUS MET XR may cause serious side effects including":**

- **Bladder cancer.** There may be an increased chance of having bladder cancer when you take ACTOPLUS MET XR. You should not take ACTOPLUS MET XR if you are receiving treatment for bladder cancer. Tell your doctor right away if you have any of the following symptoms of bladder cancer:
    - ~~you see~~ blood or a red color in your urine.
    - ~~you have~~ an increased ~~urgent~~ need to urinate ~~or pain while urinating~~
    - ~~you have pain in your back or lower abdomen~~
    - pain while you urinate

~~In studies of pioglitazone (one of the medicines in ACTOPLUS MET XR), bladder cancer occurred in a few more people who were taking pioglitazone than in people who were taking other diabetes medicines. There were too few cases to know if the bladder cancer was related to pioglitazone.~~

For DUETACT:

Under **PRECAUTIONS, General:** ***Pioglitazone hydrochloride:***

A five-year interim report of an ongoing 10-year observational cohort study found a non-significant increase in the risk for bladder cancer in subjects ever exposed to ACTOS, compared to subjects never exposed to ACTOS (HR 1.2 [95% CI 0.9 – 1.5]). Compared to never exposure, a duration of ACTOS therapy longer than 12 months was associated with an ~~40%~~ increase in risk (HR 1.4 [95% CI 0.9 – 2.1]), which reached statistical significance after more than 24 months of ACTOS use (HR 1.4 [95% CI 1.03 – 2.0]). Interim results from this study suggested that taking ACTOS ~~A duration of therapy~~ longer than 12 months increased the relative risk of developing bladder cancer in any given year by 40% which equates to an absolute increase of 3 cases in 10,000 (from approximately 7 in 10,000 [without ACTOS] to approximately 10 in 10,000 [with ACTOS]) ~~was associated with 27.5 excess cases of bladder cancer per 100,000 person-years of follow-up, compared to never use of ACTOS~~.

Under **Information for Patients:**

Patients should be told to promptly report any signs ~~of~~ of macroscopic hematuria or other symptoms such as dysuria or urinary urgency that develop or increase during treatment ~~of blood in the urine, urinary urgency, pain on urination, back or abdominal pain~~ as these may be due to bladder cancer.

To the Medication Guide, under "**What are other possible side effects of DUETACT? DUETACT can cause other serious side effects including":**

- **Bladder cancer.** There may be an increased chance of having bladder cancer when you take DUETACT. You should not take DUETACT if you are receiving treatment for bladder cancer. Tell your doctor right away if you have any of the following symptoms of bladder cancer:
    - ~~you see~~ blood or a red color in your urine.
    - ~~you have~~ an increased ~~urgent~~ need to urinate ~~or pain while urinating~~
    - ~~you have pain in your back or lower abdomen~~
    - pain while you urinate

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