ACTOS®

Pioglitazone Hydrochloride

INDICATIONS

Type 2 diabetes mellitus

ACTOS tablets should be used only in patients who do not sufficiently respond to any of the following treatments and are suspected to be insulin resistant.

1 1) Dietary treatment and/or exercise therapy alone
2) Using sulfonylureas in addition to dietary treatment and/or exercise therapy
3) Using α-glucosidase inhibitors in addition to dietary treatment and/or exercise therapy
4) Using biguanides in addition to dietary treatment and/or exercise therapy
2 Using insulin preparation in addition to dietary treatment and/or exercise therapy

Precautions for INDICATIONS

The administration of ACTOS tablets should be limited to the patients who have been definitely diagnosed as having diabetes mellitus. It should be noted that in addition to diabetes mellitus, there are such diseases as abnormal glucose tolerance and positive urine sugar that represent diabetes-like symptoms (renal glucosuria, senile abnormal glucose tolerance, abnormal thyroid function, etc.).

DOSAGE AND ADMINISTRATION

1. **When ACTOS tablets are used in addition to dietary treatment and/or exercise therapy alone or in combination of dietary treatment and/or exercise therapy and sulfonylureas, α-glucosidase inhibitors or biguanides**
Usually, for adults, 15-30 mg of pioglitazone is orally administered once a day before or after breakfast. The dosage may be appropriately adjusted according to the patient's sex, age and symptom within the upper limit of 45 mg.
2. **When ACTOS tablets are used in combination of dietary treatment and/or exercise therapy and insulin preparations**
Usually, for adults, 15mg of pioglitazone is orally administered once a day before or after breakfast. The dosage may be appropriately adjusted according to the patient's sex, age and symptom within the upper limit of 30mg.

Precautions for DOSAGE AND ADMINISTRATION

1. Edema has been reported relatively more often in women. It is, therefore, desirable to **start the administration with 15 mg once a day in women paying attention to the development of edema.**
2. Edema has been most often observed after increase in the dosage from 30 mg to 45 mg once a day. **Attention should be paid to the development of edema when the dosage is increased to 45 mg.**
3. Since edema has been reported relatively more frequently **in combination use with insulin preparations, the administration should start with 15 mg once a day. Dose should be increased carefully with close observation on edema and signs and symptoms of cardiac failure.**
4. Physiological function is decreased in elderly in general. It is, therefore, **desirable to start the administration with 15 mg once a day.**

CONTRAINDICATIONS

1. Patients with cardiac failure or a history of cardiac failure [In animal studies, increases in heart weight likely due to a compensatory change from an increase in the circulating plasma volume have been observed, and clinical cases in which the aggravation or occurrence of cardiac failure have been reported.]
2. Patients with severe ketosis, in a state of diabetic coma or precoma, or with type 1 diabetes mellitus [It becomes essential to quickly rectify hyperglycemia with administration of intravenous fluid or insulin.]
3. Patients with severe hepatic dysfunction [This drug may accumulate in the body because it is mainly metabolized in the liver.]
4. Patients with severe renal dysfunction
5. Patients with severe infections, before or after operation, or with serious trauma
[It is desirable to control blood sugar with the injection of insulin. Therefore, administration of this drug is not appropriate.]
6. Patients with a history of hypersensitivity to any of the ingredients of this drug.
7. Pregnant women or women having possibilities of being pregnant.

PRECAUTIONS

1. **Careful Administration** (ACTOS tablets should be administered with care in the following patients.)
(1) The following patients or conditions
1) Patients with cardiac diseases such as myocardial infarction, angina pectoris, cardiomyopathy and hypertensive cardiac diseases which may cause cardiac failure [An increase in the circulating plasma volume may induce cardiac failure.] (See 2. Important Precautions and Clinically significant side effects.)
2) Hepatic or renal dysfunction. (See CONTRAINDICATIONS.)
3) Pituitary insufficiency or adrenal insufficiency [Hypoglycemia may occur.]
4) Malnutrition, starvation, irregular food intake, deficiency of food intake, or weakness [Hypoglycemia may occur.]
5) Extreme muscle movement [Hypoglycemia may occur.]
6) Excessive alcohol drinkers [Hypoglycemia may occur.]
7) Elderly patients (See Use in the Elderly.)
(2) Patients who are receiving other antidiabetic drugs (See Drug Interactions and Clinically significant side effects.)
2. **Important Precautions**
(1) Since edema likely due to increase in the circulating plasma volume may occur in a short period of time, and cardiac failure may be aggravated or occur, careful attention should be paid to the following. (See CONTRAINDICATIONS and 1. Careful Administration.)
1) ACTOS tablets should not be administered to patients with cardiac failure or a history of cardiac failure.
2) Close observation should be made during administration of ACTOS tablets. If edema, abrupt body weight gain, symptoms of cardiac failure, etc. are observed, appropriate measures such as discontinuation of ACTOS tablets and administration of loop diuretics (furosemide, etc.) should be taken.
3) Instruction should be given for patients to pay attention to any edema, abrupt body weight gain or changes in the symptoms that occur during taking ACTOS tablets and to discontinue this drug immediately and consult a physician when any abnormalities are noted.
(2) Since ECG abnormality and increase in cardiothoracic ratio may occur, close observation, such as periodic ECG, should be performed. When abnormality is observed, careful administration should be performed, such as temporary discontinuation or reduction of dosage. (See Other side effects.)
(3) ACTOS tablets may induce hypoglycemic symptoms when it is concomitantly used with other antidiabetic drugs. In concomitant use with these drugs, full explanation should be given to patients on hypoglycemic symptoms and countermeasures thereof, and the patients' attention should be called to such symptoms. (See Drug Interactions and Clinically significant side effects.)
(4) In epidemiological studies conducted overseas in patients with diabetes mellitus, potential increased risk of bladder cancer was observed in patients who received pioglitazone. The risk tended to increase with long-term use. Therefore, caution should be exercised for the following points. (See Other Precautions.)
1) ACTOS tablets should not be administered to patients with active bladder cancer. ACTOS tablets should be administered carefully to patients with a prior history of bladder cancer, by fully taking into account the benefit and risk of pioglitazone.
2) Before initiating treatment, the patient or his/her family should be given a full explanation of the risk of bladder cancer. The patient must be instructed to immediately consult a physician when any sign or symptom of blood in the urine, urinary urgency, pain on urination, etc. is observed.
3) Periodic examination, such as urinalysis, should be performed during taking ACTOS tablets. Appropriate measures should be taken when abnormality is observed. Also, careful observation should be continued after stop taking ACTOS tablets.
(5) The application of ACTOS tablets should be considered only when sufficient effect has not been obtained in patients already undergoing dietary treatment and/or exercise therapy that are the basic treatment for diabetes mellitus.
(6) When ACTOS tablets are used, the administration should be limited to patients with suspected insulin resistance. A rough standard for insulin resistance is set at a body mass index (Body Mass Index: BMI kg/m2) of 24 or more or insulin secretion as a fasting blood insulin level of 5 μU/mL or more.
(7) During the administration of ACTOS tablets, blood and urinary sugar levels should be monitored periodically to determine the effect of this drug. If the effect is insufficient after administration for 3 months, this drug should be promptly switched to other drugs.
(8) During administration, the administration may become no longer necessary or the dosage may need to be reduced. In addition, the effect may be reduced or deprived due to the patient's intemperance or a complication with infection, etc. Therefore, attention should be paid to food intake, progress of body weight, blood sugar, presence of infection, etc. Caution should always be exercised in the judgement on appropriateness of continued administration, dosage, and selection of drugs, etc.
(9) Aggravated cases of diabetic retinopathy are known with rapid decrease in blood glucose level. Attention should be paid to this symptom since it has been reported on ACTOS tablets.
(10) The safety has not been established in concomitant use of ACTOS tablets at the daily dose of 45 mg and α-glucosidase inhibitors (There are few such clinical experiences.)
(11) The safety has not been established in concomitant use of ACTOS tablets with α-glucosidase inhibitors and sulfonylureas (Increasing tendency of incidence of adverse reactions has been observed in clinical trials.)
(12) The safety has not been established in concomitant use of ACTOS tablets at the daily dose of 45 mg and biguanides (There are few such clinical experiences.)

Use in the Elderly

Since physiological function is decreased in elderly in general, ACTOS tablets should be administered carefully, such as starting with 15 mg once a day, while close observation of the course of disease condition with attention to the development of adverse reactions.

Use during Pregnancy, Delivery or Lactation

(1) ACTOS tablets should not be administered to pregnant women or women having possibilities of being pregnant. [The safety of this drug in pregnant women has not been established. In an administration study during the organogenesis period in rats, high embryo-fetal mortality and low survival rate of newborns were observed in the groups given 40 mg/kg or more. In a similar study in rabbits, one each of death and abortion of mother animal and high embryo-fetal mortality were observed in the groups given 160 mg/kg.]
(2) Administration to nursing women should be avoided. However, if the administration is indispensable, nursing should be discontinued. [Transfer to mother's milk has been reported in rats.]

Pediatric Use

The safety of ACTOS tablets in children has not been established (no clinical experience).

Other Precautions

(1) In studies giving pioglitazone via gavage for 24 months in mice and rats, bladder tumor was observed in male rats of the groups given 3.6 mg/kg/day or more.
(2) In an interim analysis of an epidemiological study conducted overseas in patients with diabetes mellitus, full analysis did not show a significant difference in the risk of bladder cancer (hazard ratio 1.2 [95%CI 0.9 – 1.5]), however stratified analysis indicated a significant increase in the risk of bladder cancer for patients who received pioglitazone for 2 years or longer (hazard ratio 1.4 [95%CI 1.03 – 2.0]).2) Also, in another epidemiological study, the risk of bladder cancer was significantly increased in patients who were taking pioglitazone (hazard ratio 1.22 [95%CI 1.05 – 1.43]). In addition, there was a significantly increased risk of bladder cancer in patients who received pioglitazone for 1 year or longer (hazard ratio 1.34 [95%CI 1.02 – 1.75]).
(3) It has been reported that the number and size of colon tumor have been increased after an analogous drug (troglitazone or rosiglitazone) was orally administered to Min mice, an experimental model animal for familial adenomatous polyposis (FAP).
(4) It has been reported that (diabetic) macular edema developed or worsened after thiazolidine drugs such as ACTOS tablets were administered. If reduced visual acuity occurs, a possibility of macular edema should be considered.

SIDE EFFECTS

Adverse reactions, including abnormalities in laboratory data, were observed in 364 (26.6%) of 1,368 patients given 15 mg, 30 mg, or 45 mg of pioglitazone once a day in the clinical trials performed up to the time of approval in Japan. Edema has been observed more frequently in women and in combination with insulin [ACTOS tablets alone and combination with other antidiabetic drugs except for insulins: males 3.9% (26/665), women 11.2% (72/643), in combination with insulin: males 13.6% (3/22), women 28.9% (11/38)], and frequency of edema in patients with diabetic complications tends to be higher compared with the patients without diabetic complications [patients with diabetic retinopathy: 10.4% (44/422), patients with diabetic neuropathy: 11.4% (39/342), patients with daiabetic nephropathy: 10.6% (30/282)]. In additon, hypoglycemic symptoms have been observed more frequently in combination with insulins [ACTOS tablets alone and combination with other antidiabetic drugs except for insulins: 0.7% (9/1,308) , in combination with insulin: 33.3% (20/60)]. Adverse reactions, including abnormalities in laboratory data, were observed in 556 (16.3%) of 3,421 patients in the post-marketing drug use surveillance (as of the end of the reexamination period). Adverse reactions listed below have been found in the above-mentioned clinical trials and surveillance, or spontaneous reports.

Clinically significant side effects

1. **Since cardiac failure may be aggravated or occur**, close observation should be made during administration of ACTOS tablets. If edema, abrupt body weight gain, and symptoms/signs of cardiac failure (shortness of breath, palpitations, increased cardiothoracic ratio, pleural effusion, etc.) are observed, appropriate measures, such as discontinuation of ACTOS tablets and administration of loop diuretics, etc., should be taken. In particular, careful attention to **signs of cardiac failure should be paid when ACTOS tablets are used in cardiac disease patients with potential risk of cardiac failure or used in combination with insulins.** (See 1. Careful Administration and 2. Important Precautions.)
2. Edema may occur probably due to the increase in the circulating plasma volume (8.2%, 112/1,368 patients). Close observation should be made, and if edema is observed, appropriate measures, such as reduction of the dosage or discontinuation of ACTOS tablets, should be taken. When the symptom does not improve with these measures, the administration of loop diuretics (furosemide, etc.) should be considered, if necessary. **Edema has been observed more frequently in women, in combination with insulins, or in patients with diabetic complication and there were several cases that edema occurred after the dosage was increased from 30 mg to 45 mg once a day. These patiens should be particularly paid attention for occurrence of edema.** (See Precautions for DOSAGE AND ADMINISTRATION.)
3. **Hepatic dysfunction**, accompanied by significant increases in AST(GOT), ALT(GPT), AL-P, etc., or **jaundice** may occur (< 0.1%). Therefore, hepatic function test should be periodically performed if necessary, i.e. in patients with underlying hepatic dysfunction. If abnormality is observed, appropriate measures, such as discontinuation of ACTOS tablets, should be taken.
4. **Hypoglycemic symptoms** may occur when ACTOS tablets are concomitantly used with other antidiabetic drugs (0.1 - < 5%). When hypoglycemic symptom is observed, careful administration should be made, such as temporary discontinuation or reduction of the dosage of this drug or concomitantly using antidiabetic agents. Sucrose is usually administered when hypoglycemic symptom is observed after administration of this drug. However, **glucose should be administered when hypoglycemic symptom is observed after concomitant use with α-glucosidase inhibitors. Hypoglycemic symptoms have been observed more frequently in combination with insulins.**
5. **Rhabdomyolysis** characterized by muscle ache, weakness, increased CK(CPK), and increased blood and urinary myoglobin may occur (frequency unknown). In such a case, administration of ACTOS tablets should be discontinued, and appropriate measures should be taken.
6. Since **interstitial pneumonia** may occur (frequency unknown), tests such as chest X-ray, chest CT or serum marker should be performed immediately after fever, cough, dyspnoea or abnormal chest sounds (crepitations) etc. are observed. If abnormality is observed, ACTOS tablets should be discontinued and appropriate measures, such as administration of adrenal corticosteroid, should be taken.
7. **Relapse of gastric ulcer** has been reported.

Other side effects

	≥ 5%	0.1 - < 5%	< 0.1%	frequency unknown
HematologicNote1)		**Anemia, leukopenia, or thrombocytopenia**		
Cardiovascular		Increased blood pressure, **increased cardiothoracic ratio**Note2), abnormal ECGNote2), palpitations, pressure sensation of chest, or facial hot flushes		
HypersensitivityNote3)		**Rash, eczema, or pruritus**		
Gastrointestinal		Nausea/vomiting, stomach discomfort, heartburn, abdominal pain, feeling of enlarged abdomen, diarrhea, constipation, increased appetite, or anorexia		
HepaticNote4)		**Increased AST(GOT), ALT(GPT), AL-P, or γ-GTP**		
Psychoneurologic		Dizziness, light-headedness, headache, sleepiness, malaise, weakness, or numbness		
Others	**Increased LDH and CK (CPK)**Note5)	Increased BUN or potassium, decreased total protein or calcium, weight increase, increased urinary protein, or shortness of breath	Arthralgia or tremor, aggravation of diabetic retinopathy due to rapid decrease in blood sugar	**Bone fracture**Note6)

Note 1) Blood examination should be performed periodically (about once every 3 months).
Note 2) See 2. Important Precautions (2).
Note 3) In such a case, ACTOS should be discontinued.
Note 4) Frequency: increased AST(GOT) 0.86% (11/1,272 patients), increased ALT(GPT) 0.94% (12/1,276), increased AL-P 0.47% (6/1,272), and increased γ-GTP 0.95% (12/1,263)
Note 5) Increased LDH (5.63%, 71/1,261 patients) or CK(CPK) (5.00%, 61/1,221) may occur. When such abnormality is observed, close observation should be made, such as re-examination.
Note 6) Increased frequency of bone fracture in women has been observed in foreign clinical studies.

Drug Interactions

Precautions for coadministration (Caution should be taken for coadministration.)

Drugs	Signs, Symptoms, Treatment, Mechanisms, etc.
Antidiabetic drugs Sulfonylureas: glimepiride, glibenclamide, gliclazide, tolbutamide, etc. Sulfonylamides: glyburide Biguanides : metformin hydrochlo-ride buformin hydrochloride Nateglinide Mitiglinide calcium hydrate α-Glucosidase inhibitors: voglibose, acarbose, etc. Insulin preparations	• Since hypoglycemic symptoms may occur when ACTOS tablets are used with antidiabetic drugs listed in the left column, this drug should be administered with care, such as starting with lower dose, when used in combination with any of the drugs listed left. • When hypoglycemic symptom is observed in combination use with α-glucosidase inhibitors, glucose should be administered instead of sucrose.
For the concomitant use of antidiabetic drugs and the drugs which intensify or diminish the hypoglycemic action of antidiabetic drugs • Drugs intensifying the hypoglycemic action of antidiabetic drugs: β-blockers, salicylic acid preparations, monoamine oxidase inhibitors, fibrate derivatives for treatment of hyperli-pidemia, warfarin, etc. • Drugs diminishing the hypoglycemic actions of antidiabetic drugs: adrenaline, adrenocortical hormone, thyroid hormone, etc.	When ACTOS Tablets are further administered concurrently, in addition to the concomitant use with a drug among those listed left, attention should be paid to the drug interactions listed in the PRECAUTIONS of these antidiabetic drugs. Further attention should also be paid to the additional influence that may be caused by the improving effect of insulin resistance of this drug.
CYP2C8-inducing drugs such as rifampicin	It has been reported that AUC of pioglitazone decreased by 54% in concomitant use with rifampicin. Therefore, when ACTOS Tablets are used in combination with rifampicin, the state of patients' glycemic control should be closely observed, and the dose should be increased if necessary.

STORAGE

Store between 15-30°C, protected from moisture and humidity.

PRESENTATIONS

Tablets "Pack of 30"

ACTOS 15 mg:	Pioglitazone (Hydrochloride) 15 mg/tablet
ACTOS 30 mg:	Pioglitazone (Hydrochloride) 30 mg/tablet
ACTOS 45 mg:	Pioglitazone (Hydrochloride) 45 mg/tablet

Excipients: Lactose, carmellose calcium, hydroxylpropylcellulose, magnesium stearate.

Council of Arab Health Ministers, Union of Arab Pharmacists

THIS IS A MEDICAMENT

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous.
- Follow the doctor's prescription strictly, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

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