MEDICATION GUIDE
ACTOPLUS MET XR (ak-TŌ-plus-met eX-R)
(pioglitazone hydrochloride and metformin hydrochloride extended-release) Tablets

Read this Medication Guide carefully before you start taking ACTOPLUS MET XR and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about ACTOPLUS MET XR, ask your doctor or pharmacist.

What is the most important information I should know about ACTOPLUS MET XR?
ACTOPLUS MET XR can cause serious side effects, including **new or worse heart failure.**

- Pioglitazone, one of the medicines in ACTOPLUS MET XR, can cause your body to keep extra fluid (fluid retention), which leads to swelling (edema) and weight gain. Extra body fluid can make some heart problems worse or lead to heart failure. Heart failure means your heart does not pump blood well enough.
- If you have severe heart failure, you cannot start ACTOPLUS MET XR.
- If you have heart failure with symptoms (such as shortness of breath or swelling), even if these symptoms are not severe, ACTOPLUS MET XR may not be right for you.

Call your doctor right away if you have any of the following:

- swelling or fluid retention, especially in the ankles or legs.
- shortness of breath or trouble breathing, especially when you lie down.
- an unusually fast increase in weight.
- unusual tiredness.

Metformin, one of the medicines in ACTOPLUS MET XR, can cause a rare but serious condition called lactic acidosis (a buildup of an acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital.

Most people who have had lactic acidosis with metformin have other things that, combined with the metformin, led to the lactic acidosis. Tell your doctor if you have any of the following, because you have a higher chance for getting lactic acidosis with ACTOPLUS MET XR if you:

- have kidney problems or your kidneys are affected by certain x-ray tests that use injectable dye. People whose kidneys are not working properly should not take ACTOPLUS MET XR.
- have liver problems.
- drink alcohol very often, or drink a lot of alcohol in short-term "binge" drinking.
- get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids.
- have surgery.
- have a heart attack, severe infection, or stroke.
- are 80 years of age or older, and your kidneys are not working properly.

The best way to keep from having a problem with lactic acidosis from metformin is to tell your doctor if you have any of the problems in the list above. Your doctor may decide to stop your ACTOPLUS MET XR for a while if you have any of these things.

Lactic acidosis can be hard to diagnose early, because the early symptoms could seem like the symptoms of many other health problems besides lactic acidosis. You should call your doctor right away if you get the following symptoms, which could be signs of lactic acidosis:

- You feel very weak or tired.
- You have unusual (not normal) muscle pain.
- You have stomach pains, nausea or vomiting.
- You have trouble breathing.

- You feel dizzy or lightheaded.
- You have a slow or irregular heartbeat.

ACTOPLUS MET XR can have other serious side effects. See "What are the possible side effects of ACTOPLUS MET XR?"

What is ACTOPLUS MET XR?
ACTOPLUS MET XR is a prescription medicine used with diet and exercise to improve blood sugar (glucose) control in adults with type 2 diabetes.

ACTOPLUS MET XR contains 2 prescription diabetes medicines called pioglitazone hydrochloride (ACTOS) and metformin hydrochloride extended-release (FORTAMET).
Your doctor will decide if you should take ACTOPLUS MET XR.

ACTOPLUS MET XR can be used for adults with type 2 diabetes who:
- are taking pioglitazone alone and do not have good enough blood sugar control,
- are taking metformin alone and do not have good enough blood sugar control, or
- are already taking both pioglitazone and metformin

If you are taking pioglitazone or metformin, check with your healthcare provider and make sure you understand exactly how your healthcare provider wants you to switch over to ACTOPLUS MET XR.

It is important to eat the right foods, lose weight if needed, and exercise regularly in order to manage your type 2 diabetes. Diet, weight loss, and exercise are the main treatment for type 2 diabetes and they also help your diabetes medicines work better for you.

ACTOPLUS MET XR has not been studied in children and is not recommended for children under the age of 18. The risks of giving ACTOPLUS MET XR to a child are not known. See "What are some other possible side effects of ACTOPLUS MET XR?"

Who should not take ACTOPLUS MET XR?
Do not take ACTOPLUS MET XR if you:
- are allergic to any of the ingredients in ACTOPLUS MET XR**.** See the end of this Medication Guide for a complete list of ingredients in ACTOPLUS MET XR.
- have kidneys which are not working properly.
- have a condition called metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- are going to have an x-ray procedure with an injection of dyes (contrast agents) in your vein with a needle. Talk to your doctor about when to stop ACTOPLUS MET XR and when to start it again.

People with severe heart failure should not start taking ACTOPLUS MET XR. See "What is the most important information I should know about ACTOPLUS MET XR?"

What should I tell my doctor before taking ACTOPLUS MET XR?
Before starting ACTOPLUS MET XR, ask your doctor about what the choices are for diabetes medicines and what the expected benefits and possible risks are for you in particular.

Tell your doctor about all of your medical conditions, especially if you:
- **have heart failure.**
- **have kidney problems.**
- **are going to have dye injected into a vein for an x-ray, CAT scan, heart study, or other type of scanning.**
- **drink a lot of alcohol** (all the time or short binge drinking).
- **have type 1 ("juvenile") diabetes or had diabetic ketoacidosis.** These conditions should be treated with insulin.

- **are 80 years old or older.** People over 80 years should not take ACTOPLUS MET XR unless their kidney function is checked and it is normal.
- **have a type of diabetic eye disease called macular edema** (swelling of the back of the eye).
- **have liver problems.** Your doctor should do blood tests to check your liver before you start taking ACTOPLUS MET XR and during treatment as needed.
- **are pregnant or planning to become pregnant.** ACTOPLUS MET XR should not be used during pregnancy. It is not known if ACTOPLUS MET XR can harm your unborn baby. Talk to your doctor about the best way to control your blood glucose levels while pregnant.
- **are a premenopausal woman (before the "change of life"), who does not have periods regularly or at all.** ACTOPLUS MET XR may increase your chance of becoming pregnant. Talk to your doctor about birth control choices while taking ACTOPLUS MET XR. Tell your doctor right away if you become pregnant while taking ACTOPLUS MET XR.
- **are breastfeeding or plan to breastfeed.** It is not known if ACTOPLUS MET XR pass into your milk and if it can harm your baby. You should not take ACTOPLUS MET XR if you breastfeed your baby. Talk to your doctor about the best way to control your blood glucose levels while breastfeeding.

Tell your doctor about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. ACTOPLUS MET XR and some of your other medicines can affect each other. You may need to have your dose of ACTOPLUS MET XR or certain other medicines adjusted. Certain other medicines can affect your blood sugar (glucose) control.

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist before you start a new medicine. They will tell you if it is okay to take ACTOPLUS MET XR with other medicines.

How should I take ACTOPLUS MET XR?

- Take ACTOPLUS MET XR exactly as prescribed. Your doctor may need to change your dose of ACTOPLUS MET XR to control your blood glucose. Do not change your dose unless told to do so by your doctor.
- Take ACTOPLUS MET XR once a day with the evening meal to lower your chance of an upset stomach.
- Take ACTOPLUS MET XR **tablets whole. Do not chew, cut, or crush the tablets.** If you cannot swallow ACTOPLUS MET XR whole, tell your doctor. You may need a different medicine.
- If you take ACTOPLUS MET XR, you may see something that looks like the ACTOPLUS MET XR tablet in your stools. This is normal.
- If you miss a dose of ACTOPLUS MET XR, take your next dose as prescribed unless your doctor tells you differently. Do not take two doses at one time the next day.
- If you take too much ACTOPLUS MET XR, call your doctor or poison control center right away.
- If your body is under stress, for example: due to fever, infection, trauma (such as a car accident), or surgery, the dose of your diabetes medicines may need to be changed. Call your doctor right away.
- Stay on your diet and exercise programs and test your blood sugar regularly while taking ACTOPLUS MET XR.
- Your doctor should do blood tests before starting ACTOPLUS MET XR and from time to time to check your liver, kidneys, and blood cells.
- Your doctor should also do regular blood tests (for example, hemoglobin A1C) to check how well your blood sugar is controlled with ACTOPLUS MET XR.
- Your doctor should check your eyes regularly. Some people have had vision changes due to swelling in the back of the eye, called macular edema, while taking ACTOPLUS MET XR.
- It may take 2-3 months to see the full effect on your blood sugar level.

You may need to stop ACTOPLUS MET XR for a short time. Call your doctor for instructions if you:

- are sick with severe vomiting, diarrhea, or fever or if you drink a much lower amount of liquid than normal.
- plan to have surgery.
- are having an x-ray procedure with injection of dye.

What are other possible side effects of ACTOPLUS MET XR?
ACTOPLUS MET XR can cause other serious side effects including:

- **Weight gain.** Pioglitazone, one of the medicines in ACTOPLUS MET XR, can cause weight gain that may be due to fluid retention or extra body fat. Weight gain due to fluid retention can be a serious problem for people with certain conditions, including heart problems. See "What is the most important information I should know about ACTOPLUS MET XR?"
- **Liver problems**. It is important for your liver to be working normally when you take ACTOPLUS MET XR. Your doctor should do blood tests to check your liver before you start taking ACTOPLUS MET XR and during treatment as needed. Call your doctor right away if you have unexplained symptoms such as:
  - nausea or vomiting.
  - stomach pain.
  - unusual or unexplained tiredness.
  - loss of appetite.
  - dark urine.
  - yellowing of your skin or the whites of your eyes.
- **Macular edema** (diabetic eye disease with swelling in the back of the eye). Tell your doctor right away if you have any changes in your vision. Your doctor should check your eyes regularly.
- **Fractures (broken bones),** usually in the hand, upper arm, or foot in women. Talk to your doctor for advice on how to keep your bones healthy. It is not known if ACTOPLUS MET XR can affect the bones of children.
- **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:
  - blood or a red color in your urine
  - an increased need to urinate
  - pain while you urinate
- **Low red blood cell count (anemia).**
- **Low blood sugar (hypoglycemia).** Lightheadedness, dizziness, shakiness, or hunger may indicate that your blood sugar is too low. This can happen if you skip meals, if you use another medicine that lowers blood sugar, or if you have certain medical problems. Call your doctor if low blood sugar levels are a problem for you.
- **Ovulation** (release of an egg from an ovary in a woman) leading to pregnancy. Ovulation may happen when premenopausal women who do not have regular monthly periods take ACTOPLUS MET XR. This can increase the chance of pregnancy. See "What should I tell my doctor before taking ACTOPLUS MET XR?"

The most common side effects of ACTOPLUS MET XR reported in clinical trials included diarrhea, nausea, and upset stomach. These side effects usually happen during the first few weeks of treatment. Taking ACTOPLUS MET XR with meals can help lessen these side effects. However, if you have unusual or unexpected stomach problems, talk with your doctor. Stomach problems that start up later during treatment may be a sign of something more serious.

Other common side effects of ACTOPLUS MET XR:

- cold-like symptoms (upper respiratory infection)
- headache
- urinary tract infection
- dizziness
- sinus infection
- anemia

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the side effects of ACTOPLUS MET XR. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ACTOPLUS MET XR?

- Store ACTOPLUS MET XR at 59° to 86°F (15° to 30°C). Keep ACTOPLUS MET XR in the original container to protect from light.
- Keep the ACTOPLUS MET XR bottle tightly closed and protect from getting wet (away from moisture and humidity).

Keep ACTOPLUS MET XR and all medicines out of the reach of children.

General information about ACTOPLUS MET XR

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ACTOPLUS MET XR for a condition for which it is not prescribed. Do not give ACTOPLUS MET XR to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about ACTOPLUS MET XR. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about ACTOPLUS MET XR that is written for healthcare professionals. For more information, go to www.actoplusmetxr.com or call 1-877-825-3327.

What are the ingredients in ACTOPLUS MET XR?

Active Ingredients: pioglitazone hydrochloride and metformin hydrochloride

Inactive Ingredients for ACTOPLUS MET XR**:** candelilla wax, cellulose acetate, povidone, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, hypromellose, polyethylene glycols (PEG 400, PEG 8000), sodium lauryl sulfate, titanium dioxide, and triacetin. Ink contains shellac, iron-oxide red (15 mg/1000 mg tablet strength), FD&C Blue No. 2 Lake (30 mg/1000 mg tablet strength), propylene glycol, and ammonium hydroxide.

Always check to make sure that the medicine you are taking is the correct one. ACTOPLUS MET XR tablets look like this:

- 15 mg/1000 mg strength tablets—white to off-white, round tablet imprinted with “15/1000” and “4833X” in red on one side.
- 30 mg/1000 mg strength tablets—white to off-white, round tablet imprinted with “30/1000” and “4833X” in light blue on one side.

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