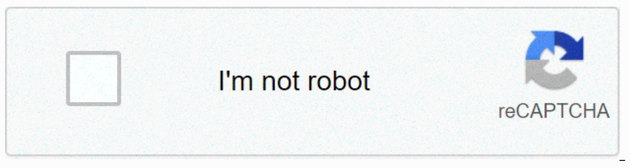

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Metformin side effects kidney stones

Jaga PinterestCreated for Greatist Experts at Healthline. Read moreDiabebee diagnosis is not a sentence of life-free fun. People with diabetes can travel the world, climb the corporate ladder, show off their outfits at the gram, and be on the life side. But don't break out the red Solo Cups just yet. It is important to consider how alcohol can affect diabetes treatment. Metformin is the most commonly prescribed medicine for the treatment of type 2 diabetes. It helps regulate and manage blood sugar levels and can even prolong your life. However, combining metformin with articling can cancel out the benefits of the drug and cause harmful side effects. That's about five drinks for men or four drinks for women in about 2 hours. Prolonged alcohol consumption while taking metformin can cause life-threatening problems associated with diabetes and potentially persistent liver damage. Your doctor should explain the possible side effects and interactions of metformin, including alcohol-related side effects. Unlike people with type 1 diabetes, people with type 2 diabetes have a type 2 diabetes mellitus. But they may have trouble doing it. Their cells may not react to insulin as they used it – it is called low insulin sensitivity. Insulin allows your body to use glucose as energy or store it for later use. This function will keep your blood sugar balanced. Doctors often prescribed drugs like metformin to increase insulin sensitivity. Metformin reduces the production of glucose in the liver, while improving glucose movement through the body. Adding a lot of alcohol to the mix complicates things - it tinkers with liver glucose production, can cause very low blood sugar. Low blood sugar increases the risk of life-threatening conditions such as lactic acidosis (more of this per second). Your liver has its limits If you're binge drinking, your liver works to remove toxins from your body instead of producing and regulating glucose. It tires out of the liver, reducing its ability to produce and circulate enough glucose. Plus, excess alcohol prevents your cells from absorbing glucose properly, so glucose levels in the bloodstream begin to increase, putting stress on your organs and nerves. Whether you have diabetes, prolonged alcohol consumption can damage your liver, leading to dangerous complications such as hepatitis and cirrhosis of the liver. From time to time, a cocktail may not be a big deal, but a long-term combination of binge drinking and taking metformin can be potentially life-threatening. Here's why. Hypoglycemia: How low can you go? Both metformin and excessive alcohol consumption lower your blood sugar levels, but they don't work together. When combined, they overwork your system and cause more harm than good. Hypoglycaemia (insulin shock) occurs when blood glucose levels reach an unstable low - less than 70 milligrams per deciliter for most Those who use insulin to regulate their blood sugar know that this is when they need to hold or reduce their insulin dose. While alcohol and metformin may be a recipe for hypoglycemia, it is not the worst combination. Studies show that sulphonylureas, a type of type 2 diabetes medication, carry a 4.5 times higher risk of hypoglycemia that metformin does. No matter how it happens, hypoglycemia is something. If you become hypoglycemia during drinking, it can be difficult to distinguish the symptoms of your normal buzz. Some of these symptoms are: dizziness confusion in visionheadachedrowsinessslurred speechFriends do not let friends have low blood sugar Hypoglycemia is treatable, so teach your friends (especially your designated manager) how to recognize symptoms. If they notice any symptoms, they should take a glass out of their hands and replace it with some food that raises blood sugar. While this isn't the trendiest accessory, bust out your blood sugar monitor to confirm your blood sugar reading. Taking glucose tablets for you is another good idea, but a pinch of hard candy, regular soda, juice, or a tablespoon of honey or sugar can do the trick. Check your blood sugar 15 minutes later. If you lose consciousness, someone should call 911.If you have had severe hypoglycaemia before and are taking metformin, your doctor may advise you to apply a glucagon hypoglycaemia rescue kit containing a syringe to inject glucagon. This fast-acting substance helps the liver to make more glucose within 15 minutes. Glucagon is also available as a nasal spray. Ask your doctor if you need glucagon and which medicine is best for you. Do not supercalifragilistic lactic acidosis While it is much rarer than hypoglycaemia, lactic acidosis can happen if you drink alcohol while taking metformin. Metformin increases your body's natural lactic acid production and alcohol consumption makes it difficult for your body to destroy it. Accumulation of lactic acid can cause serious complications in your heart, lungs, kidneys and blood vessels. Lactic acidosis requires treatment in a hospital. If left untreated, it can be life-threatening. If you notice any of the following symptoms, call 911: fatigue cramps in muscles that usually don't cramp breathing weakness Fast heart rate, headache aches, nausea, or other stomach discomfort chillyMis B-12 got to do with it? Vitamin B-12 is a nutrient the body absorbs from food. Clams and beef liver have the highest concentration, but if they're not on the menu, you can also get B-12 fish, meat, poultry, milk and eggs. Most people get all the B-12 they need from food, but those who take metformin have a higher risk of B-12 deficiency. One study found that over the course of 4 years, metformin reduced people's B-12 levels by 19 percent. Other studies up to 52%. B-12 deficiency may cause tiredness, weakness or loss of appetite. If left untreated, it can cause damage to the nervous system. If you have diabetes, it is important to consume alcohol only in moderation. For women, moderation is defined as not more than one drink per day. For men, it's not more than two drinks a day. It is important to monitor your glucose levels before drinking, if you drink, before bedtime, and 24 hours later. Alcohol can lower blood sugar levels up to 24 hours after the first drink. Low blood sugar can make you feel lethargic, so don't plan on doing anything other than Netflix and cooling after a night of drinking. Metformin gets used to it - especially its effects on the gut. Many side effects are similar to binge drinking. If you mix these two, prepare to get these symptoms worse. The more alcohol you drink and the faster you drink, the more these symptoms will intensify: vomiting excessive gassiness from the abdomen to the muscle cramps in the abdomen discomfort in rare cases, increased blood flow can cause facial redness and flushing. You can drink alcohol while taking metformin, but there are side effects. Metformin and alcohol can both lower your blood sugar, putting you at risk of hypoglycaemia and life-threatening lactic acidosis. If your blood sugar level is very unstable, it is probably best to avoid drinking until you get them under control. Be sure to talk to your doctor about the risks and interactions with any medicines you are taking. Once you have it, have your B-12 levels checked because both metformin and alcohol reduce them. General name: pioglitazone hydrochloride and metformin hydrochloride Form: tablet Medically reviewed Drugs.com. Last updated 23.11.2020. Congestive heart failure Thiazolidinediones, including pioglitazone, which is an ingredient in pioglitazone and metformin hydrochloride tablets, cause or exacerbate congestive heart failure in some patients [see warnings and precautions (5.1)] . Following the use of pioglitazone and metformin hydrochloride tablets and increasing the dose, closely monitor patients for signs and symptoms of heart failure (e. g. excessive, rapid weight gain, dyspnoea and/or oedema). If heart failure occurs, it should be treated in accordance with current treatment standards and discontinuation or dose reduction of pioglitazone and metformin hydrochloride tablets should be considered [see Warnings and Precautions (5.1)]. Pioglitazone and metformin hydrochloride tablets are not recommended for use in patients with symptomatic heart failure. The use of pioglitazone and metformin hydrochloride tablets in patients with class III or IV heart failure is contraindicated in new York Heart Association (NYHA) class III or IV heart failure (see contraindications (4) and warnings and precautions (5.1)]. Lactic acid In post-marketing experience, cases of metformin-related lactic acidosis have resulted in death, hypothermia, hypotension and resistant bradyarrhythmia. The onset of metformin-related lactic acidosis is often subtle, accompanied only by non-specific symptoms such as malaise, myalgia, respiratory distress, somnolence and abdominal pain. Metformin-related lactic acidosis was characterised by increased lactate levels in the blood (above 5 mmol/l), anion acidosis (without signs of ketoneuria or ketonemia), increased lactate-pyrumate ratio; metformin plasma concentrations are generally greater than 5 µg/ml [see warnings and precautions (5.2)]. Risk factors for metformin-related lactic acidosis include renal impairment, concomitant use with certain medicinal products (e.g. carbonic anhydrase inhibitors such as topiramate), 65 years of age or older, radiological examination of contrast, surgery and other procedures, hypoxic conditions (e. g. acute congestive heart failure), excessive alcohol consumption, and hepatic impairment. These high-risk groups include measures to reduce and manage the risk of metformin-related lactic acidosis in these high-risk groups [see posology and administration (2.2), contraindications (4), warnings and precautions (5.2), drug interactions (7) and use in specific populations (8.6, 8.7)]. If metformin-related lactic acidosis is suspected, pioglitazone and metformin hydrochloride tablets should be discontinued immediately and general supportive measures should be initiated in hospital. Rapid haemodialysis is recommended (see warnings and precautions (5.2)]. Indications and use of pioglitazone and metformin tablets Pioglitazone and metformin hydrochloride tablets are indicated in addition to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with pioglitazone and metformin is appropriate (see clinical trials (see clinical trials (14)). There are significant limitations with pioglitazone that only have an antihyperglycaemic effect in the presence of endogenous insulin. Pioglitazone and metformin hydrochloride tablets should not be used to treat type 1 diabetes mellitus or diabetic ketoacidosis as they are not effective under these conditions. Be careful in patients with liver disease [see warnings and precautions (5.5)]. Pioglitazone and metformin tablets Doses and recommendations for administration to all patients Pioglitazone and metformin hydrochloride tablets should be taken with food to reduce gastrointestinal adverse reactions associated with metformin. If treatment with pioglitazone and metformin combination tablet is considered appropriate, the recommended starting dose is: 15 mg/500 mg twice daily or 15 mg/850 mg once daily and, if necessary, gradually titrated, after assessing the adequacy of response and tolerability, for patients with new York heart connection Class I or II heart failure: 15 mg/500 mg or 15 mg/850 mg once daily and titrated gradually, as appropriate, following an assessment of the therapeutic effect and tolerability of patients whose disease is not adequately controlled with metformin monotherapy: 15 mg/500 mg twice daily or 15 mg/850 mg once or twice daily (depending on the dose of metformin already taken) and is gradually titrated as necessary after evaluation of response and tolerability, patients whose disease is not adequately controlled by pioglitazone monotherapy: 15 mg/500 mg twice daily or 15 mg/850 mg once daily and gradually titrated, as appropriate after evaluation of response and tolerability in patients who switched from pioglitazone to metformin in separate tablets:glitazone and metformin hydrochloride tablets should be taken at doses as close as possible to the dose of pioglitazone and metformin already taken. Pioglitazone and metformin hydrochloride tablets can be titrated to a maximum daily dose of 45 mg pioglitazone and 2550 mg metformin. Doses of metformin above 2000 mg may be more tolerated when administered three times a day. Following the use or dose increase of pioglitazone and metformin hydrochloride tablets, closely monitor patients for adverse reactions related to fluid retention such as weight gain, swelling and signs and symptoms of congestive heart failure (see Warnings and Warnings and Precautions (5.1)). Liver tests (serum alanine and aspartate aminotransferase, alkaline phosphatase and total bilirubin) should be perform before pioglitazone and metformin hydrochloride tablets. In patients without liver disease, regular monitoring of liver tests during treatment with pioglitazone and metformin hydrochloride tablets is not recommended. Patients who have liver test abnormalities prior to administration of pioglitazone and metformin hydrochloride tablets, or who experience liver tests with abnormalities while taking pioglitazone and metformin hydrochloride tablets, should be treated as described in Warnings and precautions (see warnings and precautions (5.5) and clinical pharmacology (12.3)]. Recommendations for use in renal impairment Prior to administration of pioglitazone and metformin hydrochloride tablets and periodically thereafter. Pioglitazone and metformin hydrochloride tablets are contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 ml/min/1.73 m at 2. The use of pioglitazone and metformin hydrochloride tablets in patients with eGFR between 30 and 45 ml/min/1.73 m2 is not recommended. In patients taking pioglitazone and metformin hydrochloride tablets with eGFR below 45 ml/min/1.73 m2, evaluate the risk of continued treatment. Pioglitazone metformin hydrochloride tablets should be discontinued if the patient's eGFR falls later in the 30 ml/min/1.73 m 2[see contraindications (4) and warnings and precautions (5.2)]. Concomitant use with strong CYP2C8 inhibitors Pioglitazone (one of the ingredients of pioglitazone and metformin hydrochloride tablets) and gemfibrozil, a potent CYP2C8 inhibitor, increases the exposure of pioglitazone approximately 3-fold. Therefore, the maximum recommended dose of pioglitazone and metformin hydrochloride tablets is 15 mg/850 mg/day when used in combination with gemfibrozil or other potent CYP2C8 inhibitors (see drug interactions (7.1) and clinical pharmacology (12.3)]. Treatment with iodized contrast images discontin pioglitazone and metformin hydrochloride tablets during or before iodized contrast image in patients with eGFR between 30 and 30 patients with a history of liver disease, alcoholism or heart failure; patients receiving intra-arterial iodine contrast. Re-evaluation of EGFR 48 hours after shooting; metformin hydrochloride tablets when renal function is stable [see Warnings and Precautions (5.2)]. Pharmaceutical forms and strengths 15 mg/500 mg tablets: white to off-white coloured capsule-shaped, biconvex, film-coated tablets debossed with 15/500 on one side and 1280 15 mg/850 mg tablets on the other side: white to off-white coloured, capsule-shaped, biconvex film-coated tablets debossed with 15/850 on one side and 1281 Initiation of contraindications in patients with NYHA class III or IV heart failure [see box 1281] Severe renal impairment (eGFR less than 30 ml/min/1.73 m 2[see warnings and precautions (5.2)]. Use in patients with known hypersensitivity to pioglitazone, metformin or pioglitazone and any other component of metformin hydrochloride. Metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin. Warnings and precautions Congestive heart failure Pioglitazone Pioglitazone, like other thiazolidinediones, may cause dose-dependent fluid retention when used alone or in combination with other antidiabetic medicines, and is most common when pioglitazone is used in combination with insulin. Fluid retention may cause or exacerbate congestive heart failure. Patients treated with pioglitazone and metformin hydrochloride should be monitored for signs and symptoms of congestive heart failure. If congestive heart failure occurs, it should be treated in accordance with current treatment standards and discontinuation or dose reduction of pioglitazone and metformin hydrochloride should be considered (see box warning, contraindications (4) and adverse reactions (6.1)). Lactic acidosis Metformin hydrochloride Cases of metformin-related lactic acidosis, including fatal cases, have been reported in post-marketing experience. These cases with non-specific symptoms such as malaise, myalgia, abdominal pain, respiratory distress or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmia have been reported with severe acidosis. Metformin-related lactic acidosis was characterised by increased levels of lactate in the blood (above 5 mmol/l), anion intermediate assembly (without signs of ketoneuria or ketonemia) and elevations in lactate-pyruxia ratios;metformin plasma concentrations are generally above 5 µg/ml. Metformin reduces the increase in lactate levels in the liver, which may increase the risk of lactic acidosis, especially in patients at risk. If metformin-related lactic acidosis is suspected, general supportive measures should be taken immediately in the hospital environment with immediate discontinuation of pioglitazone and metformin hydrochloride tablets. In patients treated with pioglitazone and metformin hydrochloride tablets who have been diagnosed or suspected of having severe lactic acidosis, it is recommended that acidosis be adjusted and accumulated metformin is used to remove metformin (metformin hydrochloride is a dialysis, clearance up to 170 ml/min under good haemodynamic conditions). Hemodialysis often results in reversal and recovery of symptoms. Educate patients and their families about the symptoms of lactic acidosis and, if symptoms occur, instruct them to stop taking pioglitazone and metformin hydrochloride tablets and report these symptoms to their healthcare provider. For known and potential risk factors for metformin-related lactic acidosis, recommendations for reducing the risk of metformin-related lactic acidosis are available below: renal impairment Metformin-related lactic acidosis in post-marketing experience was mainly observed in patients with significant renal impairment. The risk of metformin accumulation and metformin-related lactic acidosis is increased with the severity of renal impairment, as metformin is significantly excreted by the kidneys (see Clinical Pharmacology (12.3)). Before you use pioglitazone and metformin hydrochloride tablets, you will receive eGFR. Pioglitazone and metformin hydrochloride tablets are contraindicated in patients with eGFR below 30 ml/min/1.73 m2. The use of pioglitazone and metformin hydrochloride tablets is not recommended in patients with eGFR between 30 and 45 ml/min/1.73 m2. all patients taking pioglitazone and metformin hydrochloride tablets can receive eGFR at least once a year. Renal function should be evaluated more frequently in patients at increased risk of renal impairment (e.g. elderly). In patients taking pioglitazone and metformin hydrochloride tablets with eGFR below 45 ml/min/1.73 m2, evaluate the benefits and risks of continued treatment [see Posology and contraindications (4) and clinical pharmacology (12.3)]. Interactions Concomitant use of pioglitazone and metformin hydrochloride with specific medicinal products may increase the risk of metformin-related lactic acidosis: those that affect renal function cause significant haemodynamic changes, interfere with acid-base balance or increase the accumulation of metformin (e.g. cationic medicinal products) [see drug interactions (7)]. Therefore, consider monitoring more often. Age 65 or more The risk of metformin-related lactic acidosis increases with the patient's age, as elderly patients are more likely to experience liver, kidney or heart damage than younger patients. Renal function should be evaluated more frequently in elderly patients [see use in specific populations (8.5)]. Radiological studies with contrast agents Administration of ioded contrast agents in patients treated with metformin has led to acute decreased renal function and lactic acidosis. Stop pioglitazone and metformin hydrochloride tablets during or before the iodized contrast procedure in patients with eGFR between 30 and 60 ml/min/1.73 m2; patients with a history of hepatic impairment, alcoholism or heart failure; patients receiving intra-arterial iodine contrast. Re-evaluate eGFR 48 hours after taking and restart pioglitazone and metformin hydrochloride tablets if renal function is stable. Surgery and other procedures Adherence to food and fluids during surgery or other procedures may increase the risk of volume reduction, hypotension and renal impairment. Pioglitazone and metformin hydrochloride tablets should be temporarily discontinued if patients have restricted food and fluid intake. Hypoxic conditions There were several cases of metformin-related lactic acidosis (especially in hypoperfusion and hypoxaemia) in acute congestive heart failure. Cardiovascular collapse (shock), acute myocardial infarction, sepsis and other conditions associated with hypoxaemia have been associated with lactic acidosis and may also cause prerenal azotaemia. If such events occur, pioglitazone and metformin hydrochloride tablets should be discontinued. Excessive alcohol consumption Alcohol increases the effect of metformin on lactate metabolism and may increase the risk of metformin-related lactic acidosis. Warn patients against excessive alcohol consumption while receiving pioglitazone and metformin hydrochloride tablets. Hepatic impairment Cases of metformin-related lactic acidosis have occurred in patients with hepatic impairment. This may be due to a disorder of lactate clearance resulting in an increase in lactate levels in the blood. Therefore, the use of pioglitazone and metformin hydrochloride tablets should be avoided in patients clinical or liver disease. Oedema Oedema Oedema In controlled clinical trials with pioglitazone, oedema was reported more frequently in pioglitazone-treated patients than in placebo-treated patients and is dose-dependent (see adverse reactions (see adverse reactions (6.1)). In the post-marketing experience, new oedema has been reported or worsened. Pioglitazone and metformin hydrochloride should be used with caution in patients with oedema. Since thiazolidinedione ions, including pioglitazone, may cause fluid retention that may exacerbate or cause congestive heart failure, pioglitazone and metformin hydrochloride should be used with caution in patients at risk of congestive heart failure. Patients treated with pioglitazone and metformin hydrochloride should be monitored for signs and symptoms of congestive heart failure (see boxed Warning, Warnings and Warning (5.1) and patient counselling information (17.1)). Hypoglycaemia Patients receiving pioglitazone and metformin hydrochloride in combination with insulin or other antidiabetic medicines (especially medicines that promote insulin secretion such as sulphonyllureas) may be at risk of hypoglycaemia. In order to reduce the risk of hypoglycaemia, a dose reduction of the concomitant diabetes drug may be necessary [see posology and administration (2.2)]. Hypoglycaemia may also occur when calorie intake is incomplete or if strenuous exercise is not compensated for by a calorie supplement. Elderly, debilitating or malnourished patients and patients with adrenal or pituitary insufficiency or intoxication are particularly sensitive to hypoglycaemic effects. Hypoglycaemia may be difficult to recognise in the elderly, and in people taking beta-adrenergic blocking agents. Hepatic effects Fatal and non-fatal cases of hepatic failure have been reported in post-marketing experience in patients taking pioglitazone, although these data do not contain sufficient information necessary to establish the probable cause. The database of clinical trials controlled with pioglitazone has not yet been available for drug-induced hepatotoxicity [see adverse reactions (6.1)). Patients with type 2 diabetes may have fatty liver disease or heart disease with episodic congestive heart failure, both of which can cause abnormal liver function tests, and may have other forms of liver disease, many of which can be treated or treated. Therefore, it is recommended to obtain a liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase and total bilirubin) and to evaluate the patient prior to initiation of pioglitazone and metformin hydrochloride therapy. In patients with liver tests, treatment with pioglitazone and metformin hydrochloride should be initiated with caution. Immediate measurement of liver tests in patients with symptoms suggestive of hepatic impairment, including anorexia, upper right abdomen, dark urine or In this clinical context, if abnormalities in liver tests are observed in the patient (ALT exceeds the upper limit of the reference range three times), pioglitazone and metformin hydrochloride should be discontinued and investigated to determine the probable cause. Pioglitazone and metformin hydrochloride should not be restarted in these patients without a second explanation of liver test abnormalities. Patients with serum ALT levels greater than three times the reference range with total serum bilirubin greater than twice the reference range without alternative etiologies are at risk of severe drug-induced liver damage and should not be restarted with pioglitazone and metformin hydrochloride. In patients with lower serum ALT or bilirubin and with alternative probable cause, treatment with pioglitazone and metformin hydrochloride may be used with caution. In a two-year carcinogenicity study, bladder tumours were observed in male rats in the bladder (see non-clinical toxicology (13.1)). In addition, in a three-year PROactive clinical trial, 14 out of 2,605 patients (0.54%) were randomised to pioglitazone and 5/2633 (0.19%) randomised to bladder cancer in the placebo group. After excluding patients who had less than one year at the time of diagnosis of bladder cancer, 6 (0.23%) pioglitazone and two cases (0.08%) placebo-treated patients. A large subgroup of patients was observed for up to 10 additional years after the end of the study, with low additional exposure to pioglitazone. For both PROactive and post-follow-up monitoring over 13 years, the incidence of bladder cancer did not differ between pioglitazone or placebo randomised patients (HR =1.00; [95% Cl: 0.59 to 1.72]). The findings on the risk of bladder cancer in patients exposed to pioglitazone are different in observational studies; some did not find an increased risk of bladder cancer associated with pioglitazone, while others did not. A large prospective 10-year observation cohort study conducted in the United States did not find a statistically significant increase in bladder cancer risk in diabetic patients who were never exposed to pioglitazone compared to those who never received pioglitazone (HR =1.06 [95% Cl 0.89-1.26]). A retrospective cohort study conducted based on UK data found a statistically significant link between pioglitazone and bladder cancer exposure (HR: 1.63; [95% Cl: 1.22 to 2.19]). In some studies, including a 10-year observational study in the U.S., no relationship between the cumulative dose or cumulative duration of pioglitazone and bladder cancer was detected, but in others. Conflicting findings and limitations on these and other studies are an exclusion of the final interpretation of the observational data. may be associated with an increased risk of bladder tumours. There are insufficient data to determine whether pioglitazone is a tumour promoter of bladder tumours. Therefore, pioglitazone and metformin hydrochloride tablets should not be used in patients with active bladder cancer and the benefit of glycaemic control should be considered in patients with a history of glycaemic control compared to the unknown risk of recurrence of cancer with pioglitazone and metformin hydrochloride tablets. Fractures in PROactive (prospective pioglitazone clinical trial for macrovascular events) were randomised in addition to standard standard 5238 patients with type 2 diabetes mellitus with macrovascular disease and a history of macrovascular disease. During the mean follow-up period of 34.5 months, the incidence of fractures in women was 5.1% (44/870) for pioglitazone and 2.5% (23/905) for placebo. This difference was observed after the first year of treatment and persisted during the study. Most of the fractures observed in female patients were non-vertebral fractures, including lower limbs and distal upper limbs. In men treated with pioglitazone (1.7%) compared to placebo (2.1%). The risk of caution in patients treated with pioglitazone and metformin hydrochloride, especially female patients, should be considered and attention should be paid to bone health assessment and maintenance in accordance with current medical standards. Macular oedema in diabetic patients receiving pioglitazone or other thiazolidinedione has been reported in post-marketing experience. Some patients had blurred vision or decreased visual acuity, while others were diagnosed with routine ophthalmological examinations. Most patients had peripheral oedema at the time of diagnosis of macular oedema. In some patients, macular oedema improved after discontinuation of thiazolidinedione. Patients with diabetes should have regular eye examinations by an ophthalmologist according to the current standards of treatment. Patients with diabetes mellitus who report visual symptoms should be referred immediately to an ophthalmologist, regardless of the patient's medicinal products or other physical findings [see adverse reactions (6.1)). Vitamin B12 levels in controlled clinical trials of 29-week metformin were observed in approximately 7% of patients with pre-existing normal vitamin B 12 levels as subnormal without clinical manifestations. However, this reduction, which may be due to interference with the absorption of b 12 from the B12 insphoric factor complex, is very rarely associated with anaemia and appears to be rapidly reversible when stopping the addition of metformin or vitamin B 12. Haematological measurement pioglitazone and metformin hydrochloride tablets are recommended annually and all visible abnormalities should be adequately investigated and treated. Certain individuals (those with insufficient vitamin B 12 or calcium intake or absorption) appear to be predisposed to develop subnormal B 12 levels. Routine vitamin B 12 measurements may be useful in these patients at intervals of two to three years. Macrovascular results Pioglitazone and metformin hydrochloride or any other oral antidiabetic medicinal product have not been conclusive evidence of a reduction in macrovascular risk. Adverse reactions Labelling: Congestive heart failure (Warnings and warnings and precautions (5.1)] Lactic acidosis (see Boxed Warning and Warnings and Precautions (5.2)] Oedema (5.2)] the rate of adverse reactions observed in clinical trials cannot be directly compared to the frequency obtained, which may not reflect the rates observed in practice. Pioglitazone More than 8,500 patients with type 2 diabetes mellitus have received pioglitazone in randomised, double-blind, controlled clinical trials involving 2,605 patients with type 2 diabetes mellitus and patients with macrovascular disease treated with pioglitazone in a PROactive clinical trial. In these studies, more than 6,000 patients have been treated with pioglitazone for 6 months or more, more than 4,500 patients have been treated with pioglitazone for one year or more and more than 3,000 patients have been treated with pioglitazone for at least two years. The sixth 16- The most common withdrawal symptoms were associated with insufficient glycaemic control, although the incidence of these adverse reactions was lower (1.5%) pioglitazone compared to placebo (3.0%). In the PROactive study, the incidence of discontinuations due to adverse reactions was 9.0% in pioglitazone-treated patients and 7.7% in placebo-treated patients. Congestive heart failure was the most common serious adverse reaction, which led to withdrawal in 1.3% of pioglitazone-treated patients and 0.6% of patients receiving placebo. Common side effects: 16 to 16 The terms given represent those patients treated with pioglitazone >5% and more frequently than in placebo-treated patients. None of these adverse reactions were related to the dose of pioglitazone. Common side effects: 16 to 16 The reported terms refer to those that occurred >5% and more frequently with the highest dose of pioglitazone tested. adverse reactions from a 16-week placebo-controlled study in addition to metformin in addition to metformin in a 16-week placebo-controlled study reported in >5% of patients and more frequently in patients with treated with placebo + metformin compared to placebo + metformin % of patients Placebo + metformin N=160 Pioglitazone 30 mg + metformin N=168 Oedema 2.5 6.0 Headache 1.9 6.0 24 weeks of controlled double-blind pioglitazone Adverse reactions reported in >5% of patients and more frequently in patients treated with pioglitazone 45 mg + metformin as in patients treated with treated with pioglitazone 30 mg + metformin % of patients Pioglitazone 30 mg + metformin N=411 Pioglitazone 45 mg + metformin N=416 Upper respiratory tract infection 12.4 13.5 oedema 5.5 8 13.9 Headache 5.4 5.8 Weight gain 2.9 6.7 Common : in a 24-week clinical study of pioglitazone and metformin hydrochloride tablets, Table 3 summa s summa s , the incidence and types of adverse reactions reported in a 24-week double-blind clinical trial administered twice daily to patients who do not have sufficient glycaemic control in diet and exercise (N=600). Table 3 Adverse reactions (≥5% for ACTOPLUS) 15 mg twice daily N=190 Metformin 850 mg twice daily N=209 Diarrhoea 9.0 2.6 15.3 Headache 5 2.6 4.8 In this 24-week study, abdominal pain was reported in 2.0% in the pioglitazone and methozin hydrochloride groups, 1.6% in the pioglitazone monotherapy group and 3.3% in the metformin monotherapy group. Common Adverse reactions: PROactive study Summary of overall frequency and types of proactive study is presented in Table 4. The reported terms are >5% in pioglitazone-treated patients and more frequently than in patients receiving placebo. Congestive heart failure The summary of the frequency of adverse reactions associated with congestive heart failure is presented in Table 5 16 to 16.5. None of the Fatal. Congestive heart failure, which led to hospitalisation during the PROactive study, is summa described in Table 8. Cardiovascular safety In the PROactive study, 5,238 patients with type 2 diabetes mellitus with macrovascular disease and a history of macrovascular disease were randomised to pioglitazone (N=2,605) with force titration up to 45 mg/day or placebo (N=2,633). Almost all patients (95%) cardiovascular medicines (beta-blockers, ACE inhibitors, angiotensin II receptor blockers, calcium channel blockers, nitrates, diuretics, aspirin, statins and fibrates). At baseline, the mean age of patients was 62 years, the mean diabetes duration was 9.5 years and the mean HbA1c was 8.1%. The median follow-up was 34.5 months. The primary objective of this study was to investigate the effects of pioglitazone on mortality and macrovascular morbidity in patients with type 2 diabetes mellitus at high risk of macrovascular events. The primary efficacy variable was the time for the first occurrence of any event in the composite cardiovascular endpoint, which included all causes, non-fatal myocardial infarction (MI), including silent MI, stroke, acute coronary syndrome, cardiac intervention, including coronary artery bypass graft or percutaneous intervention, major leg amputation above the ankle, and shunting or revascularisation on the leg. Total 514 (19.7%) pioglitazone-treated patients and 572 (21.7%) placebo-treated patients had at least one primary composite endpoint (HR 0.90; 95% CI: 0.80, 1.02; p=0.10) Although there was no statistically significant difference in the incidence of the first three-year adverse reaction in this composite, no increase in pioglitazone mortality or total macrovascular events was observed. Table 9 shows the total number of first cases and individual adverse reactions contributing to the primary composite endpoint. Dose increase Dose-dependent weight gain occurs when pioglitazone is used alone or in combination with other antidiabetic medicines. The mechanism of weight gain is unclear, but apparently involves a combination of fluid retention and fat accumulation. Tables 10, 11 and 12 summally take into account changes in pioglitazone and placebo body weight 16 to 16 hours. If pioglitazone is discontinued, there is no edema due to taking pioglitazone. Swelling usually does not require hospitalization unless there is co-existent congestive heart failure. In a 24-week study of pioglitazone and metformin hydrochloride tablets, oedema was reported in 3.0% of the pioglitazone and metformin hydrochloride groups, 4.2% for pioglitazone and metformin hydrochloride monotherapy and 1.4% in the metformin monotherapy group. A summary of the frequency and types of adverse reactions observed in clinical trials with pioglitazone is presented in Table 13. Hepatic effects In the pioglitazone-controlled clinical trial database, no hepatotoxicity caused by pioglitazone has been observed to date. One randomised, double-blind, three-year study comparing pioglitazone with glycuritis in addition to metformin and insulin therapy was specifically designed to evaluate the incidence of elevations of serum ALT more than three times the upper limit of the reference range measured every eight weeks during the first 48 weeks of the study. Total 3/1051 (0.3%) pioglitazone-treated patients and 9/1,046 (0.9%) patients treated with glyburide developed ALT values that exceeded the upper limit of three times the reference range. None of the pioglitazone-controlled clinical trials in the pioglitazone-controlled clinical trial database has more than three times the upper limit of serum ALT than the upper limit of the reference range and the corresponding total bilirubin did not exceed the upper limit of the reference range, which is a combination of the potential for severe hepatic impairment due to the drug. Hypoglycaemia In clinical trials with pioglitazone, adverse reactions to hypoglycaemia were reported on the basis of a clinical evaluation by investigators and did not require confirmation by finger stick glucose testing. In a 16-week study of sulphonylurea, the incidence of hypoglycaemia was 3.7% for pioglitazone 30 mg and 0.5% for placebo. In a 16-week insulin study, the incidence of hypoglycaemia was reported with pioglitazone 15 mg, 15.4% for pioglitazone 30 mg and 4.8% for placebo, 7.9%. The reported incidence of hypoglycaemia was higher with pioglitazone 45 mg compared to pioglitazone 30 mg in both the 24-week segment of the sulphonylurea (15.7% versus 13.4%) and 24-week insulin study (47.8% versus 43.5%). Three patients in these four studies were hospitalized for hypoglycaemia. All three patients received pioglitazone 30 mg (0.9%) 24-week insulin study. A further 14 patients reported severe hypoglycaemia (defined as a significant intervention in the patient's normal activities) that did not require hospitalisation. These patients received pioglitazone 45 mg in combination with a sulphonylurea (n=2) or pioglitazone 30 mg or 45 mg in combination with insulin (n=12). In a two-year carcinogenicity study, bladder tumours were observed in male rats in the bladder (see non-clinical toxicology (13.1)). In a three-year PROactive clinical trial, 14 out of 2,605 patients (0.54%) were randomised to pioglitazone and 5/2633 (0.19%) randomised to bladder cancer in the placebo group. After patients who had exposure to the study drug less than one year at the time of diagnosis of bladder cancer, 6 (0.23%) pioglitazone and two cases (0.08%) placebo-treated patients. A large subgroup of patients was observed for up to 10 additional years after the end of the study, with low additional exposure to pioglitazone. For both PROactive and follow-up control over 13 years, the incidence of bladder cancer did not differ between patients randomised to pioglitazone or placebo (HR =1.00; 95% CI: 0.59 to 1.72) [see Warnings and Precautions (5.6)]. Metformin hydrochloride In a double-blind clinical trial of metformin in patients with type 2 diabetes mellitus, a total of 141 patients received metformin (up to 2,550 mg daily) and 145 patients received placebo. Table 15 lists the adverse reactions reported in more than 5% of metformin-treated patients and reported more frequently in metformin-treated patients than in placebo-treated patients. In this study, diarrhea led to discontinuation of treatment with study medications in 6% of patients treated with metformin. Laboratory abnormalities Haematological effects Pioglitazone may cause a decrease in haemoglobin and haematocrit. In placebo-controlled monotherapy studies, mean haemoglobin levels decreased by 2% to 4% in pioglitazone-treated patients compared to the mean change in haemoglobin from 1% to +1% in placebo-treated patients. These changes occurred mainly during the first 4 to 12 weeks of treatment and subsequently remained relatively persistent. These changes may be associated with increased plasma volume associated with pioglitazone therapy and are unlikely to be associated with clinically relevant haematological effects. Vitamin B 12 Concentrations Metformin may reduce serum B 12 concentrations. It is recommended that haematological parameters be measured annually in patients receiving pioglitazone and metformin hydrochloride and all visible abnormalities should be adequately investigated and treated (see warnings and precautions (5.9)). Creatine phosphokinase In clinical trials with pioglitazone in serum creatine phosphokinase (KFK), a single increase in kfK was observed more than 10 times above the upper limit of the reference range in nine (0.2%) pioglitazone (values 2150 to 11400 IU/l) and not in comparator-treated patients. Six of these nine patients received pioglitazone, two patients received an increase in kfK on the last dosing day and one patient discontinued pioglitazone due to an increase. These increases were resolved without obvious clinical complications. The relationship between these adverse reactions with pioglitazone therapy is not known. Post-marketing experience The following side effects have been observed with pioglitazone Pioglitazone: As these reactions have been reported voluntarily it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Development or worsening of diabetic macular oedema with reduced visual acuity [see warnings and precautions (5.8)] . Fatal and non-fatal hepatic failure [see warnings and precautions (5.5)] . Post-marketing experience has been reported in patients treated with pioglitazone, both with pre-known cardiac disease and without concomitant insulin administration. An unusually rapid weight gain and an increase in the number of cases have been reported in post-marketing experience. Patients with this increase should be evaluated for signs related to fluid accumulation and volume such as excessive swelling and congestive heart failure (see box warnings and warnings and precautions (5.1)). Interactions Strong CYP2C8 inhibitors CYP2C8 inhibitor (e.g. gemfibrozil) significantly increases pioglitazone exposure (area or AUC of the serum concentration-time curve) and half-life (t 1/2). Therefore, the maximum recommended dose of pioglitazone is 15 mg per day when used in combination with gemfibrozil or other potent CYP2C8 inhibitors (see dose and administration (2.3) and clinical pharmacology (12.3)]. The CYP2C8 inducer (e.g. rifampicin) inducer of CYP2C8 inducer may significantly reduce pioglitazone exposure (AUC). Therefore, if a CYP2C8 inducer is initiated or discontinued during pioglitazone therapy, a change in diabetes treatment based on clinical response may be necessary without exceeding the maximum recommended daily dose of 45 mg for pioglitazone (see clinical pharmacology (12.3)). Carbonic anhydrase inhibitors Topiramate or other carbonic anhydrase inhibitors (e.g. zonisamide, acetamide or dichlorphenides) often cause a decrease in serum bicarbonate and cause hyperchloric metabolic acidosis of non-anehadones. Concomitant use of these medicinal products with pioglitazone and metformin hydrochloride may increase the risk of lactic acidosis. Consider monitoring these patients more often. Medicinal products that reduce metformin clearance medicinal products that are excreted by tubular secretion of the kidneys (e.g. cationic medicinal products such as simetidine) may compete with metformin for common renal tubular transport systems and may increase the risk of metformin accumulation and lactic acidosis (see clinical pharmacology (12.3)]. Consider monitoring these patients more often. Al

hydrochloride tablets, the patient should be closely monitored for loss of blood glucose control. When taking such medicines from a patient receiving pioglitazone and metformin hydrochloride tablets, the patient should be closely monitored for hypoglycaemia. USE In specific populations Summary of pregnancy Risk Limited data on the use of pioglitazone and metformin hydrochloride or pioglitazone in pregnant women are not sufficient to determine the drug-related risk in the event of major birth defects or miscarriage. No clear link between metformin and the risk of major birth defects or miscarriage has been reported in studies published during pregnancy [see data). Poorly controlled diabetes-related maternal and fetal leaching during pregnancy (see clinical considerations). In animal reproduction studies, no adverse reactions up to 5 and 35 times the clinical dose based on body surface area were observed when pioglitazone was administered to pregnant rats and rabbits during organogenesis. Administration of metformin to pregnant Sprague Dawley rats and rabbits during the organogenesis period at doses up to 2 to 2.5 mg/kg/day. The estimated background risk of major birth defects is > > > 6 to 1000 000 000 000 000 000 000 0 The estimated background risk of miscarriage in the indicated population is not known. In the general U.S. population, the estimated background risk of major birth defects and miscarriage in clinically recognised pregnancies is 2-4% and 15-20%, respectively. Clinical considerations The risk of disease-related maternal and/or embryo-foetal disease Poorly controlled diabetes during pregnancy increases the mother's risk of diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm birth, birth and childbirth complications. Poorly controlled diabetes increases fetal risk of major births and macrosomia-related morbidity. Data Data Published data from post-marketing studies have not shown a clear association between metformin and major birth defects, miscarriage or maternal or foetal adverse outcomes during pregnancy. However, these studies cannot be identified with certainty the absence of a risk associated with metformin due to methodological limitations, including the size of a small sample and inconsistent reference groups. Animal studies In the reproductive studies of pioglitazone and metformin hydrochloride with pioglitazone and metformin hydrochloride tablets have not been performed. The following data are based on studies with individual components of pioglitazone and metformin hydrochloride tablets. Pioglitazone Pioglitazone, administered to pregnant rats during organogenesis, did not cause developmental effects at a dose of 20 mg/kg (45 mg clinical dose~5 times), but delayed calving and embryofoetal viability decreased at 40 and 80 mg/kg or ≥9 times the 45 mg clinical dose by body surface area. No adverse effects on development of 80 mg/kg (45 mg clinical dose~35-fold) were observed in pregnant rabbits administered during organogenesis, but embryofoetal concentrations reduced to 160 mg/kg or 45 mg at a clinical dose of ~69 times body surface area. When the pregnant rats received pioglitazone at the end of pregnancy and lactation, postnatal development was observed in the offspring due to weight loss at maternal doses of 10 mg/kg and ≥2 times the clinical dose of 45 mg by body surface area. Metformin hydrochloride Metformin hydrochloride did not cause adverse reactions when administered to pregnant Sprague Dawley rats and rabbits up to 600 mg/kg/day during the period of organogenesis. This is approximately 2 to 2 hours. Lactation Risk assessment No data are available on the presence of pioglitazone and metformin hydrochloride or pioglitazone in breast milk, on the effects on breast milk or on the effects on milk production. Pioglitazone is present in rat milk; however, data from animal studies do not reliably predict the level of human milk due to differences in lactation physiology. Limited published studies indicate that metformin is present in breast milk [see data]. However, there are no sufficient data on the effect of metformin on breast-fed foods and there are no sufficient data on the effect of metformin on milk production. The developmental and health benefits of breast-feeding should be taken into account in combination with the mother's clinical need for pioglitazone and metformin hydrochloride tablets and the potential side effects of pioglitazone and hydrochloride tablets or the disease of the mother. Data From published clinical lactation studies indicate that metformin is present in breast milk, resulting in infant doses of approximately 0.11 to 1.5 mg/ kg/ day. However, the purpose of the studies was not to establish the risk of metformin during lactation, as the sample size was small and the number of adverse reactions collected from infants is limited. Females and males with reproductive potential Discuss the possibility of an involuntary pregnancy with pioglitazone and metformin hydrochloride tablets in premenopausal women, which may cause ovulation in some anovulatory females. The safety and efficacy of pioglitazone and metformin hydrochloride in children have not been established. Pioglitazone and metformin hydrochloride are not recommended for use in children based on adverse reactions observed in adults, including fluid retention and congestive heart failure, fractures and bladder tumours (see Warnings and precautions (5.1, 5.3, 5.6, 5.7)]. Geriatrics Use Pioglitazone A total of 92 patients (15.2%) pioglitazone in three 16-26 weeks double-blind, placebo-controlled monotherapy studies ≥65 years and two patients (0.3%) were ≥75 years of age. Two additional 16 to 24-week additional studies in sulphonylurea studies included 201 patients (18.7%) pioglitazone-treated patients ≥65 years and 19 (1.8%) were ≥75 years of age. In two additional 16-24-week studies on metformin, 155 patients (15.5%) pioglitazone-treated patients ≥65 years and 19 (1.9%) were ≥75 years of age. In two additional 16-24-week studies, 272 patients (25.4%) pioglitazone-treated patients ≥65 years and 22 (2.1%) were ≥75 years of age. In the PROactive study, 1,068 patients (41.0%) pioglitazone-treated patients ≥65 years and 42 (1.6%) were ≥75 years of age. Pharmacokinetic studies with pioglitazone showed no significant differences in pharmacokinetic parameters in elderly and younger patients (see Clinical pharmacology (12.3)). Although clinical experience has not identified differences in efficacy and safety between elderly patients (≥65 years) and younger patients, these findings are limited to a small number of ≥ in patients 75 years of age. Metformin hydrochloride In controlled clinical trials of metformin, a sufficient number of elderly patients were not involved to determine whether they respond differently from younger patients, although no differences in responses from elderly and young patients were observed in other reported clinical products. In general, dose selection should be used with caution in elderly patients, usually starting at the low end of the dosing range, reflecting the liver, kidney or heart function, concomitant disease or other drug treatment, and the increased risk of lactic acidosis. Renal function should be evaluated more frequently in elderly patients [see warnings and precautions (5.2) and posology and administration (2.2)]. Renal impairment Metformin is significantly excreted by the kidneys and the risk of accumulation of metformin and lactic acidosis is increased in patients with renal impairment. Pioglitazone and metformin hydrochloride tablets are contraindicated in patients with severe renal impairment, patients with eGFR below 30 ml/min/1.73 m 2[see dose and administration (2.2), contraindications (4), warnings and precautions (5.2) and clinical pharmacology (12.3)]. Hepatic impairment The use of metformin in patients with hepatic impairment has been associated with lactic acidosis in certain cases. Pioglitazone and metformin hydrochloride tablets are not recommended for patients with hepatic impairment [see Warnings and Precautions (5.2)). Overdose of pioglitazone One case of pioglitazone overdose was reported in controlled clinical trials. The male patient took 120 mg per day for four days, then 180 mg per day for seven days. The patient denied clinical symptoms during this time. In the event of overdose, appropriate supportive care should be initiated according to the clinical signs and symptoms of the patient. Metformin hydrochloride Has been reported as an overdose of metformin hydrochloride, including swallowing more than 50 grams. Hypoglycaemia was reported in approximately 10% of cases, but a causal relationship to metformin hydrochloride has not been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases (see warnings and precautions (5.2)). Metformin is dialysable with a clearance up to 170 ml/min under good haemodynamic conditions. Therefore, haemodialysis may be useful for removing accumulated metformin from patients suspected of overdosing metformin. Pioglitazone and metformin tablets Description Pioglitazone and metformin hydrochloride tablets, USP is a combination of thiazolidinedones and biguanides containing two oral antidiabetic medicines: pioglitazone hydrochloride and metformin hydrochloride. Pioglitazone [(±)-5-[[4-[2-(5-ethyl-2-pyridineyl)ethoxy]phenyl]-2,4-] thiazolidinedione monohydrochloride contains one asymmetric carbon and is synthesized and used as a racemic mixture. Pioglitazone two enantiomers in vivo. No differences were found in the pharmacological activity of the two enantiomers. The structural formula is as shown: Pioglitazone hydrochloride, USP is a odourless white crystalline powder with a molecular formula of C 19H 20N 20N 2O 3S•HCl and a molecular weight of 392,90 daltons. It is soluble in N,N-dimethylformamide, which is slightly soluble in anhydrous ethanol, to a very small extent acetone and acetonitriles, insoluble in water and insoluble in ether. Metformin hydrochloride (N,N-dimethylimidodibotside diamide hydrochloride) USP is a white crystalline powder with a molecular formula C 4H 11N 5•HCl and a molecular weight of 165.62. Metformin hydrochloride dissolves freely in water and is practically insoluble in acetone, ether and chloroform. Metformin pKa is 12.4. The pH of the 1% aqueous solution of metformin hydrochloride is 6,68. The structural formula is shown as follows: Pioglitazone and metformin hydrochloride are available as tablets for oral containing 15 mg pioglitazone (as a base) with 500 mg metformin hydrochloride (15 mg/500 mg) or 15 mg pioglitazone (as a base) 850 mg metformin hydrochloride (15 mg/850 mg) formulated with the following excipients: croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc and titanium dioxide. Pioglitazone and metformin tablets - Clinical pharmacology Mechanism of action Pioglitazone and metformin hydrochloride tablets combine two antidiabetic medicinal products with different mechanisms of action to improve glycaemic control in adults with type 2 diabetes mellitus: pioglitazone, thiazolidinedione and biguanide metformin hydrochloride. Thiazolidinediones are insulin sensitising agents that act primarily by increasing peripheral glucose use, while biguanides mainly reduce endogenous glucose production. Pioglitazone Pioglitazone is a thiazolidinedione that depends on the presence of insulin in the mechanism of action. Pioglitazone reduces insulin resistance in peripheral and hepatic function, resulting in increased insulin-dependent glucose release and decreased hepatic glucose secretion. Pioglitazone is not a subtly of insulin secretion. Pioglitazone is a proliferator-activated receptor gamma (PPARγ) agonist of the peroxidoma. PPAR receptors are found in tissues that are important for the effect of insulin, such as fatty tissue, skeletal muscles and liver. Activation of PPARγ nuclear receptors modulates the transcription of several insulin-responsive genes involved in glucose and lipid metabolism control. In animal models of diabetes, pioglitazone reduces the risk of hyperglycaemia, hyperinglycaemicaemia and hypertriglyceridaemia to insulin-resistant conditions such as type 2 diabetes. Metabolic changes due to pioglitazone increase the response of insulin-dependent tissues and have been observed in many animal models where insulin resistance occurs. Since pioglitazone increases the effect of circulating insulin (by decreasing insulin resistance), it does not reduce blood glucose levels in animal models where there is no endogenous insulin. Metformin hydrochloride Metformin hydrochloride improves glucose tolerance in patients with type 2 diabetes mellitus by reducing both basal insulin and glucose content t. Metformin reduces the production of glucose in the liver, reduces the absorption of glucose from the intestine and improves insulin sensitivity by increasing peripheral glucose uptake and use. Metformin does not produce hypoglycaemia in patients with type 2 diabetes mellitus or in healthy subjects [except in specific circumstances, see warnings and precautions (5.4)] and does not cause hyperinsulinaemia. Insulin secretion levels remain unchanged when insulin levels in fasting and day-long insulin activity in plasma may actually be reduced. Pharmacodynamics Pioglitazone Clinical studies show that pioglitazone improves insulin sensitivity in insulin-resistant patients. Pioglitazone improves cellular insulin response, increases insulin-dependent glucose release and improves liver sensitivity to insulin. In patients with type 2 diabetes mellitus, a reduction in insulin resistance produced by pioglitazone results in a decrease in plasma glucose concentrations, a decrease in insulin concentrations in plasma and HbA1c values. In controlled clinical trials, pioglitazone had an additive effect on glycaemic control when used in combination with a sulphonylurea, metformin or insulin [see clinical trials (14)]. Clinical trials with pioglitazone included lipid disorders. Overall, pioglitazone-treated patients had mean decreases in serum triglycerides, mean increases in HDL cholesterol and persistent mean changes in LDL and total cholesterol. There is no conclusive evidence of macrovascular benefit with pioglitazone or any other diabetes medicine (see warnings and precautions (5.15) and adverse reactions (6.1)). In a 26-week placebo-controlled, dose-based monotherapy study, mean serum triglycerides were reduced in the pioglitazone 15 mg, 30 mg and 45 mg dose groups compared to the mean increase in the placebo group. The mean HDL cholesterol levels increased to a higher rate in pioglitazone-treated patients than in patients treated with placebo. There were no persistent differences in LDL and total cholesterol compared to placebo in pioglitazone-treated patients (see Table 16). table 16. Lipids in a 26-week placebo-controlled monotherapy dose study Placebo Pioglitazone 15 mg Once daily Pioglitazone 30 mg Once daily Pioglitazone 45 mg once daily Triglycerides (mg/dL) N=79 N=79 N=84 N=77 Baseline (mean) 263 2 84 261 260 Percent change baseline (adjusted mean*) 4.8% -9.0% † -9.6% † -9.3% † HDL cholesterol (mg/dl) N=79 N=79 N=83 N=77 Baseline (mean) 42 40 41% change from baseline (adjusted mean*) 8, 1% 14.1% † 12.2% 19.1% † LDL cholesterol (mg/dl) N=65 N=63 N=74 N=62 Baseline (mean) 139 132 136 127 Percentage change (adjusted mean*) 4.8% 7.2% 5.2% 6.0% total cholesterol (mg/dl) N=79 N=79 N=84 N=77 Baseline (mean) 225,220,223,214 Percentage change from baseline 4.4% 4.6% 3.3% 6.4% In two other monotherapy studies (16 weeks and 24 weeks) and in combination therapy studies with metformin (16 weeks and 24 weeks), the results were generally consistent with the data above. Pharmacokinetics In bioequivalence studies pioglitazone and metformin hydrochloride pioglitazone and metformin hydrochloride 15 mg/500 mg and 15 mg/850 mg were equivalent to pioglitazone 15 mg pioglitazone and the metformin component, metformin hydrochloride (500 mg or 850 mg, respectively) in healthy subjects. When pioglitazone and metformin hydrochloride 15 mg/850 mg tablets were co-administered with food, the overall exposure of pioglitazone did not change. No change in AUC was observed with metformin; however, the mean maximum serum concentration of metformin was reduced by 28% when administered with food. For both components (1.9 hours for pioglitazone and 0.8 hours for metformin), a slowed-down time to peak serum concentration was observed at full ness. These changes are unlikely to be clinically significant. Pioglitazone Steady-state concentrations of both pioglitazone and its major active metabolites M-III (pioglitazone ketoderivative) and M-IV (hydroxygeneral rivalry of pioglitazone) are achieved for 7 days over 7 days. At steady state, serum concentrations of M-III and M-IV are reached at or greater than pioglitazone concentrations. At steady state, pioglitazone in both healthy volunteers and patients with type 2 diabetes mellitus accounts for approximately 30-50%. C peak, AUC and trough serum concentrations (C min) for pioglitazone and M-III and M-I pregnant increased proportionally with the administered doses of 15 mg and 30 mg daily. Following oral administration of pioglitazone, pioglitazone was max for two hours. Food slows down T max to 3 to 4 hours, but does not alter the extent of absorption (AUC). The absolute bioavailability of metformin 500 mg metformin tablet on an empty stomach is approximately 50 to 100 mg. Studies using single oral doses of metformin tablets at doses of 500 mg to 1500 mg and 850 mg to 2550 mg indicate that the dose seidone proportionality is not higher due to reduced absorption rather than a change in elimination. At normal clinical doses and dosing regimens for metformin, steady-state plasma concentrations of metformin are reached at 24 <... In controlled clinical trials, peak plasma concentrations of metformin did not exceed 5 even at maximum doses. Food reduces the rate and extent of absorption of metformin, as shown by a 40% lower mean C max, a 25% lower AUC and a 35-minute T max prolongation after a single 850 mg tablet of metformin with food compared to the same tablet strength on an empty stomach. The clinical relevance of these reductions is unknown. Distribution Pioglitazone The mean volume of distribution of pioglitazone (Vd/F) after a single dose is 0.63 ± 0.41 (mean ± SD) l/kg body weight. Pioglitazone is highly protein bound (>99%) serum, mainly serum albumin. Pioglitazone also binds to other serum proteins, but with a lower affinity. M-III and M-IV are also extensively involved (>98%) albumin. Metformin hydrochloride Metformin Vd/ F after single oral doses of 850 mg immediate-release metformin was on average 654 ± 358 l. Metformin binds negligibly to plasma proteins. Metformin is divided into erythrocytes, probably as a function of time. Metabolism Pioglitazone pioglitazone is extensively metabolised by hydroxylation and oxidation; metabolites should also be partially converted into glucuronide or sulphate conjugates. Metabolites M-III and M-IV are the major circulating active metabolites in humans. In vitro data indicate that pioglitazone is metabolised by several CYP isoforms containing CYP2C8 and to a lesser extent CYP3A4, plus various other isoforms, including mainly extrahepatic CYP1A1. An in vivo study of pioglitazone in combination with gemfibrozil, a potent CYP2C8 inhibitor, and gemfibrozil showed that pioglitazone is a substrate for CYP2C8 [see posology and administration (2.3) and drug interactions (7.1)]. The urinary ratio of 6ß hydroxycortisol/cortisol in pioglitazone-treated patients showed that pioglitazone is not a potent CYP3A4 enzyme inducer. Metformin hydrochloride Intravenous single dose studies in healthy subjects indicate that metformin is excreted unchanged in the urine and does not receive hepatic metabolism (no metabolites have been established in humans) or excreted via the bile. Elimination and elimination of pioglitazone After oral administration approximately 15 to 15 ml/ day, the elimination and elimination of pioglitazone is excreted in approximately 15 to 15%. Renal elimination of pioglitazone is negligible and is primarily excreted as metabolites and conjugates. The majority of the oral dose is expected to be excreted in the bile either unchanged or as metabolites and excreted in faeces. The mean serum half-life of pioglitazone and its metabolites (M-III and M-IV) is three to seven hours and 16 to 24 hours, respectively. Pioglitazone has a apparent clearance of CL/F calculated at 5 to 7 l/h. Metformin hydrochloride Renal clearance is approximately 3.5-fold higher than creatinine clearance (CLcr), indicates that tubular secretion is the main route of elimination of metformin. After oral administration, approximately 90% of the absorbed medicinal product is eliminated by the kidneys within the first 24 hours, with plasma elimination t 1/2 approximately 6.2 hours. In the blood, elimination t 1/2 is approximately 17.6 hours, suggesting that red blood cell mass may be a distribution space. Specific populations Renal impairment Pioglitazone Pioglitazone, The elimination half-life of M-III and M-I remains unchanged with moderate (CLcr 30-50 ml/min) and severe (CLcr <30 ml/min)= renal= impairment= when= compared= to= subjects= with= renal function.= therefore,= no= dose= adjustment= in= patients= with= renal= impairment= is= required.= metformin= in= patients= with= decreased= renal= function= (based= on= egfr),= the= plasma= and = blood= t= 1/2= of= metformin= is= prolonged= and= the= renal= clearance= is= decreased= in= in= to= decrease= in= [see= dosage= and = administration= (2.2),= contraindications= (4)= and= warnings= precautions= 5.2)]= because= metformin= is= contraindicated= in= patients= with= renal= impairment,= pioglitazone= and = metformin= hydrochloride= are= also contraindicated= in= these= patients= hepatic impairment= pioglitazone= compared= with= healthy= (child-turcotte-= pugh= grade= b/c)= have= an= approximate= 45%= reduction= in= pioglitazone= and= total= pioglitazone= (pioglitazone=,= m-iii,= and= m-iv)= mean= c= max= but= no= change= in= mean= auc= values.= therefore,= no= dose= adjustment= in= patients= with= hepatic= impairment= is= required.= there= postmarketing= reports= of= liver= failure= with= clinical= clinical= trials= have= generally= excluded= patients= with= serum= alt=>2, 5 times the upper limit of normal). Pioglitazone and metformin hydrochloride should be used with caution in patients with liver disease [see Warnings and Precautions (5.5)]. Metformin hydrochloride No pharmacokinetic studies of metformin have been performed in patients with hepatic impairment. [see warnings and precautions (5.5)]. Geriatric patients Pioglitazone In healthy elderly subjects pioglitazone did not differ significantly from the max of Pioglitazone, but AUC values were approximately 21% higher than in younger subjects. The mean t 1/2 of pioglitazone was prolonged in the elderly (about 10 hours) compared to younger subjects (about seven hours). These changes were not of an order of magnitude considered clinically relevant. Metformin hydrochloride Data from controlled pharmacokinetic studies of metformin in healthy elderly patients indicate that total CL/F is reduced, t 1/2 is prolonged and C max increases compared to healthy subjects. These data suggest that the change in the pharmacokinetics of metformin with age is mainly related to change in the use of the Pediatricians </30> </30> The safety and efficacy of pioglitazone in children have not been established. Pioglitazone and metformin hydrochloride are not recommended for use in children (see Use in specific populations (8.4)). Metformin hydrochloride Following administration of a single oral metformin 500 mg tablet with food, geometric mean metformin max and AUC differed by less than 5% between patients with type 2 paediatric diabetes mellitus (12 to 16 years) and healthy adults (20 to 45 years of age) and adults with normal renal function matched by sex and body weight. Gender Pioglitazone Mean C max and AUC values of pioglitazone increased by 20 to 100 mg/m1 in women. In controlled clinical trials, the reduction of HbA1c from baseline in women was generally higher than in males (mean mean difference from HbA1c 0.5%) Since treatment should be individualised for each patient to achieve glycaemic control, dose adjustment is not recommended based on gender only. Metformin hydrochloride Pharmacokinetic parameters of metformin did not differ significantly between normal subjects and patients with type 2 diabetes when analysed by gender (male=19, women=16). Similarly, in controlled clinical trials in patients with type 2 diabetes mellitus, the antihyperglycaemic effect of metformin was comparable in males and females. Ethnic pioglitazone Pharmacokinetic data between different ethnic groups are not available. Metformin hydrochloride Pharmacokinetic parameters of metformin have not been studied according to race. In controlled clinical trials with metformin in patients with type 2 diabetes mellitus, the antihyperglycaemic effect was comparable to that of whites (n=249), blacks (n=51) and Hispanics (n=24). Drug interactions No pharmacokinetic interaction studies have been conducted with pioglitazone and metformin hydrochloride tablets, although such studies have been conducted with the components of pioglitazone and metformin. Table 17 of pioglitazone Effect of pioglitazone Co-administration of systemic exposure of other medicinal products administered by the co-administered dosing regimen (mg)* Change in NAME and dosing regimens AUC† C max change† 45 mg (N = 12) Warfarin‡ Daily saturation, then maintenance doses based on pt and INR values Quick's Value = 35 ± 5% R-warfarin ↓3% R-warfarin ↓2% S-warfarin ↓1% S-warfarin ↑1% 45 mg (N = 12) Digoxin 0.200 mg twice daily (loading dose) , followed by 0.250 mg daily (maintenance dose , 7 days) ↑15% ↑17% 45 mg daily for 21 days (N = 35) Oral contraceptives [Ethinyl estradiol (EE) 0.035 mg plus EE ↓11% EE ↓13% Noretindrone (NE) 1 mg] for 21 days NE ^3% ↓7% 45 mg (N = 23) Fexofenadine 60 mg twice daily for 7 days ↑30% ↑37% 45 mg (N = 14) Glipizide 5 mg daily for 7 days ↓3% ↓8% 45 mg daily for 8 days (N = 16) Metformin 1000 mg single dose 8.45 mg =21) Midazolam 7.5 mg single dose 15 ↓26% ↓26% 45 mg (N = 24) Ranitidine 150 mg twice daily for 7 days ↑1% ↓1% 45 mg daily for 4 days (N = 24) NifedipineER 30 mg daily for 4 days ↓13% ↓13% ↓↓ 17% 45 mg (N = 25) Atorvastatin Ca 80 mg daily for 7 days ↓14% ↓23% 45 mg (N = 22) Theophylline 400 mg twice daily for 7 days ↑2% ↑5% Metformin hydrochloride table 19. Effect on plasma metformin Co-administered Dose of metformin* Geometric mean ratio (with or without co-administered) No effect = 1.00 AUC † Cmax No dose adjustment is necessary for the following signs: Glyburide 5 mg 500 mg § 0.98 0.99 ‡ Furosemide 40 mg 850 mg 1, 09 ‡ 1.22 ‡ Nifedipine 10 mg 850 mg 1.16 1.21 Propranolol 40 mg 850 mg 0.90 0.0.0.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.10.1.1.10.100.1.1.1.1.10.1.10.10.1.1 Ibuprofen 400 mg 850 mg 1.05 ‡ Medicinal products eliminated by renal tubular secretion may increase the accumulation of metformin [see warnings and precautions (5) and drug interactions (7)] . Csimetidine 400 mg 850 mg 1.40 1.61 Carbonic anhydrase inhibitors may cause metabolic acidosis: use caution [see Warnings and precautions (5) and drug interactions (7)] . Topiramate 100 mg ¶ 500 mg ¶ 1,25 ¶ 1.17 Table 20. Effect of metformin on systemic exposure to co-administered medicinal product Dose of the drug administered at the same time * Metformin dose * Geometric mean ratio (ratio with or without co-administered) No effect = 1.00 AUC † C max No dose adjustment is required for the following signs: Glyburide 5 mg 500 mg§ 0, 78 0‡ 63‡ Furosemide 40 mg 850 mg 0.87‡ 0.69‡ Ni fedipine 10 mg 850 mg 1.10§ 1.08 Propranolol 40 mg 850 mg 1.01§ 0, 94 Ibuprofen 400 mg 850 mg 0.97 mg¶ 1.01¶ Simeticin 400 mg 850 mg 0.95§ 1.01 Non-clinical toxicology carcinoton, mutagenic, decreased fertility Piotazone and metformin hydrochloride tablets Pioglitazone and metformin hydrochloride have not been animally performed. The following data are based on the results of separate studies with pioglitazone or metformin. Pioglitazone A two-year carcinogenicity study in male and female rats was conducted at oral doses up to 63 mg/kg (approximately 14 times the maximum recommended human dose of 45 mg/m2). Drug-induced tumours were not observed on any organ except in the bladder of male rats. In male rats, benign and/or malignant transition cell tumours at a dose of 4 mg/kg/day and above (approximately equivalent to the maximum recommended human dose of mg/m2) were observed. The mechanism of bladder tumours observed in male rats. In 2009, a two-year mechanistic study was completed in male rats using food acidification to reduce the formation of kaltolite. Food acidification decreased, but did not lose the bladder's hyperplastic changes. The presence of kaltsilites pioglitazone, but this was not considered to be the main cause of hyperplastic changes. The relevance of the bladder effects of male rats to humans cannot be excluded. A two-year carcinogenicity study was also conducted in male and female mice at oral doses up to 100 mg/kg/day (approximately 11 times the maximum recommended human dose based on mg/m2). No drug-induced tumours were observed in any organ. Pioglitazone was not mutagenic in genetic toxicology studies, including the Ames bacterial test, the mammalian cell progression gene mutation test (CHO/HPRT and AS52/XPRT), the in vitro cytogenetics test using CHL cells, an unscheduled DNA synthesis test and an in vivo micronucleus test. No adverse effects on fertility were observed in male and female rats at oral doses up to 40 mg/kg pioglitazone daily prior to and during pregnancy (approximately nine times the maximum recommended human dose based on mg/m2). Long-term carcinogenicity studies with metformin hydrochloride I have been conducted in rats (104 weeks dosing duration) and mice (91 weeks dosing duration) at doses up to 900 mg/kg/day inclusive and 1,500 mg/kg/day, respectively. These doses are approximately four times higher than the daily dose of pioglitazone and metformin hydrochloride tablets of 2000 mg, based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in male or female mice. Similarly, no tumourigenic potential was observed when metformin was used in male rats. The incidence of benign uterine polyps was increased in female rats treated with 900 mg/kg/day. The mutagenic potential of metformin was not observed in the following in vitro tests: the Anesthetic test (S. typhimurium), gene mutations (mouse lymphoma cells) or chromosomal aberrations test (human lymphocytes). The results of the in vivo mouse micronucleus test were also negative. Metformin did not affect fertility in male or female rats at doses up to 600 mg/kg/day, approximately three times the maximum recommended daily dose of the metformin component of pioglitazone and metformin hydrochloride tablets, based on body area comparisons. Animal toxicology and/or pharmacology In mice (100 mg/kg), rats (4 mg/kg and above) and dogs (3 mg/kg) treated orally with pioglitazone (approximately 11. and twice the maximum recommended human oral dose in mice, rats and dogs, mg/m2, respectively). In a one-year rat study, drug-related early death due to cardiac dysfunction was observed at an oral dose of 160 mg/kg/day (approximately 35 times the maximum recommended human dose based on mg/m2). Cardiac enlargement was observed in a 13-week study in monkeys annustega 8,9 mg/kg and the maximum recommended human recommended oral dose based on mg/m 2) but not in a 52-week study at oral doses up to 32 mg/kg (approximately 13 times the maximum recommended human dose based on mg/m2). Clinical trials Patients with insufficient glycaemic control in a 24-week randomised, double-blind clinical trial in 600 patients with type 2 diabetes mellitus who have not responded adequately to diet and exercise only (mean baseline HbA1c 8.7%) pioglitazone and metformin hydrochloride 15/850 mg, 15 mg pioglitazone or metformin 850 mg twice daily. Statistically significant improvements in HbA1c and fasting plasma glucose were observed in patients treated with pioglitazone and metformin hydrochloride tablets compared to pioglitazone or metformin monotherapy (see Table 21). The efficacy and safety of pioglitazone in addition to metformin have been established in two clinical trials in patients previously treated with metformin. The bioequivalence of pioglitazone and metformin hydrochloride tablets with concomitantly administered pioglitazone and metformin tablets was demonstrated for the strength of both pioglitazone and metformin hydrochloride tablets (see Clinical Pharmacology (12.3)). In two clinical studies in which pioglitazone was used in addition to metformin, patients with type 2 diabetes mellitus included metformin at any dose either alone or in combination with another diabetes medicine. All other diabetes medicines were withdrawn at least three weeks before treatment was started. In the first study, 328 patients were randomised to receive either pioglitazone 30 mg or placebo once daily for 16 weeks in addition to the current metformin regimen. Treatment with pioglitazone in addition to metformin resulted in statistically significant improvements in HbA1c and FPG at the endpoint compared to the addition of placebo to metformin (see Table 22). In the second study, 827 patients were randomised to receive either 30 mg or pioglitazone 45 mg once daily for 24 weeks in addition to the current metformin regimen. Mean reduction in HbA1c from baseline at baseline at baseline fpg at baseline at 24. Combination therapy with pioglitazone and metformin was observed in patients regardless of the dose of metformin. How pioglitazone and metformin hydrochloride tablets are supplied/stored and handled, USP is available in 15 mg pioglitazone (as a base)/500 mg metformin hydrochloride and 15 mg pioglitazone (as a base)/850 mg metformin hydrochloride tablets as follows: 15 mg/500 mg tablet: white to off-white, capsule-shaped, biconvex, film-coated tablets debossed with 15/500 on one side and 1280 on the other side, available in the following bottles: Pudelid, mis sisaldavad 180 NDC 13668-280-33 Pudelid 500 NDC 13668-280-05 Pudelid 1000 NDC 13668-280-100 100 Üheannuselised tabletid NDC 13668-280-74 15 mg/850 mg tablett: valge kuni valkjas värviline, kujuline kapsel, kaksikkumer, õhukese polümeerikattega tabletid, mille ühele küljele on pressitud 15/850 ja teisele küljele 1281, mis on saadaval: pudelid 60 NDC 13668-281-60 Pudelid 180 NDC 13668-281-33 Pudelid 500 NDC 13668-281-05 pudelit, 750 NDC 13668-281-49 100 Üheannuselised tabletid NDC 13668-281-74 Säilitamine: Hoida temperatuuril 2 kuni 25°C (68°–77°F); 15°C to 30°C (59°-86°F) [See USP controlled room temperature]. Keep the package tightly closed and in order to protect from moisture. Patient Counseling Info See FDA-approved Patient Labeling (Drug Guide) It is important to instruct patients to follow dietary guidelines and to have blood glucose levels and glycosylated hemoglobin regularly tested. During stress such as fever, trauma, infection, or surgery, the need for medication may change and patients should be reminded to seek medical advice. Immediately inform patients of any signs or other symptoms of macroscopic haematuria, such as dysuria or need to urinate, which occur or increase during treatment, as these may be due to bladder cancer. Explain to patients the risks of lactic acidosis, its symptoms and conditions that contribute to its development, as indicated in warnings and precautions (5.2). Advise patients to stop taking pioglitazone and metformin hydrochloride tablets immediately and to inform your healthcare professional immediately if unexplained hyperventilation, myalgia, gastrointestinal symptoms, malaise, unusual sleepiness or other non-specific symptoms occur. Ask patients to inform their doctor that they are taking pioglitazone and metformin hydrochloride tablets before surgery or radiological procedure, as temporary discontinuation of pioglitazone and metformin hydrochloride tablets may be necessary until renal function is normal. Advise patients on excessive alcohol consumption while receiving pioglitazone and metformin hydrochloride tablets. Tell patients immediately to report symptoms of unusually rapid body weight or swelling, shortness of breath or other symptoms of heart failure while receiving pioglitazone and metformin hydrochloride tablets. Tell patients to stop taking pioglitazone and metformin hydrochloride tablets immediately and seek medical advice immediately if unexplained nausea, vomiting, abdominal pain, fatigue, anorexia or dark urine are present, as these symptoms may be due to hepatotoxicity. Inform patients of the importance of regular testing of renal function and haematological parameters with pioglitazone and metformin hydrochloride tablets. Inform female patients that the and metforminvesinichloridega metforminvesinichloridega in some premenopausal anovulatory women may result in unwanted pregnancy due to the effects of ovulation [see use in specific populations (8,3)] . In the event of overdose with pioglitazone and metformin hydrochloride tablets, patients should be informed by their healthcare professional or immediately to the Poison Center. Combination antihyperglycaemic therapy may cause hypoglycaemia. When initiating the use of pioglitazone and metformin hydrochloride tablets, patients and their family members should be identified with the risks of hypoglycaemia, its symptoms and treatment and the conditions that contribute to its development. Patients should be instructed to take pioglitazone and metformin hydrochloride tablets as instructed by their doctor and to instruct them to change dosing only if their doctor has found it. If a dose is missed one day, the dose should not be doubled the next day. Licensed - United States patents No. 5,965,584, 6166,042, 6166 043 and 6,172,090. Manufacturer: TORRENT PHARMACEUTICALS LTD., Indrad-382 721, Dist. Mehsana, INDIA. For: TORRENT PHARMA INC. 150 Allen Road, Suite 102 Basking Ridge, NJ 07920. 8063241 Modified March 2017 INTRODUCTION PIOGLITAZONE AND METFORMIN HYDROCHLORIDE (PYE o GLI ta zone and met for min HYE-droe-KLOR) tablets, USP Before taking pioglitazone and metformin hydrochloride tablets read this instructions carefully and each time you can re-fill. There may be new information. This information does not take into account your medical condition or treatment when talking to your doctor. If you have any questions about pioglitazone and metformin hydrochloride tablets, ask your doctor or pharmacist. What is the most important information I need to know about pioglitazone and metformin hydrochloride tablets? or worse for the treatment of heart failure. Pioglitazone, one of the tablets of pioglitazone and metformin hydrochloride, may cause you to keep additional fluids (fluid retention) on your body, which causes swelling (night) and weight gain. Extra bodily fluid can make some heart problems worse or cause heart failure. Heart failure means your heart is not pumping blood well enough. Do not take pioglitazone and metformin hydrochloride tablets if you have severe heart failure If you have heart failure with symptoms such as shortness of breath or swelling), even if these symptoms are not severe, pioglitazone and metformin hydrochloride tablets may not be right for you if you experience any of the following signs: swelling or fluid retention: swelling or fluid retention: , especially in the ankles or feet, shortness of breath or difficulty breathing, especially if you shed an unusually rapid weight gain unusual tiredness of lactic acidosis. Metformin, one of the tablets of pioglitazone and metformin hydrochloride, may cause rare but serious called lactic acidosis (accumulation of acid in the blood), which can cause death. Lactic acidosis is a medical emergency and should be treated in a hospital. Call your doctor immediately if you experience any of the following symptoms, which may be signs of lactic acidosis: you have a cold in your hands or feet, if you feel dizzy or dizzy, have a slow or irregular heartbeat, you feel very weak or tired, have unusual (not normal) muscle pain, if you have difficulty breathing or sleepiness, if you have abdominal pain Nausea or vomiting In most people who have had lactic acidosis with metformin, there are other things that led to lactic acidosis in combination with metformin. Tell your doctor if you have any of the following, as you are more likely to have lactic acidosis with pioglitazone and metformin hydrochloride tablets if you have: severe kidney problems or if your kidneys are affected by certain X-rays using injectable dye. have liver problems drink alcohol very often, or drink a lot of alcohol in the short term with excessive drinking to get dehydrated (lose large amounts of bodily fluids). This can happen if you have a sick fever, vomiting, or diarrhea. Dehydration can also occur if you sweat a lot of activity or exercise and don't drink enough fluids in surgery to have a heart attack, a serious infection, or stroke The best way to keep the problem of lactic acidosis metformin is to tell your doctor if you have any problems with the list above. If you get any of these things, your doctor may decide to stop pioglitazone and metformin hydrochloride tablets for a while. Pioglitazone and metformin hydrochloride tablets may also have other serious side effects. See What are the possible side effects of pioglitazone and metformin hydrochloride tablets? What are pioglitazone and metformin hydrochloride tablets? Pioglitazone and metformin hydrochloride tablets contain two prescription treatments called pioglitazone and metformin hydrochloride. Pioglitazone and metformin hydrochloride tablets can be used in combination with diet and exercise to improve blood sugar (glucose) control in adults with type 2 diabetes mellitus. Pioglitazone and metformin hydrochloride tablets are not intended for people with type 1 diabet