

Drug Therapy for 'Prediabetes' Held Premature

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NEW YORK — Drug treatment that is designed to prevent patients with “pre-diabetes” from progressing to outright, type 2 diabetes by controlling hyperglycemia is not ready for routine use, according to a Food and Drug Administration official.

Although lifestyle interventions have proved effective and make sense for

this indication—as has aggressive control of cardiovascular risk factors—the routine administration of an agent that controls blood sugar levels “is not generally applicable to any prediabetes patient,” Dr. Mary H. Parks said at a meeting sponsored by the American Diabetes Association.

“For drug intervention we need to look at efficacy and side effects. If there is a side effect profile of concern, is

there a benefit that offsets that?” So far, the answer is no because the benefit derived from the use of drugs that control hyperglycemia in patients who have prediabetes has not been clearly shown, while these drugs might produce adverse effects such as liver toxicity or increased cardiovascular disease risks, said Dr. Parks, who is director of the division of metabolism and endocrinology products at the Center for Drug

Evaluation and Research of the FDA.

Dr. Parks reviewed results from five separate, placebo-controlled assessments of the ability of oral hypoglycemic drugs to cut the progression from prediabetes to type 2 diabetes. Results from the five studies, published during the past 7 years, showed that treatment with a single drug such as metformin, acarbose (Precose), or a thiazolidinedione cut the rate of progression to diabetes by a relative rate of about 25%-60%, compared with placebo.

Despite this success, the data are not persuasive because “the risk reduction was modest, and less than with intensive lifestyle modification except when an insulin sensitizer [a thiazolidinedione] was used,” Dr. Parks said. Perhaps more important, all of the results were flawed by uncertainty as to “whether diabetes was

MICARDIS[®] Telmisartan Tablets

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, MICARDIS tablets should be discontinued as soon as possible. See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

MICARDIS tablets are indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS

MICARDIS tablets are contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

Fetal/Neonatal Morbidity and Mortality Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, MICARDIS tablets should be discontinued as soon as possible. The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of MICARDIS tablets as soon as possible. Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment. If oligohydramnios is observed, MICARDIS tablets should be discontinued unless they are considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. There is no clinical experience with the use of MICARDIS tablets in pregnant women. No teratogenic effects were observed when telmisartan was administered to pregnant rats at oral doses of up to 50 mg/kg/day and to pregnant rabbits at oral doses up to 45 mg/kg/day. In rabbits, embryolethality associated with maternal toxicity (reduced body weight gain and food consumption) was observed at 45 mg/kg/day [about 12 times the maximum recommended human dose (MRHD) of 80 mg on a mg/m² basis]. In rats, maternally toxic (reduction in body weight gain and food consumption) telmisartan doses of 15 mg/kg/day (about 1.9 times the MRHD on a mg/m² basis), administered during late gestation and lactation, were observed to produce adverse effects in neonates, including reduced viability, low birth weight, delayed maturation, and decreased weight gain. Telmisartan has been shown to be present in rat fetuses during late gestation and in rat milk. The no observed effect doses for developmental toxicity in rats and rabbits, 5 and 15 mg/kg/day, respectively, are about 0.64 and 3.7 times, on a mg/m² basis, the maximum recommended human dose of telmisartan (80 mg/day). **Hypotension in Volume-Depleted Patients** In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with MICARDIS tablets. This condition should be corrected prior to administration of MICARDIS tablets, or treatment should start under close medical supervision with a reduced dose. If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

PRECAUTIONS

General. Impaired Hepatic Function: As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. MICARDIS tablets should be used with caution in these patients. **Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with MICARDIS tablets. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of MICARDIS tablets in patients with unilateral or bilateral renal artery stenosis but an effect similar to that seen with ACE inhibitors should be anticipated. **Dual Blockade of the Renin-Angiotensin-Aldosterone System:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function (including acute renal failure) have been reported. Dual blockade of the renin-angiotensin-aldosterone system (e.g., by adding an ACE-inhibitor to an angiotensin II receptor antagonist) should be used with caution and should include close monitoring of renal function. **Information for Patients. Pregnancy:** Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible. **Drug Interactions. Digoxin:** When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. It is, therefore, recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing telmisartan to avoid possible over- or under-digitalization. **Warfarin:** Telmisartan administered for 10 days slightly decreased the mean warfarin trough plasma concentration; this decrease did not result in a change in International Normalized Ratio (INR). **Other Drugs:** Co-administration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glibenclamide, simvastatin, hydrochlorothiazide or ibuprofen. Telmisartan is not metabolized by the cytochrome P450 system and had no effects *in vitro* on cytochrome P450 enzymes, except for some inhibition of CYP2C19. Telmisartan is not expected to interact with drugs that inhibit cytochrome P450 enzymes; it is also not expected to interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19. **Carcinogenesis, Mutagenesis, Impairment of Fertility** There was no evidence of carcinogenicity when telmisartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1000 mg/kg/day) and rats (100 mg/kg/day) are, on a mg/m² basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD) of telmisartan. These same doses have been shown to provide average systemic exposures to telmisartan >100 times and >25 times, respectively, the systemic exposure in humans receiving the MRHD (80 mg/day). Genotoxicity assays did not reveal any telmisartan-related effects at either the gene or chromosome level. These assays included bacterial

mutagenicity tests with *Salmonella* and *E. coli* (Ames), a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with human lymphocytes, and a mouse micronucleus test. No drug-related effects on the reproductive performance of male and female rats were noted at 100 mg/kg/day (the highest dose administered), about 13 times, on a mg/m² basis, the MRHD of telmisartan. This dose in the rat resulted in an average systemic exposure (telmisartan AUC as determined on day 6 of pregnancy) at least 50 times the average systemic exposure in humans at the MRHD (80 mg/day). **Pregnancy** Pregnancy Categories C (first trimester) and D (second and third trimesters). See WARNINGS, Fetal/Neonatal Morbidity and Mortality. **Nursing Mothers.** It is not known whether telmisartan is excreted in human milk, but telmisartan was shown to be present in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use** Of the total number of patients receiving MICARDIS tablets in clinical studies, 551 (18.6%) were 65 to 74 years of age and 130 (4.4%) were 75 years or older. No overall differences in effectiveness and safety were observed in these patients compared to younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

MICARDIS tablets have been evaluated for safety in more than 3700 patients, including 1900 treated for over six months and more than 1300 for over one year. Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. In placebo-controlled trials involving 1041 patients treated with various doses of telmisartan (20-160 mg) monotherapy for up to 12 weeks, an overall incidence of adverse events similar to that of placebo was observed. Adverse events occurring at an incidence of 1% or more in patients treated with telmisartan and at a greater rate than in patients treated with placebo, irrespective of their causal association, are presented in the following table.

	Telmisartan n = 1455 %	Placebo n = 380 %
Upper respiratory tract infection	7	6
Back pain	3	1
Sinusitis	3	2
Diarrhea	3	2
Pharyngitis	1	0

In addition to the adverse events in the table, the following events occurred at a rate of 1% but were at least as frequent in the placebo group: influenza-like symptoms, dyspepsia, myalgia, urinary tract infection, abdominal pain, headache, dizziness, pain, fatigue, coughing, hypertension, chest pain, nausea and peripheral edema. Discontinuation of therapy due to adverse events was required in 2.8% of 1455 patients treated with MICARDIS tablets and 6.1% of 380 placebo patients in placebo-controlled clinical trials. The incidence of adverse events was not dose-related and did not correlate with gender, age, or race of patients. The incidence of cough occurring with telmisartan in six placebo-controlled trials was identical to that noted for placebo-treated patients (1.6%). In addition to those listed above, adverse events that occurred in more than 0.3% of 3500 patients treated with MICARDIS tablets monotherapy in controlled or open trials are listed below. It cannot be determined whether these events were causally related to MICARDIS tablets: **Autonomic Nervous System:** impotence, increased sweating, flushing; **Body as a Whole:** allergy, fever, leg pain, malaise; **Cardiovascular:** palpitation, dependent edema, angina pectoris, tachycardia, leg edema, abnormal ECG; **CNS:** insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoaesthesia; **Gastrointestinal:** flatulence, constipation, gastritis, vomiting, dry mouth, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, non-specific gastrointestinal disorders; **Metabolic:** gout, hypercholesterolemia, diabetes mellitus; **Musculoskeletal:** arthritis, arthralgia, leg cramps; **Psychiatric:** anxiety, depression, nervousness; **Resistance Mechanism:** infection, fungal infection, abscess, otitis media; **Respiratory:** asthma, bronchitis, rhinitis, dyspnea, epistaxis; **Skin:** dermatitis, rash, eczema, pruritus; **Urinary:** micturition frequency, cystitis; **Vascular:** cerebrovascular disorder; and **Special Senses:** abnormal vision, conjunctivitis, tinnitus, earache. During initial clinical studies, a single case of angioedema was reported (among a total of 3781 patients treated). **Clinical Laboratory Findings** In placebo-controlled clinical trials, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of MICARDIS tablets. **Hemoglobin:** A greater than 2 g/dL decrease in hemoglobin was observed in 0.8% telmisartan patients compared with 0.3% placebo patients. No patients discontinued therapy due to anemia. **Creatinine:** A 0.5 mg/dL rise or greater in creatinine was observed in 0.4% telmisartan patients compared with 0.3% placebo patients. One telmisartan-treated patient discontinued therapy due to increases in creatinine and blood urea nitrogen. **Liver Enzymes:** Occasional elevations of liver chemistries occurred in patients treated with telmisartan; all marked elevations occurred at a higher frequency with placebo. **Post-Marketing Experience** The following adverse reactions have been identified during post-approval use of MICARDIS tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to MICARDIS tablets. The most frequently spontaneously reported events include: headache, dizziness, asthenia, coughing, nausea, fatigue, weakness, edema, face edema, lower limb edema, angioneurotic edema, urticaria, hypersensitivity, sweating increased, erythema, chest pain, atrial fibrillation, congestive heart failure, myocardial infarction, blood pressure increased, hypertension aggravated, hypotension (including postural hypotension), hyperkalemia, syncope, dyspepsia, diarrhea, pain, urinary tract infection, erectile dysfunction, back pain, abdominal pain, muscle cramps (including leg cramps), myalgia, bradycardia, eosinophilia, thrombocytopenia, uric acid increased, abnormal hepatic function/liver disorder, renal impairment including acute renal failure, anemia, increased CPK, anaphylactic reaction, and tendon pain (including tendonitis, tenosynovitis). Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers, including MICARDIS tablets.

OVERDOSAGE

Limited data are available with regard to overdosage in humans. The most likely manifestation of overdosage with MICARDIS tablets would be hypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

DOSE AND ADMINISTRATION

Dosage must be individualized. The usual starting dose of MICARDIS tablets is 40 mg once a day. Blood pressure response is dose related over the range of 20-80 mg. **Special Populations:** Patients with depletion of intravascular volume should have the condition corrected or MICARDIS tablets should be initiated under close medical supervision (see WARNINGS, Hypotension in Volume-Depleted Patients). Patients with biliary obstructive disorders or hepatic insufficiency should have treatment started under close medical supervision (see PRECAUTIONS, General, Impaired Hepatic Function and Impaired Renal Function). Most of the antihypertensive effect is apparent within two weeks and maximal reduction is generally attained after four weeks. When additional blood pressure reduction beyond that achieved with 80 mg MICARDIS tablets is required, a diuretic may be added. No initial dosing adjustment is necessary for elderly patients or patients with renal impairment, including those on hemodialysis. Patients on dialysis may develop orthostatic hypotension; their blood pressure should be closely monitored. MICARDIS tablets may be administered with other antihypertensive agents. MICARDIS tablets may be administered with or without food.

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prevented or if there was masking of the disease by treatment.”

The studies also failed to address whether drug treatment did more than simply slow the appearance of hyperglycemia and actually reduced the rate of clinical complications.

Dr. Parks summarized the findings from three lifestyle-intervention studies, also placebo controlled, that were published between 1997 and 2002.

The studies involved three diverse populations, in China, Finland, and the United States. In all three groups a diet and exercise intervention program led to relative drops in the rate of diabetes onset of 31%-58%, compared with placebo. Lifestyle interventions are also safe, and so Dr. Parks endorsed them without reservation. The only problem, she acknowledged, is that they are not easy to implement or maintain.

Prediabetes is usually defined as a fasting blood glucose level of 100-125 mg/dL, or a 2-hour postchallenge level of 140-199 mg/dL. Over several years, the general trend for most people with blood glucose levels like these is for the level to rise and reach the threshold for a diagnosis of diabetes.

Study results have shown that about 5%-10% of people with prediabetes based on either their fasting glucose or postchallenge glucose level will progress to outright diabetes during the following year.

But as these numbers suggest, the short-term prognosis for any one individual is difficult to predict. Over the course of a few years, roughly a third progress to having outright diabetes, about a third will remain with prediabetes, and about a third will have their glycemia levels improve to the normal range, Dr. Parks said.