Pregnancy

Pregnancy Category C

Safety in pregnant women has not been established. There are no adequate and well controlled studies of fenofibrate in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In female rats given oral dietary doses of 15, 75, and 300 mg/kg/day of fenofibrate from 15 days prior to mating through weaning, maternal toxicity was observed at 0.3 times the MRHD, based on body surface area comparisons; mg/m^2.

In pregnant rats given oral dietary doses of 14, 127, and 361 mg/kg/day from gestation day 6-15 during the period of organogenesis, adverse developmental findings were not observed at 14 mg/kg/day (less than 1 times the MRHD, based on body surface area comparisons; mg/m^2). At higher multiples of human doses evidence of maternal toxicity was observed.

In pregnant rabbits given oral gavage doses of 15, 150, and 300 mg/kg/day from gestation day 6-18 during the period of organogenesis and allowed to deliver, aborted litters were observed at 150 mg/kg/day (10 times the MRHD, based on body surface area comparisons: mg/m^2). No developmental findings were observed at 15 mg/kg/day (at less than 1 times the MRHD, based on body surface area comparisons; mg/m^2).

In pregnant rats given oral dietary doses of 15, 75, and 300 mg/kg/day from gestation day 15 through lactation day 21 (weaning), maternal toxicity was observed at less than 1 times the MRHD, based on body surface area comparisons; mg/m^2.

Nursing Mothers

It is not known whether fenofibrate is excreted into milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from fenofibrate, a decision should be made whether to discontinue nursing or administration of fenofibrate taking into account the importance of the drug to the lactating woman.

Pediatric Use

Safety and efficacy in pediatric patients have not been established.

Geriatric Use

Fenofibric acid is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Fenofibric acid exposure is not influenced by age. However, elderly patients have a higher incidence of renal impairment, such that dose selection for the elderly should be made on the basis of renal function. Elderly patients with normal renal function should require no dose modifications.

ADVERSE REACTIONS

Adverse events reported by 2% or more of patients treated with fenofibrate during the double-blind, placebo-controlled trials, regardless of causality, are listed in the table below. Adverse events led to discontinuation of treatment in 5.0% of patients treated with fenofibrate and in 3.0% treated with placebo. Increases in liver function tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

BODY SYSTEM Adverse Event	Fenofibrate* (N=439)	Placebo (N=365)
BODY AS A WHOLE		
Abdominal Pain	4.6%	4.4%
Back Pain	3.4%	2.5%
Headache	3.2%	2.7%
Asthenia	2.1%	3.0%
Flu Syndrome	2.1%	2.7%
DIGESTIVE		
Liver Function Tests Abnormal	7.5%**	1.4%
Diarrhea	2.3%	4.1%
Nausea	2.3%	1.9%
Constipation	2.1%	1.4%
METABOLIC AND NUTRITIONAL DISORDERS		
SGPT Increased	3.0%	1.6%
Creatine Phosphokinase Increased	3.0%	1.4%
SGOT Increased	3.4% **	0.5%
RESPIRATORY		
Respiratory Disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

* Dosage equivalent to 145 mg TRICOR.
** Significantly different from Placebo.

Additional adverse events reported during post-marketing surveillance or by three or more patients in placebo-controlled trials or reported in other controlled or open trials, regardless of causality are listed below.

Body as a Whole

Accidental injury, allergic reaction, chest pain, cyst, fever, hernia, infection, malaise and pain (unspecified).

Cardiovascular System

Angina pectoris, arrhythmia, atrial fibrillation, cardiovascular disorder, coronary artery disorder, electrocardiogram abnormal, extrasystoles, hypertension, hypotension, migraine, myocardial infarct, palpitation, peripheral vascular disorder, phlebitis, tachycardia, varicose vein, vascular disorder, vasodilatation, venous thromboembolic events (deep vein thrombosis, pulmonary embolus) and ventricular extrasystoles.

Digestive System

Anorexia, cholecystitis, cholelithiasis, colitis, diarrhea, duodenal ulcer, dyspepsia, eructation, esophagitis, flatulence, gastritis, gastroenteritis, gastrointestinal disorder, increased appetite, jaundice, liver fatty deposit, nausea, pancreatitis, peptic ulcer, rectal disorder, rectal hemorrhage, tooth disorder and vomiting.

Endocrine System

Diabetes mellitus.

Hemic and Lymphatic System

Anemia, ecchymosis, eosinophilia, leukopenia, lymphadenopathy, and thrombocytopenia.

Laboratory Investigations

Alkaline phosphatase increased, bilirubin increased, blood urea nitrogen increased, serum creatinine increased, gamma glutamyl transpeptidase increased, lactate dehydrogenase increased, SGOT and SGPT increased.

Metabolic and Nutritional Disorders

Edema, gout, hyperuricemia, hypoglycemia, peripheral edema, weight gain, and weight loss.

Musculoskeletal System

Arthralgia, arthritis, arthrosis, bursitis, joint disorder, leg cramps, myalgia, myasthenia, myositis, rhabdomyolysis and tenosynovitis.

Nervous System

Anxiety or nervousness, depression, dizziness, dry mouth, hypertonia, insomnia, libido decreased, neuralgia, paresthesia, somnolence and vertigo.

Respiratory System

Allergic pulmonary alveolitis, asthma, bronchitis, cough increased, dyspnea, laryngitis, pharyngitis, pneumonia and sinusitis.

Skin and Appendages

Acne, alopecia, contact dermatitis, eczema, fungal dermatitis, herpes simplex, herpes zoster, maculopapular rash, nail disorder, photosensitivity reaction, pruritus, rash, sweating, skin disorder, skin ulcer and urticaria.

Special Senses

Abnormal vision, amblyopia, cataract specified, conjunctivitis, ear pain, eye disorder, otitis media and refraction disorder.

Urogenital System

Abnormal kidney function, cystitis, dysuria, gynecomastia, prostatic disorder, unintended pregnancy, urinary frequency, urolithiasis and vaginal moniliasis.

OVERDOSAGE

There is no specific treatment for overdose with TRICOR. General supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status, should an overdose occur. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Because fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.

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Timing an Issue When Calibrating CGMs

Lag time between serum glucose and interstitial fluid can cause chaos with sensor readings.

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — The physiological lag between glucose levels in the blood and in interstitial fluid can wreak havoc in continuous glucose monitoring if the lag isn't considered when calibrating the monitors, according to Dr. Howard A. Wolpert.

Patients with diabetes who want to use continuous glucose monitors need to be instructed to calibrate the devices when their glucose levels are in a steady state rather than during a period of changing glucose levels, Dr. Wolpert said at a meeting sponsored by the American Diabetes Association.

'If patients calibrate the [CGM] devices when their glucose is changing and they're not in steady state, their sensor is going to be calibrated inaccurately.'

Finger-stick monitors and the electrochemical sensors in continuous glucose monitors (CGMs) work on the same principle, based on glucose oxidase breaking down glucose and generating electrons, which are measured by the monitor's sensors. Finger-stick monitors measure serum glucose, and continuous monitors measure glucose in the interstitial fluid. When glucose levels are changing—such as rising glucose levels seen particularly after meals—there can be as much as a 30-minute delay before a changed glucose level in blood is reflected in interstitial fluid.

"If patients calibrate the continuous glucose monitoring devices when their glucose is changing and they're not in steady state, their sensor is going to be calibrated inaccurately and not give them reliable readings," said Dr. Wolpert of the Joslin Diabetes Center, Boston.

This has implications not only for accuracy but also for the patient's confidence in the device and willingness to monitor glucose levels. It also can affect the choices the patient makes when recovering from a hypoglycemic episode, and when setting the monitor's alarms at optimal levels, he said.

Dr. Wolpert gave the example of a person's blood glucose increasing 3 mg/dL per minute, which is not uncommon after a meal. If that patient has a 10-minute physiological lag, there's a 30-mg/dL discrepancy between the blood glucose and interstitial fluid glucose. By calibrating a continuous glucose monitor at that time, the patient might tell the monitor that the 140 mg/dL that it's measuring in the interstitial fluid should be 170 mg/dL instead, which would be inaccurate. That throws off future readings.

"It's something that patients need to be aware of—otherwise, they'll lose confidence in the technology. They'll think it's an inaccurate device rather than just a biologic lag," he said.

Data from a study of one model of continuous glucose monitor show that when it was calibrated as glucose levels were rapidly changing—either increasing or decreasing by more than 2 mg/dL per minute—only 50%-60% of its readings were in the clinically accurate Clarke error grid A zone, with a mean absolute relative difference of around 17%, Dr. Wolpert said. When the monitor was calibrated while glucose was relatively stable, accuracy improved, with up to 85% of readings in the A zone and a mean absolute relative difference of 9%.

In addition, when glucose is changing rapidly, the physiological lag results in the monitor not fully registering the rate of change, which can mislead the patient. Patients recovering from hypoglycemia may think they need more carbohydrates because the monitor reading is 55 mg/dL although the plasma glucose has come up to normal, above 70 mg/dL. These patients should do a finger-stick measurement before deciding whether to take any more carbohydrates, Dr. Wolpert said.

The lag also has implications for sensor alarm settings. One patient who had set his continuous glucose monitor alarms to alert him when glucose levels hit a high of 200 mg/dL or a low of 60 mg/dL was awakened by a high alarm at night. A finger-stick test showed a glucose level of 238 mg/dL. He gave himself a bolus of insulin and went back to sleep. In the morning, his finger-stick glucose measurement was 52 mg/dL, but the continuous glucose monitor hadn't warned him with a low alarm because it still read a level of 70 mg/dL. "This is a reflection of the lag," Dr. Wolpert said.

He recommended that the patient increase the low alarm to a higher level of 70-75 mg/dL. The patient tried that but complained of too many false alarms, and reverted to the former settings. Dr. Wolpert noted that wider settings for alarm levels will reduce the number of irritating and intrusive false alarms, but patients won't know of all their high and low glucose levels.

The narrower alarm settings may be best for patients with severe hypoglycemia or frequent hypoglycemic reactions, to be sure they're alerted of those situations, he suggested. Wider alarm settings may be best for patients new to continuous glucose monitors, "until they really get a handle on their glucose fluctuations," he said. "As they improve their control, tighten up those thresholds."

Dr. Wolpert has relationships with several companies that make continuous glucose monitors and other monitoring equipment, including Medtronic Inc., Lifescan Inc., Roche Diagnostics, and Novo Nordisk. ■