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 0.3 times the MRLD, based on body surface area comparisons; mg/m².

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, altered litter was observed at 150 mg/kg/day (10 times the MRLD), based on body surface area comparisons; mg/m².

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 MRLD, based on body surface area comparisons; mg/m².

Women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Safety in pregnant women has not been established. There are no adequate and well controlled studies of fenofibrate in pregnant women. Fenofibrate is a pregnancy category C drug. Pregnancy category C: There is no adequate and well controlled study in pregnant women; however, there is adequate and well controlled study in animal reproduction studies. It is not known whether fenofibrate is excreted into human 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

Fenofibrate 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. Fenofibrate, acid excretion 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 10% of patients treated with fenofibrate. 5.0% reacted with placebo. Increased in frequency tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

BODY SYSTEM

Fenofibrate

Acute worldwide: C556G

** Significantly different from Placebo.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal Pan</td>
<td>4.4%</td>
</tr>
<tr>
<td>Black Pain</td>
<td>3.8%</td>
</tr>
<tr>
<td>Headache</td>
<td>3.2%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>2.6%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2.1%</td>
</tr>
<tr>
<td>Flatus</td>
<td>2.4%</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>2.1%</td>
</tr>
<tr>
<td>Gastrointestinal Disorder</td>
<td>1.9%</td>
</tr>
<tr>
<td>Metabolic and Nutritional Disorders</td>
<td>3%</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>3.0%</td>
</tr>
<tr>
<td>Obstructive Renal Failure</td>
<td>3.6%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>6.2%</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

**Weight gain associated to 145 mg TRICOR.**

** Significantly different from Placebo.

Additional adverse events reported during post-marketing surveillance or by fewer than two patients in placebo-controlled trials or reported in open or control trials, regardless of causality are listed below.

Body as a Whole

Accidental injury, allergic reaction, rash, pain, cry, fever, herpes, malaise and pain (unspecified).

Cardiovascular System

Angina pectoris, arhythmia, atrial fibrillation, cardiovascular disorder, coronary artery disorder, electrocardiogram abnormal, esophageal disorder, hypotension, myocardial infarction, myocarditis, neuropathy, pericarditis, syncope, transient ischemic attack, palpitation, peripheral vascular disorder, phlebitis, tachycardia, tachyarrhythmia, vascular disorder, vasodilation, ventricular extrasystoles, deep vein thrombosis, pulmonary embolism and valvular entrenchment.

Diabetes System

Anemia, achlorhydria, cholestasis, collins, diabeta, duodenal ulcer, dyspepsia, eructation, esophagitis, flatulence, gastritis, gastrorrhoea, gastrointestinal disorder, increased appetite, jaundice, liver failure, jaundice, nausea, paresthesia, peptic ulcer, rectal disorder, renal hemorrhage, tooth disorder and vomiting.

Endocrine System

Diabetes mellitus

Hematologic System

Anemia, anemia aplastic, anemia hypoplastic, leukopenia, lymphadenopathy and thrombocytopenia.

Laboratory Investigations

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

Metabolic and Nutritional Disorders

Erythema, gestosis, hypoglycemia, peripheral edema, weight gain, and weight loss.

Musculoskeletal System

Arthritis, arthritis, arthralgia, back pain, joint disorder, leg cramp, myalgia, myositis, myopathy, myosthenia and tenosynovitis.

Nervous System

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

Respiratory System

Allergic reaction, asthma, bronchitis, cough increased, dyspnea, laryngitis, pharyngitis, pneumonitis and sinusitis.

Skin and Appendages

Acne, dermatitis, cutaneous, eczema, fungal dermatitis, herpes simplex, herpes zoster, muscoserous rash, nail disorder, psoriasis, dermatitis, pruritus, rash, skin disorder, skin ulcer and eczema.

Special Senses

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

Urogenital System

Abnormal kidney function, cystitis, dysuria, genitourinary, prostatic disorder, urolithiasis, pregnancy, amenorrhea, galactorrhea and vaginitis.

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 the clinical status, should be an overriding concern. 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 is not expected to be considered.

Manufactured for Abbott Laboratories, North Chicago, IL 60064, U.S.A.

by Procter & Gamble Laboratories, Cincinnati, and Ciba-Geigy Corporation Co., Kirk, Ireland or Laboratories Frontier SA, Rue de Pres, 21121 Porren-tat-Dijon, France.

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Timing an Issue When Calibrating CGMs

San Francisco — The physiological lag between glucose levels in the blood and in intracellular fluid can wreak havoc in continuous glucose monitoring if the lag isn’t considered when calculating 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.

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 monitors’ sensors. Finger-stick monitors measure serum glucose, and continuous monitors measure glucose in the intracellular 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 intracellular fluid. Patients who 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,” Dr. Wolpert said.

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.”

BY SHERRY BOSCHERT

San Francisco Review

When it was calibrated as glucose levels were rapidly changing—or 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 test 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 alarm 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 remain alert to those situations, he suggested. Wider alarm settings may be best for patients new to continuous glucose monitors, “until they really get a feel for what their glucose is doing,” Dr. Wolpert said.