APPENDIX (CURRENT LABELING) EFFICACY ISSUES

GLITAZONES ARE LESS EFFECTIVE AS MONOTHERAPY IN DIABETIC PATIENTS PREVIOUSLY TREATED WITH ANOTHER ORAL ANTI-DIABETIC DRUG

Current Glitazone Labeling (Under "Clinical Studies")		
Troglitazone1	Rosiglitazone2	Pioglitazone3
"…patients who switched from a sulfonylurea to Rezulin monotherapy also demonstrated increases in FSG* and HbA1C."	"Patients who were inadequately controlled on a maximum dose (2.5 grams/day) of metformin and who were switched to monotherapy with Avandia demonstrated loss of glycemic control, as evidenced by increases in FPG and HbA1c."	"…however, for the previously-treated group, washout from previous anti-diabetic medication resulted in deterioration of glycemic control and increases in HbA1c and FBG."** "For many previously-treated patients, HbA1c and FBG had not returned to screening levels by the end of the study."

*FSG Fasting Serum Glucose; **FBG fasting blood glucose (blood sugar level)

GLITAZONES ARE NOT AS EFFECTIVE AS OLDER DRUGS WHEN USED ALONE IN REDUCING BLOOD SUGAR AND HbA1c

Current Glitazone Labeling (comparative)		
Troglitazone	Rosiglitazone	Pioglitazone
No information in label	See Fig. 2 in label	No comparative study was done.

SAFETY ISSUES
1) ALT ELEVATIONS

Current Glitazone Labeling (Under "Laboratory Abnormalities")		
Troglitazone	Rosiglitazone	Pioglitazone
Black box warning at beginning of label: "Hepatotoxicity Severe idiosyncratic hepatocellular injury has been reported during marketed use (see ADVERSE REACTIONS). The hepatic injury is usually reversible, but very rare cases of hepatic failure, leading to death or liver transplant, have been reported." Under "lab abnormalities": During all clinical studies in North America, a total of 48 of 2510 (1.9%) Rezulin-treated patients and 3 of 475 (0.6%) placebo-treated patients had ALT levels greater than 3 times the upper limit of normal." "Twenty of the rezulin-treated and one of the placebo-treated patients were withdrawn from treatment. Two of the 20 Rezulin-treated patients developed jaundice; one of these	"In clinical studies in 4598 patients treated with Avandia encompassing approximately 3600 patient years of exposure, there was no evidence of drug-induced hepatotoxicity or elevated ALT levels." (plus under PRECAUTIONS, there is information on ALT measurements, lack of clear causality, etc.)	"During placebo-controlled clinical trials in the U.S., a total of 4 of 1526 (0.26%) ACTOS-treated patients and 2 of 793 (0.25%) placebo-treated patients had ALT values greater or equal to 3 times the upper limit of normal. All patients with follow-up values had reversible elevations in ALT." (plus under PRECAUTIONS, there is information on ALT measurements, lack of clear causality, etc.)

1 Rezulin (troglitazone) Professional Product Labeling at www.rezulin.com/ obtained 9/22/99.
2 Avandia (rosiglitazone) Professional Product Labeling at www.avandia.com obtained 9/22/99.
3 Actos (pioglitazone) Professional Product Labeling at www.actos.com obtained 9/22/99.

patients had a liver biopsy which was consistent with an idiosyncratic drug reaction."		

2) EFFECTS ON THE HEART

Current Glitazone Labeling (Under "Precautions")		
Troglitazone	Rosiglitazone	Pioglitazone
"Heart enlargement without microscopic changes has been observed in rodents at exposures of parent compound and active metabolite exceeding 7 times the AUC of the 400 mg human dose. . ." "Increased heart weights without microscopic changes were observed in mice and rats treated for up to 1 year at exposure (AUC) of parent and active metabolite exceeding 7 times the human AUC at 400 mg/day." "In the lifetime carcinogenicity studies, microscopic changes were noted in the hearts of rats…. In control and treated rats, microscopic changes included myocardial inflammation and fibrosis and karyomegaly of atrial myocytes. …at twice the AUC of the 400 mg human dose."	"In preclinical studies, thiazolidinediones, including rosiglitazone, cause plasma volume expansion and pre-load-induced cardiac hypertrophy. Two ongoing echocardiography studies in patients with type 2 diabetes (a 52-week study with Avandia 4 mg twice daily [n=86] and a 26-week study with 8 mg once daily [n=90], have shown no deleterious alteration in cardiac structure or function."	"In preclinical studies, thiazolidinediones, including pioglitazone, cause plasma volume expansion and pre-load-induced cardiac hypertrophy (see PRECAUTIONS, Animal Toxicology)." "In clinical trials that excluded patients with New York Heart Association Class III and IV cardiac status, no increased incidence of serious cardiac adverse events potentially related to volume expansion (e.g., congestive heart failure) was observed."

3) WEIGHT GAIN (GLUCOSE CONVERSION INTO FAT)

Current Glitazone Labeling (Under "Pharmacodynamics and Clinical Effects")		
Troglitazone	Rosiglitazone	Pioglitazone
No mention of weight gain in label.	"Reduction in hyperglycemia was associated with increases in weight. In the 26-week clinical trials, the mean weight gain in patients treated with Avandia was 1.2 kg (4 mg daily) and 3.5 kg (8 mg daily) when administered as monotherapy and 0.7 kg (4 mg daily) and 2.3 kg (8 mg daily) when administered in combination with metformin. A mean weight loss of about 1 kg was seen for both placebo and metformin alone in these studies."	"In all clinical trials, a reduction in HbA1c was accompanied by increased body weight in ACTOS-treated patients in a dose-related manner. The change in average weight in US placebo-controlled monotherapy trials ranged from 0.5 kg to 2.8 kg for ACTOS-treated patients and –1.3 kg to –1.9 kg for placebo-treated patients."

4) EDEMA

Current Glitazone Labeling (Under "Precautions")		
Troglitazone	Rosiglitazone	Pioglitazone
"In animal studies, troglitazone	"In preclinical studies,	"ACTOS should be used with caution

treatment was associated with increase of 6% to 15% in plasma volume. In a study of 24 normal volunteers, an increase in plasma volume of 6% to 8% compared to placebo was observed. . .” “No increased incidence of adverse events potentially related to volume expansion (eg, congestive heart failure) have been observed during controlled clinical trials.”	thiazolidinediones, including rosiglitazone, cause plasma volume expansion and pre-load-induced cardiac hypertrophy.” “Avandia should be used with caution in patients with edema. In a clinical study in healthy volunteers who received 8 mg once daily for 8 weeks, there was a statistically significant increase in median plasma volume (1.8 ml/kg) compared to placebo.” “In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was reported in patients treated with Avandia.”	in patients with edema. In double-blind clinical trials of patients with type 2 diabetes, mild to moderate edema was reported in patients treated with ACTOS (see ADVERSE REACTIONS).”

5) ANEMIA

Current Glitazone Labeling (Under “Precautions” and “Adverse Reactions”)		
Troglitazone	Rosiglitazone	Pioglitazone
Under “Precautions”: “Across all clinical studies, hemoglobin declined by 3% to 4% in troglitazone-treated patients compared with 1% to 2% in those treated with placebo. White blood cell counts also declined slightly in troglitazone-treated patients compared to those treated with placebo. These changes occurred within the first four to eight weeks of therapy. Levels stabilized and remained unchanged for up to two years of continuing therapy. These changes may be due to the dilutional effects of increased plasma volume and have not been associated with any significant hematologic clinical effects.” Under “Adverse Reactions”: “Small decreases in hemoglobin, hematocrit, and neutrophil counts (within the normal range) were more common in Rezulin-treated patients than placebo-treated patients and may be related to increased plasma volume observed with Rezulin treatment. Hemoglobin decreases to below the normal range occurred in 5% of Rezulin-treated and 4% of placebo-treated patients.”	Under “Precautions”: “Across all controlled clinical studies, decreases in hemoglobin and hematocrit (mean decreases in individual studies up to ≤1.0 gram/dL hemoglobin and up to ≤3.3% hematocrit) were observed for both Avandia alone and in combination with metformin. The changes occurred primarily during the first 4 to 8 weeks of therapy. . .” “White blood cell counts also decreased slightly in patients treated with Avandia. Decreases in hematologic parameters may be related to increased plasma volume observed with treatment with Avandia. The observed changes may be related to the increased plasma volume observed with treatment with Avandia and have not been associated with any significant hematologic clinical effects” Under “Adverse Reactions”: “The time course and magnitude of decreases were similar in patients treated with a combination of Avandia and metformin or monotherapy.”	Under “Precautions” and “Adverse Reactions”: “ACTOS may cause decreases in hemoglobin and hematocrit. Across all clinical studies, mean hemoglobin values declined by 2% to 4% in ACTOS-treated patients. These changes generally occurred within the first 4 to 12 weeks of therapy and remained relatively stable thereafter. These changes may be related to increased plasma volume associated with ACTOS therapy and have not been associated with any significant hematologic clinical effects.”

6) BLOOD PRESSURE LOWERING

Current Glitazone Labeling		
Troglitazone	Rosiglitazone	Pioglitazone

No information	No information	No information

7) PLASMA LIPIDS

Current Glitazone Labeling (Under "Clinical Pharmacology")		
Troglitazone	Rosiglitazone	Pioglitazone
"In clinical trials of Rezulin, an increase in LDL (up to 13%), HDL (up to 16%), and total cholesterol (total-C) (up to 5%) occurred while total-C/HDL and LDL/HDL ratios did not change. The increase in total cholesterol is due to the increase in HDL and LDL cholesterol."	"Avandia as monotherapy was associated with increases in total cholesterol, LDL, and HDL and decreases in free fatty acids."	"Overall, patients treated with ACTOS had mean decreases in triglycerides, mean increases in HDL cholesterol and no consistent mean changes in LDL and total cholesterol."