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January 6, 1999

Minnie Baylor-Henry, R.Ph., J.D.
Director, Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
Rm. 17B20 HFD-40
5600 Fishers Lane
Rockville, MD 20857

Dear Ms. Baylor-Henry:

Enclosed is an extremely misleading direct-to-consumer (DTC) advertisement that lacks fair balance for the dangerous diabetes drug troglitazone (Rezulin), made by Parke Davis, a division of Warner Lambert, of Morris Plains, NJ. This ad, with the good news and promotional information in Spanish but the official labeling with warnings and risks in English, appeared in the December 1998 *El Tiempo Latino* a publication distributed with newspapers in cities with large Spanish speaking populations that is promoted as "The Magazine for All Hispanics."

El Tiempo Latino has a total average circulation of 1,139,568 and 397,713 copies are distributed in California alone. A list of newspapers in which El Tiempo Latino is distributed and its circulation is enclosed for your reference. Also enclosed is an English language translation of the advertisement.

At the end of the ad consumers are instructed in Spanish to "... read the important information which appears on the back," referring to a brief summary of the full professional product labeling or package insert. However, the brief summary is not in Spanish but in English. It is our opinion that this ad violates provisions of the Federal Food, Drug and Cosmetic Act and Food and Drug Administration (FDA) advertising regulations by being misleading and lacking in fair balance.

Many Spanish speaking Americans have excellent bilingual language skills and are fluent in both Spanish and English. However, the interpretation of the brief summary (a drug's professional product labeling) that must accompany DTC print ads by regulation can be difficult to understand even for those consumers whose first language is English. The brief summary contains some risk information that is

important for consumers but it is written for health professionals, in dense technical jargon, and assumes a high level of medical knowledge on the part of the reader.

The December issue of *El Tiempo Latino* does contain an ad for another prescription drug, this time with consumer directed text and the required brief summary and both are in English. The troglitazone ad appears to be directed primarily at Spanish speaking only consumers who are only presented with the alleged benefits of troglitazone and no balancing risk information in Spanish with which to make an informed decision about using this drug.

The careful choice of words by Parke Davis in the ad's Spanish language text minimizes the risks of troglitazone by telling consumers:

In a few cases, Rezulin has been associated with serious hepatic problems, which generally are reversible, although in a few cases have resulted in insufficient hepatic function and death. Your doctor can advise you in regard to the new recommendations for hepatic monitoring with Rezulin, which require routine blood tests.

The box warning contained in troglitazone's English language brief summary, though in technical language, informs consumers in bold type "... rare cases of hepatic failure, leading to death or liver transplant, have been reported. Injury has occurred after both short- and long-term troglitazone treatment." The brief summary goes on to say that 11 blood tests are required during the first year of treatment with the drug, rather than simply that "routine blood tests" are required.

The FDA must immediately ban the distribution of this dangerously misleading ad. Because vital risk information about troglitazone has been hidden from the Spanish speaking public, Parke Davis must be required to run corrective ads in all publications in which this ad has appeared. The corrective ad must run for the same period of time that this misleading ad appeared in the publication. The corrective ad must clearly inform Spanish speaking diabetics--in Spanish--of the potentially life-threatening liver toxicity associated with this drug.

Ultimately, the FDA must address the multitude of problems that have been seen with DTC drug ads, such as this ad for troglitazone, by finalizing, and vigorously enforcing, regulations that directly address these unique problems of DTC advertising as the Agency promised to do 15 years ago.

We look forward to the FDA's prompt action on this critical public health issue.

Sincerely,

Larry D. Sasich, Pharm.D., M.P.H., FASHP Public Citizen's Health Research Group

Sidney M. Wolfe, M.D.

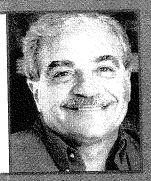
Director

Public Citizen's Health Research Group

# REZULIN, BUNA VEZ AL DÍA,

PODRÍA

"MI MÉDICO me recetó REZULIN Y ME DIJO QUE PODRÍA REDUCIR MI DOSIS DIARIA DE INSULINA."



CAMBIAR LA



"SÓLO TENGO QUE TOMAR REZULIN UNA VEZ AL DÍA, LO QUE ME SIMPLIFICA MUCHO LA VIDA."

FORMA EN OUE

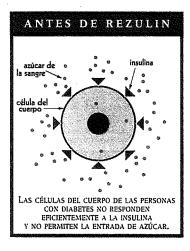
SU MÉDICO TRATA LA DABETESTIPO



"AHORA FINALMENTE TENGO CONTROLADO EL AZÚCAR DE MI SANGRE, REZULIN ME ESTÁ DANDO RESULTADOS.

# REZULINº: MEJORA EL CONTROL DE LA DIABETES TIPO 2.

Rezulin (troglitazone), una píldora para la diabetes que se toma una sola vez por día ayuda al cuerpo a utilizar su propia insulina para mejorar el control del azúcar de la sangre. Rezulin puede ser usado en pacientes no bien controlados con dieta y ejercicio solamente, o con píldoras orales de sulfonilureas o con insulina.





Puede reducir y quizás eliminar la necesidad de invectarse insulina. Debido a que Rezulin meiora la utilización de la insulina, podría hacer una diferencia si el tratamiento de su diabetes tipo 2 incluye invecciones de insulina. Con Rezulin, es posible que usted pueda reducir la dosis de insulina o el número de inyecciones que se administra. Quizás podría eliminar las invecciones por completo.

Aumenta la eficacia de muchos medicamentos Orales. Es posible que su médico descubra que Rezulin proporciona un mejor control del azúcar en la sangre cuando se agrega a un régimen de píldoras para la diabetes que contienen una sulfonilurea, tal como Amaryl, \*\* Glucotrol XL, \*\* Glynase \*\* PresTab, \*\* \* glipizide, o glyburide.

Preguntele a su médico si usted se beneficiará tomando Rezulin. Rezulin puede ofrecerle a millones de personas con diabetes tipo 2 opciones de tratamiento útiles. Por favor, tenga en cuenta que los pacientes con diabetes tipo 1 no deben tomar Rezulin. Como es el caso con todos los medicamentos disponibles en la actualidad para tratar la diabetes tipo 2, Rezulin se ha asociado a efectos colaterales. Si bien éstos no son por lo general serios, usted debe hablar de estas posibilidades con su médico. En casos poco frecuentes, Rezulin se ha asociado a problemas hepáticos serios, que por lo general son reversibles, si bien en casos muy poco frecuentes han llevado a la insuficiencia hepática y a la muerte. Su médico le puede aconsejar con respecto a las nuevas recomendaciones de monitorización hepática con Rezulin, que requieren pruebas de sangre de rutina. Los efectos colaterales más comunes descritos en los estudios médicos fueron similares a los observados con un placebo (una tableta sin medicamento) e incluyen los siguientes: infección (placebo 22% vs. Rezulin 18%), dolor de cabeza (placebo 11% vs. Rezulin 11%), y dolor (placebo 14% vs. Rezulin 10%). Hable con su médico de inmediato si llega a tener náusea, vómitos, dolor de estómago, cansancio, falta de apetito, orina de color oscuro, o coloración amarillenta de la piel (ictericia), ya que estas manifestaciones podrían ser signos o síntomas de un problema del hígado. Siga todas las recomendaciones que su médico le haga con respecto a dieta, ejercicio y pérdida de peso. Como corresponde con cualquier medicamento, dígale a su médico o profesional de atención a la salud acerca de cualquier otro medicamento que esté tomando. Si su tratamiento incluye Rezulin v píldoras de una sulfonilurea, existe la posibilidad de tener un aumento de peso controlable. Si usted es una mujer premenopáusica que ya no ovula, debe tener presente que el tratamiento con Rezulin puede causar que se reinicie la ovulación, lo que crearía un riesgo de embarazo.

Más de 1.000.000 de personas han comenzado a tomar Rezulin para meiorar el control de su diabetes. Y esta cifra continúa aumentando. La mejor manera de averiguar si a usted le beneficiaría tomar Rezulin es consultando a su médico. Para mayor información, vea la importante información que aparece en la parte posterior, y llame sin cargo telefónico al número:

1-888-900-TYPE2

# UNA VEZ AL DÍA

PREGÚNTELE A SU MÉDICO Cómo Rezulin Es Diferente.

Por favor vea la importante información que aparece al dorso.

PD-168-NJ-2381-A2(068)

(1998 Parke-Davis Pharmaceuticals Limited

Amaryl es una marca de comercio registrada de Hoechst Marion Roussel; Glucotrol XL es una marca de comercio registrada de Pfizer, Inc.; Glynase and PresTab son marcas de comercio registradas de Pharmacia & Upjohn.

English translation of Rezulin ad done by pharmacists at The West Texas Regional Poison Control Center, El Paso, TX.

## Page One

(Headline):

REZULIN, ONCE A DAY, COULD CHANGE THE WAY YOUR DOCTOR TREATS TYPE 2 DIABETES.

(Photo captions, counter-clockwise)

Man: My doctor prescribed Rezulin and told me that I could reduce my daily dose of insulin.

Woman #1: I only have to take Rezulin once a day, which really makes my life easier.

Woman #2: Now I finally have my blood sugar level under control; Rezulin has given me results.

# Page Two

(Header):

REZULIN: ENHANCES CONTROL OF TYPE 2 DIABETES.

Rezulin (troglitazone), a pill for diabetes that is taken only once a day, helps the body utilize its own insulin to enhance the control of blood sugar. Rezulin can be used by patients (who have not been able to control their diabetes well through diet and exercise only)(?), with oral sulfonilureas, or with insulin.

(Illustrations, left to right)

#### Box 1

(header): BEFORE REZULIN

(counter-clockwise): blood sugar, cell in a body, insulin

(caption): THE CELLS OF A PERSON WITH DIABETES DO NOT RESPOND EFFICIENTLY TO INSULIN AND DO NOT PERMIT SUGAR TO ENTER.

#### Box 2

(header): AFTER REZULIN

(caption): REZULIN ACTS WITHIN THE CELL TO HELP INSULIN PERMIT

SUGAR TO ENTER.

You can reduce and possibly eliminate the need to inject insulin. Because Rezulin enhances the utilization of insulin, this could make a difference if your Diabetes Type 2 treatment includes insulin injections. With Rezulin, it's possible that you can reduce your insulin dose or the number of required injections. It could also be possible to completely eliminate the injections.

Increases the efficacy of many oral medications. It is possible that your doctor will find that Rezulin provides better control of blood sugar levels when added to a regimen of other pills being taken for diabetes which contain a sulfonilurea such as Amaryl, Glucotrol XL, Glynase, PresTab, glipizide, or glyburide.

Ask your doctor if you would benefit from taking Rezulin. Rezulin can offer millions of people with diabetes type 2 useful treatment options. Please take into consideration that patients with diabetes type 1 should not take Rezulin. As is the case with all medications currently available to treat diabetes type II, Rezulin is known to cause side effects. Although these are not generally serious, you should talk about the possibility of these side effects with your doctor. In a few cases, Rezulin has been associated with serious hepatic problems, which generally are reversible, although in a few cases have resulted in insufficient hepatic function and death. Your doctor can advise you in regard to the new recommendations of hepatic monitoring with Rezulin, which require routine blood tests. The most common side effects found in medical studies were similar to those observed under a placebo (an inactive pill) and include the following: Infection (placebo 22% vs. Rezulin 18%), headache (placebo 11% vs. Rezulin 11%), and pain (placebo 14% vs. Rezulin 10%). Talk to your doctor immediately if you experience nausea, vomiting, stomachache, fatigue, loss of appetite, dark-colored urine, or a vellowish coloring to your skin (jaundice), since these manifestations could be signs or symptoms of liver problems. Follow all of your doctor's instructions with regard to diet, exercise, and weight loss. As with any medication, tell your doctor or healthcare professional about any other medications you are taking. If your treatment includes Rezulin and pills of a sulfonilurea, there is a possibility of weight gain which is controllable. If you are a pre-menopausal woman who no longer ovulates, you should keep in mind that Rezulin treatment could cause ovulation to occur, which would create a risk for pregnancy.

More than 1,000,000 people have begun to take Rezulin to better control their diabetes. And this figure continues to grow. The best way to determine if you would benefit from taking Rezulin is to talk to your doctor. For further information, read the important information which appears on the back of this page, and call toll free: 1-888-900-TYPE 2

ONCE A DAY
REZULIN
TROGLITAZONE

# ASK YOUR DOCTOR ABOUT THE REZULIN DIFFERENCE

Please read the important information which appears on the back.



#### WARNINGS

#### Hepatic

Rare cases of severe idiosyncratic hepetocellular injury have been reported during marketed use (see ADVERSE REACTIONS). The hepetic injury is usually reversible, but very rare cases of hepatic failure, leading to death or liver transplant, have been reported. Injury has occurred after both short- and long-term troglitezone treatment.

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 gatients developed reversible jaundice; one of these patients had a liver biopsy which was consistent with an idiosyncratic drug reaction. An additional Rezulin-treated patient had a liver biopsy which was also consistent with an idiosyncratic drug reaction. (See ADVERSE REACTIONS, Laboratory Abnormalities.)

Serum transaminase levels should be checked at the start of therapy, monthly for the first eight months of therapy, every two months for the remainder of the first year of Rezulin therapy, and periodically thereafter. Rezulin therapy should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT>1.5 times the upper limit of normal). Liver function tests also should be obtained for patients at the first symptoms suggestive of hepatic dysfunction, eg, nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine. If serum transaminase levels are moderately increased (ALT>1.5 to 2 times the upper limit of normal), liver function tests should be repeated within a week and then weekly until the levels return to normal. If at any time a patient has joundice or ALT rises above 3 times the upper limit of normal, Rezulin should be discontinued.

#### BRIEF SUMMARY

Consult Package Insert for full Prescribing Information.

#### INDICATIONS AND USAGE

Rezulin may be used concomitantly with a sulfonylurea or insulin to improve glycemic control. Rezulin, as monotherapy, is indicated as an adjunct to diet and exercise to lower blood glucose in patients with type II diabetes (see DOSAGE AND ADMINISTRATION in Package Insert for full Prescribing Information), Rezulin should not be used as monotherapy in patients previously well-controlled on sulfonylurea therapy. For patients inadequately controlled with a sullonyluroa alone, Rezulin should be added to, not substituted for, the sullonylurea.

Management of type II diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the

diabetic patient. This is important not only in the primary treatment of type II diabetes, but in maintaining the efficacy of drug therapy. Prior to initiation of Rezulin therapy, secondary causes of poor glycemic control, eg, infection or poor injection technique, should be investigated and treated. CONTRAINDICATIONS

Rezulin is contraindicated in patients with known hypersensitivity or allergy to Rezulin or any of its components.

#### WARNINGS

# SEE BOXED WARNING. PRECAUTIONS

Because of its mechanism of action. Rezulin is active only in the presence of insulin. Therefore, Rezulin should not be used in type I diabetes or for the treatment of diabetic keto-acidosis.

Hypoglycemia: Patients receiving Rezulin in combination with insulin or oral hypoglycemic agents may be at risk for hypoglycemia and a reduction in the dose of the concomitant agent may be necessary. Hypoglycemia has not been observed during the administration of Rezulin as monotherapy and would not be expected based on the mechanism of action.

Ovalation: In premenanguisal anovulatory patients with insulin resistance, Rezulin treatment may result in resumption of ovulation. These patients may be at risk for pregnancy.

ue at 18% for pregnanter.

Hematologic Across all clinical studies, hemoglobin declined by 3 to 4% in troglitazona-treated patients compared with 1 to 2% in those treated with placebo. White blood cell counts also declined slightly in troglitazona-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 be 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 (see ADVERSE REACTIONS, Laboratory Abnormalities).

#### Use in Patients With Heart Failure

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 (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility, and Animal Toxicology). Serial echocardiographic evaluations in monkeys treated chronically at exposures at 4-9 times the human exposure to parent compound and active metabolite at the 400 mg dose did not reveal changes in heart size of function. In a 2-year echocardiographic clinical study using 600 to 800 mg/day of Rezulin in patients with type II diabates, no increase in left ventricular mass or decrease in cardiac output was observed. The methodology employed was able to detect a change of about 10% or more in left ventricular mass.

In animal studies, trogitazone treatment was associated with increases of 6% to 15% in plasma volume. In a study of 24 normal volunteers, an increase

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#### Information for Patients

Rezulin should be taken with meals. If the dose is missed at the usual meal, it may be taken at the next meal. If the dose is missed on one day, the dose

should not be doubled the following day. It is important to adhere to dietary instructions and to regularly have blood glucose and glycosylated hemoglobin tested. During periods of stress such

as lever, trauma, infection, or surgery, insulin requirements mey change and patients should seek the advice of their physician.
Patients who develop nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine or other symptoms suggestive of hepatic dysfunction or jaundice should immediately report these signs or symptoms to their physician. Patients should be informed that blood will be drawn to check their liver function at the start of therapy, monthly for the first eight months of therapy, every two months for the remainder of the first year of Rezulin therapy, and periodically thereafter.

When using combination therapy with insulin or oral hypoglycemic agents, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.

Use of Rezulin can cause resumption of ovulation in women taking oral contraceptives and in patients with polycystic ovary disease. Therefore, a higher dose of an oral contraceptive or an alternative method of contraception should be considered.

Rezulin may affect other medications used in diabetic patients. Patients started on Rezulin should ask their physician to review their other medications to make sure that they are not affected by Rezulin.

Drug Interactions

Oral Contraceptives: Administration of Rezulin with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the plasma concentrations of both by approximately 30%, which could result in loss of contraception. Therefore, a higher dose of oral contraceptive or an alternative

Terlegadine: Coadministration of Rezulin with terlegadine decreases the plasma concentration of both terlegadine and its active metabolite by 50-70%

Internations: Coannaissance of the coannaissance of

cholestyramine and Rezulin is not recommended.

Glyburide: Coadministration of Rezulin and glyburide does not appear to alter troglitazone or glyburide pharmacokinetics.

Digoxin: Coadministration of Rezulin with digoxin does not after the steady-state pharmacokinetics of digoxin.

Warfaria: Rezulin has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

Acstammopheu: Coadministration of acetaminophen and Rezulin does not after the pharmacokinetics of either drug.
Metformia: No information is available on the use of Rezulin with metformin.

Ethanol: A single administration of a moderate amount of alcohol did not increase the risk of acute hypoglycemia in Rezulin-treated patients with type

The above interactions with terfenadine and oral contraceptives suggest that troglitazone may induce drug metabolism by CYP3A4. Studies have not been performed with other drugs metabolized by this enzyme such as: astemizole, calcium channel blockers, cisapride, corticosteriois, cyclosporine, HMG-CoA reductase inhibitors, tacrolimus, triazolam, and trimetrexate. The possibility of aftered sefety and efficacy should be considered when Rezulin is used concomitantly with these drugs.

Patients stable on one or more of these agents when Rezulin is started should be closely monitored and their therapy adjusted as necessary.

Patients stable on one or more of these agents when Rezulin is started should be closely monitored and their therapy adjusted as necessary. Carcinogenesis, Mutagenesis, Impairment of Fertility Troglitazone was administered daily for 104 weeks to male rats at 100, 400, or 800 mg/kg and to female rats at 25, 50, or 200 mg/kg. No tumors of a were increased at the low and mid doses. Plosmo drug exposure based on AUC of parent compound and total metabolites at the low and mid dos up to 24-fold higher than human exposure at 400 mg/kg in highest dose in each sex exceeded the maximum acroated dose. In a 104-week is mice given 50, 400, or 800 mg/kg, incidence of hemangiosarcoma was increased in females at 400 mg/kg and in both sexes at 800 mg/kg; incid hepatocellular carcinoma was increased in females at 800 mg/kg. The lowest dose associated with increased tumor incidence (400 mg/kg) incidence with increased (400 mg/kg) incidence with increased tumor incidence (400 mg/kg) incidence with increased (400 mg/kg) incidence with increased

Troulitazone was neither mutagenic in bacteria nor clastogenic in bone marrow of mice. Equivocal increases in chromosome aberrations were of in an in vitro Chinese hamster lung cell assay. In mouse lymphoma cell gene mutations assays, results were equivocal when conducted with a mit technique and negative with an ager plate technique. A liver unscheduled DNA synthesis assay in rats was negative.

No adverse effects on fertility or reproduction were observed in male or female rats given 40, 200, or 1000 mg/kg daily prior to and throughout and gostation. AUC of parent compound at these doses was estimated to be 3- to 9-fold higher than the human exposure.

Animal Toxicology
Increased heart weights without microscopic changes were observed in mice and rats treated for up to 1 year at exposure (AUC) of parent and metabolite exceeding 7 times the human AUC at 400 mg/day. These heart weight increases were reversible in 2- and 13-week studies, were pre by coadministration of an ACE inhibitor, and 14 days of troglitazone administration to rats did not affect left ventricular performance. In the lifetii cinogenicity studies, microscopic changes were noted in the hearts of rats but not in mice. In control and treated rats, microscopic changes in myocardial inflammation and fibrosis and karyomegaly of atrial myocytes. The incidence of these changes in drug-treated rats was increased co to controls at twice the AUC of the 400 mg human dose.

Pregnancy Category B. Troglitazone was not teratogenic in rats given up to 2000 mg/kg or rabbits given up to 1000 mg/kg during organog Compared to human exposure of 400 mg daily, estimated exposures in rats (parent compound) and rabbits (parent compound and active met based on AUC at these doses were up to 9-fold and 3-fold higher, respectively. Body weights of fetuses and offspring of rats given 2000 mg/kg. gestation were decreased. Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rars given 40, 200, mg/kg during late gestation and lactation periods; no effects were observed in offspring of rats given 10 or 20 mg/kg.

There are no adequate and well-controlled studies in pregnant women. Rezulin should not be used during pregnancy unless the potential bene fies the potential risk to the felus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence genital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to n blood glucose levels as close to normal as possible.

#### Norsing Mothers

It is not known whether troglitazone is secreted in human milk. Troglitazone is secreted in the milk of lactating rats. Because many drugs are e in human milk, Rezulin should not be administered to a breast-feeding woman

#### Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

### Twenty-two percent of patients in clinical trials of Rezulin were 65 and over. No differences in effectiveness and safety were observed betwee

patients and younger patients.
ADVERSE REACTIONS

Two patients in the clinical studies developed reversible jaundice; one of these patients had a liver biopsy which was consistent with an idios; Two patients in the clinical studies developed reversible jaundice; one of these patients had a liver biopsy which was also consistent with an idiosyncratic drug reaction. Symptoms that are ass with hepatic dysfunction or hepatitis have been reported, including; nausea, vomiting, abdomand japin, fatigue, anorexia, dark urine, abnormal liv tion tests (including increased ALT, AST, LOH, alkaline phosphatase, bilirubin. Also sae WARNINGS.

The overall incidence and types of adverse reactions reported in placebo-controlled clinical trials for Resulin-treated patients and placebo patients are shown in Table 1. In patients treated with Resulin in glyburide-controlled studies (N-550) or uncontrolled studies (N-510), the safet of Rezulin appeared similar to that displayed in Table 1. The incidence of withdrawals during clinical trials was similar for patients treated with

#### **TABLE 1. North American Placeho-Controlled Clinical Studies:** Adverse Events Reported at a Frequency ≥ 5% of Rezulin-Treated Patients

#### O/ of Dodloom

W OI L STIERT							
	Placebo N = 492	Rezulin N = 1450		Placebo N = 492	Rezulin N = 1450		
Infection	22	18	Nausea	4	6		
Headache	11	11	Rhinitis	7	5		
Pain	14	10	Diarrhea	6	5		
Accidental Injury	6	8	Urinary Tract Infection	6	5		
Asthenia	5	6	Peripheral Edema	5	5		
Dizziness	5	6	Pheryngitis	4	5		
Rack Pain	Ä	6	• •				

Types of adverse events seen when Rezulin was used concomitantly with insulin (N=543) were similar to those during Rezulin monotherapy (I although hypoglycemia occurred on insulin combination therapy (see PRECAUTIONS).

Laboratory Absormalities

Hematologic: Small decreases in hemoglobin, hematocrit, and neutrophil counts (within the normal range) were more common in Rezulin-trea placebo-treated patients and may be related to increased plasma volume observed with Rezulin treatment. Hemoglobin decreases to below the range occurred in 5% of Rezulin-treated and 4% of placebo-treated nationts.

Lipids: Small changes in serum lipids have been observed (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects in Packag for full Prescribing Information).

Sortini Transamiaase Levals: During all clinical studies in North America, a total of 48 of 2510 (1.9%) Rezulin-treated patients and 3 of 475 (16.6% bo-treated patients had ALT levels greater than 3 times the upper limit of normal. During controlled clinical trials, 2.2% of Rezulin-treated patie reversible elevations in AST or ALT greater than 3 times the upper limit of normal, compared with 0.6% of patients receiving placebo. Hyperblinic 12.125 upper limit of normal) was found in 0.7% of Rezulin-treated patients compared with 1.7% of patients receiving placebo. In the popupatients treated with Rezulin, mean and median values for billimbin, AST, ALT, alkaline phosphatase, and 66T were decreased at the ficompared with baseline, while values for LDH were increased slightly (see WARNINGS).

#### Postintroduction Reports

Adverse events associated with Rezulin that have been reported since market introduction, that are not listed above, and for which causal rela to drug has not been established include the following: congestive heart failure, weight gain, edema, fever, abnormal lab tests including increa and creatinine, hyperglycemia, syncope, anemia, malaise. Rx only

@1997-'98, PDPL July 1998

Manufactured by: Parke Davis Pharmaceuticals, Ltd. Vega Baja, PR 00694 Distributed by: PARKE-DAVIS Div of Warner-Lambert Co Morris Plains N.I 07950 IISA

Marketed by: PARKE-DAVIS Div of Warner-Lambert Co and SANKYO PARKE DAVIS Parsippany, NJ 07054 USA



	Villa de la companya			
	STATE	NEWSPAPER	VISTA CIRCULATION	DISTRIBUTIO DAY
	ARIZONA 11,597	Arlzona Republic	11,597	Friday
1/12	CALIFORNIA	•Alahambra Post/Wave	72.607	C=tt.
	<b>397</b> ,713	•City Terrace Tribune/Wave	22,687 12,600	Saturday
		•East Los Angeles Tribune/Wave	30,334	Saturday
200		•El Sereno News Herald/Wave	5,250	Saturday
KYT FF X		The Fresno Bee	76,500	Saturday
20.74 <b>-</b> 41.70 C.		Hanford Sentinel		Saturday
		Highland Park News/Wave	13,958	Saturday
		•Huntington Park Press/Wave	12,850	Saturday
		•Lincoln Heights News Herald/Way	10,488	Saturday
		Los Angeles Daily News		Saturday
100		•Maywood Press/Wave	46,084	Tuesday
			12,116	Saturday
		Mt. Washington Star Review/Wave     Montager Bark Branner 1976		Saturday
		Monterey Park Progress/Wave     Postorville Baseville	15, <u>4</u> 88	Saturday
		Porterville Recorder	11,706	Monday
		San Francisco Direct	<b>30</b> ,000	
04.24 N. S.		•San Pedro News Pilot	12,283	Saturday
		•South Gate Press/Wave	6,227	Saturday
		Tulare Advance-Register	8,014	Monday
ADD THE		Ventura County Star	29,850	Saturday
		Visalia Times-Delta	21,928	Monday
		Watsonville Register-Pajaronian	9,890	Monday
	FLORIDA	Miami Herald-El Nuevo Herald	90,000	Cumday
	128,000	Tampa Tribune	38,000	Sunday Tuesday
	ILLINOIS 24,500	Chicago Direct	24,500	
,	•			
	NEW MEXICO	Albuquerque Tribune	28,364	Saturday
	52,497	Santa Fe New Mexican	24,133	Monday
15-5/00-34	NEW YORK**	El Diario/La Prensa	53,000	Sunday
	100,184	The Jersey Journal	25,684	Saturday
		El Nuevo Hudson	21,500	Saturday
	TEXAS	Austin American-Statesman	28,782	Saturday
	398,914	Brownsville Herald	18,639	Sunday
(A) (A)		Dallas Morning News	59,530	Sunday
		El Paso Times	54, <b>556</b>	
		El Paso Other/Direct	1,660	Tuesday
		Harlingen Valley Morning Star	25,5 <b>9</b> 0	Cundo
		Houston Direct	25,590 23,500	Sunday
WAY WELL		Laredo Times	23,500 24,055	Sunday
MEN W		San Antonio Express-News	1 <b>5</b> 0,466	Sunday
N. West and		San Antonio Other/Direct	2,000	Monday
		Waco Tribune Herald	10,136	Sunday
	WASHINGTON, D.C.	El Tiempo Latino	26,163	Friday
	26,163			•
- Anna pagina	• LA ADI Circulation 225,71	RCULATION 1,	139,568	9/1/98
	**NY ADI	•		