CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020720, S12, S14

MEDICAL REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: 3/16/99

/S/

JUN 10 1999

From: Saul Malozowski
Acting Medical Team Leader

Subject: NDA 20-720 Rezulin triple therapy

To: File

I second Dr. Misbin's recommendation for approval of the supplement on triple therapy as well as his position of requesting the sponsor to withdraw the monotherapy indication and the removal of the UGDP wording from the current label. This last step should be conducted for all oral diabetic agents in a coordinate manner with agreement from the Office Director, Dr. James Bilstad.

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NDA 20-720

Troglitazone – Efficacy Supplement

Submitted November 18, 1998

Reviewed by Robert I Misbin MD
March 12, 1999

Concur
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3/16/99

INTRODUCTION:

Troglitazone is currently approved for treatment of type 2 diabetes as monotherapy or in combination with insulin or sulfonylureas. This review deals with an efficacy supplement that contained a new study showing that troglitazone improves hyperglycemia in patients inadequately treated with sulfonylureas plus metformin, protocol 991-105. Other new data submitted regarding other aspects of troglitazone treatment are discussed. These include a comparison of troglitazone, monotherapy and the combination , protocol 991-075, a comparison of troglitazone and metformin monotherapy (Glaxo 3002), and a study of the effects of troglitazone on body composition, protocol 2019. There is no new safety information except as noted. I also give a brief chronology of the development of liver failure in patients on troglitazone with details of findings of transaminase elevations that occurred during the clinical trials. A discussion of the post-marketing cases of liver failure will be presented to the Endocrine and Metabolic Advisory Committee by Dr David Graham on March 26, 1999.

NEW TRIALS

Protocol 991-105

Troglitazone vs Placebo in patients inadequately controlled on a sulfonylureas plus metformin

This protocol was for patients with type 2 diabetes, over the age of 40, who had HbA1c value greater than 8.4% after being on the combination of maximal dose sulfonylurea (20 mg glyburide or equivalent) plus metformin (1.5 g per day or greater) for at least 8 weeks. The study was a double –blind comparison of placebo to 400 mg Troglitazone that lasted 24 weeks and had change in HbA1c as the primary efficacy variable. Patients had a mean age of 59 years, and men duration of diabetes of 11.3 years. Mean body/mass index was 30.1. There were 57% males and 87% white. There were no baseline inequalities for any of these characteristics. Baseline values of HbA1, glucose, insulin and C peptide are shown in table 1. Inclusion charactersitics state that patients should have HbA1c of 8.4% or above at screening. Based on a mean of 9.7% and standard deviation of 1.2 it appears that several patients with HbA1c lower than 8.4 were studied. The placebo and troglitazone groups have minimum HbA1c values at baseline of 7.3% and

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7.5% respectively. I consider this to be a minor protocol violation which does not prejudice the results.

TABLE 4. Patients Characteristics at Baseline—All Randomized
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Characteristic	Sulfonylurea/Metformin		
	Placebo N = 99	Troglitazone N = 101	Total N = 200
Waist-Hip Ratio			
Mean	0.97	0.97	0.97
SD	0.07	0.08	0.08
Median	0.97	0.97	0.97
Min, Max	0.8, 1.2	0.7, 1.2	0.7, 1.2
Hemoglobin A_{1c} (%)			
Mean	9.7	9.6	9.7
SD	1.2	1.2	1.2
Median	9.4	9.3	9.4
Min, Max	7.3, 13.7	7.5, 13.6	7.3, 13.7
Fasting Plasma Glucose (mmol/L)			
Mean	12.9	13.1	13.0
SD	2.9	3.3	3.1
Median	12.6	12.8	12.6
Min, Max	7.9, 20.5	4.2, 29.8	4.2, 29.8
Serum Total Insulin (pmol/L)			
Mean	82	90	86
SD	63	46	55
Median	64	76	71
Min, Max	16, 536	13, 251	13, 536
C-Peptide (nmol/L)			
Mean	1.1	1.1	1.1
SD	0.5	0.5	0.5
Median	1.0	1.0	1.0
Min, Max	0.13, 3.59	0.12, 2.32	0.12, 3.59

SD = standard deviation

99 patients were assigned to placebo, and 86 patients completed the study. 101 patients were assigned to troglitazone and 92 patients completed. There were 8 dropouts due to lack of efficacy among the placebo patients and 3 among the troglitazone patients. 2 placebo patients and 3 troglitazone patients dropped out due to an adverse event.

Efficacy –

Glycemia: As shown in table 2 and figure 1, troglitazone –treated patients had a mean reduction of HbA1c of 1.3% after 24 weeks compared to a rise of 0.1% in placebo-treated patients. This net treatment effect of 1.4% was highly significant (p<.001). There were also significantly more patients in the troglitazone arm who met the HA1c " targets" of 8% and 7% (table 3).

Table 2

TABLE 7. Change from Baseline in HbA_{1c} after 24 Weeks of Double-Blind Treatment

Parameter	Sulfonylurea/Metformin	
	Placebo	Troglitazone
HbA_{1c} (%)		
N	96	97
Baseline Mean (SD)	9.7 (1.2)	9.6 (1.2)
Adjusted[a] Mean Change from Baseline (SE)	0.1 (0.1)	-1.3 (0.1)
Adjusted[a] Mean Difference from Placebo (SE)		-1.4 (0.2)
95% Confidence Interval for Difference		(-1.7, -1.1)
P-value		<0.001

[a] Adjusted for center and baseline.

Figure 1

Fig 1

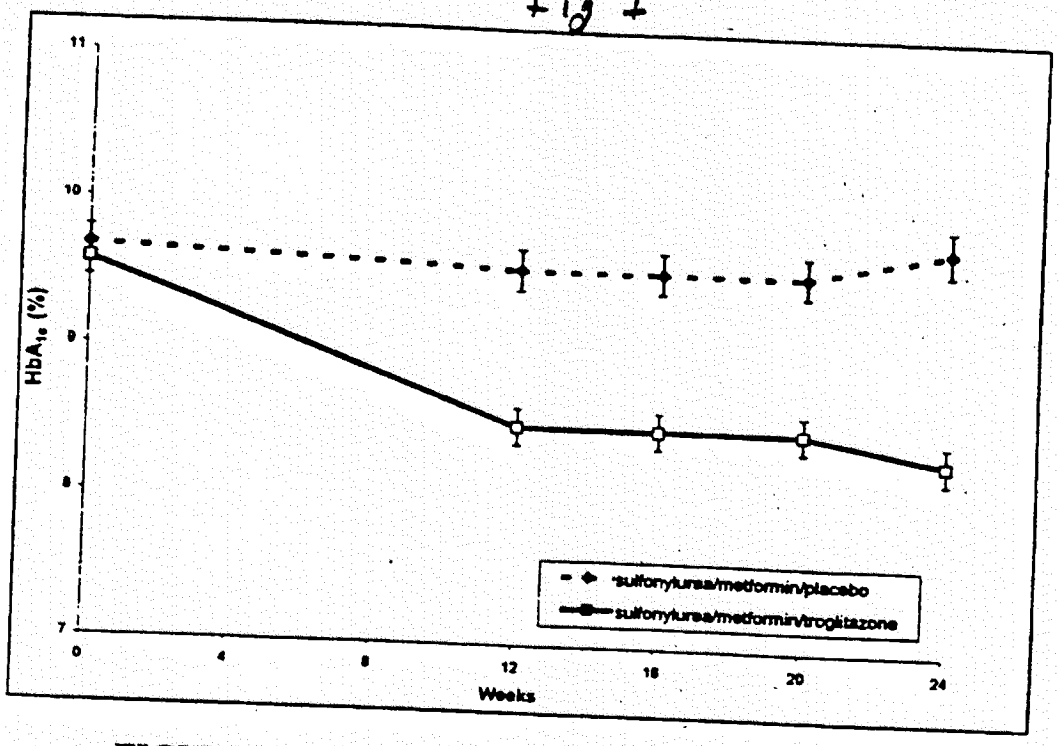

FIGURE 3: Mean (±SE) HbA_{1c} Over Time

Table 3

TABLE 9. Frequency Distribution of Patients with Target HbA_{1c} Levels ≤8% or ≤7% and FPG Levels ≤7.8 mmol/L or ≤7.0 mmol/L at Week 24 by Treatment Group

	Sulfonylurea/Metformin				
	Placebo		Troglitazone		P-value*
	%	n/N	%	n/N	
HbA_{1c} levels ≤8%	6	6/96	43	42/97	<0.001
HbA_{1c} levels ≤7%	1	1/96	14	14/97	<0.001
FPG levels ≤7.8 mmol/L	4	4/98	17	17/98	0.003
FPG levels ≤7.0 mmol/L	2	2/98	10	10/98	0.017

* Based on CMH test for general association.

As shown in table 4, mean fasting serum glucose rose from 12.9 mM to 13.2 mM the placebo group but fell from 12.9 to 10.5 mM in the troglitazone group. This was associated with a fall in fasting serum insulin from 91 to 76 pM in the troglitazone group compared to a rise from 78 to 83 pM in the placebo group (p<001). C peptide also fell slightly in troglitazone patients but the change was not statistically significant. (Note 100 pM insulin =16 uU/ml)

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.E 8. Change from Baseline in Secondary Glycemic Parameters after 24 Weeks of Double-Blind Treatment TABLE 4

Parameter	Sulfonylurea/Metformin	
	Placebo	Troglitazone
FPG (mmol/L)		
N	98	98
Baseline Mean (SD)	12.9 (2.9)	12.9 (2.8)
Adjusted[a] Mean Change from Baseline (SE)	0.3 (0.3)	-2.4 (0.3)
Adjusted[a] Mean Difference from Placebo (SE)		-2.7 (0.4)
95% Confidence Interval for Difference		(-3.4, -1.9)
P-value		<0.001
Serum Total Insulin (pmol/L)		
N	96	95
Baseline Mean (SD)*	78 (43)	91 (47)
Adjusted[a] Mean Change from Baseline (SE)	5 (4)	-15 (4)
Adjusted[a] Mean Difference from Placebo (SE)		-20 (5)
95% Confidence Interval for Difference		(-30, -10)
P-value		<0.001
C-Peptide (nmol/L)		
N	96	95
Baseline Mean (SD)	1.1 (0.4)	1.1 (0.5)
Adjusted[a] Mean Change from Baseline (SE)	-0.0 (0.0)	-0.1 (0.0)
Adjusted[a] Mean Difference from Placebo (SE)		-0.1 (0.1)
95% Confidence Interval for Difference		(-0.2, 0.0)
P-value		0.165

[a] Adjusted for center and baseline.

* 100 pmole/L = 16 μU/ml

Lipids and weight: There were small differences in serum lipids. As shown in Table 5 there was a fall in serum triglycerides in troglitazone – treated patients with rises in both LDL cholesterol and HDL cholesteroi. The total chol/HDL chol ratio was unchanged. Body weight fell 0.1 kg in placebo patients but rose 2.3 kg in troglitazone patients. The net change of 2.4 kg (from baseline of 85 kg) was highly significant (p<. 001). This was associated with a placebo- subtracted rise in body mass index of 0.9 kg/m2 (p<0.001). Mean waist circumference decreased 1.5 cm in placebo patients but increased 1.1 cm (p<0.001) in troglitazone patients. Waist/hip ratio fell slightly in placebo patients compared to troglitazone patients but the difference was not significant.

Table 5

TABLE 10. Change from Baseline in Lipid Parameters after 24 Weeks of Double-Blind Treatment

Parameter	Sulfonylurea/Metformin	
	Placebo	Troglitazone
Triglycerides (mmol/L)		
N	96	96
Baseline Mean (SD)	2.56 (1.41)	2.73 (1.74)
Adjusted[a] Mean Change from Baseline (SE)	0.46 (0.30) (41 mg/dl)	-0.29 (0.30) (25.7 mg/dl
Adjusted[a] Mean Difference from Placebo (SE)		-0.75 (0.42)
95% Confidence Interval for Difference		(-1.58, 0.07)
P-value		0.073
HDL Cholesterol (mmol/L)		
N	96	96
Baseline Mean (SD)	1.13 (0.29)	1.13 (0.28)
Adjusted[a] Mean Change from Baseline (SE)	0.03 (0.02) (1)	0.09 (0.02) (4 mg/dl)
Adjusted[a] Mean Difference from Placebo (SE)		0.06 (0.03)
95% Confidence Interval for Difference		(0.01, 0.11)
P-value		0.012
Total Cholesterol (mmol/L)		
N	96	96
Baseline Mean (SD)	5.30 (0.94)	5.40 (0.98)
Adjusted[a] Mean Change from Baseline (SE)	0.13 (0.12)	0.26 (0.12)
Adjusted[a] Mean Difference from Placebo (SE)		0.12 (0.17)
95% Confidence Interval for Difference		(-0.21, 0.46)
P-value		0.459
LDL Cholesterol (mmol/L)		
N	96	96
Baseline Mean (SD)	3.18 (0.75)	3.21 (0.83)
Adjusted[a] Mean Change from Baseline (SE)	0.03 (0.06) (1)	0.27 (0.05) (10 mg/dl)
Adjusted[a] Mean Difference from Placebo (SE)		0.24 (0.08)
95% Confidence Interval for Difference		(0.09, 0.39)
P-value		0.002
Total Cholesterol/HDL Cholesterol Ratio		
N	96	96
Baseline Mean (SD)	5.0 (1.5)	5.1 (1.5)
Adjusted[a] Mean Change from Baseline (SE)	0.2 (0.2)	0.0 (0.2)
Adjusted[a] Mean Difference from Placebo (SE)		-0.2 (0.3)
95% Confidence Interval for Difference		(-0.8, 0.5)
P-value		0.648

[a] Adjusted for center and baseline.

Comments about efficacy:

Results of this study demonstrate the efficacy of addition of troglitazone to patients whose glycemic control was inadequate despite treatment with the combination of glyburide plus metformin. In previous studies with "add-on" therapy, DEMDP has taken the position that the new drug should be added to a maximum dose of the previous drug. Using this approach, one can say rigorously that any improvement in glycemic control could not have been achieved simply be increasing the dose of the previous drug. Results of studies using this design have led to claims of 'synergy' in labeling. Thus, labels for both troglitazone and metformin have claims that each drug works synergistically with sulfonylureas.* This demonstration of synergy in clinical trials is consistent with the known mechanisms of action of these drugs. Sulfonylurea promotes insulin secretion, while troglitazone and metformin work through mechanisms other than increasing insulin secretion (further elaboration on mechanism of actions of metformin and troglitazone come in the following trial). But what about the addition of troglitazone to patients inadequately controlled on metformin plus a sulfonylurea?

Unlike sulfonylureas, metformin has non-glycemic related effects, which limit tolerability in many patients. Therefore, it is frequently not possible to increase the dose of metformin to the maximally labeled dose in order to try to achieve the theoretically maximal efficacy of metformin alone. Study 105 used patients who were on a maximal effective dose of glyburide (15 mg) but a sub-maximal dose of metformin. Although troglitazone improved glycemic control for the group as a whole, it is also important to determine whether this effect was seen, even in those patients who were on a near maximal dose of metformin. At the reviewer's request, the Sponsor has analyzed the efficacy data for patients on 2 g per day of metformin in comparison to patients who are less than 2 g per day.

(Although the 20 mg of glyburide is the maximal dose in the label, little additional efficacy is generally found when doses over 10 mg are used. Thus, I am accepting the dose 15 mg used in the present study to be a maximally effective dose. Similarly, athough the maximally labeled dose of metformin is 850 mg tid, 1000 mg bid appears to be the dose being promoted by the metformin Sponsor, thus to insist that patients be on the maximally labeled dose of 2.55 g/day would make a study impossible to do. In recognition of this problem, I advised Bayer prior to their trial of acarbose add-on to metformin, that it would be acceptable to study patients who were taking 2g per day of metformin or greater. Thus, to be consistent with all Sponsor's, I asked Parke Davis to analyze their data based on less than 2g/day of metformin or 2g/ day or greater.)

METFORMIN DOSE, grams/day

	Under 2.0 g/d		2.0 g/d or greater	
	Placebo	Troglitazone	Placebo	Troglitazone
N	47	35	47	60
Baseline, A1C	9.6	9.6	9.6	9.5
Change	0.3	-1.7	0	-1.1
Difference		-1.9		-1.1
Baseline, FSG	231	221	228	234
Change	6	-57	3	-38
Difference		-63		-41

Change means value at 24 weeks minus value at baseline
Difference means placebo subtraction
All patients were on 15 g glyburide

From the table shown above it can be seen that troglitazone improves hyperglycemia even in patients on a near-maximal dose (2g/d or greater) of metformin. However, the addition of troglitazone appears to have a greater effect in patients who are on a submaximal dose of metformin. This is shown in the table below, which includes statistical analysis to demonstrate that, the confidence intervals for patients on < 2g/day versus those on 2g per day or above do not overlap. The reduction of HbA1c of 1.1% in patients on near maximal dose of metformin is about 2/3 of the 1.9% reduction seen in patients on submaximal metformin.

Thus, broadly speaking, I tentatively conclude that about 2/3 of the reduction in HbA1c caused by troglitazone in patients on a submaximal dose of metformin was related to a troglitazone-specific mechanism and about 1/ 3 was due mechanisms that metformin and troglitazone appear to share. This conclusion is consistent with studies of a euglycemic clamp which showed that metformin increased glucose disposal to some extent, but less than troglitazone (see below, protocol 075)

	METFORMIN DOSE	
	< 2g per day	2 g per day or over
Change in A1c, % units (SE)	-1.7(0.2)	-1.1(0.1)
Difference (SE)	-1.9 (0.3)	-1.1(0.2)
95% confidence interval	(-2.5 , -1.4)	(-1.4, -0.7)

* I have always understood the term "synergy" to mean a positive interaction which is more than simply additive. Although the term is already used in labels for metformin and troglitazone, I do not believe the data would support use of this term in a strict sense. Since there is no hope of trying to change this terminology now, I shall use the term synergy the way I think it is now being used in current labels, a positive interaction between two classes of drugs with different mechanisms of action such that the effect of both used in combination is roughly the same as what would be predicted from the sum of their effects when used alone.

Safety: There was one death of a placebo-treated patient "due to atrial fibrillation". One troglitazone-treated patient was reported in the text to have had a transient rise in ALT to 144 U/l. (the ALT value in the data tabulation is 444) on day 86 but this returned to normal limits by day 107, and was attributed by the investigator to methotrexate which the patients received for rheumatioid arthritis on day 73. There were no other patients reported to have had ALT > 3 xULN. No patients were withdrawn because of a liver abnormality. 7/98 patients on troglitazone had a fall in hematocrit of over 5% compared to 3/98 patients on placebo. The greatest reduction among the placebo patients was 6.9% from 47.6 to 40.7 (normal > 42) taken as the lower limit of normal. There were three troglitazone patients with falls in hematocrit over 7%, including one with a reduction of 50 to 39.2 (normal > 42) and a second with a reduction from 35.6 to 29 (normal > 36). A table of mean changes for hematocrit and hemoglobin is shown below. No other safety issues were raised by the results of this study.

		PLACEBO	TROGLITAZONE
Hemoglobin	Baseline	14.39	14.40
	24 weeks	14.34	13.69
	Change	-0.05	-0.71
	SE	(0.06)	(0.08)
Hematocrit	Baseline	42.74	42.83
	24 weeks	42.17	40.43
	Change	-0.57	-2.40
	SE	(0.21)	(0.25)

Conclusion: This study shows that troglitazone is effective in treating hyperglycemia in patients inadequately treated on the combination of a sulfonylurea plus metoformin. No new safety issue emergend from this study. The major safety concern is liver toxicity (see later discussion about the risk of troglitazone hepatitis in sulfonylurea-treated patients) but these patients have no therapeutic alternative other than insulin, which is also associated with risk and inconvenience.

Protocol 075 (Manuscript published NEJM vol 338, 867 March 26, 1998) Individual data submitted December 15, 1998 in response to a request for information)

This is a 12-week comparison of troglitazone 400-mg monotherapy to metformin 2g monotherapy followed by a 12-week extension study in which patients receive both treatments combined. Patients were washed

out for two weeks from previous antidiabetic therapy. Patients were excluded if they had used metformin or troglitazone within two months before screening. Glucose clamps were done at the end of the three month periods to investigate mechanism of action. 15 patients were randomized to metformin and 14 to troglitazone. One of the troglitazone patients dropped out after 2 weeks because of FSG > 350 mg/dl. Two troglitazone patients who completed the monotherpy period did not go on to combined therapy.

The authors stated in their NEJM article that metformin and troglitazone were equally effective in lowering fasting plasma glucose levels (58 mg/dl for metformin and 54 mg/dl for troglitazone), but by different mechanisms. Metformin decreased endogenous glucose production while troglitazone increased glucose disposal. They also stated that "HbA1c levels did not change significantly during the first three months with either drug resulting in three month HbA1c levels essentially equal to that achieved by the subjects on their former therapy."

An examination of the individual patients' data, however, shows that the situation is more complex.

	Baseline	3 months	6 months
FPG: M to M+T	287	229	194
T to T+M	275	221	169
Hemoglobin A1c			
M to M+T	10.0	9.3	8.7
T to T +M	9.6	9.7	7.8

FPG – fasting plasma glucose, mg/dl
HbA1c in % units
M to M+T means that patients got metformin for three months followed by metformin +trogltiazone for 3 months. T to T+M means that patients got troglitazone for 3 months followed by T+M for 3 months

As monotherapy we see that the fall in FSG on metformin (58 mg/dl, 287 to 229) is about the same as that with troglitazone (54 mg/dl, 275 to 221). Not included in this table is data from one patient who dropped out of troglitazone monotherapy after two weeks because of lack of efficacy. An ITT analysis including this patient with LOCF might have shown that troglitazone was not as good as metformin even with respect to FSP. It should also be noted that metformin monotherapy resulted in a decline of HbA1c of 0.7% units compared to a rise of 0.1 with troglitazone. Admittedly, the short duration of the study is inadequate to show the full effect of a drug on HbA1c, particularly for troglitazone, which takes about 2 months to realize a full therapeutic effect even on FSG.

An alternative approach to examine efficacy is to determine a response rate using a fall in FPG of at least 30 mg/dl. Parke- Davis had previously used a fall of 30 mg/dl after six weeks in their initial NDA. Three months of monotherapy employed in this study should be adequate to determine a response.

There were 3/15 patients (20 %) on metformin who failed to show a drop in FPG of 30 mg/dl. By contrast, there were 7/13 patients (54%) on troglitazone who failed to drop their FPG of 30 mg/dl after 3 months. If on includes the additional patient on troglitazone who dropped out early, the non-responder rate would be 57% (8/14 patients) compared to 20% for metformin monotherapy ($p<0.05$ by chi square). One might also observe that the addition of troglitazone to metformin monotherapy does not seem to make as clear a difference in hyperglycemia as when metformin is added to troglitazone monotherapy. One possibly explanation is that the full effect of troglitazone monotherapy had not been achieved after the first 3 months, so that part of the improvement of hyperglycemia from combination therapy during the second three months was a carry-over effect of troglitazone montherapy . However, based on thess data, one cannot exclude the explanation that metformin is simply more effective than troglitazone either alone or in the combination.

The results of the glucose clamp data are as follows: