CENTER FOR DRUG EVALUATION AND RESEARCH

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MEDICAL REVIEW(S)

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REVIEW OF SECOND SAFETY UPDATE (submitted 19-Aug-1998)

NDA #	20-850	DRUG NAME:	Micardis™
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On 19-Aug-1998, the sponsor submitted a second safety update to this NDA being reviewed. The sequence of safety parameters that were reviewed for this second safety update report is kept in the same manner as that in my review of the NDA safety database and the first safety update report to provide easy reference and comparison.

1 Source Documents

The second safety update report covers the same clinical trials as in the NDA safety database and the first safety update report. It covers aspects of safety obtained from the 25 clinical trials of which 21 have been completed and 4 [redacted] are on-going. Safety information on 87 additional patients participating in on-going, blinded clinical trials [redacted] was reported. It also covers the 233 patients in the previously blinded study 502.224, which has now been unblinded and allocated to appropriate treatment groups for analysis.

2 Patient Characteristics and Demographics

For the second safety update, a total of 5,287 adult patients were enrolled in telmisartan clinical trials of hypertension, representing an increase of 846 (19%) patients from that reported in the NDA safety database and an increase of 87 (2%) patients from that reported in the first safety update report. (Table 2-i).

Table 2-i. Total number of patients enrolled in clinical trials of hypertension in the second safety update report compared to the NDA safety database and the first safety update report

	Telmisartan	*Comparator*	*Placebo*	*Blinded*	*Total†*
ISS total patients	3445§	1076	396	N/A	4441
1st Safety Update patients	3781§	1191	524	223	520
2nd Safety Update patients	3892§	1248	579	87	5287
Increase from NDA report to 2nd Safety Update (%)	447 (13.0)	172 (16.0)	183 (46.2)	87 (100)	846 (19.1)

† Categories are not mutually exclusive. Patients may have received placebo, a comparator or blinded medication and subsequently get telmisartan; therefore, the total is not the sum of the groups
§ includes initial randomized, *de novo* and open label extension trials

No changes in the demographics resulted from the additional 87 patients. Overall, 59.6% of the patients exposed to any dose of telmisartan were male and 83.7% were non-black. The mean age was 55.8 years (compared to 55.5 years in the NDA safety database). The baseline (mean ± SD) supine DBP and SBP were similar between the population in the NDA safety database (101.4±5.1 mmHg and 159.3±16.6 mmHg, respectively) and that in the second safety update report (101.4±5.2 mmHg and 159.3±16.5 mmHg, respectively).

The 87 additional patients in this second safety update report were randomized in two blinded telmisartan trials [redacted] and consisted of 76% male, and 98% non-black, with mean age of 58.7 years, baseline sitting SBP and DBP being, respectively, 155.4 and 90.2 mmHg with 75% of patients having baseline sitting DBP < 95 mmHg (because the entry criteria of study [redacted] required patients to have a DBP of < 95 mmHg). The mean duration of hypertension of patients in these trials is 7 years.

3 Extent of Exposure

3.1 Overall Duration of Telmisartan Exposure in Clinical Trials

For the first safety update, the exposure to telmisartan is increased by 3 months (from 5.7 to 8.7 months) compared to that in the NDA safety database. For this second safety update, the mean exposure is increased further to 10.9 months. This is due to an almost three-fold increase in exposure in the long-term follow up trials (from 7.7 months in the NDA safety database to 15.2 months in the first safety update report, and to 20.9 months in this second safety update report).

Thus, in the long-term follow up trials of telmisartan, 1,373 patients have been exposed to telmisartan for >6 months, 1,249 for > 1 year and 1,046 for >1.5 years.

3.2 Telmisartan Exposure According to Dose

3,892 patients were treated with telmisartan alone or as part of a treatment regimen (with HCTZ) and had a mean exposure time of 10.9 months. A total of 610 patients have been exposed to telmisartan 40 mg, and 843 patients to telmisartan 80 mg (as monotherapy or in combination with HCTZ) for over one year. The mean exposure to telmisartan 40 mg in 1,438 patients was 12.2 months, and to telmisartan 80 mg in 1,765 patients was 12.7 months.

4 Adverse Events

4.1 Overall Incidence of Adverse Events

Overall 2,608 (67%) of 3,892 patients in the second safety update database treated with telmisartan experienced at least one treatment-emergent adverse event, compared with 2,144 (62.2%) of 3,445 patients reported in the NDA safety database and 2,501 (66.1%) of 3,781 patients in the first safety update report. This increase in the incidence of adverse events was attributed to the second safety update database containing a greater number of patients in the long-term follow-up trials for which the mean duration of exposure to telmisartan has nearly tripled.

Also, the likelihood of a patient progressing from monotherapy to combination therapy (telmisartan + HCTZ) increases with increasing study duration; thus, compared with the incidence of adverse events previously reported in the NDA safety database, a 4.4% increase in the incidence of adverse events in patients treated with telmisartan monotherapy and a 11.3% increase in the incidence of adverse events in patients treated with telmisartan + HCTZ combination were reported in this second safety update.

The most frequently reported adverse events remained the same as those reported in the NDA safety database, and include: upper respiratory tract infections 13.6% (previously 10.7%), headache 12.6% (previously 11.8%), pain 12.1% (previously 7.6%), back pain 9.4% (previously 6.0%), dizziness 7.8% (previously 6.6%), bronchitis 6.6% (previously 4.1%), sinusitis 5.7% (previously 4.1%), fatigue 5.3% (previously 4.6%), diarrhea 5.2% (previously 4.4%), influenza-like symptoms 5.1% (previously 3.0%), coughing 4.7% (previously 3.2%), dyspepsia 3.8% (previously 2.7%), chest pain 3.3% (previously 2.5%), pharyngitis 3.2% (previously 3.1%), urinary tract infections 3.1% (previously 2.1%), myalgia 3.0% (previously 2.4%), abdominal pain 3.0% (previously 1.7%), nausea 2.6% (previously 2.2%), and rhinitis 2.4% (previously 1.7%), arthritis 2.4% (previously 1.6%), insomnia 2.0% (previously 1.3%) and arthralgia 2.0% (previously 1.2%). All other adverse events were reported in < 2% of patients.

Two patients classified under abnormal hepatic function are re-classified as follows:

Patient #3612. She was diagnosed with Wilson's syndrome by another physician. This diagnosis was not supported by clinical findings and the patient's liver function tests were within normal limits. She was found to have autoimmune vasculitis, and was treated with steroids, plaquenil and T3. The patient discontinued due to tinnitus and an abdominal mass.

Patient #4144. This patient was screened positive hepatitis B, and was thus discontinued. This patient was re-classified under "hepatitis" and not under abnormal hepatic function.

In on-going blinded trials[redacted] 21 (24.1%) patients were reported to have experienced an adverse event, with 4.6% having adverse events classified as cardiovascular events (compared to 4.7% in the NDA safety database). all of which were reported as hypertension.

4.2 **Adverse Events in Long-Term Uncontrolled Trials**

The duration of long-term observation and treatment in the second safety update report population is almost three times that in the NDA safety database, which may have contributed to an increase in the overall incidence rate of adverse events: 1,451 (84.6%) of 1,716 patients experienced at least one adverse event during the 4 long-term uncontrolled trials in the second safety update report compared to 938 (58.4%) patients as re-calculated by the sponsor from the NDA safety database using a different algorithm (there were 40 less patients - all from study[redacted]

In these long-term uncontrolled trials, too, the most frequently reported adverse events remained the same as those reported in the NDA safety database: pain 18.4% (previously 6.3%), upper respiratory infection 17.2% (previously 8.2%), back pain 15.4% (previously 6.5%), headache 13.6% (previously 9.2%), and bronchitis 11.9% (previously 5.1%).

5 **Serious Adverse Events**

5.1 **Overall Incidence of Serious Adverse Events**

For patients treated with telmisartan, the overall incidence of serious adverse events had increased from 2.9% (100 of 3,445) patients in the NDA safety database to 5.2% (196 of 3,781) patients in the first safety update, and to 6.2% (242 of 3,892 patients) in the second safety update. This increase in the incidence of serious adverse events is attributed to an increase in the incidence of serious adverse events in long-term uncontrolled trials resulting from a three-fold increase in exposure.

The most frequently reported serious adverse events were myocardial infarction 0.5% (previously 0.3 % in NDA safety database and in the first safety update report), pain 0.4% (previously 0.2% in the NDA safety database and 0.4% in the first safety update report), angina, chest pain and cerebrovascular disorder 0.3% each (previously 0.2% each in the NDA safety database as well as in the first safety update report).

The narratives of all patients who experienced serious adverse events are given in the sponsor's second safety update report - volume M32.2, page 450-629.

5.2 **Serious Adverse Events in Long-Term Uncontrolled Trials**

The overall incidence of serious adverse events during the long-term uncontrolled trials (2.4%) in the NDA safety database increased to 7.9% in the first safety update report, and to 10.3% in the second safety update report.

The incidences of serious adverse events associated with telmisartan monotherapy and telmisartan + HCTZ treatment groups increased by 3.8% and 3.5%, respectively in the first safety update report, and by 5.6% and 5.1%, respectively, in this second safety update report. This increase was attributed to the three-fold increase in the period of observation in these long-term follow-up trials.

The incidences of serious adverse events in the long term uncontrolled trials that have increased are: myocardial infarction 0.7% (from 0.6% in the first safety report, and 0.2% in the NDA safety database), neoplasm 1.4% (from 1.1% in the first safety update report and 0.3% in the NDA safety database), and vascular (extracardiac) disorder 1.1% (0.8% in the first safety update report and 0.2% in the NDA safety database). The neoplasm category is increased due to an increase in the number of different types of growths recorded (up to 16 from 5 in the NDA safety database).

The following serious adverse events occurred at a rate of ≥ 0.3%: myocardial infarction and pain 0.7%, cerebrovascular disorder 0.6%, and back pain,

hypertension, syncope, diverticulitis, arthrosis, angina pectoris and coronary artery disease 0.3% each.

6 Discontinuations Due to Adverse Events

6.1 Overall Incidence of Discontinuations

The overall incidence of discontinuations due to adverse events increased to 7.4% (288 of 3,892 patients with mean exposure 10.9 months) from 7.1% (270 of 3,781 patients with mean exposure 8.7 months) in the first safety update report, and from 5.5% (188 of 3,445 patients with mean exposure 5.7 months) in the NDA safety database. Among these discontinuations, 198 (5.5%) were receiving telmisartan monotherapy, and 82 (5.5%) were receiving telmisartan plus HCTZ, at the time of discontinuation.

As in the NDA safety database, the most common adverse events which lead to discontinuation were hypertension (0.7%), headache (0.5%), dizziness (0.5%), fatigue (0.4%) and myocardial infarction (0.4%).

The incidence of discontinuations in long term uncontrolled trials is higher in the second safety update report - 8.7% - for the total telmisartan group (compared to 4.0% in the NDA safety database). Fatigue and headache accounted for the largest proportion of discontinuations.

In the blinded trials, one patient experienced an adverse event (hypertension) resulting in discontinuation from the study for this second safety update report.

7 10-Day IND Safety Reports

Included in this section are all events associated with the telmisartan hypertension trials and congestive heart failure trials that have qualified as 10-day IND safety reports between 01-Dec-1997 and 01-Jun-1998 (Table 7): these comprise 3 initial reports and 2 follow-up reports from hypertension trials in which these patients received either telmisartan monotherapy or telmisartan plus hydrochlorothiazide at the time of the events.

TABLE 7. 10-Day IND Safety Reports[a] in Hypertension Studies and Congestive Heart Failure studies between 01-Dec-1997 and 01-Jun-1998.

Study Number	Patient Number	Date of Initial/Follow-up Submission	Study Drug and Dose at Onset (mg/day)	Adverse Event (Preferred Term)
502.219	6060	08-Dec-1997	Telmisartan 80 mg + HCTZ 12.5 mg	Syncope
502.219	3021	02-Feb-1996 08-Dec-1997	Telmisartan 40 mg	Hypertension and Headache
	6079	22-Apr-1998	Telmisartan 40 mg	Hepatic Neoplasm
	5629*	04-May-1998 13-May-1998	Telmisartan 40 mg	Myocardial Infarction Cardiac Failure

[a] Sorted by date of initial submission;
*Two IND reports (one initial and one safety report) for the same patient during this reporting period.

{Note: The above list does not include the following two IND safety reports:
A 75 year-old female in UK in a long-term open-label follow-up study (after participating in blinded trial 502.215) and receiving telmisartan 80 mg and HCTZ 12.5 mg since 1995 and on telmisartan since 13-Oct-1996 (and Diclofenac, unknown indication, dose and duration) who was hospitalized on 01-Jun-1998 with a suspected GI bleed following 9 days of diarrhea, nausea and vomiting. Colonoscopy revealed no abnormalities. She also had hyperkalemia. She was rehydrated, telmisartan, HCTZ and Diclofenac were stopped on 11-Jun-1998 and her blood pressure was controlled with lisinopril 10 mg qd. The IND report did not contain any information with regard to whether the patient had peptic ulcer disease, whether upper GI endoscopy was done, and what treatment (e.g., blood transfusion, histamine H-2 blockers, etc.) were given.

Pt # 5105 A 72-yr old WM entered a long-term open label follow-up telmisartan 40 mg qd since 04-Sep-1995 (for 33 months after completing a 26-week blinded study - trial 502.216 –

in which she received telmisartan) in Germany. She experienced an episode of orthostatic hypotension on 03-Jun-1998, and was hospitalized till 12-Jun-1998. There was no concomitant therapy. She was treated by bed rest (supine position) and required no drug treatment. Telmisartan was d/c on 02-Jun-1998 and re-introduced on 07-Jun-1998: her mean BP on 23-Jun-1998 was 130/82 mmHg.}

8 Deaths

The total number of deaths that had been reported in hypertension trials was 8 (3 reported in the NDA safety database and 5 more reported in the first safety update report). No new deaths were reported in this second safety update report.

There were also 8 deaths reported from congestive failure trials in the NDA safety database, but no new deaths from these congestive heart failure trials are reported in the first or second safety update reports.

In addition, 3 deaths were reported to have occurred during run-in, screening or post-study treatment period in the clinical hypertension trials in the NDA safety database.

{Note: Narratives of the above deaths are presented in the NDA safety review and the first safety update report review.}

9 Clinical Laboratory Analyses

Median changes in laboratory parameters from baseline to final available value on active (or placebo) study therapy and median changes over defined intervals in the course of the trials reported in NDA safety database were compared to median changes from baseline in laboratory parameters among cumulative telmisartan-treated second safety update population (excluding the long-term follow-up trials 502.219). The values remained unchanged, which the sponsor used as evidence to suggest that there is no treatment-by-time effect on the laboratory test parameters within the period of observation.

Table 9 shows the percentage of patients in the safety update treated with telmisartan in long-term uncontrolled trials whose laboratory values exceeded thresholds for the laboratory parameters from study entry to anytime during the trial. While the exposure had increased three-fold from the NDA safety database to the second safety update, there was no proportional increase in the percentage of patients above threshold for the laboratory parameters.

TABLE 9 Percentage of telmisartan-treated patients exceeding laboratory threshold levels in long-term follow-up trials in the second safety update and in hypertension trials from the NDA safety database.

			Long-term follow-up trials in the second safety update		Hypertension trials from NDA safety database	
Laboratory Test	Threshold	No. tested	% outside at baseline	% outside	% outside at baseline	% outside
Alkaline Phosphatase (U/l)	>200	1374	4.3	6.6	1.6	2.3
BUN (mg/dl)	>40	1375	0	0.4	0.2	0.6
Creatine P-Kinase (U/l)	>350	1300	3.3	5.3	4.2	5.4
Creatinine (mg/dl)	>2	1376	7.3	0.1	6.0	6.9
Hematocrit (%)	<30	1374	0.1	0.6	0.1	0.3
Hemoglobin (g/dl)	<10	1374	0.1	0.4	0.3	0.4
LDH (U/l)	>450	1366	1.2	1.2	1.0	1.4
Potassium (mEq/l)	<3	1373	0.1	0.7	0.4	0.6
SGOT (U/l)	>100	1375	0	0.4	0.1	0.3
SGPT (U/l)	>100	1374	0.1	1.2	0.3	0.7
Sodium (mEq/l)	<130	1375	0.2	0.6	0.1	1.2
Total Bilirubin (mg/dl)	>1.5	1374	1.6	2.8	1.5	1.7
Uric Acid (mg/dl)	>10	1373	0.6	2.1	0.6	3.0
Exposure (months)			18.1		5.7	

In Table 9, the percentage of patients with abnormalities in liver function tests rose slightly, and, for some unexplained reason, the percentage of patients with abnormal serum creatinine levels decreased.

While it was reported that all laboratory adverse events occurred with an incidence of < 1% in all telmisartan-treated patients in the NDA safety database (n = 3445), no new laboratory adverse events were reported in this second safety update report.

10 **Overall Summary and Conclusions**

Telmisartan has been evaluated for safety in 3,892 patients with mild to moderate hypertension with a mean exposure of 10.9 months at the time of the second safety update report. Patients in long-term follow-up trials had an exposure of 20.9 months (almost 3 times that (7.7 months) in the NDA safety database.

610 patients have been treated with 40 mg dose regimen for over 1 year and 843 patients have been treated with the 80 mg dose regimen for over 1 year. The mean exposure to telmisartan was 12.2 months in 1,438 patients on the 40 mg dose and 12.7 months in 1,765 patients on the 80 mg dose.

The incidence of adverse events was higher in the second safety update report compared to that for the NDA safety database, due largely to an increase in incidence of adverse events from the long-term uncontrolled trials, the exposure to telmisartan having tripled in the long-term uncontrolled trials in the second safety update report.

The most common adverse events also remained the same as in the NDA safety database with their incidences increased that are attributed to the increased incidences of adverse events in long-term uncontrolled trials.

The incidence of serious adverse events increased overall, again attributed to the three-fold increase in exposure to telmisartan in the long-term follow-up trials during the period of observation for the second safety update report. The most frequent serious adverse events were myocardial infarction, pain, angina, chest pain and cerebrovascular disorder.

The overall incidence of discontinuations due to adverse events also increased (from 5.5% in the NDA safety database to 7.1% in the first safety update report and to 7.4% in this second safety update report). The adverse events associated with discontinuations remained the same, namely, hypertension, headache, dizziness and fatigue.

No new deaths were reported in this second safety update report.

Cumulative laboratory data remained similar to that reported previously in the NDA safety database.

Thus, the overall safety profile of telmisartan (monotherapy or in combination with HCTZ) has remained relatively similar to that reported previously in the NDA safety database and the first safety update report despite an increased duration of exposure to telmisartan.

/S/

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	Overall trials			Long-term Uncontrolled trials		
	NDA Database	First Safety Update Report	Second Safety Update Report	NDA Database	First Safety Update Report	Second Safety Update Report
Adverse events per 100 patients (number/population x100/exposure)	2144 x100 / 3445 x 5.7 = 10.9	2501 x 100 / 3781 x 8.7 = 7.6	2608 x 100 / 3892 x 10.9 = 6.1	938 x 100 / 1606 x 7.7 = 7.6	1367 x 100 / 1716 x 15.2 = 5.7	1451 x 100 / 1716 x 20.9 = 4.0
Serious Adverse events per 100 patients (number/population x100/exposure)	100 x100 / 3445 x 5.7 = 0.51	196 x 100 / 3781 x 8.7 = 0.60	242 x 100 / 3892 x 10.9 = 0.57	2.4 /7.7 = 0.31	7.9 / 15.2 = 0.52	10.3 20.9 = 0.49
Discontinuations per 100 patients (number/population x100/exposure)	188 x100 / 3445 x 5.7 = 0.96	270 x 100 / 3781 x 8.7 = 0.82	288 x 100 / 3892 x 10.9 = 0.68	4.0 / 7.7 = 0.52	7.1 / 15.2 = 0.47	8.7 / 20.9 = 0.42

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AUG 10 1998

REVIEW OF SAFETY UPDATE

1 Source Documents

The safety update review covers the same clinical trials as in the NDA review plus new information from studies that were completed after the cutoff date for the original NDA submission, namely 502.219[ ],502.222, 502.223, 503.224, 502.228, 502.235 and 502.238. Thus, for this safety update report there are 5200 patients who have entered clinical trials of telmisartan (up from 4441 in the ISS), with 759 new patients (293 received telmisartan (plus 43 more who were later assigned to telmisartan), 223 are on blinded medication in study 502.224), 128 received placebo and 115 received a comparator drug).

The sequence of safety parameters reviewed for this safety update report is kept in the same manner as that in the NDA safety review to afford easy reference and comparison with the latter.

Table 1-i *Clinical Efficacy Trials*

Study #	Type	Total N=	Patients	Duration	Dose	Groups
Pivotal Clinical Trials						
502.202	db, r, pc, pg, in mmh	207	mmh	4 wk	T 40, 80, 120 mg, vs Placebo vs enalapril 20mg	5
502.203	db, r, pc, pg, in mmh	274	mmh	4 wk	T 20, 40, 80, 120, 160 mg vs Placebo	6
502.204	db, r, pc, pg, factorial	818	mmh	8 wk	T 20 - 160 mg ± HCTZ 6.25 - 25 mg vs Placebo	20
504.206	db, r, pc, pg	440	mmh	12 wk	T 40 - 160 mg vs Placebo vs enalapril 20 mg	6
502.207	db, r, pc, pg, dt	236	mmh	8 wk	T 40-120 mg vs Atenolol 50-100 mg vs Placebo	4
502.208	db, r, pc, pg, dt	232	mmh	12 wk	T 40- 120 mg vs Amlodipine 5-10 mg vs Placebo	3
Double-Blind, Active Drug-Controlled, Long-Term studies						
502.210	db, r, dd, pg, dt	278	elderly mmh	26 wk	T 20 - 80 mg vs Enalapril 5-20 mg	2
502.214	db, r, dd, pg	578	mmh	52-60 wk	T 40 - 160 mg vs Lisinopril 10 - 40 mg	2
502.215	db, r, dd, pg, dt	363	mmh	26 wk	T 40 - 80 mg + HCTZ 12.5 mg combination	4
502.216	db, r, dd, pg, dt	533	mmh	26 wk	T 40 - 120 mg vs Atenolol 50 - 100 mg	2
Double blind, Active Drug-Controlled, Special Population Studies						
502.209	db, r, pg	21	severe HTN	12 wk	T 80 - 160 mg vs Enalapril 10 - 20 mg	2
502.211	db, r, pg, dt	71	mod renal failure	12 wk	T 40 - 80 mg vs Enalapril 10 - 20 mg	2
502.213	db, r, pg	30	mmh (renal effect)	8 wk	T 80 mg vs T 80 mg + HCTZ 12.5 mg	2
502.238	db, r, pg	86	severe HTN	8 wk	T 80 - 160 mg vs Enalapril 20 - 40 mg	2
Uncontrolled, Long-Term Studies						
502.219	ol, fu, dt	596	mmh	> 52 wk	T 40 - 80 mg; T80 H125-25 mg; T+ H + other	3
502.220	ol, fu, dt	888	mmh	> 52 wk	T 40 - 80 - 160 mmHg, T+H; T+H+other	3
502.221	ol, fu, dt	100	mmh	> 52 wk	T 40-80 mg; T80mg+H12.5-25 mg, T+H+other	3
502.228	ol, fu, dt	132	mmh	> 52 wk	T 40-80-160 mg, T+H, T+H+other.	3
Clinical Trials in Patients with Congestive Heart Failure						
502.217	db, dd, r, pc, pg (og)	Blinded	NYHA II-III	single dose	T 10, 20, 40, 80 vs Placebo	5
502.218	db, dd, r, pc, pg (rs)	378	NYHA II-III	12 wk	T 10, 20, 40, 80 mg vs Enalapril 20 mg	5
Ongoing Clinical Trials						
502.222	db, r, pg (og)	119	mmh+ACEI cough	8 wk	T 80 mg vs Enalapril 20 mg vs HCTZ 25 mg	3
502.223	db, r, pg (rs)	92	mmh+ACEI cough	8 wk	T 80 mg vs Lisinopril 20 mg vs Placebo	3
502.224	db, r, pg (rs)	223	mmh	6 wk	T 40mg vs T 80mg vs Losartan 50mg vs Placebo	4
502.235	db, r, pg (rs)	287	mmh + fasting/food	4 wk	T 40 mg or T 80 mg, fasting / fed vs Placebo	5
	db, r, pg (og)	NA	mmh + DM + NP	60 wk	T 40 - 80 mg vs Enalapril 10 - 20 mg	2
	db, r, pg (og)	NA	mmh+LVH	12 wk	T 80 mg vs Losartan 25 mg vs Placebo	3
Clinical Pharmacology Trials						
502.201	PK	80	mmh	7 days	10, 20, 40, 60, 80, 100, 120, 160 mg oral solution vs Placebo vs Enalapril 20 mg	10
502.202	db, r, pc, pg	207	mmh	4 wk	T 40, 80, 120 mg, vs Placebo vs Enalapril 20mg	5
502.203	db, r, pc, pg	274	mmh	4 wk	T 20, 40, 80, 120, 160 mg vs Placebo	6

db = double blind; r = randomized; ol = open-label; pc = placebo-controlled; dd = double dummy; co = crossover; pg = parallel group; fu = follow up; dt = dose-titration; mmh = mild to moderate hypertension; og = ongoing; rs = completed, report submitted and reviewed; DM = diabetes mellitus; NP = nephropathy; LVH = left ventricular hypertrophy; H = hydrochlorothiazide; C = number of patients who had completed the study; T = Telmisartan; Bolded = contributing new information since the safety review of NDA

Thus, this review of safety covers aspects of safety obtained from the 21 clinical trials (19 unblinded, 2 blinded) in hypertensive patients, two trials in patients with congestive heart failure and 23 clinical pharmacology trials (Tables 1-i and 1-ii).

Table 1-ii. Clinical Pharmacology Trials

Study #	Type	N=	Duration	Dose	Groups
502.101	Single dose tolerance	4	single dose	1, 2.5, 5, 10, 20, 40, 80, 160 mg, vs Placebo	8
502.102	Relative bioavailability	12	single dose	20, 160 mg x 2 (oral solution, capsules)	4
502.103	PK-PD	18	single dose	20, 40, 80 mg vs Placebo	3
504.105	PK, IV tolerability	6	single dose	10, 20, 40 mg IV x 30 min vs Placebo	4
502.106	Absolute/Relative bioavailability	12	single dose	40 mg (IV, oral solution, tablet)	3
502.109	Relative bioavailability	12	single dose	20, 80, 80 mg (tablet, capsule)	3
502.110	Metabolic profiling (^{14}C-labeled)	10	single dose	40 mg (IV x 20 min or oral)	2
502.111	PK, IV tolerability	6	single dose	80, 120 mg IV infusion	2
502.112	Absolute/Relative bioavailability	12	single dose	160 mg (IV vs oral (80 + 80 mg) tablet)	3
502.113	Food interaction	12	single dose	40, 160 mg with or without high fat meal	2x2
502.114	HCTZ interaction	12	7 days	160 (80 + 80) mg ± HCTZ 25 mg	3
502.115	PK, oral tolerability	12	7 days	320 mg (80 mg x 4 tablets)	1
502.118	PK, Renal insufficiency	8	single dose	120 mg (80 + 40 mg)	1
502.119	Digoxin interaction	12	7 days	Digoxin 0.25 mg ± 120 (80 + 40) mg	2
502.120	Warfarin interaction	12	30 days	Warfarin ± 120 (80 + 40) mg	2
502.121	Acetaminophen interaction	12	single dose	Acetaminophen 1 G ± 120 (80 + 40) mg	2
502.122	Glibenclamide interaction	12	13 days	Glibenclamide 1.75 mg ± 120 (80 + 40) mg	2
502.123	PK, Hepatic insufficiency	12	single dose	20, 120 (60/120) in 30 min IV infusion	4
502.124	PK, Elderly	12	7 days	20, 120 (40 + 80) mg	2
502.125	Ibuprofen interaction	12	7 days	Ibuprofen 400 mg ± 120 (80 + 40) mg	2
502.126	Amlodipine interaction	12	9 days	Amlodipine 10 mg ± 120 (80 + 40) mg	2
502.127	Pivotal Bioequivalence Study	29	single dose	80 mg (Tab Clin vs Tab Prod)	2
502.128	Relative bioavailability	24	multiple doses	Oblong (120 mg) vs Round (40 + 80mg) tabs	2
502.201	PK in patients with hypertension	80	7 days	10, 20, 40, 60, 80, 100, 120, 160 mg oral solution vs Placebo vs Enalapril 20 mg	10
502.202	db, r, pc, pg, in patients with mmh	207	4 wk	T 40, 80, 120 mg, vs Placebo vs Enalapril 20mg	5
502.203	db, r, pc, pg, in patients with mmh	274	4 wk	T 20, 40, 80, 120, 160 mg vs Placebo	6

db = double blind; r = randomized; pc = placebo-controlled; pg = parallel group; mmh = mild to moderate hypertension

2 Patient Characteristics and Demographics

For the safety update, a total of 5,200 adult patients were enrolled in telmisartan clinical trials of hypertension, representing an increase of 759 (17.1%) patients (Table 2-I).

Table 2-i Total number of patients enrolled in clinical trials of hypertension in safety update report compared to original NDA submission

	Telmisartan	*Comparator*	*Placebo*	*Blinded*	*Total†*
ISS total patients	3445§	1076	396	N/A	4441
Safety Update patients	3781§	1191	524	223	520
Increase (%)	336 (9.8%)	115 (10.7%)	128 (32.2%)	223 (100%)	759 (17.1%)

† Categories are not mutually exclusive. Patients may have received placebo, a comparator or blinded medication and subsequently get telmisartan; therefore, the totalis not the sum of the groups
§ includes initial randomized, *de novo* and open label extension trials

The demographics in TABLE 2-ii show that in all treatment groups, approximately 60% of the patients were male. About 13.2% of the overall treatment population were black (compared to 10.4% black in the original NDA submission). About 60% of the patients were between 45 and 64 years of age, with a mean age of 55.3, 53.7 and 57.0 years in the telmisartan, placebo and comparator groups, respectively. The percentage of patients aged 75 years or higher ranged between 1.1% and 6.0% of the population across treatment groups. More than 35% of patients in each of the treatment groups of the overall study population had had hypertension for ten years or more. The baseline supine DBP and SBP were similar between the three treatment groups with the mean baseline DBP ranging between 100.8 mmHg and 101.5 mmHg and the mean baseline SBP ranging between 156.6 mmHg and 161.1 mmHg. Mean body mass index was similar for all groups ranging from 28.9 kg/m^2 to 29.7 kg/m^2.

TABLE 2-ii Demographics and Baseline Characteristics of All Patients Enrolled in Clinical Trials of Hypertension

	Telmisartan	Placebo	Comparator
	%	%	%
TOTAL TREATED	3262 (100%)	524 (100%)	1191 (100%)
GENDER			
Male	59.8	61.6	59.4
Female	40.2	38.4	40.6
RACE			
Black	13.8	13.2	7.9
Non-black	84.9	86.8	89.9
Not asked	1.4	0	2.2
AGE (years)			
2 34	3.0	2.3	1.8
35-44	14.3	15.3	13.6
45-54	29.9	35.9	26.4
55-64	30.8	31.7	29.3
65-74	17.8	13.7	23.0
≥ 75	4.1	1.1	6.0
Mean	55.3	53.7	57.0
S.D.	11.3	9.7	11.3
SUPINE DBP (mmHg)			
< 95	2.8	5.0	4.5
95 - < 100	39.9	41.6	42.1
100 - < 105	33.9	35.3	28.7
105 - < 110	14.0	12.0	13.6
110 - < 115	7.7	5.5	8.3
≥ 115	1.7	0.6	2.6
Mean	101.5	100.8	101.2
S.D.	5.3	5.0	6.0
SUPINE SBP (mmHg)			
< 140	8.5	4.8	7.1
140 - < 160	46.5	57.8	43.6
160 - < 180	33.7	30.0	33.5
180 - < 200	9.4	6.9	12.6
3 200	1.8	0.6	3.2
Mean	158.7	156.6	161.1
S.D.	16.4	14.1	17.7
HYPERTENSION DURATION (yrs)			
Missing	1.6	3.1	1.4
< 1	10.5	8.0	12.1
1 - < 4	23.8	20.8	20.3
4 - < 10	28.6	30.9	28.0
≥ 10	35.6	37.2	38.2
Mean	8.8	10.0	9.2
S.D.	8.5	9.3	8.4

The demographic makeup of patients in this safety update report has remained virtually identical to that reported in original NDA submission.

3 Extent of Exposure

3.1 Overall Duration of Telmisartan Exposure in Clinical Trials

For this safety update, the exposure to telmisartan is increased by 3 months (from 5.7 to 8.7 months) compared to that in the original NDA submission (TABLE 3.1), reflecting the on-going nature of the long term uncontrolled trials (501.219, [redacted]). In these long-term follow up trials, the exposure had increased from 7.7 months in the original NDA to 15.2 months in this safety update report.

In the long term follow-up trials, 1370 patients have been exposed to telmisartan for >6 months, 1088 patients have been exposed to telmisartan for >1 year, and 436 patients have been exposed to telmisartan for > 2 years. Overall, telmisartan had been evaluated in 1937 patients treated for over 6 months, and 1360 patients treated for over 1 year (TABLE 3.1).

TABLE 3.1 Overall Telmisartan Exposure in Clinical Trials of Hypertension

Duration of Therapy (Days)	*Patients Receiving Telmisartan Monotherapy*	*Patients Receiving Telmisartan/HCTZ Combination*	*All[a] Patients Receiving Telmisartan (%)*
1-14	414	47	150
15-31	573	95	482
32-61	520	370	568
62-91	581	144	391
92-182	387	264	253
183-335	345	311	383
336-365	146	45	194
365-547	490	176	877
≥548	317	21	483
Total	3500	1474	3781
Mean (days)	204.9	175.2	263.9
Mean (months)	6.7	5.8	8.7

Patients may have received both monotherapy and combination therapy, thus the sum does not equal all telmisartan treated

3.2 Telmisartan Exposure According to Dose

3781 patients were treated with telmisartan alone or as part of a treatment regimen (with HCTZ), and had a mean exposure time of 8.7 months (Table 3.2). A total of 554 patients have been exposed to telmisartan 40 mg, and 737 patients to telmisartan 80 mg (as monotherapy or in combination with HCTZ) for over one year. The mean exposure to telmisartan 40 mg was 9.9 months in 1401 patients, and for telmisartan 80 mg was 9.8 months in 1691 patients.

TABLE 3.2 Overall Telmisartan Exposure by Dose in Clinical Trials of Hypertension

	Telmisartan									
Duration	*10 mg*	*20 mg*	*40 mg*	*60 mg*	*80 mg*	*100 mg*	*120 mg*	*160 mg*	*Total*	
(Days)	n	n	n	n	n	n	n	n	n	%
1-14	6	19	54	6	26	6	13	20	150	4.0
15-31	0	30	117	0	174	0	65	36	482	12.7
32-61	0	42	154	0	243	0	9	120	568	15.0
62-91	0	2	101	0	118	0	65	105	391	10.3
92-182	0	1	77	0	133	0	21	21	253	6.7
183-335	0	2	157	0	200	0	6	18	383	10.1
336-365	0	0	127	0	60	0	0	7	194	5.1
365-547	0	0	324	0	484	0	0	69	877	23.2
≥548	0	0	230	0	253	0	0	0	483	12.8
Total	6	96	1401	6	1691	6	179	396	3781	100
Mean (days)	7.0	42.1	302.8	7.0	296.9	7.0	68.0	138.6	263.9	263.9
Mean (months)	0.2	1.4	9.9	0.2	9.8	0.2	2.2	4.6	8.7	8.7

4 Adverse Events

4.1 Overall Incidence of Adverse Events

Overall 2,501 (66.1%) of 3,781 patients in the updated safety database treated with telmisartan experienced at least one treatment emergent adverse event, compared with 2,144 (62.2%) of 3,445 patients reported in the NDA review. This increase in the incidence of AE was attributed to the proportionately greater number of patients in the long-term follow-up trials in the safety update database, the mean duration of observation for patients in this category having nearly doubled. Also, the likelihood of a patient progressing from monotherapy to combination therapy (telmisartan + HCTZ) increases with increasing study duration; thus, compared with that incidence of adverse events previously reported in the NDA submission, there was a 3.9% increase observed in the incidence of adverse events in patients treated with telmisartan monotherapy and a 7.6% increase in the incidence of adverse events in patients with telmisartan + HCTZ combination safety update database, (Table 4.1).

TABLE 4.1 Incidence (%)of telmisartan adverse events by treatment regimen (monotherapy versus combination with hydrochlorothiazide)

	Telmisartan Regimen					
	Telmisartan Monotherapy		Telmisartan + HCTZ		All	
	ISS	*SUR*	*ISS*	*SUR*	*ISS*	*SUR*
Total treated	3156	3500	1331	1474	3445	3781
Total with adverse event (%)	56.7	60.5	52.1	59.7	62.2	66.1
Autonomic Nervous System	**1.9**	**2.0**	**1.7**	**2.2**	**2.4**	**2.6**
Flushing	0.5	0.5	0.2	0.2	0.5	0.6
Hot flushes	0.3	0.3	0.4	0.4	0.4	0.4
Impotence	0.6	0.7	1.0	1.3	1.0	1.1
Sweating increased	0.5	0.5	0.2	0.3	0.6	0.6
Body as a Whole	**19.7**	**23.6**	**15.8**	**22.0**	**22.9**	**28.5**
Allergic reaction	0.3	0.3	0.2	0.5	0.3	0.5
Allergy, including aggravated	0.7	0.8	1.1	1.0	1.0	1.1
Asthenia	0.2	0.3	0.5	0.6	0.4	0.6
Back pain	5.1	6.7	3.8	5.4	6.0	8.1
Chest pain, including precordial	2.2	2.6	1.3	2.2	2.5	3.3
Fatigue	3.8	3.9	3.3	3.6	4.6	5.0
Fever	0.5	0.6	0.3	0.5	0.6	0.7
Influenza like symptoms	2.7	3.6	1.5	2.9	3.0	4.5
Leg pain	0.5	0.8	0.5	0.9	0.6	1.1
Malaise	0.4	0.5	0.2	0.3	0.4	0.5
Pain	6.5	8.8	5.3	7.9	7.6	10.7
Cardiovascular Disorders	**4.1**	**4.3**	**2.6**	**3.3**	**4.7**	**5.6**
ECG abnormal, including specific	0.3	0.4	0.4	0.7	0.4	0.7
Hypertension	0.8	0.7	0.4	0.5	0.9	1.0
Hypotension, including postural	0.3	0.3	0.9	0.9	0.6	0.7
Edema dependent	0.8	0.9	0.2	0.3	0.8	0.9
Edema legs	0.4	0.4	0.2	0.2	0.4	0.5
Edema peripheral	0.9	0.9	0.3	0.3	1.0	1.1
Central & Peripheral Nervous System	**18.3**	**19.9**	**14.2**	**16.2**	**20.8**	**23.0**
Dizziness	4.6	4.9	6.7	7.7	6.6	7.5
Headache	11.1	11.5	5.9	6.5	11.8	12.4
Hypoesthesia	0.4	0.4	0.1	0.1	0.4	0.4
Insomnia	1.0	1.5	0.9	1.0	1.3	1.8
Migraine, including aggravated	0.6	0.7	0.3	0.3	0.6	0.8
Muscle contractions involuntary	0.4	0.5	0.2	0.3	0.5	0.6
Paraesthesia	0.4	0.6	0.9	1.2	0.8	1.0
Somnolence	0.7	0.7	0.4	0.5	0.8	0.98
Vertigo	0.5	0.7	0.6	0.7	0.8	1.0
Gastrointestinal System	**12.8**	**15.1**	**11.0**	**14.0**	**15.1**	**18.4**
Abdominal pain	1.5	2.0	1.2	1.7	1.7	2.5
Constipation	0.6	0.7	0.8	0.7	0.9	1.0
Diarrhea	3.5	3.8	3.5	3.9	4.4	4.8
Dyspepsia	2.1	2.6	2.3	2.9	2.7	3.5
Enteritis	0.3	0.5	0	0.3	0.3	0.6
Flatulence	0.8	0.8	0.5	0.4	0.9	1.0
Gastritis	0.6	0.8	0.2	0.7	0.6	1.0
Gastrointestinal disorders NOS	0.7	1.1	0.6	1.0	0.8	1.5
Gastroenteritis	0.4	0.5	0.2	0.2	0.4	0.5
Gastroesophageal reflux	0.3	0.4	0.2	0.3	0.3	0.5
Hemorrhoids	0.4	0.6	0.2	0.5	0.5	0.7
Mouth dry	0.4	0.5	0.5	0.5	0.6	0.7
Nausea	1.7	1.8	1.7	1.9	2.2	2.4
Toothache	0.3	0.5	0.3	0.3	0.4	0.6
Vomiting	0.4	0.5	1.0	1.0	0.8	1.0
Hearing & Vestibular Disorders	**1.3**	**1.7**	**1.0**	**1.4**	**1.6**	**2.1**
Ear disorder, general	0.4	0.5	0.5	0.7	0.6	0.7
Earache	0.4	0.5	0.2	0.3	0.4	0.6
Tinnitus	0.5	0.5	0.2	0.3	0.5	0.6
Heart Rate & Rhythm Disorders	**2.2**	**3.0**	**2.5**	**3.2**	**2.9**	**4.0**
Fibrillation atrial	0.2	0.2	0.4	0.6	0.3	0.4
Palpitation	0.9	1.2	0.8	0.9	1.1	1.5
Tachycardia	0.5	0.5	0.4	0.5	0.6	0.7
Liver & Biliary System	**0.5**	**0.5**	**0.8**	**0.9**	**0.8**	**0.8**

TABLE 4.1 (continued). Incidence of telmisartan adverse events by treatment regimen (monotherapy vs combination with HCTZ)

	Telmisartan Regimen					
	Telmisartan Monotherapy		Telmisartan + HCTZ		All	
	ISS	*SUR*	*ISS*	*SUR*	*ISS*	*SUR*
Total treated	3156	3500	1331	1474	3445	3781
Total with adverse event (%)	56.7	60.5	52.1	59.7	62.2	66.1
Metabolic & Nutritional Disorders	**2.1**	**3.0**	**3.5**	**4.9**	**3.4**	**4.8**
Diabetes mellitus, incl. Aggravated	0.3	0.6	0.5	1.0	0.5	1.0
Gout	0.4	0.5	0.2	0.4	0.5	0.7
Hypercholesterolemia	0.3	0.6	0.1	0.3	0.3	0.7
Hyperuricemia	0.1	0.1	0.7	0.7	0.4	0.4
Hypokalemia	0.1	0.1	1.1	1.2	0.6	0.6
Musculoskeletal System	**6.7**	**8.4**	**5.5**	**8.2**	**8.0**	**10.6**
Arthralgia	1.0	1.3	0.8	1.4	1.2	1.7
Arthritis, including aggravated	1.4	1.9	0.8	1.2	1.5	2.1
Arthrosis	0.3	0.8	0.6	1.0	0.5	1.1
Bone disorder	0.2	0.3	0.3	0.4	0.3	0.5
Cramps legs	0.8	1.0	0.8	1.2	1.1	1.4
Myalgia	1.8	2.0	1.9	2.2	2.4	2.8
Tendon disorder	0.4	0.5	0	0.1	0.4	0.4
Myo-, Endo-, Pericardial & Valve Disorders	**1.0**	**1.6**	**0.6**	**0.9**	**1.2**	**1.9**
Angina pectoris	0.6	0.6	0.3	0.4	0.6	1.1
Neoplasm	**0.4**	**0.7**	**0.3**	**0.7**	**0.5**	**1.0**
Psychiatric Disorders	**3.5**	**4.0**	**2.5**	**3.3**	**4.0**	**5.0**
Anxiety	1.0	1.1	0.8	1.0	1.1	1.5
Depression	0.9	1.1	0.7	0.9	1.1	1.5
Libido decreased	0.2	0.2	0.4	0.4	0.3	0.4
Nervousness	0.7	0.9	0.5	0.6	0.8	1.1
Red Blood Cell Disorders	**0.3**	**0.5**	**0.3**	**0.7**	**0.4**	**0.7**
Reproductive Disorders, Female	**1.0**	**1.3**	**0.8**	**0.8**	**1.2**	**1.5**
Reproductive Disorders, Male	**0.6**	**1.1**	**0.2**	**0.3**	**0.6**	**1.2**
Prostatic disorder	0.3	0.7	0.2	0.2	0.4	0.7
Resistance Mechanism Disorders	**3.1**	**4.4**	**2.5**	**3.3**	**3.8**	**5.5**
Abscess	0.4	0.6	0.5	0.7	0.6	0.9
Herpes zoster	0.3	0.3	0.3	0.3	0.3	0.4
Infection	0.7	1.3	0.5	0.7	0.8	1.5
Infection fungal	0.5	0.7	0.2	0.3	0.6	0.8
Infection viral	0.3	0.3	0.3	0.4	0.4	0.4
Otitis media	0.3	0.6	0.3	0.3	0.4	0.7
Respiratory System	**18.9**	**22.7**	**15.9**	**20.1**	**22.0**	**26.7**
Asthma	0.3	0.4	0.2	0.3	0.3	0.4
Bronchitis	3.5	4.6	2.0	3.4	4.1	5.6
Coughing	2.6	3.3	2.0	2.7	3.2	4.2
Dyspnea	0.6	0.8	0.3	0.5	0.7	1.0
Epistaxis	0.5	0.7	0.7	0.7	0.7	0.9
Pharyngitis	1.7	2.3	1.7	2.3	2.1	3.0
Rhinitis	1.6	1.8	0.8	1.2	1.7	2.1
Sinusitis	3.3	4.0	3.3	4.1	4.1	5.1
URI	8.8	10.2	7.6	9.1	10.7	12.8
Skin & Appendages	**4.2**	**5.6**	**3.7**	**5.0**	**5.2**	**7.1**
Dermatitis	0.3	0.5	0.2	0.2	0.4	0.6
Eczema	0.7	0.9	0.5	0.5	0.8	1.0
Pruritus	0.5	0.6	0.6	0.7	0.7	0.9
Rash (Erythematous & maculopapular)	1.1	1.3	1.1	1.2	1.4	1.7
Skin disorder	0.5	0.8	0.3	0.9	0.6	1.1
Urinary System	**3.8**	**4.7**	**3.1**	**4.0**	**4.7**	**5.9**
Cystitis	0.5	0.6	0.5	0.5	0.6	0.8
Micturition frequency	0.6	0.7	0.2	0.3	0.7	0.7
UTI	1.7	2.2	1.4	1.6	2.1	2.5
Vascular (extracardiac) Disorders	**1.6**	**2.1**	**0.7**	**1.4**	**1.7**	**2.5**
Cerebrovascular disorder	0.3	0.4	0.2	0.3	0.3	0.5
Vision Disorders	**2.3**	**2.9**	**1.1**	**1.5**	**2.5**	**3.3**
Conjunctivitis	0.5	0.7	0.2	0.5	0.6	0.9
Vision abnormal	0.9	1.0	0.2	0.3	0.9	1.0
White Cell & Resistance Disorders	**0.3**	**0.3**	**0.4**	**0.5**	**0.4**	**0.5**

The most frequently reported adverse events remained the same as those reported in the NDA submission, with slight change in their order, and include: upper respiratory tract infections 12.8% (previously 10.7%), headache 12.4% (previously 11.8%), pain 10.7% (previously 7.6%), back pain 8.1% (previously 6.0%), dizziness 7.5% (previously 6.6%), bronchitis 5.6% (previously 4.1%), sinusitis 5.1% (previously 4.1%), fatigue 5.0% (previously 4.6%), diarrhea 4.8% (previously 4.4%), influenza-like symptoms 4.5% (previously 3.0%), coughing 4.2% (previously 3.2%), dyspepsia 3.5% (previously 2.7%), chest pain 3.2% (previously 2.5%), pharyngitis 3.0% (previously .1%), myalgia 2.8% (previously 2.4%), urinary tract infections 2.5% (previously 2.1%), abdominal pain 2.5% (previously 1.7%), nausea 2.4% (previously 2.2%), and rhinitis 2.1% (previously 1.7%). All other adverse events were reported in < 2% of patients.

4.2 Adverse Events in Long-Term Uncontrolled Trials

The duration of long-term observation and treatment in the safety update report population is double that of the safety report in the NDA submission which may have contributed to an increase in the overall AE incidence rate (1367 (79.7%) of 1716 patients having experienced at least one adverse event during the 4 long-term uncontrolled trials in the safety update report compared to 938 (58.4%) patients as re-calculated by the sponsor from the NDA submission using a different algorithm (there were 40 less patients - all from study

Here, also, the most frequently reported adverse events remained the same as those reported in the NDA submission: upper respiratory infection 14.9% (previously 8.2%), pain 14.3% (previously 6.3%), headache 12.4% (previously 9.2%), back pain 12.0% (previously 6.5%0 and bronchitis 9.3% (previously 5.1%).

The incidence of adverse events long term uncontrolled trials does not differ from that of the long-term (one year) controlled trial (study 502.214): 79.7% for all telmisartan treated patients in the four long-term uncontrolled trials in safety report compared to 80.5% and 83.0%, respectively, for patients treated with telmisartan and lisinopril in active drug controlled long-term trial 502.214. On the other hand, the mean exposure was greater in patients treated with telmisartan (386 days) from the long term uncontrolled trials in the safety update report compared to patients treated with telmisartan (276 days exposure) or lisinopril (270 days exposure) in long-term controlled trial 502.214.

5 Serious Adverse Events

5.1 Overall Incidence of Serious Adverse Events

For patients treated with telmisartan, the overall incidence of serious adverse events had increased from 2.9% (100 of 3,445) patients in the original NDA submission to 5.2% (196 of 3781) patients in the safety update (Table 5.1), attributable largely to serious adverse events in long-term uncontrolled trials as explained above in adverse events.

Two serious adverse events were reported in the blinded treatment group from study 502.224: one was an episode of angina and the other was a hospitalization for eye surgery due to a tearing left eye.

The most frequently reported serious adverse events were pain and myocardial infarction 0.4% each (previously 0.2% for pain and 0.3% for MI), angina 0.3% (previously 0.2%), chest pain 0.2% (previously 0.2%) and prostate disorder 0.2% (previously 01.%).

TABLE 5.1 Incidence (%)of serious adverse events by treatment regimen (monotherapy versus combination with hydrochlorothiazide)

	Telmisartan Regimen					
	Telmisartan Monotherapy		Telmisartan + HCTZ		All	
	ISS	*SUR*	*ISS*	*SUR*	*ISS*	*SUR*
Total treated	3156	3500	1331	1474	3445	3781
Total with adverse event (%)	2.2	4.0	2.2	3.8	2.9	5.2
Mean exposure (months)	4.6	6.7	3.8	5.8	5.7	8.7
Body as a Whole	**0.4**	**0.9**	**0.2**	**0.5**	**0.5**	**1.0**
Back pain	<0.05	0.1	0.1	0.1	0.1	0.1
Chest pain, including precordial	0.2	0.2	0.1	0.1	0.2	0.2
Fever	<0.05	<0.05	0	0	<0.05	<0.05
Pain	0.2	0.4	0	0.1	0.2	0.4
Cardiovascular Disorders	**0.1**	**0.1**	**0.1**	**0.2**	**0.1**	**0.2**
Hypertension	0.1	0	0.1	0.1	0.1	0.1
Central & Peripheral Nervous System	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**	**0.2**
Headache	<0.05	0	0.1	0.1	0.1	0.1
Migraine	<0.05	<0.05	0	0	<0.05	<0.05
Vertigo	<0.05	0	0	0	<0.05	<0.05
Gastrointestinal System	**0.2**	**0.4**	**0.1**	**0.3**	**0.2**	**0.5**
Abdominal pain	<0.05	0.1	0	0	<0.05	0.1
Constipation	<0.05	<0.05	0	0	<0.05	<0.05
Diverticulitis	0.1	0.1	0	0	0.1	0.1
Gastric Ulcer, Hemorrhage	<0.05	<0.05	0	0	<0.05	<0.05
Gastroenteritis	0	0	0.1	0.1	<0.05	<0.05
Hearing & Vestibular Disorders	**<0.05**	**<0.05**	**0.1**	**0.1**	**0.1**	**0.1**
Deafness	<0.05	<0.05	0.1	0.1	0.1	0.1
Heart Rate & Rhythm Disorders	**0.1**	**0.1**	**0.2**	**0.3**	**0.2**	**0.2**
Bundle Branch Block	<0.05	<0.05	0	0	<0.05	<0.05
Cardiac arrest	<0.05	<0.05	0	0	<0.05	<0.05
Atrial fibrillation	0.1	0.1	0.2	0.2	0.1	0.1
Palpitation	0	0	0.1	0.1	<0.05	<0.05
Liver & Biliary System	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**
Cholecystitis	0.1	0.1	0.1	0.1	0.1	0.1
Metabolic & Nutritional Disorders	**0**	**<0.05**	**0.2**	**0.1**	**0.1**	**0.1**
Dehydration	0	0	0.2	0.1	0.1	0.1
Musculoskeletal System	**0.2**	**0.2**	**0.2**	**0.2**	**0.2**	**0.3**
Arthritis	<0.05	<0.05	0	0	<0.05	<0.05
Arthritis, aggravated	<0.05	<0.05	0.2	0.1	0.1	0.1
Arthrosis	<0.05	0.1	0.1	0.1	0.1	0.1
Bone disorder	<0.05	<0.05	0	0	<0.05	<0.05
Tendon disorder	<0.05	<0.05	0	0	<0.05	<0.05
Myo-, Endo-, Pericardial & Valve Disorders	**0.4**	**0.6**	**0.5**	**0.7**	**0.6**	**0.9**
Angina pectoris	0.1	0.2	0.2	0.3	0.2	0.3
Coronary Artery Disorder	0.1	0.1	0	0	0.1	0.1
Myocardial Infarction	0.2	0.3	0.3	0.4	0.3	0.4
Myocardial ischemia	<0.05	<0.05	0	0	<0.05	<0.05
Pericarditis	<0.05	<0.05	0	0	<0.05	<0.05
Neoplasm	**0.3**	**0.5**	**0.2**	**0.5**	**0.3**	**0.7**
Adenocarcinoma NOS	<0.05	<0.05	0	0	<0.05	<0.05
Basal Cell Carcinoma	0.1	0.1	0	0	0.1	0.1
Bone Metastases	<0.05	<0.05	0	0	<0.05	<0.05
Breast Neoplasm Malignant female	0	0.1	0.1	0.1	<0.05	0.1
Colon carcinoma	0.1	0.1	0	0.1	0.1	0.1
Endometrial Neoplasm malignant	<0.05	<0.05	0	0	<0.05	<0.05
Hepatic Neoplasm	<0.05	<0.05	0	0	<0.05	<0.05
Melanoma, malignant	0	0	0.1	0.1	<0.05	0.1
Neoplasm, malignant	<0.05	<0.05	0.1	0.1	0.1	0.1
Pancreas Neoplasm malignant	<0.05	<0.05	0	0	<0.05	<0.05
Psychiatric Disorders	**0.1**	**0.2**	**0**	**0.1**	**0.1**	**0.2**
Depression	<0.05	0.1	0	0	<0.05	0.1
Drug Dependence	<0.05	<0.05	0	0	<0.05	<0.05
Psychosis	<0.05	<0.05	0	0	<0.05	<0.05
Suicide attempt	<0.05	0.1	0	0	<0.05	0.1

TABLE 5.1 (continued). Incidence of serious adverse events by treatment regimen (monotherapy vs combination with HCTZ)

	Telmisartan Regimen					
	Telmisartan Monotherapy		Telmisartan + HCTZ		All	
	LSS	*SUR*	*LSS*	*SUR*	*LSS*	*SUR*
Total treated	3156	3500	1331	1474	3445	3781
Total with adverse event (%)	56.7	60.5	52.1	59.7	62.2	66.1
Red Blood Cell Disorders	<0.05	0.1	0	0	<0.05	0.1
Anemia	<0.05	<0.05	0	0	<0.05	<0.05
Reproductive Disorders, Female	0.1	0.2	0.1	0.1	0.1	0.2
Endometritis	<0.05	<0.05	0	0	<0.05	<0.05
Menorrhagia	<0.05	<0.05	0	0	<0.05	<0.05
Ovarian Cyst	0	0.1	0.1	0.1	<0.05	0.1
Reproductive Disorders, Male	0.1	0.1	0.1	0.1	0.1	0.2
Prostatic disorder	0.1	0.1	0.1	0.1	0.1	0.2
Resistance Mechanism Disorders	<0.05	<0.05	0.1	0.1	0.1	0.1
Cellulitis	<0.05	<0.05	0	0	<0.05	<0.05
Sepsis	0	0	0.1	0.1	<0.05	<0.05
Respiratory System	0.1	0.2	0.1	0.3	0.1	0.3
Asthma	<0.05	0.1	0	0	<0.05	0.1
Epistaxis	<0.05	<0.05	0.1	0.1	0.1	0.1
Pulmonary edema	<0.05	<0.05	0	0	<0.05	<0.05
Urinary System	0.1	0.1	0.1	0.2	0.1	0.2
Urethral disorder	<0.05	<0.05	0	0.1	<0.05	0.1
Urinary Tract Infection	0	0	0.1	0.1	<0.05	<0.05
Urinary Tract Malformation	<0.05	<0.05	0	0	<0.05	<0.05
Vascular (extracardiac) Disorders	0.2	0.4	0.1	0.2	0.2	0.4
Cerebral Hemorrhage	<0.05	<0.05	0	0	<0.05	<0.05
Cerebrovascular disorder	0.2	0.3	0.1	0.2	0.2	0.3
Thrombophlebitis, deep	<0.05	<0.05	0	0	<0.05	<0.05
Vision Disorders	0.1	0.1	0	0	0.1	0.1
Glaucoma	<0.05	<0.05	0	0	<0.05	<0.05
Strabismus	<0.05	<0.05	0	0	<0.05	<0.05

5.2 Serious Adverse Events in Long-Term Uncontrolled Trials

The overall incidence of serious adverse events during the long-term uncontrolled trials (2.4%) in the NDA submission increased to 7.9% in the safety update, the incidences associated with telmisartan monotherapy and telmisartan + HCTZ treatment groups having increased by 3.8% and 3.5%, respectively. This increase was attributed to the doubling of the period of observation in these long-term follow-up trials.

Newly occurring serious adverse events among this patient population in the long term uncontrolled trials not previously reported in the NDA review included syncope (0.3%), abdominal pain, prostate disorder and pneumonia (0.2% each).

Serious adverse event incidences in the long term uncontrolled trials that have increased in incidence are: myocardial infarction (up to 0.6% from the previous incidence of 0.2%), neoplasm (up to 1.1% from 0.3%), and vascular (extracardiac) disorder (up to 0.8% from 0.2%). The neoplasm category is increased due to an increase in the number of different types of growths recorded (up to 10 from 3 in the NDA review).

6 Discontinuations Due to Adverse Events

6.1 Overall Incidence of Discontinuations

The overall incidence of discontinuations due to adverse events increased to 7.1% (mean exposure 8.7 months) from that previously reported in the NDA submission (5.5%, mean exposure 5.7 months) (Table 6.1). Among these discontinuations, 180 (5.1%) were receiving telmisartan monotherapy, and 78 (5.3%) were receiving telmisartan plus HCTZ, at the time of discontinuation.

TABLE 6.1 Overall Incidence of Telmisartan Adverse Events Leading to Discontinuation by Treatment Regimen (Monotherapy versus Combination with Hydrochlorothiazide)

	Telmisartan Regimen					
	Mono-therapy		Telmisartan /HCTZ		Total Telmisartan†	
	Any relationship					
	n	%	n	%	n	%
Total treated	3500		1474		3781	
Total with any AE leading to discontinuation	180	5.1	78	5.3	270	7.1
Autonomic Nervous System	11	0.3	3	0.2	14	0.4
Impotence	8	0.2	3	0.2	11	0.3
Body as a Whole - General	31	0.9	12	0.8	45	1.2
Fatigue	12	0.3	2	0.1	16	0.4
Chest pain	7	0.2	4	0.3	11	0.3
Cardiovascular Disorders	34	1.0	10	0.7	52	1.4
Hypertension	20	0.6	2	0.1	28	0.7
Central & Peripheral Nervous System	39	1.1	12	0.8	55	1.5
Dizziness	9	0.3	8	0.5	18	0.5
Headache	19	0.5	1	0.1	21	0.6
Myo, Endo, Pericardial & Valve Disorders	19	0.5	9	0.6	29	0.8
Angina Pectoris	7	0.2	3	0.2	10	0.3
Myocardial Infarction	7	0.2	6	0.4	14	0.4
Respiratory System Disorders	11	0.3	4	0.3	15	0.4
Cough	7	0.2	3	0.2	10	0.3

† Patients receiving telmisartan in combination with other antihypertensives are shown in the total column only: so T mono plus T/H does not equal T total.

The largest percentage increase in the incidence of discontinuations was found in the "central/peripheral nervous system" and "body as a whole" categories, and within these categories, fatigue and headache accounted for the largest percentages.

As in the NDA report, the most common adverse events which lead to discontinuation were hypertension, headache and dizziness.

The majority of patients who discontinued due to cough were patients participating in the cough studies (502.222 and 502.223) in which the population comprised of ACEI coughers.

There were 2 reported cases of syncope that resulted in discontinuation.

Four patients were discontinued for adverse events in ongoing study 502.224, which is still blinded.

The incidence of discontinuations in long term uncontrolled trials is higher in the safety update report than that in the NDA submission, particularly so for the telmisartan + HCTZ group for which the withdrawals had increased from 2.0% in the NDA submission to 5.3% in the safety report.

7 10-Day IND Safety Reports

Included in this section are all events associated with the telmisartan hypertension trials and congestive heart failure trials that have qualified as 10-day IND safety reports after the previous cutoff date of 30-Apr-1997 for the NDA submission.

Thus, in Table 7, all events associated with the telmisartan clinical program that have qualified as 10-day IND safety reports between 01-May-1997 and 01-Dec-1997 are shown: these comprise 5 follow-up reports from hypertension trials and 4-follow-up reports from the two congestive heart failure trials.

TABLE 7. 10-Day IND Safety Reports[a] in Hypertension Studies and Congestive Heart Failure studies between 01-May-1997 and 01-Dec-1997.

Study Number	Patient Number	Date of Initial /Follow-up Submission	Study Drug and Dose at Onset (mg/day)	Adverse Event (Preferred Term)
Hypertension Studies				
502.215	3189	06-May-1996 02-Jul-1997	Telmisartan 80 mg + HCTZ 12.5 mg	Epistaxis
502.210	4178	18-Aug-1996 09-Jun-1997	Enalapril 15 mg	Vertigo, chest pain
502.210	4239	12-Jul-1996 09-Sep-1996 10-Jun-1997	Telmisartan 20 mg	Glaucoma
502.210	4315	28-Nov-1996 02-Jul-1997	Enalapril 5 mg	Atrial fibrillation
502.219	6069	06-Oct-1997	Telmisartan 80 mg	Hypertension
Congestive Heart Failure Studies				
502.218	1021	18-Jun-1996 09-Jun-1997	Telmisartan 80 mg	Cardiac failure
502.218	1106	11-Nov-1995 02-Jul-1997	Telmisartan 80 mg	Ataxia, dizziness dyspepsia
502.218	1142	24-Jul-1995 23-Jun-1997	Telmisartan 20 mg	Cardiac failure, ventricular tachycardia, myocardial infarction
502.218	1145	24-Jul-1995 20-Jun-1997	Telmisartan 80 mg	Myocardial infarction Angina pectoris, cardiac failure, circulatory failure

[a] Sorted by date of initial submission

8 Deaths

Three patients out of 3,445 (0.1%) had fatal adverse events while receiving telmisartan treatment in clinical hypertension trials, as reported in the NDA submission. Since then, 5 additional patients died (all were receiving telmisartan) while participating in telmisartan clinical trials, bringing the total number of deaths to 8 (0.2%). Three of these five death were cardiovascular related, 1 death was from cancer and the last was a sudden death (Table 8). Also, there were 8 deaths reported from congestive heart failure trials in the NDA submission, but no new deaths from congestive heart failure trials are reported in the safety update report.

TABLE 8 Fatal Adverse Events in Clinical Hypertension Trials

Patient No. (Trial No.)	Age[a]/Race/ Gender	Study Drug/ Dose	Adverse Event Preferred Term	Treatment-Duration at Onset (days)
3023	48/W/M	Telmisartan 80 mg/HCTZ25 mg + other	Death	396
3235[b] (502.215)	54/W/M	Telmisartan 40mg	Pulmonary carcinoma	139
3536 (502.216)	70/W/M	Telmisartan 40mg	Angina pectoris	551
4157 (502.204/219)	61/W/M	Telmisartan 80mg	Myocardial infarction	297
4178 (502.210)	75/W/F	Telmisartan 80mg	Cerebral thrombosis	228

[a] Age at time of entry. Narratives indicate age at time of event.

[b] Because the patient had been lost to follow-up, the exact length of time on treatment and the date of last dose of study medication prior to the patient's death were unknown, but it was estimated that he had received at least 4 months of treatment with study drug.

Patient 3023 (Trial [illegible]) This 50 year-old white male patient with history of hyperlipidemia and hyperuricemia since 1983, and obesity, arthrosis, gonarthrosis and marked depressive psychosis since 1984, began open-label telmisartan 40 mg on 31-Oct-1995. He died suddenly on 29-Nov-1996 from a "suspected myocardial infarction". No autopsy was performed. He had been seen at the doctor's office one day before (28-Nov-1996) and had felt well then. At the time of death, he was taking 80 mg telmisartan + 25 mg HCTZ + 4 mg doxazosin for 205 days, and had received telmisartan for a total of 395 days.

Patient 3235 (Trial [redacted]) This 56 year-old white male began open-label telmisartan 40 mg on 16-Apr-1996 after having completed a blinded telmisartan trial (502.215) in which he had received telmisartan and HCTZ since 10-Oct-1995. He was last seen at study clinic on 27-Aug-1996 when no adverse symptoms were reported. He did not return for visits, and was considered lost to follow-up and discontinued from the study in January 1997. In March 1997, the investigator reported being informed that the patient had been diagnosed with lung cancer with metastases in September 1996, and had died on 19-Feb-1997. The exact length of time the patient was on treatment was not known; the sponsor estimated that the patient had received at least 4 months of treatment with the study drug.

Patient 3536 (Trial [redacted]) This 72 year-old white male with history of CAD since 1979, CABG in 1979, prostatism and TURP in 1989, began open-label telmisartan 40 mg on 30-Nov-1995 after completing a double-blind telmisartan study (502.216) in which telmisartan had been administered since 20-Jun-1995. He died of ventricular arrhythmias on 05-Jun-1997 after 1.5 years of open-label treatment with telmisartan. Concomitant medications included Acenocoumarol prn po, dipyridamole 300 mg po, both since 1979 for CAD.

Patient 4157 (Trial 502.219): This 62 year-old white male with significant obesity since 1990 and a 6-year history of hypertension, began open label treatment with telmisartan 40 mg on 21-Feb-1996. No concomitant medications were reported. On 13-Dec-1996, after 144 days on treatment, he was reported to have suffered sudden death from myocardial infarction.

Patient 4178 (Trial [redacted]) This 75 year-old white female with history of diabetes mellitus since 1992, and urinary incontinence, tremor and abdominal pain for one year, began open-label telmisartan 40 mg on 22-Apr-1996 after completing a double-blind study (502.210) during which she received enalapril since 25-Oct-1995. The patient had a stroke on 06-Dec-1996 (presenting with decreased consciousness, right hemiparesis, dysphasia and vomiting), and died on 07-Dec-1996 after 228 total days of treatment with telmisartan, of which she was on telmisartan 80 mg for 202 days. Concomitant therapies included Cetiprin 200 mg po since 01-Jul-1996, Inderal 30 mg po since 11-Oct-1996, and Minorin 200 mg.

9 Clinical Laboratory Analyses

Median changes in laboratory parameters from baseline to final available value on active (or placebo) study therapy and median changes over defined intervals over the course of the trials reported in NDA submission were compared to median changes from baseline in laboratory parameters among telmisartan-treated patients without the long-term follow-up trials 502.219[redacted] The values remained unchanged, which the sponsor used as evidence to suggest that there is no treatment-by-time effect on the laboratory test parameters within the period of observation.

Table 9 shows the percentage of patients in the safety update treated with telmisartan in long-term uncontrolled trials whose laboratory values exceeded thresholds for the laboratory parameters which showed changes of ±2% or more from study entry to anytime during the trial.

TABLE 9 Threshold Analyses Compared to Median Baseline Laboratory Parameters

	Tel (Mono) %		Tel + HCTZ %		Tel (Total) %	
	On entry	During trial	On entry	During trial	On entry	During trial
Alk. phosphatase (> ± 200 U/L)	4.5	6.7	2.5	3.1	3.9	5.9
(n)	(1131)		(481)		(1497)	
Creatinine (> ± 2 mg/dL)	7.1	0	4.4	0.2	6.7	0.1
(n)	(1133)		(482)		(1499)	
Uric acid (> ± 2.7 mg/dL)	0.5	1.1	0.4	3.1	0.5	1.9
(n)	(1132)		(480)		(1496)	

There was an increase in the percentage of patients treated with telmisartan who exceeded the threshold levels in nearly all laboratory parameters tested during the trial compared to study entry, of which alkaline phosphatase, creatinine and uric

acid showed the largest on-treatment changes (Table 9). On the other hand, there was a decrease in the percentage of patients outside the threshold for creatinine in patients treated with telmisartan monotherapy during the trial compared to study entry (i.e., from 7.1% to 0%)

While it was reported that all laboratory adverse events occurred an incidence of less than 1% in all telmisartan-treated patients (n = 3445) in the NDA safety review, no new laboratory adverse events were reported in this safety update report.

10 **Overall Summary and Conclusions**

Telmisartan has been evaluated for safety in 3,781 patients with mild to moderate hypertension including 1,937 patients treated for over 6 months, and 1,360 patients treated for over 1 year. 554 patients have been treated with 40 mg dose for over 1 year and 737 patients have been treated with the 80 mg dose regimen for over 1 year.

The mean exposure to telmisartan was 9.9 months in 1401 patients on the 40 mg dose and 9.8 months in 1691 patients on the 80 mg dose.

The overall incidence or pattern of adverse events were similar between patients in *long-term* uncontrolled trials and patients in the uncontrolled trials.

The incidence of adverse events was higher in the safety update report compared to that for the original NDA submission, due largely to an increase in incidence of adverse events from the long-term uncontrolled trials, the exposure to telmisartan having more than doubled in the long-term uncontrolled trials in the safety update report.

The most common adverse events remained the same as in the original NDA submission with their incidences increased attributed to increased incidences of adverse events in long-term uncontrolled trials.

The incidence of serious adverse events increased overall, again attributed to increased exposure from the doubling of the period of observation in the long-term follow-up trials. The most frequent serious adverse events were pain, myocardial infarction, angina, chest pain and prostate disorder.

The overall incidence of discontinuations due to adverse events also increased (from 5.5% in the original NDA submission to 7.1%); the adverse events associated with discontinuations remained the same, namely, hypertension, headache, dizziness and fatigue.

Cumulative laboratory data remained similar to that reported previously for the NDA submission.

Thus, the overall safety profile of telmisartan (monotherapy or in combination with HCTZ) has remained similar to that reported previously for the NDA submission, with adverse experiences reported being mild and transient in nature, and comparable to control group, and having required discontinuation only infrequently.

/S/

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