

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20905

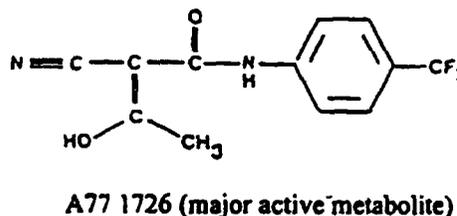
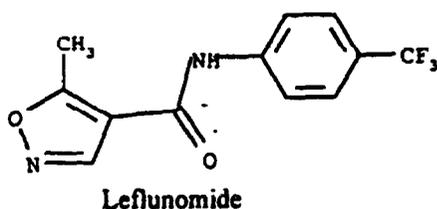
**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology/Biopharmaceutics Review

NDA:	20-905 (ORIG)	SUBMISSION DATE:	3/11/98, 4/20/98 4/24/98, 5/15/98, 5/28/98, 6/3/98 6/15/98, 6/23/98, 6/24/98
PRODUCT:	ARAVA™ Leflunomide Tablets		
SPONSOR:	Hoechst Marion Roussel Kansas City, MO 64137	REVIEWER:	Veneeta Tandon, Ph.D.

I. Background

Leflunomide is a pyrimidine synthesis inhibitor with antiproliferative effects intended for use in the treatment of rheumatoid arthritis (RA). Chemically, leflunomide is an isoxazole derivative with the chemical name N-(4'-trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide. The compound was originally developed as an anti-inflammatory agent, but due to significant immunomodulatory activity, development of the compound was directed towards the treatment of autoimmune diseases.



Following oral administration leflunomide is rapidly metabolized to A77 1726, which is presumed to be the active drug product. The active compound A77 1726, is the ring open metabolite of leflunomide with a chemical name 3-cyano-3-hydroxy-N-(4-trifluoromethylphenyl)-crotonamide.

Dosage and Administration: It is recommended that therapy be initiated with a 300 mg loading dose administered as a single 100 mg dose per day for 3 days, followed by daily maintenance dose of 20 mg. In the event of tolerability issues, the dose may be decreased to 10 mg daily.

II. Recommendation

From a biopharmaceutics standpoint of view the sponsor has adequately described the pharmacokinetics of ARAVA, based upon the plasma concentrations of the major active metabolite (A77 1726) of leflunomide in healthy subjects and patients with RA. The parent drug leflunomide was occasionally seen at very low levels. The sponsor at the

very end stages of the review requested that the use of 5 x 20 mg tablets be allowed as an alternative to the 1 x 100 mg as the loading regimen for leflunomide. This will not be an approvability issue for this application and will be addressed separately. Considering the size of the review, the labeling for leflunomide will also be dealt separately. Currently, the application is approvable from the pharmacokinetics standpoint, contingent upon addressing the issues regarding polymorphs and dissolution specifications (see comments 1 and 2 on page 52).

INDEX

I.	Background.....	1
II.	Recommendation.....	1
III.	Formulation.....	3
IV.	Review Overview.....	4
	Metabolism-Mechanistic Studies	
	(A) <u>In Vivo Studies</u>	
	Radiolabeled Study in Man (GB101).....	4
	Urinary Metabolites using F-NMR (1022).....	9
	Study with I.V. A77 1726 (1024).....	10
	(B) <u>In Vitro Studies</u>	14
	Absorption	
	(A) Bioavailability (Relative BA) (D110).....	15
	(B) Effect of Food on Bioavailability (GB103).....	16
	Multiple Dose Pharmacokinetics	
	(A) In Healthy Subjects (D111).....	18
	(B) In Patients with Rheumatoid Arthritis	
	6-month Study (YU204).....	20
	18-month Study (YU205).....	22
	Dose-pulsing Study (YU206).....	23
	Dose Proportionality.....	25
	Enhancement of Elimination	
	(A) Effect of Charcoal (GB102).....	26
	(B) Effect of Cholestyramine (GB 104).....	27
	Special Population	
	In Dialysis Patients (B101 NI).....	28
	Protein Binding.....	31
	Drug Interactions	
	(A) In Vitro Interactions.....	33
	(B) In Vivo Interactions.....	34
	With Oral Contraceptive (ZA101).....	34
	With Methotrexate (2F01).....	36
	With Cimetidine (1032).....	38
	With Rifampin (1033).....	39
	Bioequivalence.....	41
	10 mg used in clinical trial vs. 10 mg to-be marketed (1036)	41
	2x10 mg used in clinical trial vs. 20 mg	

	to-be marketed (1030).....	43
	10 mg tablets with two crystalline forms of drug (1035)....	44
	Population Pharmacokinetics	
	(A)Phase I/II Analysis.....	46
	(B)Phase III Analysis.....	47
	In Vitro Dissolution.....	49
V.	Overall Conclusions.....	51
VI.	Comments.....	52

III. Formulation

The formulation for the 10 mg, 20 mg and 100 mg tablets is shown in the table below. 10 and 20 mg are proportionally similar, except for the change in the active ingredient, other ingredients remaining the same.

Ingredient
Leflunomide
Lactose Monohydrate
Starch NF
Povidone USP
Talc USP
Colloidal Silicon Dioxide NF
Magnesium Stearate NF
Crospovidone NF
Hydroxypropyl Methylcellulose USP
Polyethylene Glycol NF
Titanium Dioxide USP
Ferric Oxide NF
Talc USP

IV. Review Overview

The sponsor has submitted 22 studies along with numerous pilot in-vitro studies. Out of these, 19 studies have been reviewed in full length and important conclusive observations from the other studies have been documented in this review. The organization of the studies is given in the Index on page 2, which will facilitate the reader to get an overview of the different studies submitted in support of the clinical pharmacology and biopharmaceutics of leflunomide. The conclusions and comments have been provided at the end of each section. The overall conclusions from the "Pharmacokinetics section" of the NDA are provided at the end of this review.

Following oral administration, leflunomide is rapidly converted to the active metabolite, A77 1726. Parent leflunomide is occasionally seen at very low levels. The outstanding characteristic of the pharmacokinetics of A77 1726 is its long half life (~15 days). Oral administration of activated charcoal or cholestyramine is effective in enhancing the elimination of A77 1726 in case of overdose or increased incidence of adverse events, decreasing the half-life to ~ 24 hours. The details of the pharmacokinetics of A77 1726 are discussed in the following sections.

METABOLISM-MECHANISTIC STUDIES

(A) In Vivo Studies

Animal studies have suggested that the metabolism of leflunomide takes place during passage through both the gut wall and the liver, although the site of first-pass metabolism has not been confirmed in man. A couple of in vivo metabolism mechanistic studies have been performed by the applicant to characterize the metabolic pathway in man and are discussed below.

Study # GB 101: Pharmacokinetics and metabolism of Leflunomide in healthy male volunteers following oral administration of ¹⁴C-labelled compound.

The pharmacokinetics and metabolism of Leflunomide after oral administration of ¹⁴C-labeled drug (for position of label, see Appendix, page A3) has been examined in three healthy volunteers in this study. The study design is sketched on page A2 of the Appendix along with analytical validation data on page A3. The metabolic fate of approximately 35% of the dose (21.7% in urine and 14.4% in feces) was established within 72 hours post dosing of 100 mg leflunomide. The observations from this study are summarized below.

Plasma metabolites

A77 1726 was the single plasma metabolite observed.

- *Total radioactivity in plasma:*

The total radioactivity and plasma A77 1726 concentrations were superimposable and pharmacokinetic parameters were about the same (see Tables below).

Table :Pharmacokinetic parameters of total radioactivity in plasma following 100 mg ¹⁴C-leflunomide containing 1.85 MBq radioactivity

Subject	C _{max} (µg.equiv/g)	T _{max} (hours)	AUC _{0-24h} (µg.equiv.h/g)	AUC _{0-∞} (µg.equiv.h/g)	T _{1/2} (days)
1	9.11	6	2432.5	2549.6	7.64
2	6.48	5	1642.4	1735.4	8.11
3	6.81	24	1861.5	1920.1	7.39
Mean	7.47	11.67	1978.8	2068.4	7.71
SD	1.43	10.69	407.9	426.9	0.37
% CV	19.2	91.7	20.6	20.6	4.7

- *A77 1726 in plasma*

Table : Pharmacokinetic parameters of A77 1726 in plasma following 100 mg ¹⁴C-leflunomide containing 1.85 MBq radioactivity

Subject	C _{max} (µg.equiv/g)	T _{max} (hours)	AUC _{0-24h} (µg.equiv.h/g)	AUC _{0-∞} (µg.equiv.h/g)	T _{1/2} (days)
1	9.23	8	2589.2	2723.3	8.03
2	6.73	6	1722.9	1820.5	8.06
3	6.82	24	1958.4	2015.5	7.18
Mean	7.59	12.67	2090.1	2186.5	7.76
SD	1.42	8.87	448	475	0.50
% CV	18.7	77.9	21.4	21.7	6.4

- *Leflunomide in plasma, urine and feces:*

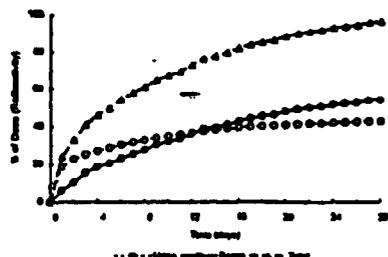
Leflunomide plasma concentrations measured up to 24 hours post-dose were below the quantitation limit (25 ng/ml), supporting extensive metabolism of leflunomide.

Reviewer's Comment:

In this study the LOQ is 25 ng/ml (assay Nov 1991) as compared to 5 ng/ml (assay Apr 1996) in the latter studies. The applicant has also not made any attempt to prevent the post sampling decomposition of leflunomide in samples by acidification of the collected plasma samples. A 30% loss of leflunomide in plasma samples was demonstrated in the assay validation at physiological pH. In the latter studies the sponsor has taken measures to prevent this loss by acidification of the collected plasma samples with hydrochloric acid (see assay validation on page A5 of the Appendix). In other studies, plasma levels of leflunomide have been observed (<25 ng/ml).

Urinary metabolites

- *Radioactivity in urine/feces:*



In the three subjects urinary excretion of radioactivity ranged from 30.8 to 58% of the dose and excretion of radioactivity in the feces ranged from 31.2 to 63.5% of the dose. The mean recovery (% of dose \pm sd) in urine, feces and total was 42.8 ± 13.9 , 48.2 ± 16.2 and 91 ± 2.9 respectively. The mean cumulative excretion of total radioactivity is shown the figure.

Fig: Mean cumulated excretion of total radioactivity

- *Identification of metabolites:*

U1 and U2 were two components detected in the urine. Deconjugation studies (incubation with β -glucuronidase) with U1 gave components U1A, U1B and U1C. Component U1A accounted for most of the radioactivity. Spectrum of U1A was consistent with X91 0228 (methyl-hydroxy A77 1726). Re-chromatography of U1A gave components U1A and U1C. Peak U1C was consistent with an isomer of X91 0228. It was postulated by the applicant that U1 was a glucuronide conjugate of methyl-hydroxy A77 1726 which after deconjugation isomerized from one isomeric form of X91 0228 to another. For easy visualization, the complete breakdown of various components detected in the urine has been shown schematically.

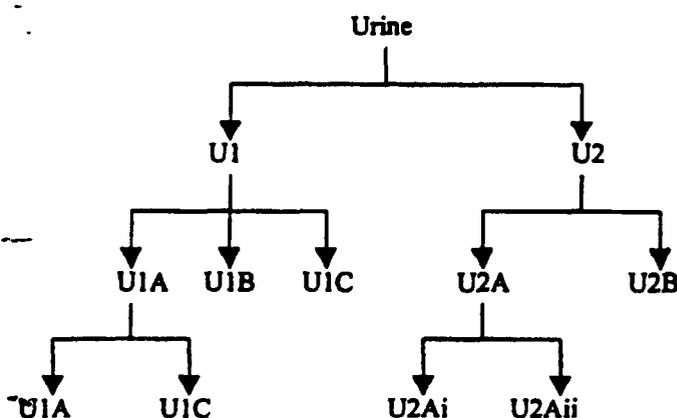


Figure: Schematic showing the components detected in the spectrum, where U1A, U1C, U2A, U2Ai and U2Aii were consistent with the spectrum of isomers of methyl-hydroxy A77 1726 and U2B was a peak consistent with TFMA-N-oxanilic acid.

Re-chromatography of U2 gave U2A and U2B. Deconjugation studies with U2A gave U2Ai and U2Aii. The spectrums of these two were consistent with that of X91 0228.

Therefore, it was postulated that U2A is also a glucuronide conjugate of methyl-hydroxy A77 1726, which after deconjugation to X91 0228, existed in two isomeric forms. Deconjugation studies with U2B gave component consistent with trifluoromethylaniline-N-oxanilic acid (TFMA-N-oxanilic acid). U3 was another component that was not identified.

In general in the urine samples TFMA-oxanilic metabolite (U2B) accounted for a mean of 9.7% of the dose. Hydroxylation of the methyl group and subsequent glucuronidation produced two isomeric forms (U1 and U2A) which accounted for a mean of 12% of the dose.

Percent of the dose excreted as these metabolites are tabulated below. After 72 hours there was insufficient radioactivity to allow further profiling.

Table : Percentage of dose corresponding to each urinary metabolite

Subject	Sampling time	% Dose Excreted	U1 (glucuronide conjugate of X91 0228)	U2A (glucuronide conjugate of X91 0228)	U2B (TFMA-N-oxanilic acid)	U3 (not identified)
1	0-24	18.10	8.31	3.31	5.30	1.19
	24-48	3.54	ND/NC	0.393	1.41	0.59
	48-72	1.63	ND/NC	ND/NC	1.30	0.326
	Total	23.27	8.31	3.7	8.01	2.11
2	0-24	21.30	8.75	4.24	7.09	1.21
	24-48	5.42	0.179	0.488	3.36	0.547
	48-72	4.20	ND/NC	0.508	3.69	ND/NC
	Total	30.92	8.93	5.24	14.14	1.76
3	0-24	15.9	5.44	3.05	3.75	1.40
	24-48	4.67	0.243	0.789	1.62	0.658
	48-72	1.77	ND/NC	0.273	1.50	ND/NC
	Total	22.34	5.68	4.11	6.87	2.06

ND/NC not detected/not calculated

Fecal metabolites

The mean recovery (% of dose \pm SD) of the radioactivity in the feces was 48.2 ± 16.2 , ranging from 31.2 to 63.5%. F1, F2 and F3 were three main fecal metabolites observed. Spectrum of F1 was consistent to A77 1726, F2 was consistent to methyl-hydroxy A77 1726 and F3 was identified as a reduced form of leflunomide. F1 accounted for 63-74% of the radioactivity in the 0-24 hour collection, corresponding to 4.7 to 6.3% of the total radioactive dose. F3 accounted for < 1% of the dose. The absence of parent leflunomide in the feces and the prolonged fecal excretion of radioactivity suggest extensive biliary elimination. The % of the dose excreted as these metabolites in the feces is given in the table below.

Table: Percentage of dose corresponding to each fecal metabolite

Subject	Sampling time	% Dose Excreted	F1 (A77 1726)	F2 (methyl-hydroxy A77 1726)	F3 (reduced leflunomide)
1	0-24	6.30	4.65	0.712	0.939
	24-48	1.74	1.32	0.155	0.266
	48-72				
	Total	8.04	5.97	0.867	1.21
2	0-24	-	-	-	-
	24-48	3.73	2.89	0.358	0.481
	48-72	6.65	5.43	0.412	0.805
	Total	10.38	8.32	0.770	1.29
3	0-24	10.00	6.28	0.760	1.88
	24-48	7.68	5.17	0.530	1.98
	48-72	4.06	4.06	ND	ND
	72-96	4.49	4.04	ND	ND
	Total	26.23	19.55	1.29	3.86

ND/NC not detected/not calculated

In brief, A77 1726 accounted for a mean of 11.3% of the dose and methyl-hydroxy A77 1726 accounted for a mean of 0.98% of the dose and reduced leflunomide accounted for a mean of 2.12% of the dose excreted in the feces.

Reviewer's Comments

- Analytical validation for the detection of metabolites in the urine and feces has not been submitted.
- Validity of the determination of radioactivity in the biological samples has also not been submitted, although the methodology has been described.

Conclusions

- A77 1726 is the major metabolite in plasma and feces. Urinary metabolites were methyl-hydroxy A77 1726 and TFMA-N-oxanillic acid. Other fecal metabolites were methyl-hydroxy A77 1726 and reduced leflunomide.
- Absence of parent drug in feces is consistent with extensive biliary elimination.
- Within the first three days of dosing the metabolic fate of only 35% of the dose (21.7% in urine and 14.4% in feces) could be established.
- At the end of 28 days the mean recovery (% of dose \pm sd) in urine, feces and total was 42.8 ± 13.9 , 48.2 ± 16.2 and 91 ± 2.9 respectively. From the results it could be speculated that renal route of elimination predominates during the first 24 hours, which is followed by a slower hepatic phase of elimination.

Study # 1022: A study to determine the urinary metabolites of leflunomide using fluorine nuclear magnetic resonance.

This was a non-radiolabeled study done in one normal healthy volunteer using a sensitive technique for analysis (Fluorine NMR), and was designed in order to allow profiling of the earlier metabolites of leflunomide by collecting urine in a series of smaller fractions instead of a single 0-24 hour collection in the radiolabeled study. This would reinvestigate whether leflunomide escapes first pass metabolism. 4 g cholestyramine was given three times daily after 96 hours of dosing with leflunomide to enhance the elimination of leflunomide (rationale discussed in the section 'Enhancement of Elimination' of this review). Post sampling decomposition of leflunomide to A77 1726 was prevented by adding 10µl of concentrated HCl to the plasma samples. Details of the study design are given on page A4 of the Appendix.

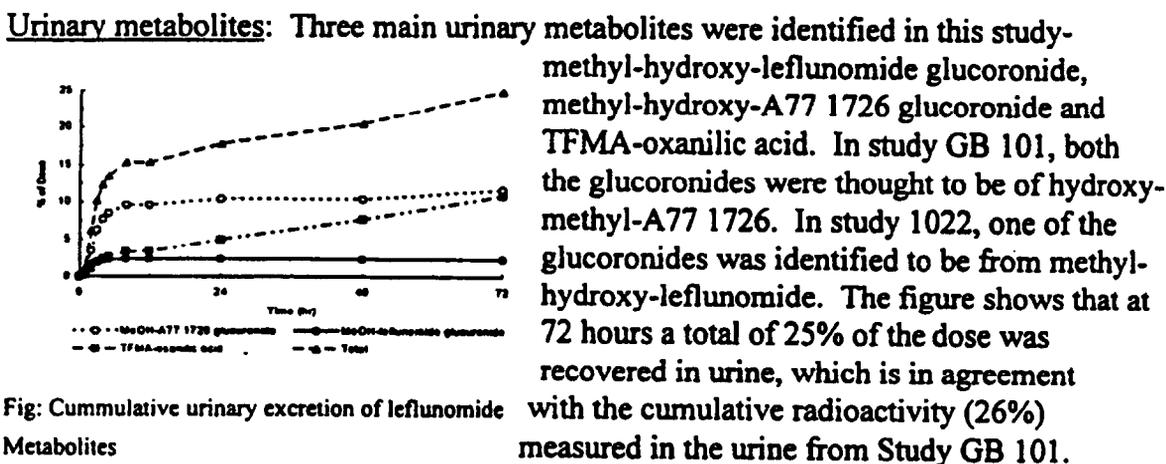
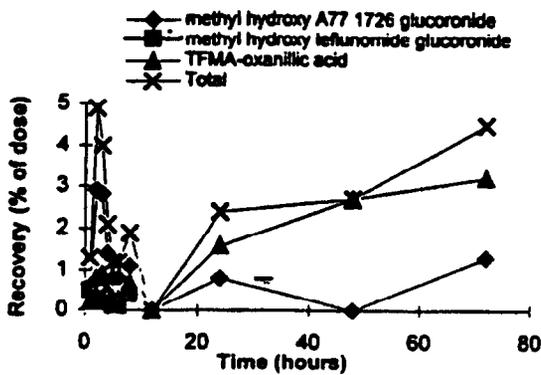
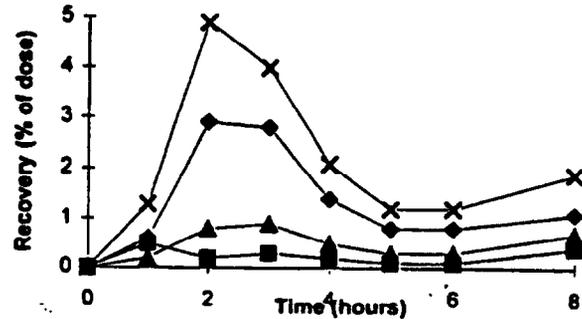


Fig: Cummulative urinary excretion of leflunomide Metabolites

The metabolic profile of these three metabolites till 72 hours post dosing and the first 8 hours post dosing is shown below. Based on the data, the excretion profiles for the metabolites submitted by the sponsor were not very accurate and has been re-plotted by the reviewer. The figure shows that the elimination of TFMA-oxanilic acid starts off slowly, but it continues for days after leflunomide dosing, whereas the glucuronides are eliminated within the first 8 hours of dosing. Methyl-hydroxy-A77 1726 glucuronide was also visible at 72 hours post dosing. By 72 hours after dosing, these metabolites accounted for 25% of the leflunomide dosed (TFMA-oxanilic acid accounted for 10.9%, methyl hydroxy A77 1726 glucuronide for 11.7% and methyl hydroxy leflunomide glucuronide for 2.4% of the leflunomide dosed). Peak hourly recoveries of the glucuronides were at two hours (2.9% of the dose) and for TFMA-oxanilic acid peak was at three hours (0.9% of the dose).



(a) Profile till 72 hours post dose



(b) Profile expanded for the first 8 hours

Figure: Excretion profiles of the major urinary metabolites following a single 100 mg oral dose

Sampling times (post-dose)	Plasma Conc	
	A77 1726 ($\mu\text{g/ml}$)	Lef (ng/ml)
predose	ND	-
5 min	-	ND
10 min	-	ND
20 min	-	ND
30 min	-	15.2
1 h	-	ND
2 h	-	ND
4 h	8.99	ND
8 h	-	ND
24 h	7.39	-
72 h	6.20	-
168 h	1.93	-
336 h	0.31	-

- = no sample taken
ND = not detected

Plasma metabolites

Plasma concentration of leflunomide and A77 1726 is shown in this Table. 0.31 $\mu\text{g/ml}$ of A77 1726 was present at 336 hours post dose. The concentration at 4 hours was 8.99 $\mu\text{g/ml}$. The mean C_{max} observed in Study # GB101 was 7.59 $\mu\text{g/ml}$ with T_{max} ranging from 6 to 24 hours.

Conclusions

- One of the glucuronides was thought to be coming from methyl-hydroxy leflunomide as opposed to from methyl-hydroxy A77 1726 as suggested in the previous study (GB101).
- At 72 hours-a-total of 25% of the dose was recovered in the urine, which is in good agreement with the urinary recovery of 26% of the total radioactivity during the same time in study GB101.
- Complete credence cannot be obtained from a study of N=1, therefore, the results can only be informative and not conclusive.

Study # 1024: Safety and pilot pharmacokinetics of i.v. A77 1726, and early investigation of urinary metabolite formation.

This study was designed with the use of labeled A77 1726 with the non radioactive isotope, ^{13}C , to allow differentiation between the formation of TFMA-oxanilic acid from metabolism of TFMA and the side chain degradation of A77 1726, i.e. to clarify the pathway from A77 1726 to the major metabolite TFMA-oxanilic acid, and to establish

the origin of methyl-hydroxy-A77 1726 and its glucuronide conjugation. Each volunteer received a 10 mg intravenous infusion of A77 1726 over 2 hours. An infusion of 2 hours was selected to approximate the concentration time profile of A77 1726 observed after oral administration of the corresponding dose of leflunomide. On day 15 of the study (336 hours after the start of infusion), 4 g of cholestyramine was given t.i.d for 72 hours. Detailed study design is given on page A6 of the Appendix along with position of the label of page A7 and individual subject data on pages A8-A10.

Plasma metabolites

- *A77 1726 in plasma*

The concentration profile characteristics of A77 1726 after constant infusion of 10 mg A77 1726 for 2 hours is shown in the table below.

Characteristic	Mean ± s.d.
C _{max} (mg/ml)	1.240 ± 0.158
t _{max} (h)	2.17 ± 0.41
AUC(0-23) (mg.h/l)	20.50 ± 1.50
AUC(0-48) (mg.h/l)	41.21 ± 3.37
AUC(0-96) (mg.h/l)	76.05 ± 8.15
AUC(0-336) (mg.h/l)	204.80 ± 28.88
AUC _{total} (extrapolated beyond 336 h)(mg.h/l)	335.13 ± 75.85
% extrap.	37.8 ± 6.2

N=6

The model-independent and model-dependent pharmacokinetic characteristics are summarized in the table below.

Characteristic	Model-independent	Model-dependent (1-compartment)
	Mean ± s.d.	Mean ± s.d.
AUC _{total} (mg.h/l)	335.13 ± 75.85	350.51 ± 96.21
% extrap.	37.8 ± 6.2	40.3 ± 8.4
CL _{tot} (ml/min)	0.5213 ± 0.1289	0.5081 ± 0.1459
CL _{tot} (ml/h)	31.28 ± 7.73	30.49 ± 8.76
CL _{tot} (ml/h/kg BW)	0.3796 ± 0.0648	0.3691 ± 0.0781
MT _{vss} (h)	350.8 ± 59.2	378.6 ± 89.4
V _{ss} (l)	10.626 ± 1.058	10.931 ± 0.792
V _{ss} (l/kg BW)	0.1301 ± 0.0087	0.1342 ± 0.0079
t _{1/2.1} (h)	242.8 ± 40.5	263.1 ± 62.0
t _{1/2.2} (h)	-	1.1114 ± 0.4782
V _c (l)	-	6.934 ± 1.012
V _c (l/kg BW)	-	0.0847 ± 0.0077

The concentration-time profiles for each subject showed a distribution phase with an average half-life of about 1h ($t_{1/2}$ in the table above). This distribution phase has only occasionally been observed after oral administration of leflunomide.

After cholestyramine administration for three days after 336 hours of infusion of A77 1726, the plasma concentration of A77 1726 decreased below the LOQ (0.1 µg/ml) in all, but one of the subjects. This subject (2) also had the highest concentration of A77 1726 before the administration of cholestyramine.

- *TFMA in plasma*

No plasma level of TFMA was detected in the plasma (LOQ 1ng/ml), and was not possible to assess any potential influence of subject acetylator status on the N-acetylation of TFMA.

Urinary metabolites

Following administration of A77 1726 intravenously to healthy volunteers, a single metabolite, 4-trifluoromethyloxanilic acid (TFMA-oxanilic acid) was eliminated to a very small extent in the 0-24 hour urine, mostly below the LOQ (50 ng/ml). The hourly rate of oxanilic acid excretion was roughly constant for each volunteer over the 24 hours. The recovery of TFMA-oxanilic acid was lower than would have been predicted from oral leflunomide studies. It was postulated that it could be possible that there exists a supplementary pathway to oxanilic acid via methyl-hydroxy-A77 1726 glucoronide and A81 3226.

¹³C₂-4-trifluoromethyloxanilic acid (¹³C₂ TFMA-oxanilic acid) was quantified (10 out of 36 urine samples), but levels were low. ¹³C₂ TFMA-oxanilic acid increased from 0.0073 µg/ml in 0-2 hour urine to 0.0702 µg/ml in 8-24 hour urine. Total recovery in the first 24 hours after starting the infusion, expressed as a percentage of dose, ranged between 0.54 and 0.99 %. 98% of ¹³C-label was retained in the metabolite, suggesting that TFMA is not a significant intermediate in the metabolic breakdown of A77 1726.

Specific assay for methyl-hydroxy-leflunomide glucoronide and methyl-hydroxy-A77

1726 glucorónide, measured as X91 0228 gave no values above the LOQ (50 ng/ml). This is in agreement with the postulation that following oral administration of leflunomide, the urinary methyl-hydroxy-leflunomide glucoronide and methyl-hydroxy-A77 1726 glucoronide are derived from the leflunomide by oxidation prior to isoxazole ring opening rather than direct metabolism of A77 1726. No other urinary metabolites were identified by the ¹⁹F-NMR spectroscopy as well.

These results agree with findings in other studies in which circulating A77 1726 is cleared slowly from the body, the routes of elimination being biliary for intact compound and renal for oxanilic acid.

Figure: Proposed Metabolic pathway of leflunomide (HWA 486) in man

Conclusions

Reviewer's Comments

- *Analytical validation report for TFMA-oxanilic acid is not submitted, but SOP reference number is given. Assay validation report for methy-hyddroxy leflunomide and methyl-hydroxy A77 1726 glucoronides are also not submitted.*
- *The sponsor has proposed the above pathway of metabolism of leflunomide (HWA 486) in man. However, the metabolism mechanistic studies submitted as part of Clinical Pharmacology do not explain the pathway in fullness. This pathway was presented in one of the documents in the NDA and was cross-referenced to document number 16639. No detail information about the pathway was obtained from this document upon its request on the 90-day meeting. This pathway has been presented as part of the review, however, it should only be considered a proposed pathway. The percentages of the dose converted to the major metabolites have not really been tied down from any of the three metabolism mechanistic studies submitted.*

The metabolism report is not very specific on terms of the site of metabolism either. However, most of the metabolism is suspected to be taking place in the liver.

(B) In Vitro Studies

Studies with human liver microsomes showed that isoxazole ring opening of leflunomide to A77 1726 was catalyzed by both catalytically active, and to a lesser extent, inactive microsomal protein. Soluble protein (cytosol) also catalyzed this ring opening. Subcellular fractions from human gastrointestinal tract were also able to catalyze this ring opening. Further metabolism of leflunomide (other than ring opening) in human liver samples in vitro was minimal. Metabolism was detectable from donor samples high in CYP3A4 activity. Further details of the role of isoenzymes of CYP 450 has been discussed on page 34 of this review.

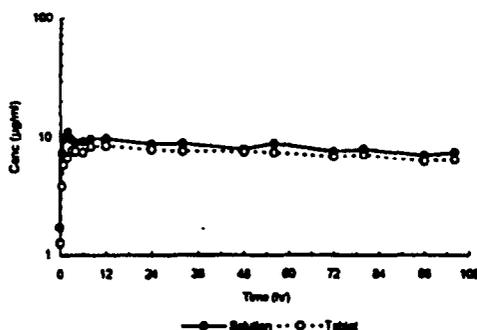
ABSORPTION

(A) Bioavailability (Relative BA)

The bioavailability of 100 mg leflunomide tablet relative to a solution (aqueous alcoholic PEG 400) was studied in the following study.

Study # D110:

Leflunomide has low aqueous solubility (21 mg/l at pH 4.8 and 6.8), hence the bioavailability of a tablet formulation has been compared to a standard aqueous alcoholic PEG 400 solution. The maximum plasma concentrations were lower with the tablet and reached at later time after administration of the tablet. This would be an expected difference between the two formulations. Based upon the treatment ratios for C_{max} , AUC_{0-104} and $AUC_{0-\infty}$, the bioavailability of the tablet relative to the solution was 80%.



Elimination half-life averaged 8 to 9 days and was essentially the same regardless of treatment. Although plasma concentrations were measured for approximately one-half of the half-life (104 hrs or 4.3 days), plasma concentrations after either formulation showed monoexponential decay from 12 hours through 104 hours with the same slope (see figure) and the AUC_{0-104} and $AUC_{0-\infty}$ ratios, tablet to solution, were the comparable (0.87 and 0.80, respectively). This suggests that collection of data through 104

hours provided a reasonable comparison of the tablet and solution. The mean \pm SD of the pharmacokinetic parameters are tabulated below. For details see page A11-A12 of the Appendix.

Parameter	Solution	Tablet
C_{max} ($\mu\text{g/ml}$)	11.7 ± 1.5	9.5 ± 1.7
T_{max} (hr)	3.1 ± 4.4	5.7 ± 4.3
AUC_{0-104} (hr x $\mu\text{g/ml}$)	872 ± 152	761 ± 138
$AUC_{0-\infty}$ (hr x $\mu\text{g/ml}$)	3324 ± 1480	2661 ± 771
$t_{1/2}$ (days)	9.0 ± 3.0	8.4 ± 3.0

(B) Effect of food on bioavailability

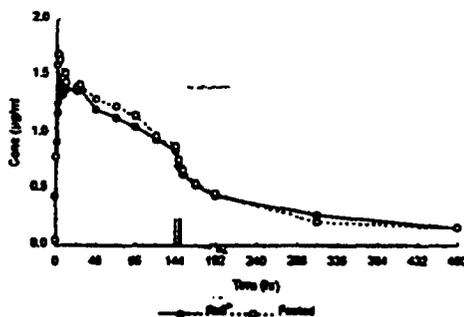
Study # GB 103:

The effect of food on the bioavailability of leflunomide from the 10 mg tablet was examined in 10 healthy volunteers receiving a single 20 mg (2x10 mg tablets) dose. Plasma samples were collected for 20 days (480 hours) after each treatment with a 7 week washout separating each phase. 50 g of charcoal was administered at 144, 147 and 150 hours after drug administration, to test the hypothesis that charcoal enhances the elimination of A77 1726. Details of the study design is given on page A13 of the Appendix. Since charcoal enhances elimination (discussed in section 'Enhancement of Elimination' of the review), it is more appropriate to use data only through 144 hours for pharmacokinetic analyses.

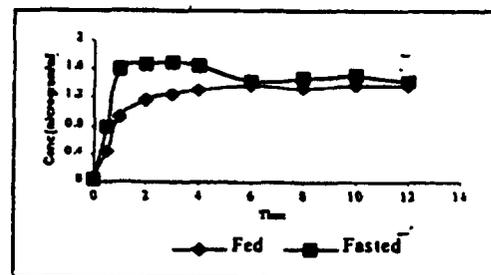
A standard breakfast was taken within 15 minutes prior to the administration of leflunomide. The standard breakfast under fed conditions consisted of two egg muffins with 100 ml orange juice with a nutritional value of :

fat	30 g
protein	41.8 g
carbohydrate	51.8 g
fibre	3.8 g
energy	640 Kcals

This diet is lower in fat content as compared to the recommended FDA high fat breakfast (30.8 g vs 55 g). The volume of fluid intake along with the food is also lower. The content of food as well as the volume of fluid intake would affect the drug absorption.



(a) For 480 hours



(b) The first 12 hours expanded

Figure: Mean plasma A77 1726 concentrations after administration of 20 mg of leflunomide under fed and fasted conditions to healthy volunteers (the vertical lines in figure (a) indicate the time of administration of activated charcoal)

The results of the study show that food had minimal effect on the plasma concentrations of A77 1726 with difference being observed for the first 6 hours of dosing reflecting the

T_{max} . The pharmacokinetic parameters under fed and fasted conditions are tabulated below. There was a decrease in the rate of appearance of A77 1726, as evidenced by an approximate 3-fold increase in T_{max} and a slight decrease in C_{max} . However, the 90% confidence intervals were within the 80%→125% window.

Parameter	Fed	Fasted	90% Equivalence Interval
C_{max} (µg/ml)	1.5 ± 0.3	1.8 ± 0.4	81→95%
t_{max} (h)	11.5 ± 11.2	3.5 ± 4.1	
AUC ₀₋₁₄₄ (µg.hr/ml)	163 ± 31.2	175 ± 53.4	83→105%
AUC _{0-∞} (µg.hr/ml)	422 ± 271	420 ± 193	80→115%
$t_{1/2}$ (days)	7.8 ± 3.9	7.4 ± 2.2	

The individual subject data and statistical analysis is attached in the Appendix on pages A14 to A16. Further the effect of oral charcoal administration on the $t_{1/2}$ of A77 1726 showed consistent results as that seen in a single volunteer study (GB102 on page 26) and the $t_{1/2}$ (hr) are tabulated below.

Study Period	Fed	Fasted
Before charcoal (24→144 h)	178	182
During charcoal (144→150 h)	20	15
After charcoal (168→480 h)	184	189

Conclusions

Based on the study design and diet, food does not seem to have an impact on the pharmacokinetics of leflunomide at the 20 mg dose.

Reviewer's Comment:

- *The food study was conducted on a 2x10 mg tablets, however, it is generally recommended to conduct the food study on the highest strength available (i.e. 100 mg is the highest strength available). The 20 mg dose did not show any food effect in terms of extent of absorption. Upon consultation with the medical reviewer, it was found out that the pivotal clinical trials (US 301 and MN 302) were done without any dietary restrictions. However, in study MN 301, specifications were given that the doses should be given with the meals. In all the PK studies with 100 mg leflunomide, the dose was administered after an overnight fast. The Medical Reviewer did not see any difference in the toxicity profile of the two studies with and without diet restrictions. Appropriate labeling comments with the consultation of the Medical Reviewer should be made.*
- *The high fat diet was also different as compared to the recommended FDA high fat diet, but given the long half-life of the drug the impact of the diet may not be significant.*

MULTIPLE DOSE PHARMACOKINETICS

(A) In healthy subjects:

Study # D111:

The objective of this study was to evaluate the degree of accumulation of A77 1726 in plasma and its tolerance in healthy subjects after administration of a single dose of 100 mg of leflunomide for 14 days. Details of study design are on page A17 of the Appendix.

A77 1726 in plasma

Plasma profiles of A77 1726 from the first dose of leflunomide in the multiple-dose regimen were fitted using the curve-fitting program and the parameters obtained are tabulated below. Plasma samples were collected only till 24 hours after the first dose. Determination of $T_{1/2}$ of A77 1726 from the first dose of leflunomide led to considerable underestimation, which led to poor multiple dose predictions. Better agreement was obtained between predicted and observed 14-day levels using data from a separate single dose study (#D110) in which sampling was extended beyond 24h to 104h. (compare $C_{ss(min)}$ values and $T_{1/2}$ from the two studies in the table below). Individual subject means are provided on pages A18-A19 of the Appendix.

Parameter \pm SD	Study # D111	Study # D110
$T_{1/2}$ (h)	72.8 \pm 27.6	183.6 \pm 72.3
C_{max} (μ g/ml)	12.11 \pm 2.08	9.5 \pm 1.7
T_{max} (h)	5.2 \pm 4	5.7 \pm 4.3
$C_{ss(min)}$ (predicted) (μ g/ml)	46.1 \pm 20.7	98.7 \pm 45.3
$C_{ss(min)}$ (observed) (μ g/ml)	83.4 \pm 35.3	

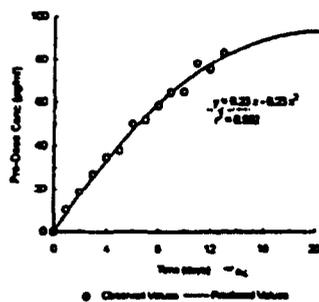


Fig: Mean pre-dose A77 1726 concentration after 100 mg/day leflunomide after 14 days

Steady state levels were not attained even after the 14th day of dosing. Because of the very long half life calculated for the single dose profiles, the predicted time to steady state plasma concentrations was much longer (> 20 days). As shown in the figure the steady state pre-dose concentration would be ~93 μ g/ml. After 14 days of dosing the mean pre-dose concentration was 83 μ g/ml which is about 90% of steady state. The accumulation of A77 1726 was quite considerable during this time, giving serum levels approximately 10 times higher than those from a single dose. Meaningful estimates of A77 1726 half life after the last dose are difficult to obtain from this study, due to the relatively infrequent sampling after the dose. The very large standard deviation with the half-life (338.1 \pm 210.4 h) reflects the poor confidence in the measurement. The C_{max} after 14 days of dosing was 92.1 \pm 34.3 μ g/ml as opposed to 12.11 \pm 2.08 μ g/ml after the first dose (8

fold increase). The long half-life of A77 1726 explains for this accumulation after multiple dosing. The ratio of area under the mean plasma concentration-time curve from 0-24 hours after last (2053 µg.h/ml) and first doses (242 µg.h/ml), 8.5 is another estimate of the accumulation ratio and is consistent with ratio of mean C_{max} s (7.8).

The concentrations of TFMA in plasma have been presented in the Appendix on page A20. The concentrations ranged from 1.5 to 7.1 ng/ml during 312-336 hours post initial dose. The sponsor has assessed the TFMA plasma concentration in the pharmacokinetic studies due to the concern of TFMA being mutagenic in animal studies. However, the C_{max} of TFMA was about 5000 times lower than that of A77 1726 levels.

A77 1726 in urine

The recovery of A77 1726 is shown on page A20 of the Appendix. The highest concentration of A77 1726 in urine was 0.4 µg/ml, although in most samples A77 1726 concentrations were below the limit of quantification (0.1 µg/ml). Full method development for the detection of A77 1726 was not done due to negligible amounts in the urine. Only between 272 and 934 µg (0.02 and 0.07% respectively, of the single 100 mg leflunomide administered for 14 days) was recovered in 6 out of 10 subjects treated with leflunomide.

Reviewer's Comment

- *In this study the applicant states that most urine samples for A77 1726 were below the limit of quantitation (0.1 µg/ml), but in the report for study D110 (Vol 1.68) also conducted at the same year (Mar 1982), the limit of detection for analysing samples in the urine was set to 20 ng/ml. As mentioned above full method development was not done.*

Loading and maintenance dose rationale for healthy subjects

The long $t_{1/2}$ and subsequent long time required to reach steady state indicates that a loading dose would be appropriate for leflunomide. Assuming that loading (D_L) and maintenance (D_M) doses are related through

$$D_L = \frac{D_M}{1 - e^{-\beta\tau}}$$

where β is the elimination rate constant and τ the dosing interval, a $t_{1/2}$ of $\sim 7 \rightarrow 8$ days (Studies GB101 and D110) predicts that the loading dose should be $\sim 10 \rightarrow 12$ fold higher than the maintenance dose. Consequently, a 100 mg loading dose would be suitable for a 10 mg maintenance dose.

Conclusions

- After 2 weeks of dosing of 100 mg leflunomide, the serum concentrations were 10 times higher than after a single dose of 100 mg.
- The ratios of the AUCs after the last and first dose is 8.5 and the ratio of the mean C_{max} is 7.8 suggesting the high accumulation of A77 1726 on multiple dosing, which is consistent with the observed plasma half-life.

(B) In Patients with Rheumatoid Arthritis

Study # YU 204:

This study was designed to assess the pharmacokinetics and pharmacodynamics of leflunomide in patients with severe RA receiving daily doses of leflunomide for 6 months. 3 groups of RA patients (18 in each group) received daily doses of 5 mg/day (50 mg loading dose), 10 mg/day (100 mg loading dose) and 25 mg/day (100 mg loading dose). The loading dose was given on Day 0 and the maintenance dose on the next day. Plasma samples were collected over a 32-week period and analyzed for A77 1726 and TFMA. Details on page A21.

The mean \pm SD and ranges of the pharmacokinetic parameters obtained for A77 1726 after administration of leflunomide for 24 weeks are summarized below. The mean data is attached in the Appendix on pages A22-A24. The 25 mg/day dosage regimen showed high inter-patient variability. A dose proportional increase in trough concentrations was seen in the 5 and 10 mg dosing regimen. Following 25 mg/day the mean trough concentrations were not truly dose proportional. There were two subjects (10 and 32) that were outliers with extremely high $C_{24}(ss)$ concentrations. Due to this high inter-patient variability definite conclusions cannot be made. The variability in the $t_{1/2}$ values was also very high, especially in the 25 mg/day group, ranging from 6-40 days. Mean concentrations 24 hours after administration of a 50 mg loading dose were one-half of those observed after administration of 100 mg and the 2 groups receiving 100 mg loading doses (10 mg/day and 25 mg/day) had essentially the same values (see Table). Due to small subject number and high inter-patient variability, no conclusion regarding dose proportionality could not be obtained from this study.

TFMA was only detected in 9/18 samples of the 25 mg/day dosage regimen, with C_{max} ranging from 2-4 ng/ml and a t_{max} of 56-112 hours. No detectable TFMA were found at the end of the post-treatment observation period in all the groups.

Parameter	Maintenance (Loading) Dose		
	5 mg (50 mg)	10 mg (100 mg)	25 mg (100 mg)
C_{24} (Day 1) (μ g/ml)	4.0 \pm 0.6	8.4 \pm 2.1	8.5 \pm 2.2
$C_{24}(SS)$ (μ g/ml)	8.8 \pm 2.9	18 \pm 9.6	63 \pm 36

Time to SS (weeks)	7.0 ± 1.4	6.8 ± 2.5	8.5 ± 4.3
t _{1/2} (days)	15 ± 3	14 ± 5	18 ± 9

Age Trend Analysis

The covariance analysis using dose, age and BMI as independent variables performed to investigate if the concentrations of A77 1726 after 6 months of treatment are dependent on the age or BMI of patient, showed that the plasma concentrations were dose-dependent ($p < 0.001$), but neither age nor BMI had a significant influence. Two patients of age 60 years (8 and 32) had unusually high plasma concentrations, which lead to a small p-value for the variable "age". The t_{1/2} analysis with respect to age and BMI is also tabulated below. No subjects less than 40 years were included in 25 mg/day regimen and there was high variation in this group as well, hence, difficult to draw conclusions regarding the effect of age on the t_{1/2} of this group. The figures showing the effect of age on the plasma concentration and t_{1/2} are attached in the Appendix on page A25.

Source (adjusted for all other variables in model)	DF	Sum of Squares	Mean Sum of squares	F-value	p-value
Css					
dose	3	36665.4	12221.8	21.13	0.0001
BMI	1	160.8	160.8	0.28	0.6006
age	1	2146.0	2146.0	3.71	0.0604
Model	5	102778.1	20555.6	35.55	0.0001
Error	45	26023.0	578.3		
T _{1/2}					
dose	3	131.8	43.9	1.16	0.3339
BMI	1	12.1	12.1	0.32	0.5748
age	1	168.4	168.4	4.46	0.0403
Model	5	12634.8	2527.0	66.9	0.0001
Error	45	1698.8	37.8		

Loading and maintenance dose rationale in patients

Based upon a t_{1/2} of ~ 15.7 days (see Table p20, averaged across doses), the loading dose in the target population should be 23 times the maintenance dose, or 230 mg for a 10 mg per day regimen. Since 100-200 mg per day was the highest single daily dose that had been studied in clinical trials, a loading regimen of 100 mg per day for 3 days was thought by the sponsor to be sufficient in most patients. Based on the calculation and the poor solubility of the drug, the three day loading regimen of 100 mg daily seems reasonable.

Further steady state pharmacokinetics of leflunomide from patients with RA was obtained from studies US 201, YU 210/202 and YU 206. In studies US 201 and YU 201/202,

patients received 5 mg/day (50 mg loading dose), 10 mg/day (100 mg loading dose), or 25 mg/day (100 mg loading dose) for 6 weeks. The plasma concentrations after the final dose $C_{6\text{ weeks}}$ increased in a dose related manner. The $t_{1/2}$ averaged between 10-19 days with a range of 9 to 30 days across patients. The mean \pm SD pharmacokinetic parameters from these studies are summarized below:

Maintenance (Loading) Dose			
Parameter	5 mg (50 mg)	10 mg (100 mg)	25 mg (100 mg)
C_{max} ($\mu\text{g/ml}$)	8.3 \pm 4.2	24.4 \pm 28.8	57.2 \pm 29.6
$C_{6\text{ weeks}}$ ($\mu\text{g/ml}$)	6.3 \pm 3.4	17.4 \pm 9.7	29.5 \pm 13.7
$t_{1/2}$ (days)	12 \pm 3	16 \pm 7	13 \pm 4

C_{max} values are from study US 201 and $C_{6\text{ weeks}}$ $t_{1/2}$ from study YU 201/202

Age Trend analysis

No correlation was seen age, BMI and serum levels of A77 1726, although a weak positive correlation was found between age and half-life from study YU 201/202.

Study # YU 205:

This study was an open-label extension study for patients in studies YU 204 and YU 203 to obtain more information on long term treatment (18-month) in RA patients. In the 6 month studies YU 203 and YU 204, patients were randomized to one of three daily leflunomide dosages: 5 mg with 50 mg loading dose, 10 mg with 100 mg loading dose or 25 mg with 100 mg loading dose. Study YU 203 also contained a fourth arm in which patients were randomized to placebo. Patients from study 203 entered study 205 directly without interrupting study medication and did not receive a loading dose. Patients from study 204, however, interrupted their study medication for 8 weeks before entering study 205. Therefore, they were given a single loading dose of 100 mg leflunomide at the start of the study. Patients from both studies received a daily maintenance dose of 10 mg for the first 4 weeks. The dose was then increased or decreased by 5 mg (range from 5 mg to 25 mg) every 4 weeks depending upon the efficacy or toxicity. Trough concentrations of A77 1726 were measured every 3 months and prior to a dosage change. The study description is on page A26.

Mean trough concentrations at 10 mg per day (19 $\mu\text{g/ml}$) and 25 mg per day (54 $\mu\text{g/ml}$) were in agreement with those measured in study YU 204 (18 and 63 $\mu\text{g/ml}$, for 10 and 25 mg/day, respectively). The number of measurements made at 5, 10, 15, 20 and 25 mg/day regimens were 14, 310, 251, 188 and 94 respectively. A log-log plot of A77 1726 concentration vs. dose between 10 mg and 25 mg/day was linear with a slope of 1.09 ($r^2=0.995$) (see section dose proportionality), supporting the linearity of A77 1726 kinetics. However, a discrepancy was seen at the 5 mg/day regimen. Due to the small

number of observations (N=14), definitive conclusions would be difficult to draw with this data.

Age and Gender Trend Analysis

After normalizing to a 20 mg dose, mean trough plasma A77 1726 concentrations were higher in women than in men. The difference between the means was 10 mg/l (women 30.5 mg/l, men 20.3 mg/l). Although, men and women had similar body mass index

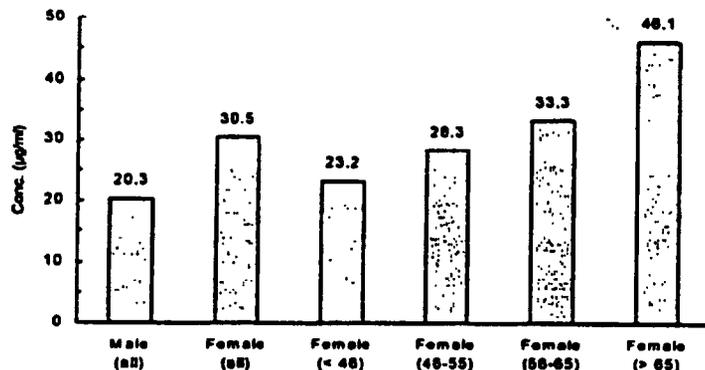


Figure: Mean A77 1726 trough plasma concentrations in male and female patients with RA after administration of 10 to 25 mg/day

ranging from 17.1-32.7 kg/m² for men and from 15.7-43.7 kg/m² for women. A clear relationship between age and plasma concentrations of A77 1726 was also observed where elderly patients had higher plasma concentrations than younger patients. This trend could be well observed with the female patients (increase in plasma concentration with increase in age). However, similar analysis was not possible in male subjects due to smaller number of male subjects. This trend has been pictured in the graph. The 5 mg dosage group has been excluded from the analysis.

Reviewer's Comment

Study YU 203 has been submitted as part of the Clinical section of this NDA. This study is similar to YU 204, but also has a placebo arm to it. In the Clinical Summary of the application the applicant has mentioned the choice of the 20 mg maintenance regimen was based on the efficacy and safety concerns from this Phase II study. Improved efficacy was observed with 25 mg dose as compared to the 10 mg, but was also associated with more adverse events. Therefore, a daily dose of between 10 and 25 mg was regarded as the optimal dose for majority RA patients.

Study # YU 206:

This multiple dose pulsing study was designed to assess the safety, tolerability and kinetic profile of leflunomide under pulsed administration up to 200 mg/week for 6 months and to determine whether deterioration in the patient's condition may occur at the end of a pulse interval. Patients were randomized to take weekly either 2 tablets of 100

mg leflunomide or 1 tablet of 100 mg leflunomide and a visually identical placebo. Both groups received a loading dose of 2x100 mg leflunomide, administered for two days (100 mg each). Details of the study design are outlined on page A27 of the Appendix.

The means \pm SD for the $C_{ss(max)}/t_{ss(max)}$ and $C_{ss(min)}/t_{ss(min)}$ values for the 100 mg and 200 mg dosage regimen is tabulated below. The individual subject parameters are attached in the Appendix on page A28 along with the plasma concentration profiles and trough profiles on page A29.

Parameter	100 mg leflunomide per week (n=20)	200 mg leflunomide per week (n=21)
$C_{ss(max)}$ ($\mu\text{g/ml}$)	45.8 \pm 15.2	85.9 \pm 37.1
$C_{ss(min)}$ ($\mu\text{g/ml}$)	29.7 \pm 15.4	59.3 \pm 37.3
$t_{ss(max)}$ (hours)	98.2 \pm 49.9	117.0 \pm 51.9
$t_{ss(min)}$ (hours)	158.2 \pm 27.7	164.0 \pm 13.4

The results show that C_{max} and C_{min} increase in proportion to the administered dose. The mean steady state comparisons of C_{min} for study YU 206 and YU 204 is shown below. YU 204 was also a multiple dose study where patients were given daily doses of 10mg/day (weekly 70 mg) and 25mg/day (weekly 175 mg).

Study YU 206 (treatment phase- 6 mo)	Study YU 204 (treatment phase- 6 mo)
100 leflunomide per week 29.7 \pm 15.4 $\mu\text{g/ml}$	10 mg leflunomide/day (70 mg per week) 17.98 \pm 9.6 $\mu\text{g/ml}$
200 leflunomide per week 59.3 \pm 37.3 $\mu\text{g/ml}$	25 mg leflunomide/day (175 mg per week) 63.0 \pm 36.2 $\mu\text{g/ml}$

TFMA plasma levels were below the detection limit in most cases (2 ng/ml). The maximum plasma concentration of TFMA was 3 ng/ml.

Conclusions

- The half live of A77 1726 in patients is \sim 15 days.

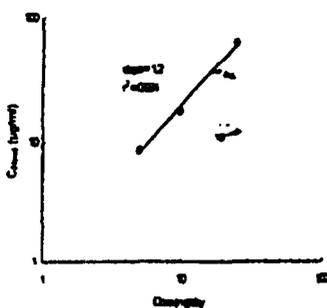
- Plasma concentrations are higher in women and increase with age as seen in study YU 205.
- It takes about 7-8 weeks to reach steady state with a single loading dose of 100 mg followed by a maintenance dose daily.

Reviewer's Comment

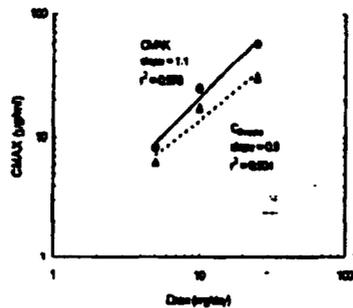
- *The maximum exposure at the maximum recommended dose (20 mg) at steady state (Study YU 204) has not been reported. The Pharmacology Reviewer would need this information for toxicity comparison with the animal data. The reviewer has calculated the rough estimation of the maximum exposure with the 25 mg tablet from study YU 204 based on the steady state trough values after the last dose to be 1512 µg.h/ml. This would however be an underestimation of the maximum exposure. The actual exposure can be calculated by taking into account the 0-12 h samples collected after the last dose at the end of 24 weeks.*
- *The 100mg D_L/20mg D_M dosage regimen has not been studied in the multiple dose PK study YU 204. However, the 10 and 20 mg tablets are dose proportional, have linear pharmacokinetics and clinical studies have been conducted in the same regimen.*
- *It was not very clear from the study design of YU 204 that trough levels of A77 1726 were measured for 24 weeks, however, the results report trough concentrations on Day 1 and at steady state.*

DOSE PROPORTIONALITY

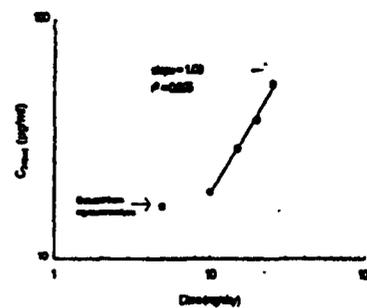
No formal dose proportionality study was conducted. Data from studies YU 204, YU 201/201, US 201 and YU 205 supported the linear pharmacokinetics of A77 1726. A log-log plot of steady state trough or C_{max} values vs. dose was linear in all these studies with a slope close to unity, indicating linear pharmacokinetics. However, high variability was also seen in some of these studies. Relationship between A77 1726 concentration at steady state and leflunomide dose after the administration of 5, 10 and 25 mg/day for different durations has been shown in the following graphs, suggesting linear pharmacokinetics of the drug in this range.



Duration: 24 weeks (YU 204)



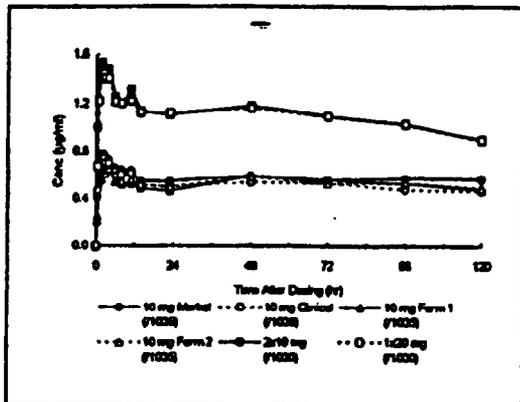
Duration: 6 weeks (YU 201/202, US 201)



Duration: up to 18 mo (YU 205)

Reviewer's Comment

The variability gets shrunk in a log-log plot. In study YU 204 the 25 mg dose was not truly dose proportional, however, there was so much variability amongst subjects that no definite conclusions could be drawn.



Additional information regarding dose proportionality was obtained from bioavailability/bioequivalence studies 1036, 1030, and 1035, 10 mg and 20 mg doses of leflunomide have been administered to healthy volunteers according to identical protocols. Details of these studies will be discussed in the section 'Bioequivalence' in the latter part of the review. Plasma concentrations after administration of 2 x 10 mg or 1 x 20 mg are essentially twice those after administration of 10 mg doses and C_{MAX} and AUC_{0-120} increase

linearly with dose (see Figures on the side and below). Taken as a whole, the data in patients with rheumatoid arthritis and in healthy volunteers provide sufficient evidence that the pharmacokinetics of A77 1726 are linear over the range of doses to be used clinically and that the 10 mg and 20 mg strengths are dose and dosage form proportional.

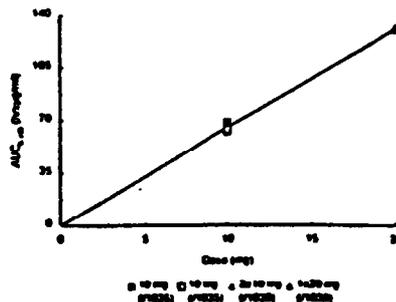
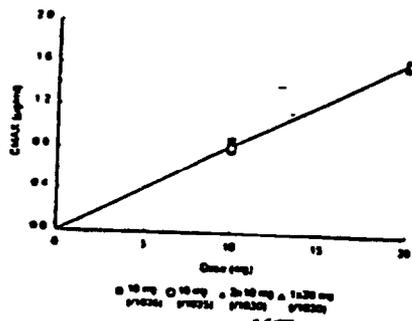


Figure: Relationship between C_{max} and AUC after administration of 10 mg and 20 doses in the bioequivalence studies (1030, 1035 and 1036)

ENHANCEMENT OF ELIMINATION

Due to the extremely long half-life of A77 1726 it would be imperative to gain insight on methods to eliminate the drug faster from the system, especially in case of overdose and increased incidence of side effects. In this attempt, activated charcoal and cholestyramine were investigated as adsorbents that would bind to the drug in the gut and interfere with entero-hepatic recycling.

(A) Effect of Activated Charcoal

Study # GB 102:

This study was designed to determine whether oral charcoal could reduce the plasma levels of A77 1726 in man by interruption of the entero-hepatic recycling. This was a pilot study conducted in one healthy male volunteer and the details of the design are outlined on page A30 of the Appendix.

The half-life values for A77 1726 were estimated using a combination of linear regression and method of residuals (Wagner). Values were estimated over the time intervals:

- 0-120 h (when leflunomide was given alone)
- 120-122 h (after the first dose of activated charcoal)
- 122-144 (after the next 2 doses of activated charcoal)
- 144-360 h (after the effect of charcoal ceased)

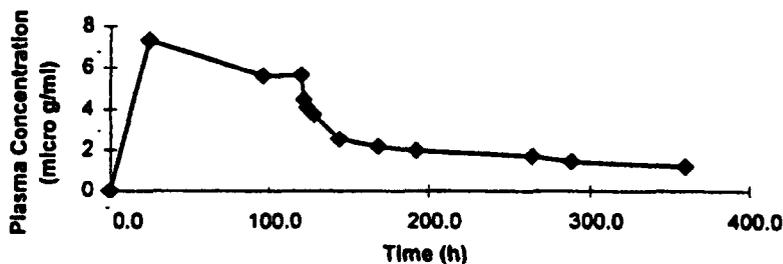


Figure: Plasma concentration of A77 1726 after 100 mg leflunomide and 3x50 g doses of activated charcoal (120, 123 and 126 hours)

After a single dose of 100 mg leflunomide, plasma concentrations of A77 1726 declined with a half life of 240 hours. In a 2 h period following the first 50 mg dose of charcoal the half life decreased to 7 h (5.8 h as calculated by the reviewer). Following the next 2 doses of charcoal (over the period of next 22 hrs) the half-life decreased to 29 h. 18 hrs after the last dose of charcoal (when the effect of charcoal had ended) the half-life returned to a value of 228 h.

(B) Effect of Cholestyramine

Study # GB 104:

In vitro experiments have shown that cholestyramine binds more than twice as much A77 1726 (per gram dry weight) as charcoal. Cholestyramine was also effective in enhancing the elimination of A77 1726. The changes in the half-lives of A77 1726 before and after administration of cholestyramine are shown in the table below. Cholestyramine (8 g each) was administered at 77.5, 83.5, 96, 215.5 and 221.5 hrs after dosing of leflunomide (20 mg dose). The half-lives have been calculated during the time interval of 77.5→96

hours. The third dose of cholestyramine was given at 96 hours (day 5). Details of study are on page A31.

The maximum drop in the half-life is observed after the first and second dose of cholestyramine which were given on day 4. This was followed by a single dose of cholestyramine on day 5. The half-life increases to ~ 104 hours at the 96→216 hr time interval. And once again after the last two doses of cholestyramine at 215.5 and 221.5 hours, the half-life again decreases to ~58 hours.

SPECIAL POPULATION

In Dialysis Patients

Study # B101 NI:

The effects of continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis of the pharmacokinetics of A77 1726 was investigated in this study. Leflunomide (100 mg) was administered to 3 patients on hemodialysis and three on CAPD after the dialysis or after a CAPD bag change. Plasma samples were collected for 28 days after administration of leflunomide and samples from dialysate fluid (CAPD patients) were obtained during the first 3 days. Dialysate of hemodialyzed patients was taken 5 minutes

after start, during (2 hours) and at the end of the first dialysis session performed after drug administration. Dialysate from CAPD patients were taken before leflunomide administration and from all subsequent dwell periods up to 3 days after drug administration. For details see page A32.

- *A77 1726 in plasma*

The individual pharmacokinetic parameters (mean \pm sd) of A77 1726, obtained following oral administration of 100 mg leflunomide to hemodialysis patients and CAPD patients is compared with another oral 100 mg leflunomide single dose study in healthy volunteers (Study GB101). In CAPD patients the pharmacokinetic characteristics of A77 1726 were similar to those obtained in healthy volunteers after single dose administration of the drug.

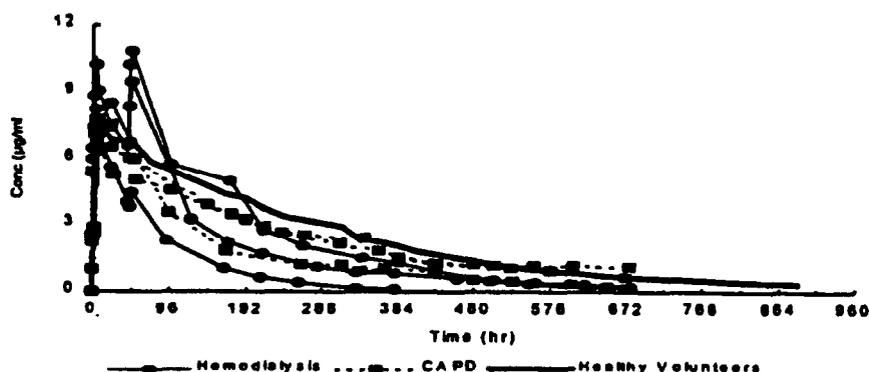


Figure: Individual patient plasma A77 1726 concentrations after administration of 100 mg leflunomide to patients undergoing hemodialysis or CAPD, compared to healthy volunteers from study GB 101.

Parameter	Hemodialysis	CAPD	Healthy Volunteers
C_{max} ($\mu\text{g/ml}$)	9.2 ± 1.8	7.5 ± 0.4	7.6 ± 1.4
t_{max} (days)	1.4 ± 1.1	0.22 ± 0.09	0.50 ± 0.4
$AUC_{0 \rightarrow \infty}$ ($\mu\text{g}\cdot\text{hr/ml}$)	1303.9 ± 623.2	1854.9 ± 467.8	2186.5 ± 475
$t_{1/2}$ (days)	4.45 ± 1.53	8.7 ± 1.82	7.8 ± 0.5

Patients undergoing hemodialysis had a shorter $t_{1/2}$ and a reduced AUC. This leads to the speculation that hemodialysis partly contributes to the elimination of the active metabolite. However, it was also seen that the AUC was highest in the patient with the highest extraction ratio (0.26). The sponsor speculates that other factors such as the

differences in protein binding may also contribute to the more rapid elimination in this group of patients.

The dialysis extraction ratio of A77 1726 in hemodialysis subjects was calculated using A77 1726 plasma concentrations in venous blood entering the dialyser (C_{in}) and in blood leaving the dialyser (C_{out}). The mean extraction ratio of A77 1726 for each hemodialysis subject is given in the table below.

The clearance rates from the dialysate were calculated for both creatinine and A77 1726 and are summarized below. The low additional contribution of CAPD to the elimination of A77 1726 is also substantiated by the low mean dialysate clearance of 0.13 ml/min. This can be explained by the high protein binding of the metabolite.

Study Group	Dialysate creatinine clearance (ml/min) ^a	Dialysate A77 1726 clearance (ml/min) ^b
Hemodialysis group (Mean ± SD)	-	32.7 ± 18.7
Subject 1	-	
Subject 2	-	
Subject 3	-	
CAPD group (Mean ± SD)	4.7 ± 0.91	0.13 ± 0.14
Subject 4		
Subject 5		
Subject 6		

^a $Cl_{creatinine} = A_{creatinine} / (t_h - t_0) (C_{creatinine})$

^b $Cl_{dial} = Q \cdot ER$, where Q = measured blood flow rate

Concentrations of TFMA in plasma were equal to or below 9.4 ng/ml. Pharmacokinetics of A77 1726 in patients with mild and moderate renal impairment has not been studied.

The effect of dialysis on plasma protein binding of A77 1726 was also determined from study B101 NI patients, the free fraction was in the range between 0.44-1.37% in dialysis patients compared to mean values of 0.52-0.67% measured in healthy subjects at similar concentrations. The results were more variable as compared to normal subjects and rheumatoid patients and showed no obvious pattern relating dialysis to the extent of protein binding. However, there are insufficient number of subjects to make any firm conclusions regarding the influence of dialysis on plasma protein binding of A77 1726.

Conclusions

- This study confirms that in patients with chronic renal failure, free fraction of A77 1726 is likely, but not certain, to be higher than healthy subjects. The free fraction was twice that seen in healthy plasma. Hemodialysis and CAPD had no clear effect on protein binding, but there were too few subjects for any firm conclusions to be drawn.
- The value of dialysis on treatment of over dosage of leflunomide is not significant. A77 1726 is negligibly cleared by dialysis.
- The results from this study are consistent with a poorly soluble drug, with a small volume of distribution and high protein binding.

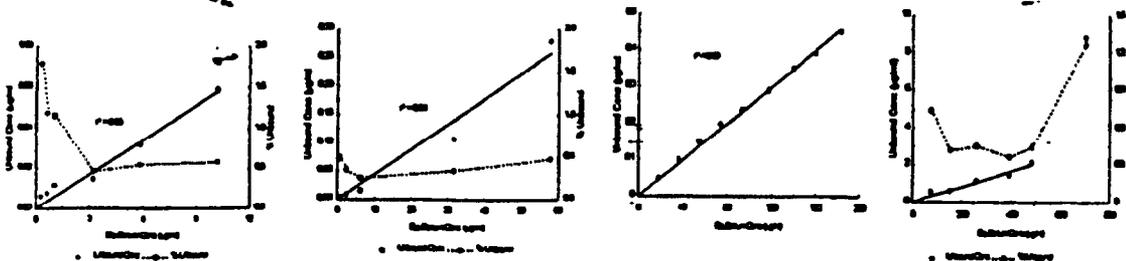
Reviewer's Comment

Leflunomide was not administered under nondialysis or intermittent hemodialysis condition to evaluate the contribution of dialysis on the elimination of A77 1726 in these patients and the patients were not at steady state either.

PROTEIN BINDING

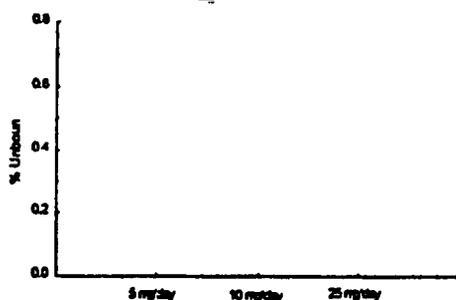
The following observations have been made from the in-vitro protein binding studies.

- There was a reasonably linear relationship between the unbound and total concentrations of leflunomide (Figure below). Although higher at the lower concentrations, the percent unbound was constant from approximately 3 → 10 µg/ml, averaging $\sim 0.53 \pm 0.06\%$.
- Binding was independent of concentration at least to ~ 60 µg/ml. The unbound fraction averaged $0.39 \pm 0.10\%$ over the concentration range of 10-60 µg/ml.
- The binding of A77 1726 to human serum proteins was examined over a wider concentration range (20 → 200 µg/ml) in vitro by equilibrium dialysis, indicating that binding was independent of concentration. The unbound fraction averaged $0.26 \pm 0.01\%$ over this concentration range, consistent with that observed at lower concentrations ($0.39 \pm 0.10\%$).
- Protein binding was also studied at higher concentration range of 89 → 839 µg/ml. At concentrations from 89 → 573 µg/ml, the mean binding was 99.5%. But at 839 µg/ml binding was diminished (98.7%) and the free fraction was over double than that seen at lower concentrations.



Plasma A77 1726 concentrations in the pharmacokinetic and clinical studies have typically not exceeded 150 µg/ml. Consequently, the protein binding and the relationship between bound and free should be constant over the range of A77 1726 plasma concentrations observed or expected in the clinical use of leflunomide.

- No relationship between albumin concentration and protein binding could be obtained in another study.



- The protein binding of A77 1726 in RA patients was further investigated using plasma from patients in the multiple dosing study YU204. Plasma was obtained from 4 patients in each of the 3 dosing groups — 5 mg/day (50 mg loading dose), 10 mg/day (100 mg loading dose) and 25 mg/day (100 mg loading dose) — and included unlabelled A77 1726 concentrations ranging from ~4 µg/ml to ~100 µg/ml. As shown in the figure, the

percent unbound was comparable in all 3 groups and averaged 0.55% across the 3 groups.

- Due to high protein binding of A77 1726, the potential for protein binding interactions with warfarin, diclofenac, ibuprofen and tolbutamide was investigated in

Drug	Conc (µg/ml)	Mean Percent Change in Unbound Conc
Warfarin	1.0	3.5
	2.5	4.3
	5.0	-14.9
Diclofenac	0.5	50.0
	2.5	22.6
	5.0	47.8
Ibuprofen	20	12.7
	50	25.0
	75	17.0
Tolbutamide	50	43.5
	250	43.9
	400	30.5

vitro using equilibrium dialysis. The mean percentage change in unbound fraction of the potential interacting drugs in the presence of A77 1726 as used in the in vitro studies are summarized in the Table. The concentration of A77 1726 used was 10, 20 and 50 µg/ml. A77 1726 did not affect binding of warfarin, increased percent unbound of diclofenac by 23 to 50%, increased for ibuprofen, for tolbutamide % unbound increased from 31 to 44%. The protein binding of A77 1726 was not altered in the presence of warfarin, diclofenac or ibuprofen.

However, tolbutamide led to an

increase in the percent unbound of A77 1726, which was dependent upon the concentration of tolbutamide, but independent of concentration of A77 1726. Mean percent change in unbound fraction¹ of A77 1726 in the presence of tolbutamide is tabulated below.

A77 1726 ($\mu\text{g/ml}$)	Tolbutamide ($\mu\text{g/ml}$)		
	50	250	400
10	50.0	125	200
20	50.0	125	200
50	40.0	80	160
Mean	47.0	110	187

¹Percent change in binding from value obtained without tolbutamide.

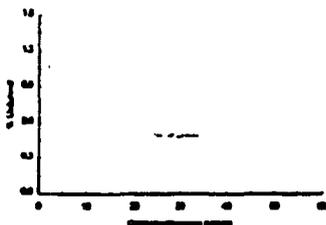
Protein Binding and dialysis

- The in vitro protein binding of A77 1726 was compared in plasma from 6 healthy volunteers, 6 patients with RA, and 12 patients with chronic renal insufficiency, most undergoing CAPD. Binding was determined in vitro with ¹⁴C-A77 1726 (100 $\mu\text{g/ml}$) using equilibrium dialysis and results summarized in the table below.

Population	% Unbound
Healthy Volunteers (n=6)	0.62 \pm 0.05
Patients with Rheumatoid Arthritis (n=6)	0.80 \pm 0.17
Patients with Chronic Renal Insufficiency (n=12)*	1.51 \pm 0.41

*Combination of groups with fresh and frozen plasma.

- The effect of dialysis on plasma protein binding of A77 1726 was also determined from study B101 NI patients, the free fraction was in the range between 0.44-1.37% in dialysis patients compared to mean values of 0.52-0.67% measured in healthy subjects at similar concentrations. The results were more variable as compared to normal subjects and rheumatoid patients and showed no obvious pattern relating dialysis to the extent of protein binding. However, there are insufficient number of subjects to make any firm conclusions regarding the influence of dialysis on plasma protein binding of A77 1726.
- Protein binding was also performed in a larger group of 50 subjects with chronic renal failure who were not part of study B101 NI. In this group the mean value of free fraction of A77 1726 was slightly higher than that seen in healthy subjects and very similar to that seen in rheumatoid patients. The values of free A77 1726 were in the range of 0.47-1.33%. There was an indication of a relationship between creatinine clearance and free fraction in that generally those patients with the lowest creatinine clearance had the highest free fraction of A77 1726. However, one patient (subject 10) did not fall into this trend (creatinine clearance 7.5 ml/min, free fraction 0.65%). Individual subject data is attached on pages A33 to A34 of the Appendix.



DRUG INTERACTIONS

(A) In Vitro Interactions

The potential inhibitory effects of leflunomide and the three metabolites, A77-1726, N-

(4'-trifluormethylphenyl)-2-cyano-acetamide (A81 3226) and TFMA-oxanilic acid, on cytochrome P450 isoenzymes were investigated using marker substrates and human liver microsomes. The specific marker enzymes and substrates are listed in the Table.

Isoenzyme	Marker Enzyme	Marker Substrate
CYP 1A2	Ethoxyresorufin deethylase	Ethoxyresorufin
CYP 2D6	Bufuralol 1'-hydroxylase	Bufuralol
CYP 3A4	Testosterone 6 β -hydroxylase	Testosterone
CYP 2C9	Tolbutamide 4-hydroxylase	Tolbutamide

The strongest inhibitions of all 4 isoenzymes were observed for leflunomide (see Table below). However, at clinical doses of leflunomide, plasma concentrations of the parent compound are rarely observed due to extensive first pass metabolism. Consequently, any interactions with other substrates could only occur during the first pass – with both substrates present – through the liver and/or gut wall. A77 1726 is the major circulating species and appears to inhibit CYP 2C9. Steady-state C_{min} values after dosing with 25 mg/day (Study YU204) averaged 63 μ g/ml, corresponding to 243 μ M, ~ 13-fold higher than the IC_{50} , implying that A77 1726 has the potential to inhibit the metabolism of CYP 2C9 substrates. Since non-protein bound drug is able to interact with the enzyme, the free plasma concentration may be a better predictor of potential inhibition. Assuming a free fraction of 1.3% in patients with RA, the free plasma concentration would be 3.2 μ M, approximately 6-fold lower than the IC_{50} , indicating the likelihood of inhibition.

IC_{50} (μ M) for leflunomide and metabolites				
Substance	CYP 1A2	CYP 2D6	CYP 3A4	CYP 2C9
Leflunomide	2.2 \pm 1.8	> 1000	51 \pm 39	210 \pm 120.4
A77 1726	> 500	> 1000	No Inhibition	17.7 \pm 71
A81 3226	No Inhibition	> 1000	81.9 \pm 133	No Inhibition
TFMA-Oxanilic Acid	No Inhibition	> 1000	No Inhibition	No Inhibition

The potential of A77 1726 to inhibit the metabolism of CYP 2C9 substrates was further investigated in vitro using diclofenac, a non-steroidal anti-inflammatory drug likely to be given concurrently with leflunomide. Non-steroidal anti-inflammatory drugs like diclofenac and piroxicam are substrates for CYP 2C9. Diclofenac (10 μ M) was incubated with A77 1726 (0.001 \rightarrow 1000 μ M, corresponding to 0.00026 \rightarrow 258 μ g/ml) in a human liver microsomal preparation and the formation of 4'-hydroxydiclofenac determined. A77 1726 inhibited the formation of 4'-hydroxydiclofenac with an IC_{50} of 64 \pm 40 μ M. The inhibition appeared to be non-competitive with a K_i of 46 μ M. Extrapolating in vitro data of this type to the in vivo situation is difficult. However, the clinical trials showed no differences between patients taking leflunomide concomitantly with diclofenac and those not taking diclofenac, indicating that any potential interaction in man may not be of clinical significance.

(B) In Vivo Interactions

With oral contraceptive, Triphasil® (Study # ZA101):

Study ZA101 examined the effect of leflunomide on antiovolatory effect of a low dose (combination) oral contraceptive agent Triphasil® (levonorgestrel/ethinyl estradiol) in 34 healthy premenopausal Caucasian females.

This study was extended over three menstrual cycles (~12 weeks). After a control cycle to demonstrate ovulation, defined as a serum progesterone concentration > 10 nmol/L, subjects received 2 cycles of Triphasil® (Akromed Products [Pty] Ltd.), the first without leflunomide and the second with leflunomide administered at a dose of 100 mg/day on Days 1 → 3 (loading dose) followed by 20 mg/day on Days 4 → 20. On Days 21 and 22 of the second cycle, 20 g of activated charcoal in 40 ml of water was administered every 6 hours to enhance the elimination of A77 1726. Pre-dose blood samples were collected through 28 days and analyzed for A77 1726 and progesterone. Plasma concentrations were measured during cycle 3 on days 1, 2, 3, 4, 10, 14 and 21 to demonstrate steady-state concentrations and on days 23 and 28 to demonstrate elimination of A77 1726 from the body. Details of study design are given on page A35 of the Appendix.

The mean plasma A77 1726 concentrations (µg/ml)-trough levels are tabulated below.

Day	Mean (µg/ml)	CV%	Range
1	0.08*	-	
2	9.29	20.4	
3	19.6	18.1	
4	29.9	18.8	
10	33.5	19.5	
14	36.3	21.3	
21	39.1	23.0	
23	19.0	53.6	
28	15.5	57.0	
40	8.50	0.00	

* All but 2 subjects had values below LOQ=0.10µg/ml
Protocol violations were made for sampling days for 7 subjects (sampled on day 11, 12, 15, 25, 28, and 32)

By reviewing the individual subject data it was observed that on Day 1 two subjects had detectable levels, 0.90 and 33.9 µg/ml. The applicant has omitted the 33.9 µg/ml value to calculate the mean of 0.08 µg/ml. This observed concentration cannot be explained based on the pharmacokinetics of leflunomide. Protocol violation states that for this subject (#14) the 0 h blood sample was taken 2 minutes after ingestion of leflunomide on day 1.

Steady state appears to have reached

between days 14 and 21. Rapid elimination was observed with the ingestion of activated charcoal on days 21 to 23, the mean levels decreased from 39 to 19 µg/ml within 2 days (days 21 to 23), thereafter, elimination was notably slower, the mean value decreasing only to 15.5 µg/ml over 5 days (days 23 to 28). The plasma concentration profile is attached on page A36 of the Appendix.

Serum progesterone concentrations were determined to prove ovulation (progesterone concentrations of 10 nmol/l or higher) during cycle 1 and to prove suppression of ovulation during cycles 2 and 3. Subjects enrolled into the study had mean plasma progesterone concentrations indicating that all were ovulating (plasma progesterone > 10 nmol/L). Administration of Triphasil® reduced mean progesterone concentrations to 1.42 nmol/L (see Figure), with a maximum value of 4.57 nmol/L, indicating an antiovolatory effect in all subjects (plasma progesterone ≤ 10

nmol/L). When leflunomide was co-administered with Triphasil®, mean progesterone concentrations were comparable (1.73 nmol/L) (see Figure) and the maximum value was 2.81 nmol/L, indicating no effect of leflunomide on the antioovulatory action of the oral contraceptive. The LOQ for progesterone was 0.3 nmol/L.

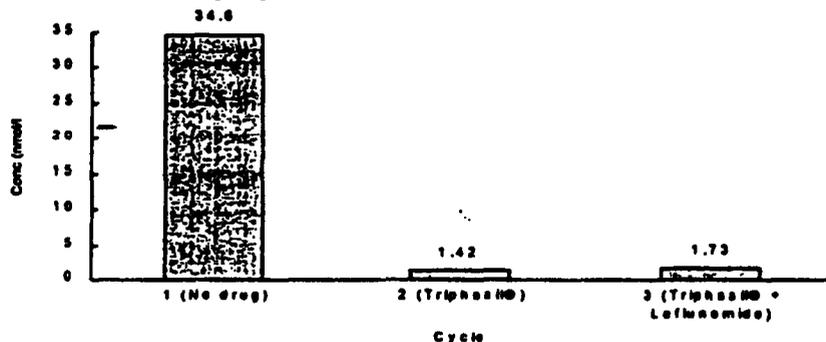


Figure: Effect of Concomitant Administration of Leflunomide and Triphasil® on Mean Plasma Progesterone Concentrations

The risk of ovulation by concomitant treatment of leflunomide and Triphasil® was calculated for solving the following equation for r ;

$$\sum_{r=0}^0 {}^{32}C_r (1-r)^{32-r} = (1-r)^{32} = 0.05$$

and was found to be 8.94%.

Methotrexate (Study # 2 F01):

Methotrexate (MTX) is considered to be the “gold standard” disease modifying antirheumatic drug (DMARD) in the treatment of RA. It is reasonable to expect that patients may receive leflunomide and MTX concomitantly. The primary objective of this study was to evaluate the safety of the addition of leflunomide treatment in subjects whose RA had remained active despite MTX therapy for at least 6 months at doses of ≥ 15 mg/wk, or ≥ 10 mg/wk in the event of documented intolerability. The secondary objectives were to evaluate the pharmacokinetics and potential efficacy of the agents used in combination.....

This study report presents data for the first 12 months of treatment. The planned therapy is for 24 months or as long as the clinical benefit continues. Patients were to have been treated with MTX for at least 6 months, on a stable dose of MTX for ≥ 4 weeks before entry into the study and have active RA. After a leflunomide loading dose of 100 mg/day for 2 days, patients received 10 or 20 mg of leflunomide per day in addition to their weekly dose of MTX, and continued on the combination therapy for 12 months or as long as clinical benefit occurred.

Plasma concentrations for measurement of MTX and/or leflunomide were collected at up to 4 visits from 11 subjects from one center. Visit 1 was prior to leflunomide administration and Visits 2 \rightarrow 4 occurred 40 to 80 days after the preceding visit, with the

exception of 2 patients for whom Visits 3 and 4 were separated by 449 and 191 days. Other details are on page A37.

As shown in the table below, there was no significant effect of visit (pre and post leflunomide) on any of the methotrexate pharmacokinetic parameters. Maximum A77 1726 plasma concentrations after the first 100 mg loading dose were consistent with that obtained in other studies and no apparent change in C_{max} during the maintenance dose was observed. Maximum concentration of TFMA was also within the limits observed in other studies. Pharmacokinetics of methotrexate and A77 1726 do not seem to be altered in this study. Parent leflunomide concentrations have not been measured.

Table: Mean \pm Sd parameters for MTX in patients receiving concomitant leflunomide

Parameter ^a	Baseline Visit 1	Week 6 Visit 2	Week 12 Visit 3	Week 24 Visit 4	p-value ^b
C_{max} (μ M/mg)	0.049 \pm 0.014	0.052 \pm 0.010	0.049 \pm 0.013	0.050 \pm 0.018	0.7920
t_{max} (hr)	2.06 \pm 0.56	1.83 \pm 0.83	1.63 \pm 0.83	1.56 \pm 0.73	0.3523
AUC _{0-8h} (hr x μ M/mg)	0.18 \pm 0.049	0.20 \pm 0.033	0.20 \pm 0.056	0.19 \pm 0.056	0.1735
AUC _{last} (hr x μ M/mg)	0.24 \pm 0.067	0.28 \pm 0.061	0.25 \pm 0.087	0.25 \pm 0.10	0.3718

^a C_{max} and the AUCs were normalized for dose. AUC_{0-8h}: area under the curve to 8 hours; AUC_{last}: area under the curve to the last time point with a concentration > LOQ.

^bp-value for visit effect from an Analysis of Variance (C_{max} and AUCs) or Wilcoxon Rank Sum Test (t_{MAX})

This can also be demonstrated by the plots of individual values for dose-normalized AUC_{last} and C_{max} as a function of visit.

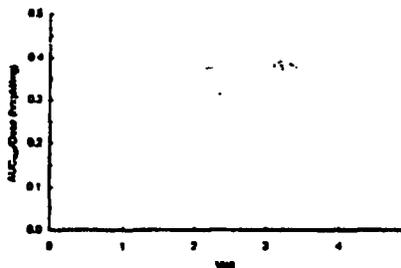


Fig: Dose-normalized MTX AUC_{last}

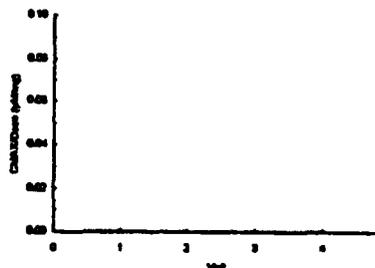


Fig: Dose-normalized MTX C_{max}

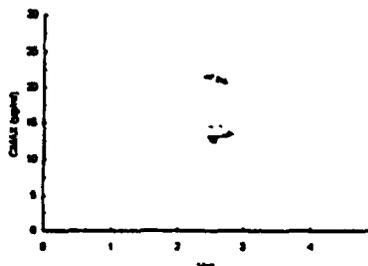


Fig: A77 1726 C_{max}

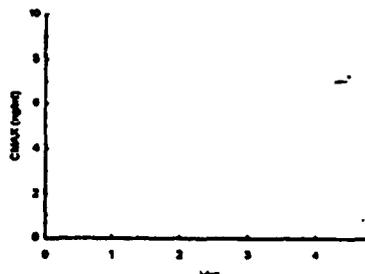
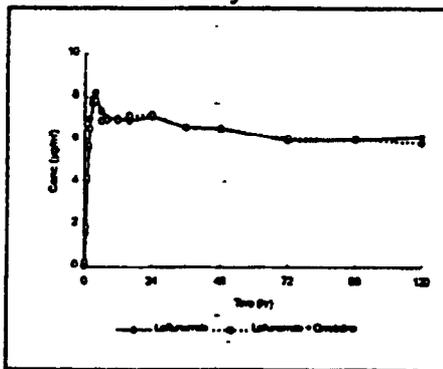


Fig: TFMA C_{max}

Two incidences (subject 55013 and 56005) of grade III-IV elevated LFTs were observed, but unfortunately PK assessment was not done in these subjects, hence the reviewer is unable to make any judgment regarding the correlation between the observed effect and the pharmacokinetic parameter observed from those individuals in this study. These subjects discontinued from the study participation.

Cimetidine (Study #1032):

Leflunomide is metabolized to A77 1726, most likely during presystemic and/or first-pass metabolism, therefore, the potential for drug-interaction exists when co-administered with drugs that affect the cytochrome P450 mixed function oxidase system. Cimetidine may alter absorption, compete for renal tubular secretion and affect hepatic blood flow. The objective of this study was to determine the single dose pharmacokinetics of leflunomide and its metabolites A77 1726 and TFMA alone and after multiple doses of cimetidine. Details of the study design are sketched on page A38 of the Appendix. Plasma samples were collected for 120 hours after each leflunomide dose from 12 male subjects and analyzed for leflunomide, A77 1726 and TFMA. Cholestyramine was also administered on day 11.



Mean plasma A77 1726 concentrations were essentially superimposable after administration of leflunomide alone or following 5 days of dosing with cimetidine (see figure). There were no differences between treatments in C_{max} or AUC and the 90% confidence intervals for both parameters were within the 80% → 125% range indicating equivalent exposure to A77 1726 under both conditions.

Fig: Mean plasma concentrations of A77 1726 after administration of leflunomide with and without cimetidine (300 mg qid x 10 days) to healthy volunteers

Mean ± SD pharmacokinetic parameters for A77 1726 and 90% confidence intervals are tabulated below.

Parameter	Leflunomide alone	Leflunomide + Cimetidine	p-value ^a	90% Confidence Interval
C_{max} (µg/ml)	8.33 ± 0.97	8.57 ± 1.58	0.661	94% → 110%
t_{max} (hr)	3.59 ± 1.08	15.0 ± 27.9	N/A	N/A
AUC_{0-120} (hr x µg/ml)	762.6 ± 88.1	768.0 ± 109	0.986	96% → 104%

^a p-value from treatment effect of the ANOVA

Leflunomide was detected in the plasma (LOQ 5 ng/ml) sporadically in about 50% of the subjects when leflunomide was administered alone and in 11 of the 12 subjects when

coadministered with cimetidine. The majority of concentrations were ≤ 50 ng/ml, although a few higher concentrations were observed. TFMA could be detected in all subjects at early times after administration of leflunomide. No pharmacokinetic or statistical analyses were performed because of the sparse data. The frequency distribution plots for leflunomide and TFMA is shown below.

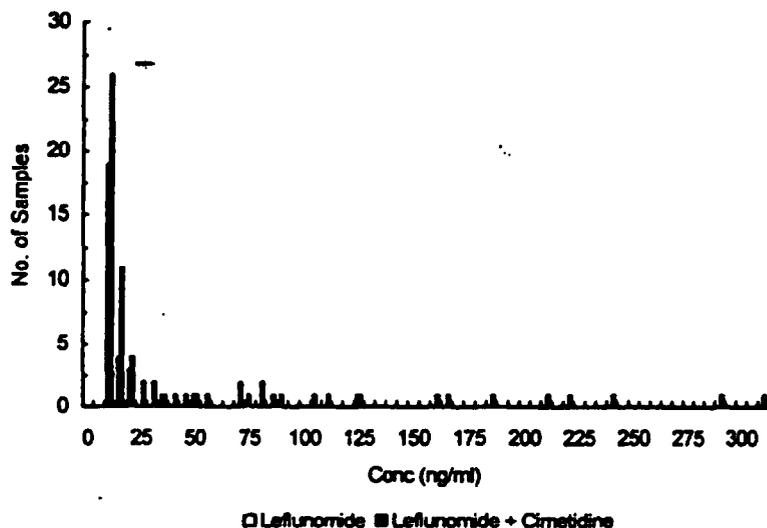


Fig: Frequency distribution of leflunomide plasma concentration

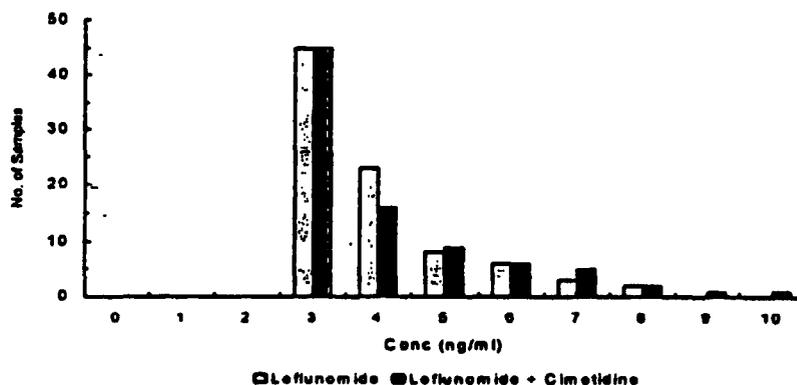
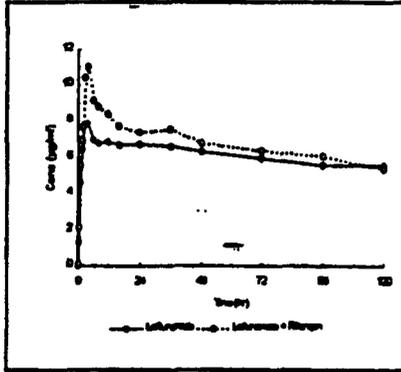


Fig: Frequency distribution of TFMA plasma concentration

The sponsor has taken measures to acidify the plasma pH to 3 to 4 for leflunomide assay upon collection of samples to prevent its breakdown to A77 1726 under basic conditions.

Rifampin (Study # 1033):

Rifampin is a non-specific cytochrome P-450 inducer. The objective of this study was to determine the single dose pharmacokinetics of leflunomide and its metabolites A77 1726 and TFMA alone and after multiple doses of rifampin. Details of study design are sketched on page A39 of the Appendix. Plasma samples were collected for 120 hours after each leflunomide dose from 12 male subjects and analyzed for leflunomide, A77 1726 and TFMA. Cholestyramine was also administered on day 13.



Mean plasma A77 1726 concentrations were higher after administration of leflunomide following 8 days of dosing with rifampin (see figure) and there was a small, but statistically significant increase in C_{max} . The individual subject increase in C_{max} is shown on page A40. Although the increase in AUC was statistically significant, the 90% confidence interval (105% → 115%) was within the 80% → 125% range, indicating that the net exposure to A77 1726 under both conditions was equivalent.

Fig: Mean plasma concentrations of A77 1726 after administration of leflunomide with and without rifampin (300 mg/day x 12 days).

Mean ± SD pharmacokinetic parameters for A77 1726 and 90% confidence intervals are tabulated below.

Parameter	Leflunomide alone	Leflunomide + Rifampin	p-value ^a	90% Confidence Interval
C_{max} (µg/ml)	8.17 ± 1.32	11.4 ± 2.02	0.001	129% → 148%
t_{max} (hr)	5.21 ± 5.98	3.17 ± 1.40	N/A	N/A
AUC ₀₋₁₂₀ (hr x µg/ml)	732.3 ± 74.0	809.5 ± 105	0.003	105% → 115%

^a p-value from treatment effect of the ANOVA

Seven out of the 12 subjects had detectable plasma concentrations of leflunomide when leflunomide was administered alone and 2 out of the 12 subjects after administration with rifampin. As illustrated in the figure below, the majority of concentrations from the leflunomide-only treatment and all from the combination were ≤ 25 ng/ml. TFMA was observed sporadically in all subjects when leflunomide was administered alone and in most subjects when leflunomide was co-administered with rifampin, with the majority of concentrations for both treatments ≤ 10 ng/ml. Based on these data, rifampin did not appear to induce the formation of TFMA.

The frequency distribution plots for leflunomide and TFMA is shown below.

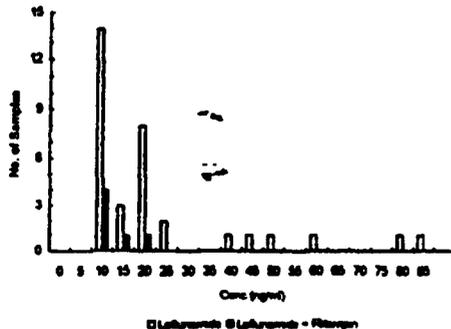


Fig: Frequency distribution of leflunomide plasma concentration

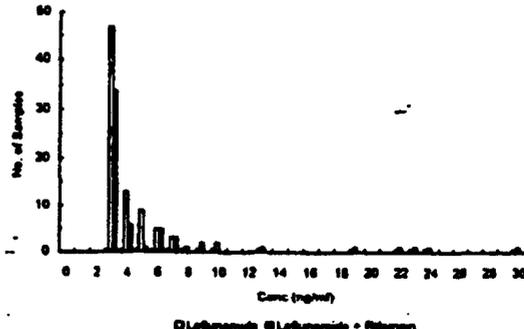


Fig: Frequency distribution of TFMA plasma concentration

Reviewers Comment

Mean plasma concentrations after a single dose of leflunomide are affected in the presence of rifampin, showing a statistically significant increase in C_{max} . The impact on the levels after chronic dosing with leflunomide in the presence of rifampin cannot be assessed from this study, hence, caution must be taken on concomitant administration of leflunomide with rifampin.

BIOEQUIVALENCE

Bioequivalence studies can be difficult for drugs with long elimination half-lives due to the extended period of time required for washouts between treatments. For leflunomide, 5 half-lives, or ~ 40 days in healthy volunteers, would be required between 2 treatments to ensure complete elimination of the previous dose. The applicant has utilized a "pseudo-simultaneous" or "semi-simultaneous" method as an alternative design that can result in comparable estimates of bioequivalence while shortening the overall length of the study.

In this approach, the administration of each study formulation is superimposed on the still-continuing elimination of A77 1726 from the preceding dose of leflunomide. Before administration of each study formulation, sufficient samples are taken over an appropriate time period to estimate the concentration time profile originating from the previous dose of leflunomide. The dosing intervals are arranged to ensure that the residual concentrations of A77 1726 in plasma from loading dose or from the first formulation are similar, when the first or second formulations, respectively are administered. Using an estimate of the elimination rate constant (λ_z) and the plasma concentration just prior to dosing, the observed plasma concentration-time curve is then "corrected" for the underlying concentration-time curve before calculation of the pharmacokinetic parameters used to estimate bioequivalence (C_{max} , t_{max} , and AUC).

The utility of the pseudo-simultaneous method for determining the bioequivalence between different formulations of leflunomide was tested in a 6 subject pilot study using 2 administrations of the same batch of 10 mg tablets. Results of this pilot study showed no significant differences between treatments in C_{max} , t_{max} , and AUCs and the 90% equivalence intervals for C_{max} and AUCs were well within the 80%→125% equivalence range in the pilot study. Hence, the applicant feels that this method would be suitable for the assessment of bioequivalence of different formulations of leflunomide. The study design was discussed with the agency during the development phase and was agreed to be an acceptable method. The details of the study design will be described in the following study with the equations used to calculate the corrected concentrations and the AUCs.

10 mg tablets used in clinical trials vs the to-be-marketed tablets (Study # 1036):

Twenty healthy male volunteers received a 20 mg loading dose (2 × 10 mg reference tablets) followed by 10 mg clinical or to-be-marketed tablets at 288 hours (13 days) and

624 hours (27 days), according to a randomized crossover. Plasma samples were collected for a total of 47 days and analyzed for A77 1726. To enhance A77 1726 elimination, 4 gm of cholestyramine was administered TID for 3 days beginning on Day 40. Details of study design and sampling schedule are attached on page A41 of the Appendix. For each treatment, plasma samples obtained 192, 144, 120, 72, and 24 hours before dosing were used to estimate the value of λ_z used to "correct" the observed plasma concentrations for the underlying concentrations from the previous dose. The different time points of the curve used to determine the $t_{1/2}$ and AUCs are also outlined in detail in the Appendix on pages A43-A44.

The main assumption behind using the psuedo-simultaneous approach for bioequivalence studies was that the concentration decline was monoexponential. With this assumption the entire mathematical approach to correcting the carryover effects from the previous dose is logical.

Details of their approach are discussed below. Separate exponential functions were adjusted to the five concentration-time data pairs obtained immediately before administration of each study formulation as follows:

$$C(t)_1 = C(0h)_1 \cdot \exp(-\lambda_1 \cdot t)$$

where, $C(t)_1$ = adjusted exponential function for the data preceding administration of the first study formulation
 $C(0h)_1$ = intercept at study time 0
 λ = rate constant

$$C(t)_2 = C(0h)_2 \cdot \exp(-\lambda_2 \cdot t)$$

where $C(t)_2$, $C(0h)_2$ and λ_2 are the corresponding term from the second study.

The corrected concentration were calculated as follows:

$$C(t)_{\text{corrected}} = C(t) - C(0h)_1 \cdot \exp(-\lambda_1 \cdot t) \quad \text{with } 288h \leq t \leq 408h$$

$$C(t)_{\text{corrected}} = C(t) - C(0h)_2 \cdot \exp(-\lambda_2 \cdot t) \quad \text{with } 624h \leq t \leq 744h$$

where $C(t)$ = observed concentration at time t

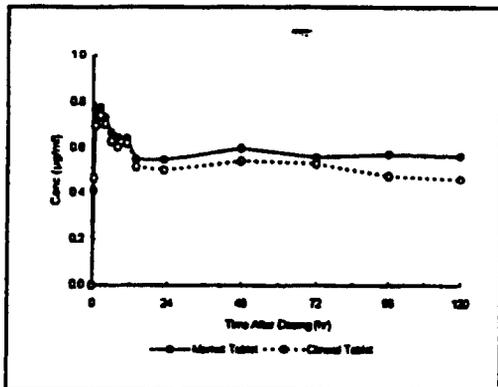
The "corrected" plasma concentration-time data were analyzed using non-compartmental methods. Data through 120 hours after each dose were used in the pharmacokinetic analyses. Although 20 subjects completed the study, only 16 could be evaluated for pharmacokinetics. Of the subjects that were not evaluated, 2 were due to lost samples and 2 were due to aberrant data that prevented calculation of elimination constant and needed to be corrected for previous doses.

AUD (area under concentration-time data) was calculated using linear trapezoidal rule for the first 23, 48, 72, 96 and 120 hours after administration of each study formulation. The area attributable to the carry over of A77 1726 was then subtracted from these AUD values according to the following formulae for the first and second study formulations, respectively.

$$\text{AUD}(288-311\text{h})_{\text{corrected}} = \text{AUD}(288-311\text{h}) - \text{AUC}(288-311\text{h})_1 \\ = \text{AUD}(288-311\text{h}) - C(288\text{h})_1 \cdot (1 - \exp(-\lambda_1 \cdot 23)) / \lambda_1$$

$$\text{AUD}(624-647\text{h})_{\text{corrected}} = \text{AUD}(624-647\text{h}) - \text{AUC}(624-647\text{h})_2 \\ = \text{AUD}(624-647\text{h}) - C(624\text{h})_2 \cdot (1 - \exp(-\lambda_2 \cdot 23)) / \lambda_2$$

where, $C(288\text{h})_1$ and $C(624\text{h})_2$ are the corrected concentrations



The mean plasma concentrations after administration of the clinical and market tablets, corrected for carryover from the previous dose or doses, were very similar (see figure). There were no significant differences between treatments in C_{max} or AUC over any of the measured time periods. As shown in the Table, 90% confidence intervals for C_{max} and all AUCs were well within the 80% → 125% equivalence range.

The results of this study demonstrate that the 10 mg

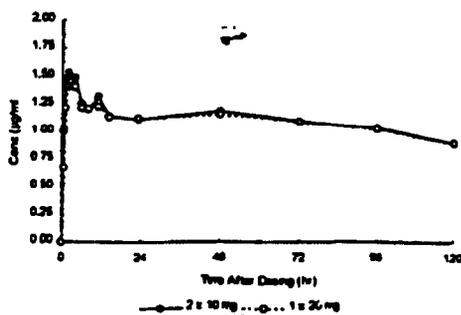
leflunomide tablet used in the clinical trials is bioequivalent to that which will be used for marketing.

Parameter	Clinical 10 mg	Market 10 mg	Ratio [%]	90% Confidence Interval
C_{max} (µg/ml)	0.83 ± 0.18	0.88 ± 0.20	107	102% → 113%
T_{max} (hr)	2.00 ± 0.95	10.4 ± 29.4	122	
AUC (hr x µg/ml)				
0 → 23 hr	13.3 ± 3.07	14.0 ± 2.70	106	101% → 111%
0 → 48 hr	26.4 ± 6.68	28.4 ± 5.39	108	101% → 117%
0 → 72 hr	39.3 ± 9.96	42.3 ± 8.38	108	101% → 116%
0 → 96 hr	51.5 ± 13.1	55.9 ± 11.6	109	102% → 116%
0 → 120 hr	62.8 ± 16.8	69.6 ± 14.9	111	103% → 120%

Leflunomide was detected in two plasma samples of one subject with concentrations of 5.3 ng/ml and 5.6 ng/ml on study days 1 and 2.

2x10 mg used in clinical trials vs. 20 mg tablet to-be-marketed (Study # 1030):

The study design was the same as the previous study and is outlined on page A42 of the Appendix. The mean plasma concentrations after administration of 20 mg doses of the 10 mg clinical and 20 mg market tablets, corrected for carryover from the previous dose or doses, were essentially superimposable as shown in the figure. There were no significant differences between treatments in C_{max} , t_{max} or AUC over any of the measured time periods. As shown in the Table, 90% confidence intervals for C_{max} and all AUCs were well within the 80% → 125% equivalence



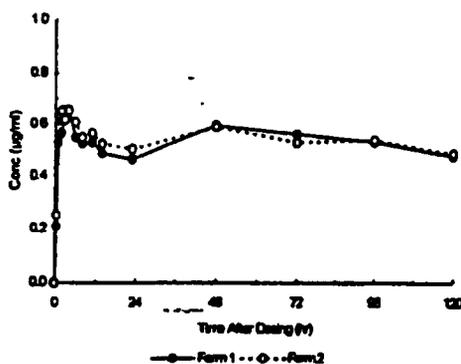
range. The results of this study demonstrate that the 10 mg leflunomide tablet used in the clinical trials is bioequivalent to the 20 mg tablet that will be used for marketing, i.e., the 2 tablets are dosage-form proportional.

Parameter	2 × 10 mg	1 × 20 mg	Ratio [%]	90% Confidence Interval
C _{max} (µg/ml)	1.68 ± 0.42	1.61 ± 0.42	96	90% → 102%
T _{max} (hr)	7.80 ± 14.1	9.20 ± 22.9	100	
AUC (hr × µg/ml)				
0 → 23 hr	26.8 ± 5.57	26.1 ± 6.04	96	92% → 102%
0 → 48 hr	55.6 ± 10.9	54.7 ± 11.8	97	92% → 105%
0 → 72 hr	83.2 ± 16.8	81.8 ± 16.5	97	92% → 105%
0 → 96 hr	109 ± 23.0	107 ± 20.7	98	93% → 105%
0 → 120 hr	132 ± 28.2	130 ± 25.0	98	93% → 105%

Plasma concentrations of leflunomide were below the lower limit of quantitation in most subjects, except in 5, where the values ranged from 5.2-7.2 ng/ml on days 2 and 3.

10 mg tablets using two different crystalline forms of the drug (Study #1035):

Form I and II are the two polymorphic forms of leflunomide which have the same solubility and dissolution profiles. The mean plasma concentrations after administration of 10 mg doses of the tablets prepared from Forms I and II, corrected for carryover from



the previous dose or doses, were essentially superimposable as shown in the figure. However, it cannot be concluded from the parametric statistical analysis that the formulations were bioequivalent. As shown in the Table, the 90% equivalence interval for C_{max} was within the 80% → 125% equivalence range. However, the lower limit for the AUCs were < 80%. This was due to a higher variability in the data (39% CV) in this study compared to that observed in previous studies

using the same design (12%). This was a consequence of longer than usual values for t_{1/2} in some subjects following the loading dose, leading to overestimation of the carryover of concentrations from that dose and affecting the AUC calculations for the first study period. The distribution of log-transformed AUC values after correction for carryover was skewed on Day 1, but not on study Day 2. This skewing was not apparent in the data from the previous two bioequivalence studies employing the same study design. The resultant skewing of AUC values adversely affected the estimates of the confidence intervals.

The sponsor has requested that a nonparametric analysis of the data be acceptable to judge the bioequivalence between two forms of leflunomide. When calculated using a post-hoc nonparametric analysis, confidence intervals for C_{max} and all AUCs were within the 80% → 125% range (see Table below).

Parameter	Form 1	Form 2	90% Confidence Interval	
			Parametric	Non-Parametric
C_{max} (µg/ml)	0.79 ± 0.16	0.81 ± 0.17	91% → 116%	91 → 112
T_{max} (hr)	11.8 ± 18.3	22.0 ± 29.0		
AUC (hr x µg/ml)				
0 → 23 hr	12.5 ± 3.39	11.7 ± 3.27	74% → 113%	88 → 112
0 → 48 hr	26.2 ± 7.42	25.0 ± 7.09	74% → 118%	87 → 112
0 → 72 hr	39.6 ± 11.5	38.8 ± 11.8	75% → 121%	87 → 119
0 → 96 hr	52.4 ± 15.2	51.9 ± 16.3	76% → 122%	88 → 119
0 → 120 hr	64.7 ± 19.3	61.1 ± 20.1	77% → 121%	87 → 117

The results of this study demonstrate that although the polymorphic forms of leflunomide were not bioequivalent when inference is based on the parametric statistical analyses, they produce comparable plasma A77 1726 concentration-time curves.

Reviewer's Comment

The non-parametric test is not acceptable from the bioequivalence standpoint. The applicant had stated that Form II is present to the extent of <10% in a batch, however, it is also mentioned that the proportion of Form II tended to increase during storage. The polymorphic composition of the batches used in clinical and pharmacokinetic studies was requested by the reviewer along with stability information of Form II in a batch of the drug product. The data showed an increase of 7% of Form II in 12 months at 25 °C/60% RH. The percentages of Form II at 3 months in the batches 31, 32 and 33 were 2%, 27% and 11%. The percent of Form II in a given batch appears to be quite random. The percentages increased to 3%, 34% and 15%, respectively for the three batches at the end of 12 months. The pure Form II is not bioequivalent to Form I, but we cannot say that what percentage of Form II in a batch would really affect the bioavailability of the drug product. Hence, it would be recommended that the sponsor is able to prove the given percent in a batch would not make any difference. Recommendations have been given at the end of the review.

POPULATION PHARMACOKINETICS

The population pharmacokinetics section was reviewed with Dr. He Sun (Pharmacometric node for DPE III)

Two kinds of population analysis was done by the sponsor:

- **Interaction with charcoal/cholestyramine:** Total CL was 10 times higher than normal values. On average the effect from a single charcoal/cholestyramine lasted 7.1 h. Approximately 18.5% and 10.5% of the available A77 1726 was extracted from the body in men and women, respectively following a single dose.
- **Kidney disease:** Patients with kidney disease showed significantly increased CL (24%) and V (43%), resulting in increased half life (16%).

RA Patients

- **Age:** Age was used as a categorical value (below and above 53 yrs). CL of older group was 18.7% lower than that of younger group and t1/2 was 18.5% higher.
- **Body Size:** Height best related to CL and V.
- **Sex:** CL in women was 22% lower than in men.

Although age, sex, and height were statistically significant as single covariates in RA patients, there was no major reduction in variability by the combined model. The median values for CL and V in healthy subjects and patients with RA are listed in the following Table. These values are in good agreement with those obtained in Study 1024, in which healthy volunteers received 10 mg of A77 1726 by intravenous infusion. The mean values for CL and V were 31.3 ml/h and 10.6 L, respectively.

Median (95% CI) Pharmacokinetic Parameter Estimates in Healthy Subjects and Patients with RA		
Parameter	Healthy Subjects	Patients with RA
CL (ml/h)	30.1	26.9
V (L)	9.9	16.1

(B) Phase III Analysis

The Phase III analysis was using data from 742 of the 816 (91%) patients in the Phase III studies that received leflunomide. The demographics of the patients from the Phase III studies are summarized in the Table.

Summary of Demographic Data for Patients from the Phase III Studies	
Parameter	Mean ± SD
Age (yr)	58 ± 11
Weight (kg)	72 ± 14
Height (cm)	164 ± 9.0
Lean Body Mass (kg)	50 ± 9.0
Liver Function Tests	
SGOT (U/L)	20 ± 6.7
SGPT (U/L)	20 ± 10
SGGT (U/L)	39 ± 46

The following covariates were examined for potential effect on CL and/or V.

Continuous: age, weight, height, lean body mass, liver function tests (SGOT, SGPT, SGGT), renal function

Discrete: age (> 65 vs ≤ 65), sex (male vs female), smoking status (active, former, non-smoker), alcohol consumption (none, < 1 drink/day, ≥ 1 drink per day), SGOT (normal – ≤ 50 U/L, high – > 50 U/L)

Model development was done using the data from 491 patients in Study 302, validated using the data from 251 patients in Studies 301 and 303, and then finalized using data from all 742 patients. Smoking status, SGOT (as a continuous variable), and lean body mass were the significant covariates. The final equations for CL and V were as follows.

$$CL = 23.0 \times (1 + SMOK \times 0.383) \times \left(\frac{20}{SGOT} \right)^{0.097}$$

and

$$V = 11.5 \times \left(\frac{LBM}{50} \right)^{0.372}$$

Conclusions

As noted above for the Phase I/II analysis, the estimates of CL and V were consistent with those estimated from i.v. administration of A77 1726.

- **Smoking:** Smoking appeared to have the greatest impact on CL, with a 38% increase in patients that were active smokers.
- **Liver Function:** The clearance was decreased in patients with increased liver enzymes (SGOT and SGPT). When SGOT increases to 100 u/L, a 15% decrease in CL was calculated.
- **Sex:** There were also modest increases in CL (20%) and V (18%) in male as compared to female patients.
- **Age:** Although age was a significant covariate in the Phase I/II analysis, age as either a continuous or discrete variable was not a significant covariate in the Phase III analysis, which is more representative of the target population.
- **Drug-Interactions:** The drugs that were most commonly administered with leflunomide were acetaminophen (40%), diclofenac (32%), prednisolone (18%), folic acid (16%), prednisone (16%), and naproxen (13%). Cimetidine and ranitidine also showed no significant interactions. None of these drugs had a demonstrable effect on the clearance of A77 1726.
- **Interaction with cholestyramine:** Of the 742 patients, only 7 received cholestyramine, and demonstrated a 40% increase in CL, consistent with observations from phase I/II analysis.
- No leflunomide was detected in any of the samples (163 samples). TFMA concentration was not detectable in 66 samples (25%) and was measurable in 202

samples (75%), although concentrations were < 25 ng/ml did not appear to increase over time.

- Based on the Phase I/II population analysis, a plasma A77 1726 concentration of 13 µg/ml appeared to give the maximum probability of a positive response. In the Phase III analysis, 96% of patients had a steady-state concentration > 13 µg/ml after daily administration of 20 mg of leflunomide, including patients with increased clearance as a consequence of smoking. Cholestyramine was the only concomitant medication to affect the pharmacokinetics of A77 1726, an interaction that is known and recommended for enhancing elimination. It appears, therefore, that 20 mg per day is sufficient for most RA patients regardless of demographics or concomitant medication.

Reviewer's Comments

- *The sponsor had three types of data set, (1) data set with blood samples with known dosing and sampling time (N=1964), (2) data set with blood samples with at least one known (N=2642) and (3) data set include large amount of samples without dosing and sampling time information (N=8013).*

Upon the reviewers request, the sponsor conducted population PK analysis for each of the three data sets. Comparison of the results showed that the structural parameters were not significantly different among the three analysis while variance parameters are somewhat different. Considering the fact that the half-life of the drug is 10-20 days and the maximum error in time recording may not exceed 1 day, increasing sample size will increase the accuracy of variance parameter, and the validation results, the analysis results based on the 2nd data set (n=2624) was accepted.

- *The treatment of outliers was questioned. Upon the review of sponsors response, since the majority outliers are those blood samples with zero observations. The treatment of outliers was acceptable.*
- *The Validation procedure is well conducted and accepted. The reviewer appreciated the sponsor's effort in the validation of the final model.*
- *The findings of the study results contributed to the overall understanding of the pharmacokinetics of A77 1726. The contributions of covariance to the CL and Vd of the drug should be included in the drug labeling for prescription information.*
- *Gender effect appears to be statistically significant. Such differences will be enhanced between male smokers and female non-smokers, and, maybe at a clinically significant level.*

IN VITRO DISSOLUTION

For leflunomide two polymorphic forms (I and II) are known which are practically insoluble in aqueous media. The solubility at 25°C was found to be at 23 mg/l at pH 1.2,

and 21 mg/l at pH 4.8 and pH 6.8 demonstrating independence of the pH of the solvent.

Test Conditions

Acceptance Criteria:

Conclusions

- **Influence of dissolution medium:** For 10 and 20 mg tablets dissolution profiles were identical for water and HCl. Dissolution complies with specification irrespective of medium.
For 100 mg tablets rapid and complete dissolution occurs
- **Influence of agitation:** 10 mg tablets were not influenced by agitation. The 20 mg and 100 mg tablet were slightly influenced by agitation.
- **Influence of different specific surface area:** Low dissolution rates were found for tablets containing leflunomide. For tablets containing drug substance having SSA within the specified range dissolution was within the specified range.
- **Influence of polymorphism:** Dissolution is not influenced by polymorphism significantly, however a lower trend towards dissolution of tablets was seen that contained the combination of I and II (75:25) and pure Form II.
- Based on the pharmacokinetic characteristic of leflunomide, dissolution of tablets has no or minimal influence of pharmacokinetics and cannot be a rate limiting step regarding bioavailability and can only be used to characterize batch to batch uniformity. T_{max} , the clinical marker for absorption rate is dependent on both absorption rate and elimination rate. Because of the elimination process being longer for leflunomide compared to absorption, the sensitivity of T_{max} to changes in absorption will be smaller than with other drugs with faster elimination. The choice of loading dose depends on the maintenance dose, dosing interval, rate of absorption

and rate of elimination. In a pilot study, a plot of ideal loading dose/maintenance dose ratio as a function of absorption rate was constant.

Reviewer's Comment

The choice of this surfactant has not been discussed by the applicant. This medium will not simulate the physiological conditions, hence the dissolution test can only be used for batch to batch uniformity and in vivo performance of the 100 mg tablet cannot be assessed from the dissolution test. However, the 100 mg tablet is to be used for a loading dose only.

- *The specifications for the dissolution could be tightened a bit. Looking at the dissolution plots it was observed that [redacted] was dissolved in 30 minutes. Upon agreement with the Chemist, the specifications for the dissolution of leflunomide tablets should be changed to not less than [redacted] in 30 minutes. The applicant had made a statement in the chemistry section of the NDA that the specifications of [redacted] in 30 minutes was agreed by the FDA division of Biopharmaceutics. However, the agency had allowed the above specification, but not agreed to it.*

V. Overall Conclusions

- Leflunomide is extensively converted to the active metabolite A77 1726 during the absorption process by presystemic and/or hepatic first pass metabolism.
- The bioavailability of a 100 mg oral tablet relative to a solution was 80%.
- Leflunomide does not show any food effect at the 20 mg dose. Clinical trials (US 301 and MN 302) have been done irrespective of diet restrictions, however, the clinical trial MN 301 specifies doses to be taken with food.
- In patients with RA, the pharmacokinetics of A77 1726 are linear at doses from 5 mg to 25 mg per day. However, the variability was high in the 25 mg group. Steady state concentrations reached within 7 to 8 weeks, the elimination half-life is ~ 15 days. The 10 and 20 mg tablet are dose and dosage form proportional.
- In Phase II studies, plasma A77 1726 concentrations appear to be higher in female RA patients than in males, and among female patients, appear to increase with increasing age. However, age and gender were not significant covariates in the population pharmacokinetic analyses of the Phase III studies.
- If required for the treatment of overdose or toxicity, the elimination of A77 1726 can be enhanced by oral administration of activated charcoal or cholestyramine.
- The percent unbound to plasma protein for leflunomide averaged $0.53 \pm 0.06\%$ at concentrations ranging from 3 → 10 $\mu\text{g/ml}$ and 0.4% for A77 1726 over the range 0.75 → 573 $\mu\text{g/ml}$. In patients with RA, the unbound fraction of A77 1726 was ~ 0.8%.
- A77 1726 caused slight changes ($\leq 50\%$) in the percent unbound of warfarin, diclofenac, ibuprofen, and tolbutamide. Warfarin, diclofenac, or ibuprofen did not alter the protein binding of A77 1726. However, tolbutamide led to an increase in the

percent unbound of A77 1726 that was dependent upon the concentration of tolbutamide but not on the concentration of A77 1726.

- In vitro data suggests that A77 1726 may inhibit cytochrome P450 isoenzyme 2C9 and thus could inhibit the metabolism of CYP 2C9 substrates, such as diclofenac. However, analysis of the safety data in the Phase III studies showed no differences between patients taking leflunomide concomitantly with diclofenac and those not taking diclofenac, indicating that any potential interaction in man is not of clinical significance.
- Leflunomide did not affect the antioovulatory effect of an oral contraceptive (Triphasil®).
- The pharmacokinetics of A77 1726 and MTX do not appear to be altered by concomitant administration of leflunomide and MTX.
- There were no differences in the pharmacokinetics of A77 1726 when leflunomide was administered with cimetidine, a nonspecific cytochrome P450 inhibitor.
- Although plasma concentrations of A77 1726 were higher when leflunomide was co-administered with rifampin, a nonspecific cytochrome P450 inducer, AUCs were equivalent, indicating that the net exposure to A77 1726 was the same under both conditions. However, it is important to give consideration to the AUCs under steady-state conditions, unlike the single dose AUCs observed in the trial.
- The 10 mg tablet used in the clinical trials is bioequivalent to the 10 mg tablet intended for marketing, and when given at the same dose, bioequivalent to the 20 mg tablet intended for marketing.

Unresolved Issue

1. The applicant has requested the agency to allow the usage of 5 x 20 mg tablets as an alternative to 1 x 100 mg tablet as the loading regimen and would like to know whether the agency concurs that an in vivo bioavailability study between 1 x 100 mg and 5 x 20 mg tablet would not be warranted. This will be addressed separately and is not an approvability issue for the application N 20-905.

VI. Comments to be sent to the sponsor

1. The bioequivalence studies showed that pure polymorphic forms I and II were bioinequivalent from the biopharmaceutics stand point by the acceptable parametric method. The non-parametric method is not acceptable by the agency. The stability of form II in leflunomide 100 mg tablets at 25°C/60% RH showed a maximum increase of 7% in form II in 12 months. The percentages of form II at 3 months in drug product batches 31, 32 and 33 were 2%, 27% and 11%, respectively. The applicant needs to either give specifications for the percent of form II in a particular drug product, or demonstrate bioequivalence in a ratio of 70:30 of form I:II or the maximum intended ratio of I:II in a given drug product, or demonstrate by clinical studies that the percentage of polymorphic form II in a particular batch does not compromise the efficacy or safety of the product.

2. The recommended dissolution specifications should be changed from Q of in 30 minutes to Q of in 30 minutes based on the dissolution data submitted.

7/15/98

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm. D. EU-7/25/98

CC: NDA 20-905 (orig)
HFD-550/Div File
HFD-550/CSO/Cook
HFD-880(Bashaw/Tandon)
HFD-880(Lazor)
HFD-344(Viswanathan)
attn:CDR.B.Murphy

AE

**APPEARS THIS WAY
ON ORIGINAL**

Clinical Pharmacology/Biopharmaceutics Review

NDA: 20-905 (053)

SUBMISSION DATE: 8/21/98

PRODUCT: Leflunomide Tablets

SPONSOR: Hoechst Marion Roussel, Inc REVIEWER: Veneeta Tandon, Ph.D.

Response to Comments

- Response to Item 3 dated August 20th, 1998

Upon consideration of the data submitted we concur with the setting of a specification of no more than _____, of leflunomide Form II in the drug product.

- Response to Item 4 dated August 20th, 1998

Examination of the data provided for the 20 mg tablet suggests that there would be up to a ~ 18% failure rate for individual tablets, using a _____ specification. On the basis of this we recommend that a dissolution specification of _____ at 30 minutes be adopted. In practice at the S1 level this would result in a specification of: _____ in 30 minutes according to the current USP 23 acceptance table for immediate release drug products.

8/26/98

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm. D. ED 8/20/98

CC: NDA 20-905 (053)
HFD-550/Div File
HFD-550/CSO/Cook
HFD-880(Bashaw/Tandon)
HFD-880(Lazor)
HFD-344(Viswanathan)
CDR ATTN: B. Murphy

CM