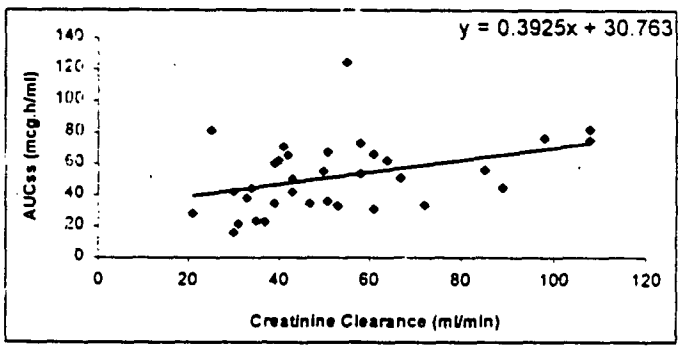
| parameter | units | CrCl 20-39 mL/min moderate | | | CrCl 40-60 mL/min mild | | | CrCl >60 mL/min normal | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | mean | %CV | median | mean | %CV | median | mean | %CV | median |
| $C_{max,ss}$ | [µg/mL] | 2.33 | 51.3 | 2.09 | 3.23 | 35.3 | 3.09 | 3.23 | 20.8 | 3.24 |
| $t_{max,ss}$ | [h] | 4.3 | 38.5 | 4.0 | 4.6 | 52.0 | 4.0 | 4.4 | 31.2 | 5.0 |
| $C_{min,ss}$ | [µg/mL] | 1.03 | 55.2 | 0.925 | 1.87 | 50.6 | 1.73 | 1.60 | 46.1 | 1.40 |
| $\lambda_z$ | [$h^{-1}$] | 0.0386 | 25.9 | 0.0392 | 0.0273 | 34.0 | 0.0302 | 0.0368 | 47.7 | 0.0309 |
| $t_{1/2}$ | [h] | 19.3 | 26.1 | 17.9 | 28.8 | 39.8 | 22.9 | 24.2 | 63.6 | 22.4 |
| $AUC_{ss}$ | [µg·h/mL] | 38.2 | 49.0 | 36.2 | 58.9 | 40.5 | 54.9 | 57.2 | 29.5 | 56.2 |
| MRTss | [h] | 30.1 | 22.7 | 30.2 | 43.8 | 30.1 | 38.1 | 39.7 | 53.3 | 33.5 |
| Cl/f | [mL/min] | 8.02 | 46.2 | 6.95 | 4 80 | 34.4 | 4.55 | 4.80 | 34.3 | 4.44 |
| Vd/f | [L] | 12.6 | 37.3 | 13.1 | 11.3 | 38.9 | 10.5 | 9.11 | 45.9 | 7.89 |
| free fraction | [%] | 0.926 | 23.3 | 0.823 | 0.661 | 34.1 | 0.695 | 0.545 | 32.4 | 0.561 |

A bar diagram in the Appendix on page 59 shows the comparison of mean pharmacokinetic parameters for each impairment group. The confidence interval and p-values for group differences is also attached in the Appendix on page 60. Significant difference between healthy and moderately impaired patients were seen in the $AUC_{ss}$, $C_{max,ss}$, $C_{min,ss}$ and CL values.

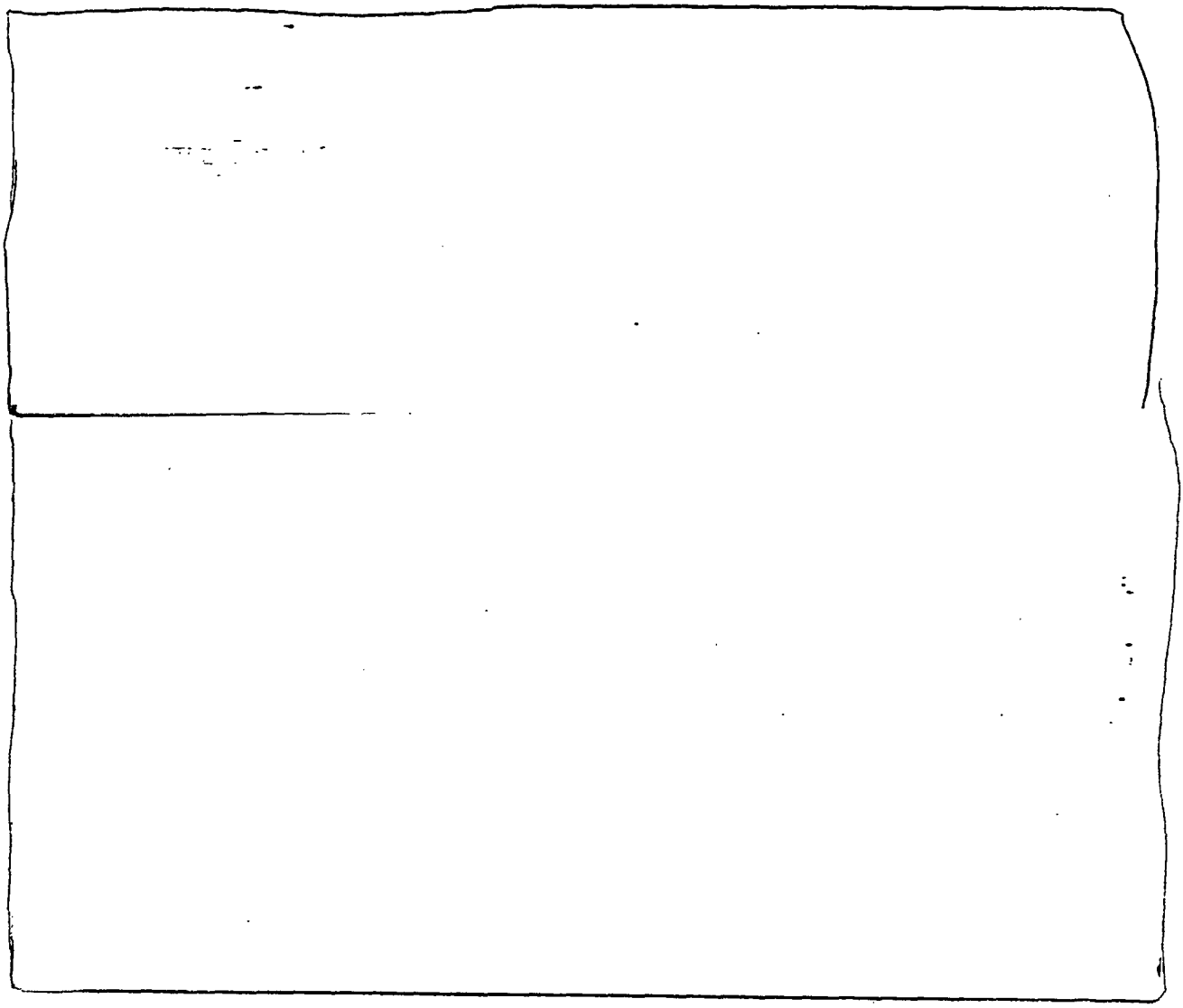
The graphical representation of renal function impairment is shown in the adjacent figure. Considering a uniform linear dependence of $AUC_{ss}$ from baseline creatinine clearance, the gradient of the regression line is +0.3925(µg.h/ml)/(ml/min). The 2-sided 95%confidence interval for this gradient is [+0.092, +0.700] (µg.h/ml)/(ml/min), indicating a significant dependence.




The higher meloxicam clearance in subjects with creatinine clearance≤40 may be due to increased fraction of unbound meloxicam which is available for hepatic metabolism and subsequent excretion.

*Protein binding in renally impaired*

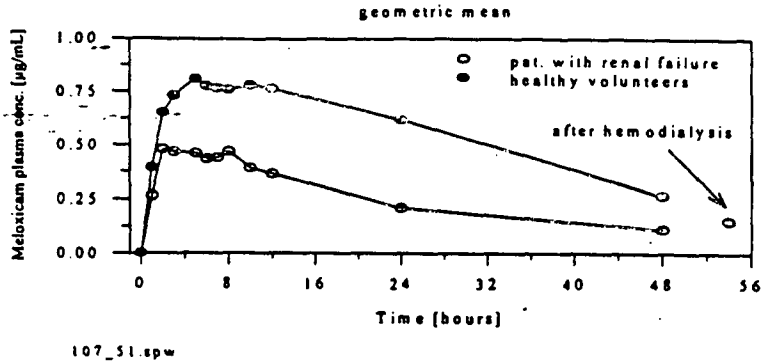
Impairment of renal function is known to affect the protein binding of highly protein bound drugs (more than 99%). The protein bound fraction of meloxicam in plasma samples from this trial was evaluated. Plasma samples obtained 240 and 264 hours after the first administration of meloxicam, were pooled 1:1 to obtain enough plasma for ultrafiltration. 40 µg meloxicam was added per ml of plasma. A validated HPLC assay was used to determine the free meloxicam fractions in the plasma samples.



*Study 107.051: Pharmacokinetics of 15 mg meloxicam as a single oral dose in patients with end-stage renal failure on chronic hemodialysis*

Twelve volunteers (6M and 6F) with end-stage renal failure undergoing chronic hemodialysis completed this study along with twelve healthy volunteers matched for age (± 5) and gender. Meloxicam was administered one hour prior to breakfast as a single 15 mg dose in the morning after the last hemodialysis. The study was performed during two-day interval between two treatments with hemodialysis. Blood samples were collected predose and serially for 48 hours after administration before the next dialysis procedure. An additional blood sample was obtained after hemodialysis to check for the dialyzability of meloxicam. Other details of the study design are attached in the Appendix on page 67 along with the individual subject demographics on page 68.

The mean meloxicam plasma concentration in patients with end stage renal failure and healthy volunteers is shown in the following figure.




The mean and median pharmacokinetic parameters are shown in the following table.

| | | renal failure n = 12 | | healthy volunteers n = 12 | | |
|---|---|---|---|---|---|---|
| parameter | units | mean | %CV | mean | %CV | CI(95%) |
| $C_{MAX}$ | [µg/mL] | 0.590 | 35.9 | 0.977 | 21.2 | 22.7-52.7 |
| $t_{MAX}$ | [h] | 4.1 | 64.8 | 6.8 | 51.4 | 24.5-81.7 |
| $\lambda_Z$ | [$h^{-1}$] | 0.050 | 73.0 | 0.032 | 43.2 | 111-241 |
| $t_{1/2}$ | [h] | 17.9 | 46.0 | 26.1 | 58.1 | 41.5-90.0 |
| $AUC_{0-TLQC}$ | [µg·h/mL] | 12.6 | 50.6 | 29.5 | 29.9 | 22.7-52.7 |
| $AUC_{0-\infty}$ | [µg·h/mL] | 16.3 | 51.3 | 44.2 | 56.8 | 22.8-52.7 |
| $MRT_{TOT}$ | [h] | 26.6 | 42.3 | 40.6 | 53.9 | 44.5-80.9 |
| Cl/f | [mL/min] | 18.9 | 43.3 | 7.1 | 43.7 | 220-438 |
| Vd/f | [L] | 25.9 | 43.6 | 13.3 | 25.7 | 118-303 |
| 8 hours | postdose | | | | | |
| total | [µg/mL] | 0.483 | 40.2 | in Study 107.071: | | |
| free | [ng/mL] | 4.24 | 30.4 | | | |
| free | [%] | 1.01 | 53.0 | 0.296 | 35.6 | |

A considerable part of the total AUC was extrapolated; about 23% in renal failure patients and 27% in healthy subjects was extrapolated. The overall results did not change considering $AUC_{0-TLQC}$ instead of $AUC_{0-\infty}$. Patients with renal failure exhibited a 57% lower $AUC_{0-TLQC}$ and a 63% lower $AUC_{0-\infty}$ than matching healthy volunteers. The $C_{MAX}$ was lowered by 40%. Total maximum plasma concentration tended to be achieved earlier in patients on chronic dialysis. However, due to the occurrence of multiple peaks one should not give over consideration to these values. The lower AUC values for patients on chronic dialysis were consequently reflected in the 2.7 times higher total clearance (bound and unbound) values (+167%). The half life was shorter (-31%) as compared to the healthy volunteers. The volume of distribution was increased (+85%), but this reflects the volume of distribution during terminal phase. Dose normalized AUCs were plotted against the body weight of males and females, no significant trend was observed. These figures are attached in the Appendix on page 69. Individual subject pharmacokinetic parameters are attached in the Appendix on pages 70-71, no gender-related differences were observed in this group of patients.

*Assessment of dialysability of meloxicam*

Renal failure patients had received the next hemodialysis treatment two days after meloxicam treatment. The time of begin and end of treatment was not constant for all patients. An additional blood sample was taken from these patients after the end of the hemodialysis procedure to look for potential dialysability of the drug. The mean pre-and post-dialysis meloxicam plasma concentrations in patients with end-stage renal failure is tabulated in the following table.

| | BLQ set to 0 µg/ml | |
|---|---|---|
| | **Mean** | **%CV** |
| 48H postdose | 0.084 | 95.3 |
| After Dialysis | 0.083 | 118 |
| | BLQ ignored | |
| 48H postdose | 0.126 | 50.4 |
| After Dialysis | 0.167 | 10.9 |
| | BLQ set to 0.025 µg/ml | |
| 48H postdose | 0.092 | 76.9 |
| After Dialysis | 0.096 | 90.9 |

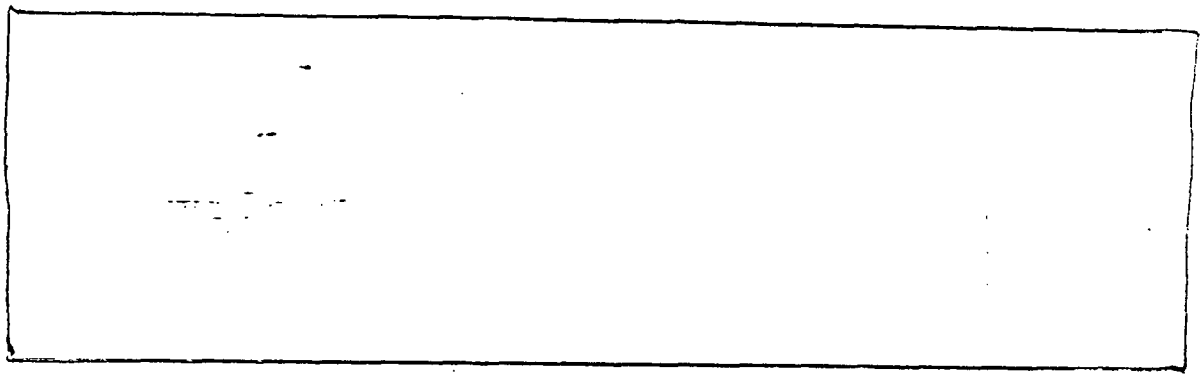
A relevant dialysability was not seen, probably due to high protein binding (>99%). These comparisons were actually hampered by the fact that only 8 out of 12 patients showed quantifiable concentrations at 48 hours after administration, of which, 2 values were close to 0.05 µg/ml (LOQ). Only 6 showed concentrations after hemodialysis. Hence, the sponsor took three approaches to calculate the concentrations, as seen in the table, all of which gave similar results. Therefore, there was no relevant decrease in plasma concentration of meloxicam after hemodialysis.

*Effect of protein binding in patients with end-stage renal failure*

The free meloxicam fractions after a single 15 mg dose for the different categories of subjects are tabulated below. The graph showing the total meloxicam clearance vs. the % free fraction of meloxicam has been attached in the Appendix on page 72 along with the individual subject free concentration data on pages 73-75.

| Category | Mean % Free Fraction |
|---|---|
| End-stage renal failure | 0.895 |
| Healthy males | 0.28 |
| Healthy females | 0.30 |

There seems to be an association between lower protein binding with higher meloxicam clearance. Due the higher free fraction in plasma, more meloxicam is metabolized per unit time, which leads to decreased values of total $AUC_{0-\infty}$. Meloxicam is eliminated by metabolism with approximately half of the dose excreted in urine and the remainder in feces; hence, a 2.7-fold increase (+167%) in clearance would not be expected based on a 63% decrease in AUC. A rough calculation of free $C_{MAX}$ and free $AUC_{0-\infty}$ values were 92% (0.0053 vs. 0.0029 µg/mL) higher in renally impaired patients in comparison to healthy volunteers while the calculated free $AUC_{0-\infty}$ was similar in both populations (0.1467 vs. 0.1326 µg·h/mL). The individual subject free $C_{MAX}$ is attached in the Appendix on page 76.



*Conclusions*

- Patients with end-stage renal failure exhibited lower total meloxicam plasma concentrations, but higher free fractions.
- Calculated maximum free concentrations were higher in patients with end-stage renal failure than healthy volunteers and calculated free AUCs were similar.
- The free fraction is considered critical for safety, therefore, a starting dose of 7.5 mg instead of 15 mg is recommended in patients with end-stage renal failure.
- No relevant decrease in plasma concentration of meloxicam after hemodialysis, hence, dialysis may not be an option for treatment of overdose.

*Study 107.081: Urinary excretion of $PGE_2$, 6-keto-$PGF_1$alpha and creatinine after administration of 3 x 50 mg diclofenac/day over four days or 30 mg meloxicam as a loading dose on Day 1 followed by 15 mg meloxicam/day for three days each (cross-over) in healthy female volunteers whose menstrual cycle is controlled by low-dose combined oral contraceptives ('minipill')*

Like all other NSAIDs meloxicam is an inhibitor of the prostaglandin biosynthesis. An intact cyclooxygenase system is needed for the production of vasodilator prostaglandins such as $PGE_2$ and $PGI_2$ to maintain renal plasma flow and glomerular filteration rate. Therefore NSAIDs which inhibit renal prostaglandin formation may cause reversible deterioration of renal function. For a large number of NSAIDs reduction of renal prostaglandin biosynthesis has been shown. Along those lines, this trial was conducted to evaluate the influence of meloxicam on intrarenal PG-synthesis. This trial was conducted only in females and urinary excretion of $PGE_2$, 6-keto-$PGF_1$alpha and creatinine were measured. It has been shown that urinary $PGE_2$ may reflect renal PG synthesis in women but not in men, since seminal fluid may contribute a highly variable fraction of the measured urinary PGs in men (*J. of Clin. Invest., 55, 763-770, 1975 and Prostagalndin, 18, 623-629, 1979*). The phases of menstrual cycle may influence the prostaglandin excretion in urine. This may be caused by an elevation of the concentration of $PGE_2$ and $PGF_2$ alpha in the endometrium which are resulting from an increased production of PGs by the endometrium during the luteal and menstrual phases of ovulatory cycles. Therefore, all volunteers were required to be in the second half of the menstrual cycle and the cycle was controlled by a minipill. A criteria was set that the $PGE_2$ baseline value of the first treatment would not be more than four-fold of the common geometric mean of the baseline value of all volunteers. As urinary volume varies greatly urinary creatinine

and creatinine clearance were measured. To determine whether therapeutic plasma levels of meloxicam were reached predose concentrations and an appropriate drug concentration-time profile on the last day of administration was measured.

Meloxicam was given as a single 30 mg loading dose followed by three 15 mg doses to achieve steady-state conditions. The meloxicam loading dose was given to ensure steady state conditions on day 4 of treatment. The reference treatment was 50 mg diclofenac (Voltaren®) enteric-coated tablets dosed t.i.d. for four days. Other details of the study design are summarized on page 77 of the Appendix.

*Results*

The total daily urinary excretion $PGE_2$ at baseline was 200 ng. The following table shows a reduction of about 38% following treatment with meloxicam compared with a reduction of about 30% following treatment with diclofenac. The percentage reduction observed after meloxicam treatment was the same in both periods, but this was not the case for diclofenac treatment, 23.5% and 37% for periods 1 and 2 respectively.

The mean total daily urinary excretion of 6-keto-$PGF_1$alpha of approximately 1 mg was reduced by approximately 20% following treatment with diclofenac and 35 % following treatment with meloxicam.

Urinary excretion of PGE2 (ng) over 24 hours in all subjects

Treatment Diclofenac

| Day | N | Mean | SD | Minimum | Maximum |
|---|---|---|---|---|---|
| 2 | 16 | 182.02 | 79.30 | 79.55 | 362.49 |
| 6 | 16 | 126.22 | 51.27 | 59.49 | 239.51 |
| 6-2 | 16 | -55.80 | 79.22 | -225.73 | 57.10 |
| Mean Reduction Day 6- Day 2 in % = 30.66 % | | | | | |

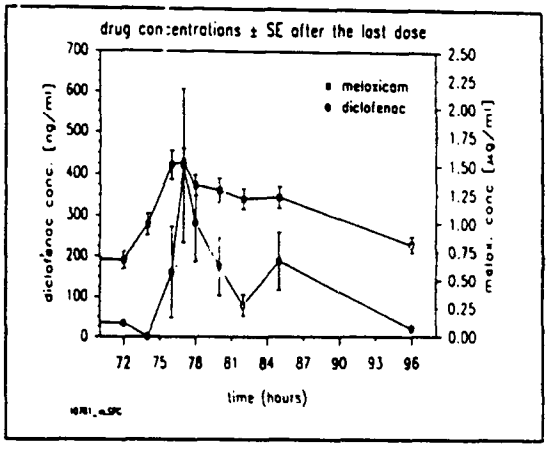
Treatment Meloxicam

| Day | N | Mean | SD | Minimum | Maximum |
|---|---|---|---|---|---|
| 2 | 16 | 211.95 | 110.557 | 76.22 | 490.20 |
| 6 | 16 | 130.55 | 59.928 | 54.43 | 251.80 |
| 6-2 | 16 | -81.40 | 98.134 | -400.42 | -2.34 |
| Mean Reduction Day 6- Day 2 in % = 38.41 % | | | | | |

Mean total daily creatinine was approximately 1.5 g. A slight increase (up to 3%) was observed following active treatment. Creatinine clearance was used as an easy monitor of renal function. A baseline mean of creatinine clearance of approximately 110 ml/min increased by 2% to 3% after both treatments. A reduction of $PGE_2$ production to levels impairing renal blood flow did not occur since no increase in creatinine or no reduction of creatinine clearance was observed. It may be possible that the 30 mg loading dose blocked the cyclooxygenase to a greater extent than it would have been if steady state was achieved gradually, because the baseline values and the values under medication would not be in the same menstrual cycle.

The mean plasma concentration profile and the pharmacokinetic parameters for meloxicam in healthy females are shown below.

| parameter | units | 15 mg meloxicam mean | %CV | median |
|---|---|---|---|---|
| $C_{MAX,SS}$ | [µg/mL] | 1.60 | 31.1 | 1.49 |
| $C_{PRE,SS}$ | [µg/mL] | 0.680 | 44.0 | 0.636 |
| $C_{MIN,SS}$ | [µg/mL] | 0.680 | 44.0 | 0.636 |
| $t_{max,ss}$ | [h] | 5.0 | 25.3 | 5.0 |
| $\lambda_z$ | [$h^{-1}$] | 0.0338 | 29.0 | 0.0329 |
| $t_{1/2}$ | [h] | 22.4 | 32.9 | 21.1 |
| $AUC_{ss}$ | [µg·h/mL] | 27.18 | 30.6 | 26.26 |
| $MRT_{TOT}$ | [h] | 35.0 | 30.2 | 33.7 |
| Cl/f | [mL/min] | 10.2 | 35.5 | 9.52 |
| Vd/f | [L] | 18.9 | 37.0 | 16.4 |




Meloxicam multiple dose pharmacokinetics was similar to those observed in the earlier studies. Diclofenac plasma concentrations varied from a mean pre-dose concentrations ($C_{PRE,SS}$) of 33.3 ng/mL (n = 10) to mean peak concentrations ($C_{MAX,SS}$) of 977.4 ng/mL

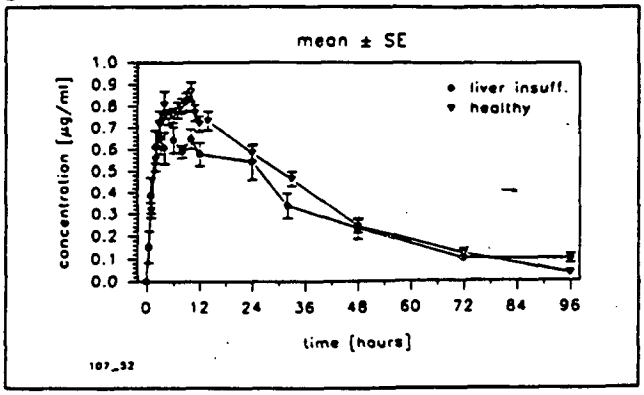
## (D) EFFECT OF HEPATIC IMPAIRMENT

*Study 107.052: Pharmacokinetics and tolerability of 15 mg meloxicam as a single oral dose in patients with liver insufficiency.*

Studies with radiolabeled meloxicam in man demonstrated that the parent compound accounted for over 90% of total radioactivity in the plasma; the drug appeared only in its metabolized form in the urine and feces. The results suggested that liver is involved in the metabolic clearance of meloxicam.

12 male subjects with mild to moderate liver insufficiency (according to Child-Pugh classification system) were enrolled in the study. 3 matching healthy volunteers were enrolled and 9 healthy volunteers were taken as historical controls. Subjects were administered a single 15 mg dose of meloxicam under fasting conditions. Other details of study design are given on page of the Appendix 78. The individual subject demographics are also attached in the Appendix on page 79.

The subjects were not analyzed based on the severity of hepatic impairment. The mean plasma concentration profile in healthy subjects and patients with liver insufficiency is shown in the adjacent figure. It was only at time points less than 2 hours that the patients with liver insufficiency showed slightly



higher plasma concentrations. At all other time points the levels were lower in the hepatic impaired subjects. A greater biological variation was seen in the patient group, as compared to the healthy subjects, as also seen in the table below.
The mean pharmacokinetic parameters are tabulated in the following table based on all subjects combined.

| | | impaired hepatic function (P) | | | healthy volunteers (H) | | | Ratio | 90% |
|---|---|---|---|---|---|---|---|---|---|
| parameter | units | mean | %CV | median | mean | %CV | median | P/H | CI |
| $C_{max}$ | [µg/mL] | 0.84 | 28.7 | 0.865 | 0.91 | 17.8 | 0.933 | 0.92 | 78-105 |
| $t_{max}$ | [h] | 10.3 | 86.5 | 8.0 | 7.0 | 55.8 | 5.0 | 1.47 | 57-185 |
| $\lambda_z$ | [$h^{-1}$] | 0.0458 | 29.9 | 0.0425 | 0.0344 | 23.1 | 0.0322 | 1.33 | |
| $t_{1/2}$ | [h] | 16.4 | 29.0 | 16.3 | 21.2 | 22.9 | 21.6 | 0.77 | 63-92 |
| $AUC_{0-tlqc}$ | [µg·h/mL] | 25.11 | 46.7 | 23.49 | 31.23 | 29.4 | 29.18 | 0.80 | 60-95 |
| $AUC_{0-\infty}$ | [µg·h/mL] | 27.24 | 45.2 | 25.28 | 35.09 | 29.8 | 31.24 | 0.77 | |
| $MRT_{tot}$ | [h] | 27.9 | 31.6 | 28.7 | 33.4 | 22.0 | 34.9 | 0.84 | 67-99 |
| Cl/f | [mL/min] | 11.1 | 44.4 | 9.92 | 7.70 | 28.5 | 8.02 | 1.44 | 110-168 |
| Vd/f | [L] | 14.4 | 29.2 | 14.5 | 13.5 | 18.9 | 12.8 | 1.06 | 87-124 |

Equivalence could not be demonstrated for all parameters tested, since the confidence intervals were beyond the limits of 0.8-1.25. The table also shows that patients with hepatic dysfunction tended towards lower peak plasma concentrations (-9.7%) and AUCs (-24.8%), with a more rapid elimination and higher clearance (+44%). The outcome of the parameters in the patient group was in the opposite direction to that expected when the role of the liver would be exclusively for elimination. A reasonable explanation of the faster elimination of meloxicam by patients with hepatic dysfunction could not be outlined, but the sponsor speculates that it could be potential perturbation of recirculation process, alterations in hepatic blood flow, extra- or intrahepatic shunting of blood or changes in bile flow. However, as meloxicam has a low clearance with a low hepatic extraction, any changes in hepatic blood flow would unlikely affect hepatic elimination of the drug. Another possible, but unlikely explanation could be the slightly higher unbound fraction as given below.

*Effect of protein binding*

The free meloxicam fraction in plasma was not different from that of the healthy controls. The percent unbound in plasma was 0.35 ± 0.215% in the hepatic impaired patients and 0.30 ± 0.105% in the healthy volunteers (from historical data). This comparison could be obtained from only 4 matched healthy volunteers. The unbound fraction also indicated higher variability in patients than in healthy controls. No correlation could be found between the extent of free fraction and the elimination behavior expressed by clearance (See figure and table in Appendix on page 82).

*Reviewer's Comment*

- *The sponsor had not analyzed the results based on the severity of liver dysfunction. The subjects were enrolled based on Child Pugh criteria for liver impairment, but then patients with mild moderate and severe impairment were not analyzed in separate groups. Additional analysis was requested from the sponsor*

- *Detailed scoring (i.e. no of ascites, albumin and prothrombin time etc) should be provided in summary tables. These scorings have been provided based on the Grade table according to Pugh, but the actual values have not been given. This table is attached in the Appendix on page 79.*
- *The study has been conducted in males only. It is recommended to use equal number of females in the study as well.*
- *One weakness of the study design is the use of historical controls in the trial, rather than concomitant controls.*

Results from the additional analysis performed by the sponsor based on the Child-Pugh Classification system upon request is summarized in the following tables.

| | | Pugh A (n=3) | | | Healthy (n=3) | | |
|---|---|---|---|---|---|---|---|
| Age | years | 48 | 21.9 | | 47.4 | 19.7 | |
| | units | gmean | g%CV | 95%CI | mean | %CV | 95%CI |
| $C_{MAX}$ | [µg/mL] | 0.74 | 36.7 | 0.38-1.45 | 0.90 | 9.4 | 0.75-1.07 |
| $t_{MAX}$ # | [h] | 6 | 2-4 | --- | 4 | 4-12 | --- |
| $AUC_{0-TLQC}$ | [µg·h/mL] | 22.1 | 86.3 | 5.4-90.0 | 29.3 | 34.4 | 15.6-55.0 |
| $AUC_{0-\infty}$ | [µg·h/mL] | 25.3 | 72.8 | 7.4-86.4 | 32.0 | 31.2 | 18.0-56.8 |
| $MRT_{TOT}$ | [h] | 29.3 | 33.9 | 15.7-54.5 | 29.0 | 23.6 | 18.7-45.0 |
| $t_{1/2}$ | [h] | 17.6 | 28.3 | 10.4-29.7 | 17.8 | 22.8 | 11.7-27.2 |
| Cl/f | [mL/min] | 9.89 | 72.8 | 2.9-33.8 | 7.81 | 31.2 | 4.4-13.9 |
| Vd/f | [L] | 15.0 | 39.5 | --- | 12.1 | 10.6 | --- |

| | | Pugh B (n=8) | | | Healthy (n=8) | | |
|---|---|---|---|---|---|---|---|
| Age | years | 46.7 | 17.6 | | 46.5 | 17.3 | |
| | units | gmean | g%CV | 95%CI | mean | %CV | 95%CI |
| $C_{MAX}$ | [µg/mL] | 0.87 | 23.3 | 0.55-1.39 | 0.92 | 22.4 | 0.71-1.19 |
| $t_{MAX}$ # | [h] | 8 | 1-24 | --- | 5 | 4-14 | --- |
| $AUC_{0-TLQC}$ | [µg·h/mL] | 23.1 | 48.7 | --- | 32.2 | 25.4 | --- |
| $AUC_{0-\infty}$ | [µg·h/mL] | 25.0 | 48 | 14.8-42.3 | 36.5 | 26.8 | 21.6-61.6 |
| $MRT_{TOT}$ | [h] | 25.2 | 37.6 | 16.6-38.3 | 35.7 | 18.3 | 29.0-44.0 |
| $t_{1/2}$ | [h] | 15.1 | 33.7 | 10.3-22.0 | 22.8 | 19.2 | 18.3-28.4 |
| Cl/f | [mL/min] | 10.0 | 47.9 | 7.4-13.5 | 6.86 | 26.7 | 3.9-12.0 |
| Vd/f | [L] | 13.0 | 33.5 | --- | 13.5 | 19.4 | --- |

#median and range

| | | Pugh C (n=1) | Healthy(n=1) |
|---|---|---|---|
| Age | years | 46 | 49 |
| | units | gmean | gmean |
| $C_{MAX}$ | [µg/mL] | 0.63 | 0.77 |
| $t_{MAX}$ | [h] | 10 | 3 |
| $AUC_{0-TLQC}$ | [µg·h/mL] | 20.5 | 18.8 |
| $AUC_{0-\infty}$ | [µg·h/mL] | 21.8 | 21.2 |
| $MRT_{TOT}$ | [h] | 30.0 | 22.7 |
| $t_{1/2}$ | [h] | 16.3 | 15.1 |
| Cl/f | [mL/min] | 11.5 | 11.8 |
| Vd/f | [L] | 16.2 | 15.4 |

As seen in the tables, no systematic trend could be obtained based on the Child-Pugh Classification system and the pharmacokinetic parameters. The 95% confidence intervals for the geometric means overlapped between the liver insufficient and the healthy matched pair. There was only one subject in Pugh C Class and the matched pair had the

lowest value for AUC and Cmax as compared with other healthy volunteers. No conclusive information could be drawn regarding the severely impaired subjects.

The relative ratios for $AUC_{0-\infty}$ and $C_{MAX}$ are shown in the following table.

| Parameter | Class | N | Relative Ratio Liver insuffieciency/Matched Control Geometric mean(%) |
|---|---|---|---|
| $AUC_{0-TLQC}$ [µg·h/mL] | All Subjects | 12 | 73 |
| | Pugh A | 3 | 79 |
| | Pugh B | 8 | 69 |
| | Pugh C | 1 | 103 |
| $AUC_{0-\infty}$ [µg·h/mL] | All Subjects | 12 | 75 |
| | Pugh A | 3 | 75 |
| | Pugh B | 8 | 72 |
| | Pugh C | 1 | 109 |
| $C_{MAX}$ [µg/mL] | All Subjects | 12 | 90 |
| | Pugh A | 3 | 82 |
| | Pugh B | 8 | 95 |
| | Pugh C | 1 | 82 |

Based on this assessment, the conclusions do not seem to be dependent on the hepatic insufficiency classification system used. The plasma concentration profiles based on the Pugh classification system and the geometric means of $C_{max}$ and $AUC_{0-\infty}$ with the matched healthy pair is attached in the Appendix on pages 80-81.

*Reviewer's Comment*

- *In classifying the patients based on Child-Pugh scores, the sponsor has given more stress on the amount of ascites present (a highly subjective variable). If the scores would be reclassified based on the albumin content, there would be 9 subjects in the mildly impaired category, 3 in the moderate and 1 in the severe. Even with this classification, looking at the tables provided, it does not seem that it would make any difference in the conclusions of the results. No obvious trend could be observed from the results. However, with only one subject in the severe category, no definitive conclusion could be drawn regarding this category. The matched healthy pair for this category too, had a lower value for $C_{max}$ and $AUC_{0-\infty}$ as compared to the other healthy volunteers. This also renders additional inconsistency to the results obtained.*

*Conclusions*

- There was no marked difference in the meloxicam pharmacokinetics between patients with mild to moderate liver impairment and healthy subjects. Hence dosage adjustment would not have to be made in these patients with hepatic dysfunction. These results are surprising given the involvement of the liver in the metabolism and recycling of meloxicam. A distinct possibility is that Child-Pugh criteria may not be appropriate for assessing drugs with this degree of recycling/metabolism.
- Patients with severe hepatic insufficiency have not been adequately studied and the use of meloxicam in this population should be done with caution using the lowest

dose and titrated up slowly.

## V.6 POPULATION PHARMACOKINETICS

*Report U97-2656: [redacted] population pharmacokinetic evaluation of meloxicam plasma concentrations derived from rheumatoid arthritis studies*

The purpose of this report was to evaluate the effect of age, weight, gender and concomitant medication on meloxicam plasma concentrations by population pharmacokinetic methods. Patients suffering from rheumatoid arthritis received repeated doses of meloxicam in order to evaluate the safety and efficacy of meloxicam as an antirheumatic agent. Doses varied from 7.5 mg to 60 mg. Compliance plasma samples were obtained at least seven days after the first dose and thus all concentrations were considered to be in steady state. Treatment lasted three weeks (Study 107.014 and 107.030) or six months (107.036) in three trials, which were included in this investigation. Drug plasma concentrations and respective times of sampling and last dose were treated as derived from a single dosing interval. The final database consisted of 1226 plasma samples derived for 586 patients and was analyzed by [redacted] using a one compartment model.

The 586 patients (141M, 445F) in the final evaluation had a mean age (range) of 54.6 (18-80) years, a mean weight of 68.6 (36-116) kg and a mean height of 164.7 (139-193) cm. A one compartment model was found to describe the plasma concentrations sufficiently well. A two compartment model and a recirculation model did not yield a relevantly better fit of the data. Sixteen patients (outliers) of the initial database (n=602) were excluded because of extreme pharmacokinetic parameters and drug plasma concentrations that were not compatible with the dosing schedule of the trial protocols. It is assumed that compliance failure influenced their drug concentrations. The final model revealed the following relationships:

Clearance = $0.1571 \cdot (age/50)^{-0.5169+0.0028\ weight} + 0.0342 \cdot (1\text{-gender})$
Volume of distribution = $1.2176 \cdot$ weight
Absorption rate constant = clearance / volume of distribution + 0.3131

The effect of different covariates in the [redacted] analysis is shown in the following table.

| Covariate | Difference in Objective Function | Significance |
|---|---|---|
| Infuluence on clearance | | |
| Body weight | 12 | P<0.095 |
| Gender | 18 | P<0.005 |
| Age | 18 | P<0.005 |
| Dose | 1 | n.s. |
| Influence on volume of distribution | | |
| Body weight | 0 | n.s.1 |
| Gender | 0 | n.s. |
| Age | 9 | P<0.005 |
| Dose | 1 | n.s |
| Influence on bioavailability etc | | |
| OCC | 36 | P<0.005 |

1 when tested as weight as covariate for clearance, p.0.05

The variable 'gender' is '0' for males and '1' for females. Using mean weights and ages clearance was 0.377 L/h in male and 0.343 L/h in female patients. The volume of distribution was 15 L and the absorption rate constant was 0.338 $h^{-1}$ for males and 0.336 $h^{-1}$ for females. Comedications, that occurred in more than 35 patients were investigated with respect to their impact on meloxicam clearance. A significant effect was found for sulfasalazine (n=55): +0.0652 L/h and corticosteroids (n=77): -0.0427 L/h. Advanced age was accompanied by a minor decrease in clearance.

The plasma samples in this investigation were primarily collected for compliance checks. The mean values for clearance and volume of distribution fit well with mean values found in a healthy population in Phase 1 trials, despite the retrospective analysis and the use of a one compartment model instead of a two compartment model with gastrointestinal recirculation, which was found adequate for Phase 1 data. Such an advanced model was not supported by the data in this evaluation. This may be due to the fact that on average not more than two drug concentrations were available per patient and three would be a minimum to detect a recirculation phenomenon. A decrease in clearance with age was already known from Phase I trials, but the [redacted] approach failed to show the known gender dependence of the age effect. This may be caused by the study population, which comprised relatively few elderly patients with ages above 70-80 years. Nevertheless, these data are derived from a representative patient population. The lack of pharmacokinetic drug-drug interactions with furosemide or methotrexate was also known from Phase 1 trials and was confirmed by this investigation. It is not known why sulfasalazine increased the meloxicam clearance by approximately 20%.

*Conclusions*

- The [redacted] analysis of plasma compliance samples revealed similar pharmacokinetic parameters in comparison to values known from formal Phase 1 trials. No new information was determined regarding the pharmacokinetic parameters of meloxicam.
- [redacted] approach failed to show gender dependence of the age effect, which was very obvious in the Phase I studies.
- Sulfasalazine appears to increase meloxicam clearance by approximately 20%.

*Reviewer's Comment*

*The analysis results have been reviewed with Dr. Dan Wang, Pharmacometrics Expert, Division of Pharmaceutical Evaluation III, and are found acceptable.*

## V.7 BIOEQUIVALENCE

### *(A) 7.5 mg tablets (to-be-marketed) vs 7.5 mg capsules*

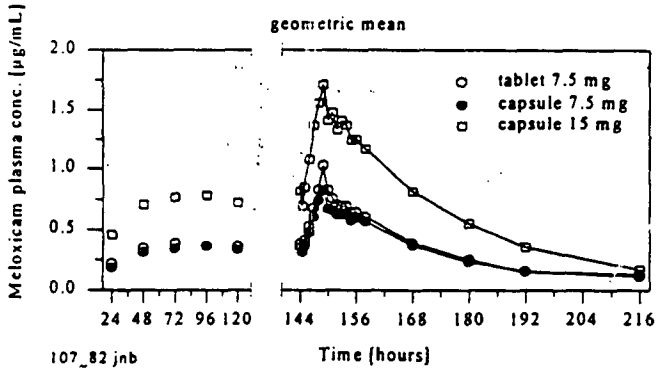
*Study 107.082: Determination of the relative bioavailability of 7.5 mg meloxicam tablets q.d. compared with 7.5 mg meloxicam capsules and dose proportionality between 7.5 mg*

*and 15 mg meloxicam capsules q.d. after oral administration over 7 days to healthy volunteers.*

This study was designed to assess the steady-state bioequivalence of 7.5 mg capsules and tablets as well as determine dose-proportionality after multiple oral doses of 7.5 and 15 mg capsules for seven days. The reviewer has checked with the review chemist regarding the adequacy of the batch size, manufacturing variables for the lot used in this study and found it to be acceptable.

This study was an open, randomized, multiple dose, three-way crossover study in eighteen healthy volunteers. Each subject received 7.5 mg meloxicam as tablet and capsule and 15 mg as capsule orally for 7 days. The drug was administered within ten minutes after breakfast. There was a seven-day washout period between each dosing period. Blood samples were obtained predose on Days 1 to 7 and serially up to 72 hours after the last dose on Day 7. Other details of study design are provided on page 83 of the Appendix. $C_{MAX,SS}$ and $AUC_{SS}$ values were used to compare the rate and extent of absorption for the two dosage forms as the primary end point. The other pharmacokinetic parameters used in the table below were used as secondary endpoints.

The mean steady state plasma concentration profile after administration of 7.5 mg capsules. 7.5 mg tablets and 15 mg tablets is shown in the figure below.




The mean and median pharmacokinetic parameters are also shown in the following table.

| | | 7.5 mg tablet | | | 7.5 mg capsule | | | 15 mg capsule | | |
|---|---|---|---|---|---|---|---|---|---|---|
| parameter | units | mean | %CV | median | mean | %CV | median | mean | %CV | median |
| $C_{MAX,SS}$ | [µg/mL] | 1.05 | 19.9 | 1.01 | 0.881 | 22.5 | 0.846 | 1.92 | 22.6 | 1.93 |
| $t_{MAX,SS}$ | [h] | 4.9 | 8.4 | 5.0 | 5.1 | 26.7 | 5.0 | 5.6 | 28.4 | 5.0 |
| $C_{MIN,SS}$ | [µg/mL] | 0.369 | 43.6 | 0.320 | 0.331 | 39.5 | 0.312 | 0.748 | 39.2 | 0.676 |
| $C_{PRE,SS}$ | [µg/mL] | 0.420 | 42.6 | 0.383 | 0.379 | 38.8 | 0.350 | 0.899 | 41.7 | 0.827 |
| $\lambda_Z$ | [$h^{-1}$] | 0.0373 | 29.9 | 0.0358 | 0.0368 | 26.6 | 0.0381 | 0.0340 | 25.9 | 0.0358 |
| $t_{1/2}$ | [h] | 20.1 | 28.7 | 19.4 | 20.4 | 31.2 | 18.2 | 22.2 | 34.6 | 19.4 |
| $AUC_{SS}$ | [µg·h/mL] | 15.37 | 29.4 | 14.53 | 13.90 | 30.2 | 13.45 | 30.00 | 31.8 | 28.45 |
| $C_{MAX,SS}/AUC_{SS}$ | | 0.0722 | 28.8 | 0.0690 | 0.0651 | 12.4 | 0.0636 | 0.0667 | 17.5 | 0.0652 |
| $MRT_{TO}$ | [h] | 30.7 | 29.1 | 28.8 | 32.1 | 26.0 | 30.5 | 34.3 | 28.8 | 31.0 |
| Cl/f | [mL/min] | 8.81 | 28.9 | 8.61 | 9.81 | 31.9 | 9.30 | 9.28 | 35.8 | 8.81 |
| Vd/f | [L] | 14.7 | 32.2 | 13.0 | 16.4 | 24.6 | 16.7 | 17.0 | 30.7 | 17.0 |

The 90% confidence intervals for the logarithimized test (7.5 mg tablet)/reference (7.5 mg capsules) ratios fer $AUC_{ss}$ was within the acceptance range of 80-125%, but not for $C_{MAX,SS}$ as shown in the following table.

| Parameter | Point estimator [%] | 90% Confidence Interval |
|---|---|---|
| $AUC_{ss}$ | 110.8 | 100.2-122.6 |
| $C_{max,ss}$ | 120.1 | 108.3-133.1 |

This table demonstrates bioinequivalence between the 7.5 mg tablets and the 7.5mg capsules.

*Reviewer's Comment*

*Several meeting were held in December 1997 with the sponsor, discussing the bioineqivalence issues and the inappropriate study design (steady-state and fed conditions). At the request of Dr. Bashaw in 1997, a re-analysis of the data was also performed using 15 mg capsules as the reference product. This analysis, using dose normalization, indicates that both 7.5 mg tablet and capsule are bioequivalent for AUC and $C_{max}$ to the 15 mg capsule. This result was still problematic, because although it shows bioequivalence to the 15 mg capsule in a dose normalized manner, but does not answer the question of 7.5 mg equivalency. It does suggest that if the clinical data base for 15 mg capsule is acceptable, then one would consider the 7.5 mg tablet as being acceptable. This is not ideally a preferred method.*

*At that time the sponsor presented the AE data showing that the rate of AE's for the 7.5 mg tablets was equivalent to that of the 7.5 mg capsules. On the basis of this the medical staff decided that the difference was insignificant and that the product should be considered clinically equivalent. As a part of the development the sponsor also undertook to study the proposed 7.5 mg tablet in US patients, such that it has its own clinical database.*
*The bioequivalency with dose-normalization is discussed in the following paragraphs.*

The adjustment to 15 mg dose was chosen by the sponsor, since this dose was the most often studied meloxicam dose in pharmacokinetic trials. Pharmacokinetics parameters were tested for dose proportionality by means of the bioequivalence approach. Dose proportionality was considered to be demonstrated if the shortest 90% confidence intervals for the ratio test versus reference were located in the range of 0.80 to 1.25. The following table shows the dose normalized mean values along with the confidence intervals for the pharmacokinetic parameters.

| Parameter | Product | Mean | Point estimator [%] | 90% Confidence Interval |
|---|---|---|---|---|
| $AUC_{ss}$ | 7.5 mg capsule (A) | 27.8 | A vs. C 0.935 | 0.845-1.04 |
| | 7.5 mg tablet (B) | 30.7 | B vs. C 1.04 | 0.937-1.15 |
| | 15 mg capsules (C) | 30.00 | - | - |
| $C_{MAX,SS}$ | 7.5 mg capsule | 1.76 | 0.918 | 0.828-1.02 |
| | 7.5 mg tablet | 2.11 | 1.10 | 0.994-1.22 |
| | 15 mg capsules | 1.92 | - | - |
| $C_{MIN,SS}$ | 7.5 mg capsule | 0.662 | 0.885 | 0.787-0.995 |
| | 7.5 mg tablet | 0.739 | 0.978 | 0.870-1.10 |
| | 15 mg capsules | 0.748 | - | - |
| $C_{PRE,SS}$ | 7.5 mg capsule | 0.757 | 0.856 | 0.752-0.975 |
| | 7.5 mg tablet | 0.840 | 0.938 | 0.824-1.07 |
| | 15 mg capsules | 0.899 | - | - |

The 7.5 mg tablets when dose normalized to 15 mg were within the acceptance criteria for all the parameters. The values for the 7.5 mg capsules were slightly lower (11.5% for $C_{MIN,SS}$ and 14.5% for $C_{PRE,SS}$, exceeding the acceptance limit by 2.4% ($C_{MIN,SS}$) and 4.8% ($C_{PRE,SS}$). The figures showing the dose normalized parameters are attached in the Appendix on pages 84-88.

*Conclusion*

Meloxicam showed a dose-proportional increase of $C_{MAX,SS}$ and $AUC_{ss}$ values in the dose range 7.5 mg and 15 mg following oral administration after dose-normalization using the 15 mg capsule as the reference.

This data along with the clinical database using the U.S. 7.5 mg tablet in question makes the inequivalence issue moot.

***(B) 15 mg tablets (marketed in Europe) vs 15 mg capsules***

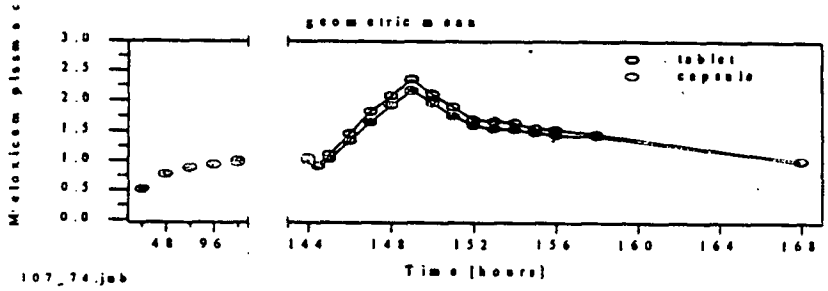
*Study 107.074: Determination of the relative bioavailability of 15 mg meloxicam tablets compared with 15 mg meloxicam capsules after oral administration over 7 days to healthy volunteers.*

This was a steady-state nonfasting bioequivalence study to bridge from a capsule formulation dosed in many European studies to the tablet formulation that is marketed in Europe. The same tablet formulation with a different shape is intended for marketing in the US. The only reason for reviewing this study now is that the sponsor intends to market the 15 mg strength also at a later date once additional clinical data is available to support it.

The study was a nonblinded, randomized, multiple-dose two-way crossover study in 24 healthy male volunteers. In each period, volunteers were administered oral 15 mg doses of meloxicam once per day for 7 days, either as the reference capsule or as the tablet. On the last dosing day of each period (Day 7), doses were given ten minutes after a

standardized light breakfast 12 hours after the last meal on Day 6. There was a washout period of at least 8 days between the two periods. Blood samples were collected predose and serially to 24 hours after dosing on Day 7. Bioequivalence was determined by comparison of mean $C_{MAX,SS}$ and $AUC_{SS}$. Secondary end points were peak trough fluctuation (%PTF), $C_{MIN,SS}$, $T_{MAX,SS}$.

The mean meloxicam plasma concentration-time profile after 15 mg doses as either capsule or tablet dosage form is shown in the following figure.




The mean and median pharmacokinetic parameters are shown below.

| | | 15 mg capsule | | | 15 mg tablet | | |
|---|---|---|---|---|---|---|---|
| parameter | units | mean | %CV | median | mean | %CV | median |
| $C_{MAX,SS}$ | [µg/mL] | 2.32 | 30.2 | 2.25 | 2.45 | 23.8 | 2.28 |
| $C_{MIN,SS}$ | [µg/mL] | 0.948 | 42.0 | 0.877 | 0.990 | 48.7 | 0.777 |
| $C_{PRE,SS}$ | [µg/mL] | 1.14 | 41.9 | 1.07 | 1.10 | 46.6 | 0.884 |
| $t_{MAX,SS}$ | [h] | 5.1 | 11.5 | 5.0 | 5.0 | 14.4 | 5.0 |
| $\lambda_z$ | [$h^{-1}$] | 0.0349 | 31.8 | 0.0345 | 0.0396 | 30.4 | 0.0391 |
| $t_{1/2}$ | [h] | 22.2 | 39.7 | 20.1 | 19.6 | 40.9 | 17.7 |
| $AUC_{SS}$ | [µg·h/mL] | 36.2 | 34.5 | 33.8 | 38.1 | 34.4 | 33.1 |
| $MRT_{TOT}$ | [h] | 34.4 | 36.2 | 31.5 | 30.6 | 37.6 | 27.5 |
| Cl/f | [mL/min] | 7.57 | 28.5 | 7.40 | 7.19 | 27.9 | 7.56 |
| Vd/f | [L] | 13.8 | 33.0 | 12.6 | 11.7 | 39.9 | 11.0 |
| %PTF | [%] | 94.6 | -- | 94.1 | 99.4 | -- | 101 |

The 90% confidence intervals for the logarithimized test/reference ratios for both $C_{MAX,SS}$ and $AUC_{SS}$ were within the acceptance range of 80-125%, as shown in the following table.

| Parameter | Point estimator [%] | 90% Confidence Interval |
|---|---|---|
| $AUC_{SS}$ | 105.4 | 100.8-110.3 |
| $C_{MAX,SS}$ | 107.1 | 100.9-113.7 |

The 15 mg tablet (currently marketed in Europe) was considered bioequivalent to the 15 mg capsule.

## V.8 DISSOLUTION

According to the biopharmaceutics drug classification system proposed by FDA, meloxicam is low solubility, high permeability drug, placing it in Class 2 of the designated categories. Meloxicam is practically insoluble in water (0.2 mg/100 ml).

Meloxicam has pKa values of 1.1 and 4.2 and exhibits increased solubility under basic conditions.

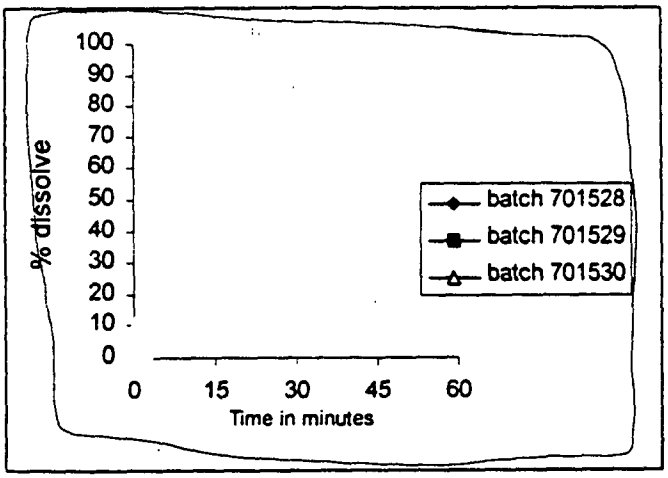
The dissolution of meloxicam tablets was evaluated at different conditions. The variables investigated included: solubility of the drug (pH range from 1.0 to 8.0), dissolution profiles of tablet in the media covering the pH range from 1.0 to 7.5, stirring speed and the discriminatory power of the selected conditions towards product differences associated with manufacturing variables and storage conditions.

The investigation was performed for different strengths ranging from 7.5 mg to 60 mg. But only the to-be-marketed strength will be discussed here.

The method selected includes the following conditions:

Apparatus:
Medium:
Temperatrure:
Sampling time:
Proposed regulatory specification

A sample of the dissolution profile of meloxicam 7.5 mg tablet, under the above given conditions is shown in the following figure.




Comparisons were also made between the batches used in the clinical trials vs. the registration batches of meloxicam. F2 was calculated to demonstrate similarity between the profiles. A F2 between demonstrates similarity. Three clinical lots (B 960913, B 960914, B 960920) were evaluated with reference to the registered lots 701528, 701529. Comparisons were made at each time point as well as the full profile. The profiles were not statistically different, that indicates that the tablets manufactured at Boehringer Ingelham (registered batches) and equivalent to those manufactured at . The tables showing the F2 values and a few profiles are attached in the Appendix on pages 89-92.

*Reviewer's Comment*

- *The pH of 7.5 is usually higher than the values measured in the upper gastrointestinal tract, but was chosen to achieve sink conditions at 7.5 and 15 mg tablet strengths.*
- *Although from the dissolution profile it appears that the specifications could be tightened, but on discussion with the review chemist it was observed that the stability batches of drug products packed in the [redacted] blisters would require a specification of [redacted] Hence, the sponsor's proposed specifications were considered more reasonable based on the drug product performance.*

## VI. OVERALL CONCLUSIONS

### *Metabolism*

- Meloxicam is almost completely metabolized in the liver into four main inactive metabolites (activity observed at extremely high doses). Only parent drug is detected in the plasma. Meloxicam metabolites are excreted in equal extent in the urine and the feces. Less than 2% of the parent drug remains unchanged in the urine and feces.
- The urinary metabolites are AF-UH 1 9% (hydroxylation product) and UH-AC 110SE 60% (formed by carboxylation of the methyl group on the thiazolyl moiety of meloxicam). In addition two other metabolites were found in the urine (DS-AC2 16% and BIBO 8032 4%). In the stool only two metabolites were found (UH-AC 110SE and AF-UH 1).
- Excretion balance of meloxicam is complete after 6 days.
- There is strong evidence that CYP2C9 is involved in the biotransformation step yielding AF-UH 1 with a minor contribution of CYP3A4 as well.
- The drug interaction trials will be summarized separately in Dr. Dan Wang's review.

### *Absorption*

- The absolute bioavailability of meloxicam was 89% following a single oral dose of 30 mg meloxicam in a capsule dosage form.
- Meloxicam has prolonged absorption with a $T_{max}$ of 5-9 hours, consistent with its poor solubility.
- A second meloxicam peak occurs at 12-14 hours post dose, suggesting gastrointestinal recirculation.
- Upon multiple dosing steady state is reached by ~ Day 5. Rate or extent of absorption is not affected by multiple dose treatment.
- High fat breakfast (75 g) did not affect the extent, but lead to a 22% higher $C_{max}$, but is not significantly different per the draft food guidance. The effect on US tablet formulation is unknown.
- Antacid use did not affect the bioavailability of meloxicam.
- Following single intravenous doses, dose-proportional pharmacokinetics were shown in the range of 5 mg to 60 mg meloxicam. Pharmacokinetics after multiple oral doses were dose-proportional in the range of 7.5 mg to 15 mg.

*Distribution*

- The mean volume of distribution (Vss) of meloxicam is approximately 10 L.
- Meloxicam is > 99% bound to human plasma proteins (primarily albumin) within the therapeutic dose range.
- Median meloxicam free fractions varied from 0.13% to 0.44% in the plasma samples from healthy volunteers as well as osteoarthritis patients.
- Lower free fractions were found in elderly healthy females (0.25%, N=16), compared to elderly males (0.48%, N=24).
- Patients with end-stage renal function (N=9) yielded a higher free fraction of 0.93%. This value was significantly higher than the value in healthy volunteers (+344%)
- Meloxicam concentrations in synovial tissues are ~40% the corresponding concentration in plasma. The free fraction in synovial fluid is 2.5 times higher than in plasma, which can be attributed to the lower albumin content in synovial fluid as compared to plasma.

*Excretion*

- The mean elimination half life ranges from 15-22 hours.
- Elimination half life is constant across dose levels, indicating linear metabolism in the therapeutic dose range.
- Plasma clearance ranges from 7-9 mL/min
- Urinary excretion of the parent and metabolites after unlabeled multiple once daily doses of 7.5 mg meloxicam (capsules) was 0.56% 6.39% and 12.6% of the dose for meloxicam, AF-UH 1SE and UH-AC 110SE, respectively. Only about 16-17% of the total dose was recovered in the urine in the form of meloxicam and two of its metabolites.

*Special Population*

*Gender*

- Young females have 22-24% lower $AUC_{ss}$ values as compared to young males.
- Young females have 22-29% higher CL values as compared to young males.
- These differences could be due to weight differences between males and females.
- Differences in $C_{max}$ could not be clearly defined, although cross study comparisons showed a 34% higher $C_{max}$ in young males.
- Half life was 9-16% lower in females.
- No clinical meaningful difference was seen in males and females regarding the adverse event profile.

*Elderly*

- Elderly males exhibited meloxicam plasma concentrations and steady state pharmacokinetics similar to young males.

- Elderly females had a larger AUC (21%) per 10 years of age vs. younger females. Despite the increased total concentrations in the elderly females, the adverse event profile was comparable for both elderly patient populations.
- A smaller free fraction was found in elderly female patients in comparison to elderly male patients.

*Renal Insufficiency*

- Mean plasma concentration decreased moderately in patients with renal impairment.
- This was associated with an increase in clearance. This increase may be due to an increase in the unbound fraction of meloxicam, leading to an increased metabolic clearance.
- Patients with end-stage renal failure exhibited lower total meloxicam plasma concentrations, but higher free fractions (0.9% in patients on chronic hemodialysis vs. 0.3% free fraction in healthy).
- Calculated maximum free concentrations were higher in patients with end-stage renal failure than healthy volunteers and calculated free AUCs were similar.
- The free fraction is considered critical for safety, therefore, a dose of 7.5 mg instead of 15 mg is recommended in patients with end-stage renal failure.
- There was no relevant decrease in plasma concentration of meloxicam after hemodialysis, hence, dialysis would not be an option for treatment of overdose and additional doses are not necessary after hemodialysis.

*Hepatic Insufficiency*

- There was no marked difference in the meloxicam pharmacokinetics between patients with mild to moderate liver impairment and healthy subjects. Hence, dosage adjustment would not have to be made in these patients with hepatic dysfunction.
- Patients with severe hepatic insufficiency have not been adequately studied and the use of meloxicam in this population should be done with caution using the lowest dose and titrated up slowly.
- Protein binding of meloxicam was not affected by hepatic insufficiency.

*Bioequivalence*

- Meloxicam showed a dose-proportional increase of $C_{MAX,SS}$ and $AUC_{SS}$ values in the dose range 7.5 mg and 15 mg following oral administration after dose-normalization using the 15 mg capsule as the reference and 7.5 mg capsules were considered bioequivalent to 7.5 mg to-be-marketed tablets of meloxicam.

*Dissolution*

Apparatus:
Medium:

Proposed regulatory specification

/S/ 8/24/99

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

Team Leader: E. Dennis Bashaw, Pharm. D. 8/28/99

CC: NDA 20-938
HFD-550/Div File
HFD-550/CSO/Lewin
HFD-880(Bashaw/Tandon)
HFD-880(Lazor)
HFD-344(Viswanathan)
CDR ATTN: B.Murphy

## CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA 20-938 **SUBMISSION DATE:** 2/5/1999
**PRODUCT:** Meloxicam Tablets, 7.5 mg 8/13/1999
**BRAND NAME:** MOBIC® **REVIEWER:** Dan Wang, Ph.D.
**SPONSOR:** Boehringer Ingelheim Pharmaceuticals, Inc
Ridgefield, CT 06877 **TYPE OF SUBMISSION:** Original

## REVIEW OF THE DRUG INTERACTION SECTION OF MOBIC® NDA

This review of the NDA covers only the "Drug Interaction" section of the "Clinical Pharmacokinetics Section". The general pharmacokinetic section was reviewed by Dr. Tandon and is provided separately. The final recommendation and the comments will be provided in Dr. Tandon's review, which will also include the summary of the entire "Clinical Pharmacokinetics section". Below is an index to facilitate perusal of this review.

## INDEX



## DRUG INTERACTION STUDIES

### Cholestyramine

Study 107.049: The influence of cholestyramine on the reabsorption of meloxicam as a single IV bolus injection of 30 mg in healthy volunteers (Report U90-0256)

Meloxicam is a NSAID in the oxicam class. The other two drugs in the oxicam class (piroxicam and tenoxicam) all show significant enterohepatic and/or enteroenteric circulation. Since half of the meloxicam dose is excreted in feces, it is important to know whether recirculating processes in the gut exist for meloxicam and to what extent they affect its pharmacokinetics. This study tested the influence of the ion exchange resin

cholestyramine, a drug trapping resin in the intestinal tract, on the reabsorption of meloxicam after a single 30 mg intravenous dose.

This was an open, randomized, two-way crossover design in healthy male volunteers. Twelve subjects received a single 30 mg intravenous bolus dose of meloxicam either alone or during concomitant oral dosing of 4 g cholestyramine three times a day. Cholestyramine treatment was started on the evening before meloxicam dosing and was repeated two hours after meloxicam injection followed by two additional doses on Day 1. Three doses of cholestyramine per day were then given on Days 2, 3 and 4 to bind any meloxicam secreted into the gastrointestinal tract. There was a two week washout period between the two periods. Blood samples were collected predose and serially up to 96 hours after the meloxicam dose. Other details of study design have been summarized on page 1 of the Appendix II. Plasma samples were analyzed by a HPLC assay. The assay validation review for this study has been conducted by Dr. Tandon and can be found in her review. The influence of cholestyramine was tested by comparison of $t_{1/2}$, $MRT_{TOT}$, Cl, $AUC_{0\text{-}TLQC}$ and $Vd_{SS}$.

**RESULTS:** Twelve healthy male volunteers completed this study. Volunteer 4 inadvertently received a paravenous application during the reference treatment (meloxicam alone) and was, therefore, excluded from the evaluation. Mean meloxicam plasma concentration time profiles are given in the figure below, and mean and median pharmacokinetic parameters are summarized in Table 1.

Figure 1. Mean meloxicam plasma concentrations after single intravenous doses of 30 mg meloxicam with or without cholestyramine treatment to eleven healthy volunteers

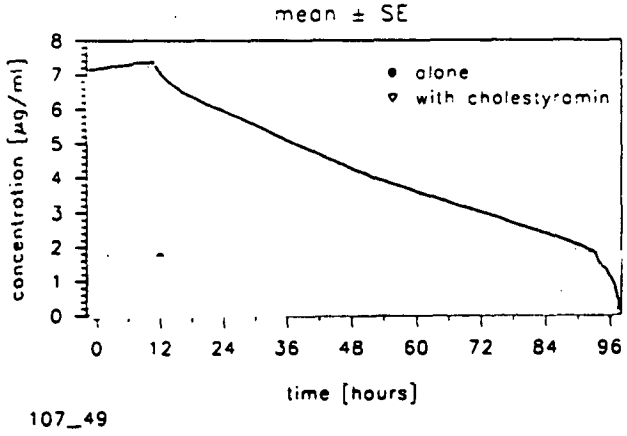



Table 1. Mean and median pharmacokinetic parameters of meloxicam after single intravenous doses of 30 mg meloxicam with or without cholestyramine treatment to eleven healthy volunteers.

| Parameter | Units | 30 mg IV alone | | | 30 mg IV with cholestyramine | | |
|---|---|---|---|---|---|---|---|
| | | mean | %CV | median | Mean | %CV | median |
| $AUC_{0-\infty}$ | [µg·h/mL] | 76.42 | 32.5 | 65.3 | 49.38 | 24.4 | 47.04 |
| $MRT_{TOT}$ | [h] | 26.0 | 34.9 | 21.6 | 16.0 | 26.3 | 13.1 |
| Cl | [mL/min] | 7.17 | 31.0 | 7.65 | 10.7 | 23.6 | 10.6 |
| $t_{1/2}$ | [h] | 19.2 | 33.5 | 15.7 | 12.5 | 26.2 | 10.2 |
| $Vd_{SS}$ | [L] | 10.3 | 12.5 | 9.94 | 9.76 | 12.0 | 9.83 |

The results showed that cholestyramine significantly increased the mean clearance of meloxicam by 50% resulting in a reduction of $t_{1/2}$, $MRT_{TOT}$ and $AUC_{0-\infty}$ (point estimate 0.659, 90% C.I. 0.601 - 0.723). The volume of distribution ($Vd_{ss}$) remained constant. This suggests the existence of a recirculation pathway for meloxicam in the gastrointestinal tract. The higher clearance of meloxicam under the influence of cholestyramine in caused by irreversible binding of meloxicam to cholestyramine with subsequent elimination of the complex. The changes observed were in the same range as reported for piroxicam (~50%) and smaller than that reported for tenoxicam (~100%). The type of recirculation, enterohepatic or enteroenteric, could not be determined using this study design.

Five volunteers showed a slight elevation of liver enzymes, Alanine Aminotransferase (GPT), Asparate Aminotransferase (GOT) and Gamma-Glutamyl Aminotransferase (GGT), following concomitant administration of the two drugs.

**CONCLUSIONS:** The clearance of meloxicam increases significantly (50%) when given concomitantly with cholestyramine. This suggests the existence of a recirculation pathway for meloxicam in the gastrointestinal tract.

**Aspirin and Cimetidine**

**Study 107.018:** Influence of aspirin and $H_2$-receptor antagonist cimetidine (Tagamet®) on pharmacokinetics and tolerance of 30 mg UH-AC 62 XX as a single oral administration in healthy volunteers (Report U89-0626)

Cimetidine is often given as part of the anti-inflammatory treatment to improve gastric tolerance of NSAIDs. In many cases, two anti-inflammatory drugs are combined, most frequently with aspirin. Therefore, this study was conducted to investigated the possible interaction between meloxicam and acetylsalicylic acid (competition for plasma protein binding) and cimetidine (limited metabolic capacity).

This was an open, randomized, three-way crossover design in healthy male volunteers. Nine subjects received single 30 mg meloxicam capsule doses on Day 1. This was given either alone, with 1000 mg acetylsalicylic acid t.i.d., or with 200 mg cimetidine q.i.d. for four days each. The concomitant treatment was extended to four days because meloxicam concentrations can be monitored up to four days after a single dose. Meloxicam was always given with one serving of yogurt. Breakfast was served two hours after the meloxicam dose. There were two week washout periods between study periods. Blood samples were serially collected for 96 hours postdose and plasma samples were analyzed by HPLC assay. The assay validation review for this study has been conducted by Dr. Tandon and can be found in her review. The influence of acetylsalicylic acid and cimetidine on meloxicam pharmacokinetics was tested by comparison of $AUC_{0-\infty}$ and Cmax values.

**Results:** Nine healthy male volunteers completed this study. Mean meloxicam plasma concentration-time profiles are shown in the figure below, and summary statistics of

pharmacokinetic parameters are given in Table 1. Other parameters can be found in Table 2.

Figure 1. Mean meloxicam plasma concentrations after single oral doses of 30 mg meloxicam capsule alone, with cimeditine or with aspirin treatments to 9 healthy volunteers

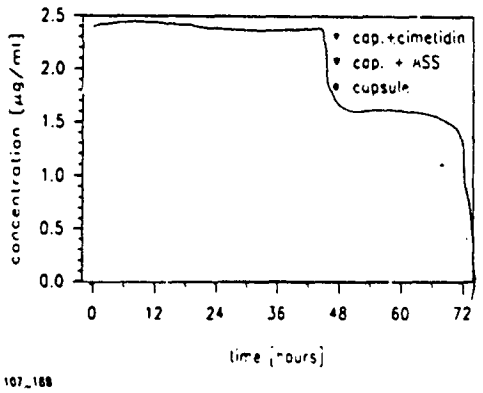



Table 1. Statistic summary of pharmacokinetic parameters of meloxicam given alone, with cimeditine or aspirin.

| | Treatment | N | Geometric Mean (±SD) | GMR | 90% CI for GMR |
|---|---|---|---|---|---|
| $AUC_{inf}$ (µg-hr/ml) | Meloxicam alone | 9 | 59.14 (12.77) | | |
| | Meloxicam + cimeditine | 9 | 63.10 (35.65) | 1.07 | (0.81, 1.40) |
| | Meloxicam + aspirin | 9 | 65.06 (34.42) | 1.10 | (0.88, 1.38) |
| $C_{max}$ (µg/ml) | Meloxicam alone | 9 | 1.78 (0.27) | | |
| | Meloxicam + cimeditine | 9 | 1.62 (0.54) | 0.92 | (0.78, 1.08) |
| | Meloxicam + aspirin | 9 | 2.20 (0.50) | 1.24 | (1.04, 1.48) |

Table 2. Mean PK parameters of meloxicam given alone, with cimeditine or aspirin.

| | | 30 mg meloxicam alone | | | 30 mg meloxicam + 1000 mg ASA t.i.d. | | | 30 mg meloxicam + 200 mg cimetidine q.i.d. | | |
|---|---|---|---|---|---|---|---|---|---|---|
| parameter | units | mean | %CV | median | mean | %CV | median | mean | %CV | median |
| $t_{MAX}$ | [h] | 7.9 | 53.9 | 8.0 | 6.2 | 48.7 | 6.0 | 9.2 | 38.3 | 12.0 |
| $t_{1/2}$ | [h] | 17.5 | 17.6 | 17.6 | 16.9 | 39.1 | 15.3 | 19.5 | 30.3 | 18.4 |
| $MRT_{TOT}$ | [h] | 28.5 | 19.7 | 26.3 | 27.1 | 34.0 | 25.6 | 31.6 | 25.9 | 29.5 |
| Cl f | [mL/min] | 8.59 | 17.8 | 9.38 | 8.45 | 44.7 | 6.88 | 8.55 | 36.3 | 9.28 |

The result showed that concomitant dosing with 1000 mg acetylsalicylic acid t.i.d. resulted in a 24% increase of mean $C_{max}$ values, while the mean $AUC_{0-\infty}$ value showed an increase of 10%. Meloxicam pharmacokinetics was not relevantly affected by 200 mg cimetidine q.i.d., with a 8.5% decrease of mean $C_{max}$ and a 7% increase of mean $AUC_{0-\infty}$ value. The reviewer agrees with the sponsor that the wide 90% CI is likely caused by the relatively low sample size (nine subjects), which precluded demonstration of bioequivalent results for the cotreatment with cimetidine.

**CONCLUSION:** When given concomitantly with a clinical anti-inflammatory dose of aspirin. the mean $C_{max}$ and $AUC_{0-\infty}$ values of meloxicam increased by 24% and 10%, respectively. Meloxicam pharmacokinetics was not affected by concomitantly cimetidine.

## Methotrexate

**Study 107.070:** An open trial to assess the pharmacokinetic interaction of meloxicam (UH-AC 62 XX) 15 mg oral q.d. with methotrexate (MTX) 15 mg IV once per week in patients with rheumatoid arthritis (Report U93-2048)

Low dose of MTX once weekly has been used in the treatment of RA recently to minimize its hepatotoxicity. As the therapeutic effect of MTX does not occur until 0.5-3 months of treatment, NSAIDs are commonly used with MTX to relieve acute symptoms and to avoid a delay in onset of the long lasting MTX effect. The potential interaction between MTX and NSAID may be caused by an altered renal prostaglandin biosynthesis resulting in a decrease in glomerular filtration rate and MTX clearance and competition between NSAIDs and MTX on the level of renal tubular secretion. A decrease in renal production of $PGE_2$ may also lead to a reduction in renal sodium excretion, which is coupled with excretion of weak organic acids. Organic acids are known to competitively inhibit renal tubular secretion of MTX. Seven-hydroxy methotrexate, the major extracellular MTX metabolite, which is highly bound to plasma proteins and may have both therapeutic and toxic effects, is filtered by the kidneys and may precipitate if the peritubular concentration exceeds its solubility. Therefore a drug-drug interaction study was conducted for meloxicam and MTX.

In this open-label pharmacokinetic study, thirteen patients suffering from rheumatoid arthritis received daily 15 mg doses of meloxicam after a washout period of three to eleven days without an NSAID with paracetamol as rescue treatment. The length of the washout period was dependent on the pharmacokinetics of the previously given NSAID. One NSAID-free day was a minimum washout. To achieve steady state conditions, one injection of 15 mg methotrexate on Day 1 was combined with daily oral doses of meloxicam from Day 3 to Day 9 with a second methotrexate dose on Day 8. Drugs were given after an overnight fast. Blood samples for methotrexate assays were obtained on Days 1 and 2 as well as on Days 8 and 9. On Days 6, 7, 8 and 9, blood was collected to verify meloxicam steady-state. Both drugs were analyzed in plasma using HPLC assays.

**Results:** Twelve patients completed this study. The trough meloxicam plasma levels indicated that steady-state was achieved at Day 6. Mean methotrexate plasma concentration time profiles are shown in the figure below, and summary statistics for AUC are summarized in Table 1. Mean values for other parameters are summarized in Table 2.

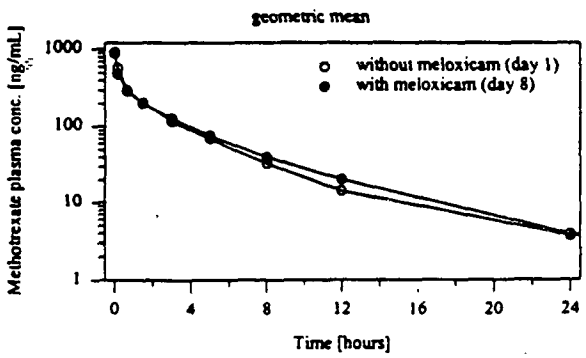


Table 1. Statistic summary of pharmacokinetic parameters of meloxicam given alone or with MTX

| | Treatment | N | Geometric Mean (±SD) | GMR | 95% CI for GMR |
|---|---|---|---|---|---|
| $AUC_{0-\infty}$ (ng-hr/ml) | Meloxicam alone | 12 | 2107 (438) | | |
| | Meloxicam + MTX | 12 | 2274 (484) | 1.08 | (0.998, 1.17) |

Table 2. Mean and median methotrexate pharmacokinetic parameters after a single 15 mg IV dose either alone or after 15 mg q.d. oral meloxicam for 6 days (Study 107.070).

| | | 15 mg methotrexate alone | | | 15 mg methotrexate with meloxicam | | |
|---|---|---|---|---|---|---|---|
| parameter | units | mean | %CV | median | mean | %CV | Median |
| Methotrexate: | | | | | | | |
| $\lambda_z$ | [$h^{-1}$] | 0.237 | 43.8 | 0.242 | 0.231 | 24.2 | 0.241 |
| $t_{1/2}$ | [h] | 3.67 | 57.2 | 2.88 | 3.23 | 33.9 | 2.87 |
| $MRT_{TOT}$ | [h] | 3.00 | 42.4 | 2.61 | 3.29 | 39.4 | 2.81 |
| Cl | [mL/min] | 122 | 24.3 | 116 | 113 | 26.3 | 106 |
| Vd | [L] | 37.7 | 55.1 | 33.0 | 31.4 | 39.5 | 28.1 |
| $Vd_{ss}$ | [L] | 21.6 | 42.5 | 19.4 | 22.2 | 42.6 | 20.9 |

The results indicated that the pharmacokinetics of MTX was not affected by concomitantly administration of meloxicam.

## CONCLUSION:

No pharmacokinetic interaction between methotrexate and meloxicam with respect to methotrexate AUC was observed. It should, however, be noted that the use of a IV dose of MTX was an unusual design feature. Normally, MTX for anti-inflammatory purpose is given orally.

### Digoxin

STUDY 107.072: Pharmacokinetic interaction of 15 mg meloxicam capsules oral once daily with 0.3 mg β-acetyldigoxin tablets (Novodigal) oral once daily during eight days in healthy volunteers (Report U93-2039)

β-acetyldigoxin (Novodigal, Germany) is a cardiac glycoside related to digoxin. In man it is thought to be a pro-drug for digoxin. Digoxin is eliminated primarily by the kidney by both filtration at the glomerulus and secretion by the tubules. Re-absorption from the tubular lumen may become significant when the rate of flow of tubular fluid is markedly reduced. NSAIDs are known to impair renal function. Through effects on renal prostaglandin, meloxicam may possibly affect the renal elimination of digoxin, leading to higher levels of digoxin. Therefore, this trial is performed in order to exclude a severe interaction with meloxicam and digoxin.

This was a double-blind, randomized, multiple-dose, two-way crossover study in twelve healthy male volunteers. In both periods, subjects were given initial loading doses of 1 mg/day β-acetyldigoxin on Day 1 and 0.5 mg/day on Day 2. This was followed by 0.3 mg/day β-acetyldigoxin doses from Day 3 through Day 7 of each period. Half the subjects were randomized to 15 mg meloxicam once per day for 7 days and the other half received placebo capsules. After a 14-day washout, the subjects were crossed-over to the

alternate regimen of meloxicam or placebo, respectively. Blood samples were collected predose on Days 1, 5, 6, 7, and serially for 48 hours after dosing on Day 7 of each period. Plasma samples were assayed for digoxin by means of a [redacted] Meloxicam was assayed by a HPLC method.

RESULTS: Twelve healthy male volunteers completed this study. Mean digoxin plasma concentration time profiles are plotted in Figure 1, and summary statistics of pharmacokinetic parameters are summarized in Table 1.

Figure 1. Steady-state mean digoxin plasma concentrations either alone or administered with 15 mg daily meloxicam

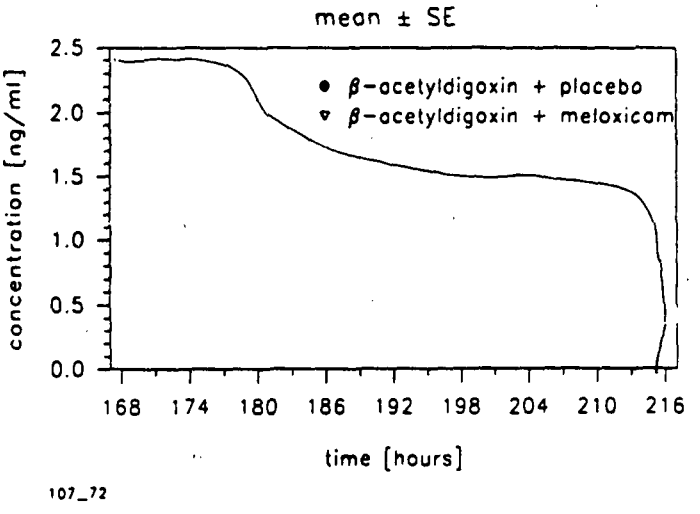



Table 1. Steady-state mean digoxin pharmacokinetic parameters either alone or administered with 15 mg daily meloxicam

| parameter | Units | digoxin alone | | | digoxin with meloxicam | | | Difference | |
|---|---|---|---|---|---|---|---|---|---|
| | | Mean | %CV | median | mean | %CV | median | point estimate (%) | 90% C.F. lower%-upper% |
| Digoxin: | | | | | | | | | |
| $C_{MAX,SS}$ | [ng/mL] | 2.0 | 12.9 | 2.0 | 2.1 | 19.0 | 2.1 | 104.6 | 93.6-115.7 |
| $C_{MIN,SS}$ | [ng/mL] | 0.7 | 22.9 | 0.6 | 0.8 | 37.8 | 0.7 | 98.4 | 88.2-114.6 |
| $C_{PRE,SS}$ | [ng/mL] | 0.7 | 22.9 | 0.7 | 0.8 | 37.8 | 0.7 | -- | -- |
| $t_{MAX,SS}$ | [h] | 1.6 | 48.1 | 1.3 | 1.8 | 47.4 | 1.5 | 100.0 | 99.9-100.3 |
| $t_{1/2}$ | [h] | 58.1 | 31.6 | 54.2 | 50.3 | 28.1 | 45.2 | 86.5 | 67.8-105.2 |
| $AUC_{SS}$ | [ng·h/mL] | 21.0 | 15.4 | 20.9 | 21.6 | 13.8 | 20.8 | 102.7 | 96.3-109.1 |
| $MRT_{TOT}$ | [h] | 69.8 | 32.5 | 64.3 | 61.7 | 28.5 | 56.0 | 88.4 | 69.5-107.3 |
| Meloxicam | | | | | | | | | |
| $C_{PRE,SS}$ | [µg/mL] | -- | -- | -- | 0.88 | 33.9 | 0.87 | -- | -- |

The results indicated that digoxin pharmacokinetics did not affected by co-administration of meloxicam.

**CONCLUSION:** Multiple doses of 15 mg meloxicam did not affect digoxin pharmacokinetics at steady state when given concomitantly with β-acetyldigoxin, which is a pro-drug of digoxin. Although this is acceptable, use of a US product in this study would have been preferred.

**Warfarin**

**Study 107.141:** Pharmacodynamic and pharmacokinetic interaction between oral meloxicam (15 mg) capsules and adjusted warfarin (1 mg/5 mg) tablets in an open label study in healthy volunteers (Report U95-2256)

Both meloxicam and warfarin are highly bound to plasma proteins and are metabolized by the same cytochrome P450 isoenzyme (CYP2C9). In animal studies, at high meloxicam dose of 4 mg/kg (therapeutic dose at 0.2 mg/kg), a prolongation of prothrombin times was noted. This study was performed to assess the possible interaction.

This was an open multiple-dose study in healthy male volunteers. Sixteen subjects were screened for the study, 13 were enrolled in the interaction treatment and 12 completed the study. Warfarin was dosed as commercially available tablets (Coumadin®). The subjects were dosed for 17 days with warfarin alone prior to the addition of meloxicam to the regimen. Initially, each subject received a fixed dose regimen (a 5 mg tablet, once per day) for five days, followed by nine days of warfarin titration to achieve an INR (International Normalized Ratio) between 1.2 and 1.8, and finally a three-day warfarin stabilization phase with the final warfarin dose after day 17. After the stabilization phase, 15 mg meloxicam capsules were dosed concomitantly once daily for seven days. The concomitant meloxicam was then terminated and the INR value monitored for a further seven days, prior to termination of warfarin dosing. The drugs were dosed once per day with 200 mL of tap water in the morning after breakfast.

INR values were determined predose on each study day except for Days 2 and 3. EDTA blood samples (5.0 mL) were drawn predose on Days 14 - 17, 21 - 26, 29 and 31 and serially up to 24 hours after dosing on days 17 and 24. Plasma was separated and frozen until later determination of R- and S-warfarin concentrations. The analysis for R- and S-warfarin was determined enantioselectively using an [redacted] Warfarin plasma concentrations were determined enantioselectively to differentiate between the five times more potent S-enantiomer metabolized by CYP 450 2C9 and the less potent R-enantiomer metabolized by 3A4 and 1A2 as well as 2C19. This was necessary, because warfarin is applied as a 1:1 racemate and there are reports on stereoselective inhibition of warfarin metabolism by several interaction partners.

EDTA blood samples for the determination of meloxicam were drawn immediately predose on Days 18 - 24. To monitor the washout of meloxicam, additional samples were taken before warfarin application on days 25, 26 and 29. Meloxicam was quantified in plasma by a [redacted]

**Result:**

1. Pharmacokinetics

Mean plasma concentration-time data for warfarin with and without concomitant meloxicam are plotted as Figure 1. Day 17 was 384-408 hours and day 24 was 552-576 hours. Summary statistics of pharmacokinetic parameters of warfarin are presented in Table 1.

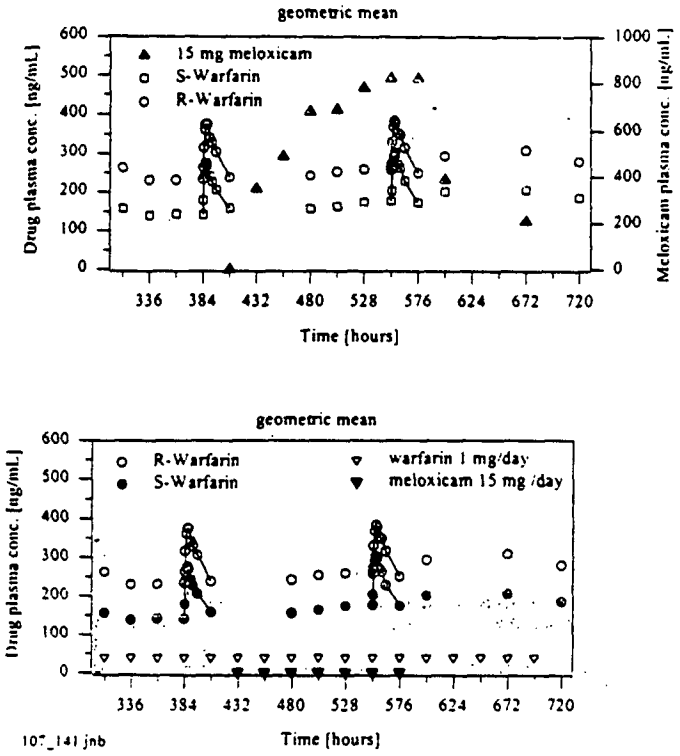



Figure 1. Mean plasma concentrations of S-, R-warfarin and meloxicam

Table 1. Summary statistics of S- and R-warfarin with and without meloxicam

| | Treatment | Geometric Mean (%CV) | GMR | 90% CI for GMR |
|---|---|---|---|---|
| R-warfarin $AUC_{ss}$(μg-hr/ml) | Warfarin alone | 7.31 (43.8) | | |
| | Warfarin + Meloxicam | 7.58 (39.1) | 1.04 | (0.991, 1.08) |
| S-warfarin $AUC_{ss}$(μg-hr/ml) | Warfarin alone | 5.07 (27.5) | | |
| | Warfarin + Meloxicam | 5.64 (28.1) | 1.11 | (1.07, 1.16) |
| R-warfarin $C_{max,ss}$(ng/ml) | Warfarin alone | 416 (42.4) | | |
| | Warfarin + Meloxicam | 413 (42.1) | 0.993 | (0.899, 1.10) |
| S-warfarin $C_{max,ss}$(ng/ml) | Warfarin alone | 309 (24.2) | | |
| | Warfarin + Meloxicam | 336 (25.5) | 1.09 | (0.986, 1.20) |

These result indicate that there is a 26% increase in S-warfarin predose concentration, which lead to about 10% increase in AUC and Cmax.

2. Pharmacodynamic

The pharmacodynamic effect of warfarin, expressed as INR-values was r
meloxicam co-administration. Geometric mean (%CV) INR-values for
(day 17) were 1.20 (10.7) and 1.25 (16.6) for warfarin with meloxicam.
was not statistically significant (p=0.13).

**Conclusion:** Co-administration of 15 mg meloxicam daily did not significantly alter t
pharmacokinetics and pharmacodynamics of warfarin.

**Furosemide**

**Study 107.089:** A study to detect a possible interaction of meloxicam with furosemide following repeated administration of meloxicam (Report U93-0784)

Indomethacin, a NSAID, has both a pharmacokinetic and pharmacodynamic interaction with furosemide. The effect of furosemide was reduced by co-administration of indomethacin. The mechanism of this pharmacodynamic interaction is thought to be the alteration in prostaglandin-mediated hemodynamic effects of furosemide. Although the interaction may not be present for all NSAIDs, this multiple dose study was conduct to investigat the effect of meloxicam on furosemide pharmacokinetics and pharmacodynamics, after single and repeated administration of furosemide with meloxicam at steady-state.

This was an open, multiple-dose study comprising 3 treatment phases plus a run-in phase. Fifteen healthy male volunteers entered the study. It started with a run-in period of 4 days where no medication was administered but subjects had to follow the instructions described in the protocol regarding food and fluid intake. This was followed by a period of 3 days where furosemide was administered as a single daily dose of 40 mg at 8:00am (Days 1-3). Thereafter, a single washout day (Day 4) was followed by a period of 10 days where meloxicam was administered as a single daily dose of 15mg at 8:00 am (Days 5-14). On Days 15 to 17, furosemide and meloxicam were administered concomitantly at the same doses described above and at the same time of the day. Blood samples were collected on Days 3 (furosemide alone) and 17 (furosemide + meloxicam) for 16 hours to determine furosemide pharmacokinetics. Samples were assayed for furosemide by HPLC assay. Meloxicam was assayed by HPLC in predose samples of the last three treatment days to validate attainment of steady-state. Urine samples were also collected for pharmacodynamic analysis.

**Results:**

1. Pharmacokinetics.

All fifteen subjects completed this study. Mean furosemide plasma concentration-time profiles are depicted in Figure 1, and summary statistics of pharmacokinetic parameters are listed in Table 1.

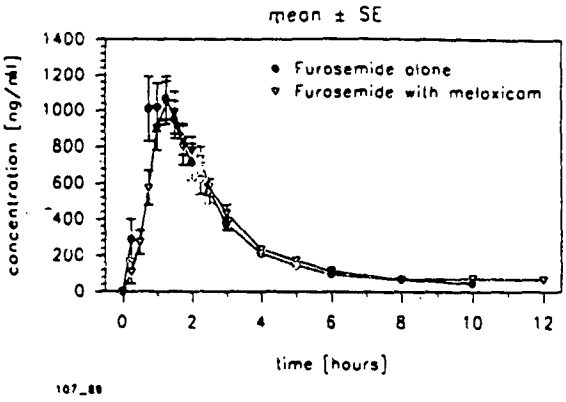



Figure 1. Mean furosemide plasma concentration-time profiles

Table 1. Summary Statistics of PK parameters (plasma) of Furosemide

| | Treatment | Geometric Mean | GMR | 90% CI for GMR |
|---|---|---|---|---|
| $AUC_{ss}$(ng-hr/ml) | Furosemide + placebo | 2921 | | |
| | furosemide + Meloxicam | 2846 | 0.974 | (0.897, 1.06) |
| Cmax (ng/ml) | furosemide + placebo | 1311 | | |
| | furosemide + Meloxicam | 1162 | 0.886 | (0.703, 1.16) |

The results showed that meloxicam did not affect the exposure of furosemide in term of mean $AUC_{ss}$. The mean Cmax of furosemide decreased by 10 % when given with meloxicam. Although the mean $AUC_{ss}$ and Cmax values were similar under two treatment conditions, individual data showed significant difference between the days studied indicating high intra-subject or inter-occasion variability with furoxemide pharmacokinetics.

The pharmacokinetics of furosemide in urine are summarized in Table 2.

Table 2. Cumulative urinary furosemide excretion (mg) on Day 3 and Day 17.

| | Treatment | Geometric Mean | GMR | 90% CI for GMR |
|---|---|---|---|---|
| 0-4 hours | Furosemide + placebo | 12.98 | | |
| | furosemide + Meloxicam | 13.08 | NC* | NC |
| 0-8 hours | furosemide + placebo | 16.17 | | |
| | furosemide + Meloxicam | 16.97 | 1.057 | (0.934, 1.18) |
| 0-24 hours | furosemide + placebo | 18.48 | | |
| | furosemide + Meloxicam | 19.52 | 1.06 | (0.972, 1.15) |

*Not calculated by the sponsor.

The pharmacokinetics results from urine indicated no interaction between furosemide and meloxicam.

2. Pharmacodynamics

The concentration of serum electrolytes and serum uric acid, and the average creatinine clearance are similar for the two treatments on both Days 1/15 and Days 3/17.

The cumulative volumes and the average specific gravity of urine are similar for the two treatments on both Days 1/15 and Days 3/17. The cumulative urinary sodium excretion is similar for the two treatments, as is the excretion of chloride. The potassium and excretion is 20% lower for the treatment furosemide +meloxicam on Day 3, and phosphate excretion 20% lower on Day 1.

**CONCLUSION:**

Meloxicam 15 mg daily at steady-state did not significantly affect the pharmacokinetics and pharmacodynamics of furosemide. However, slight decrease in furosemide Cmax (10%), and potassium and phosphate urinary excretion (20%) were observed.

Study 107.114:A study to detect the possible interaction of meloxicam with furosemide following repeated administration of meloxicam to patients with compensated chronic cardiac failure (Report U96-0238)

Although meloxicam did not significantly affect the PK and PD of furosemide when given concomitantly in healthy volunteers, there still were concerns about the interaction in patients with an ineffective circulatory volume. Therefore, this study was conducted to investigate the possible PK/PD interaction between meloxicam and furosemide in patients with compensated chronic cardiac failure (CCF).

This randomized, double-blind, placebo-controlled, multiple-dose, cross-over study. The study extended over 28 days and included a 7-day run-in period (Days 1 to 7 - furosemide 40 mg per day). During the two treatment phases (Days 8 to 14 and Days 22 to 28), patients were randomized to receive either meloxicam (15 mg per day) plus furosemide (40 mg per day) [test treatment] or placebo plus furosemide (40 mg per day) [reference treatment]. The two treatment periods were separated by a washout period of seven days (Days 15 to 21) during which furosemide (40 mg per day) was administered.
On the last day of each treatment period (Days 14 and 28), pharmacodynamic measurements were obtained of urine volume, urine electrolytes, serum electrolytes, serum uric acid and creatinine clearance. Urine and plasma samples at selected time intervals were also obtained for the measurement of furosemide concentrations. Pre-dose plasma samples were obtained on Days 12 to 14 and Days 26 to 28 for the determination of meloxicam concentrations.

**Results:** All nineteen patients completed this study.

1. Pharmacokinetics

Mean concentrations are illustrated in Figure 1. Summary statistics of pharmacokinetic parameters are summarized Table 1.

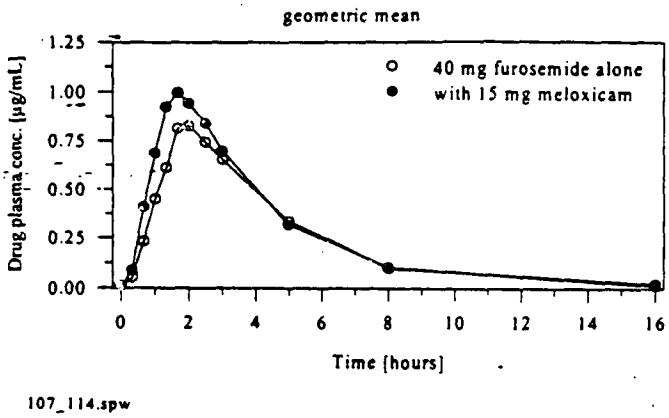



Figure 1. Mean furosemide plasma concentrations (n=19) after repeated once-daily 40 mg furosemide doses either alone or in combination with repeated once-daily 15 mg meloxicam doses

Table 1. Summary Statistics of PK parameters (plasma) of Furosemide

| | Treatment | Geometric Mean | GMR | 90% CI for GMR |
|---|---|---|---|---|
| $AUC_{ss}$(ng-hr/ml) | Furosemide + placebo | 4135 | | |
| | furosemide + Meloxicam | 4398 | 1.06 | (0.964, 1.16) |
| Cmax (ng/ml) | furosemide + placebo | 1124 | | |
| | furosemide + Meloxicam | 1367 | 1.21 | (1.01, 1.45) |

The results showed that meloxicam did not affect the exposure of furosemide in term of mean $AUC_{ss}$. The mean Cmax of furosemide increased by 21 % when given with meloxicam. Higher variability was observed with individual data (intra-subject variability was 33% and 17% for Cmax and AUCss, respectively). Some patients showed significant higher AUC and Cmax values when given furosemide alone, but some showed significant higher values when given fruosemide + meloxicam.

The pharmacokinetics of furosemide in urine are summarized in Table 2 (n=19).

Table 2. Cumulative urinary furosemide excretion (mg) on Day 14 and Day 28

| | Treatment | Geometric Mean | GMR | 90% CI for GMR |
|---|---|---|---|---|
| 0-4 hours | Furosemide + placebo | 4.78 | | |
| | furosemide + Meloxicam | 7.95 | NC* | NC |
| 0-8 hours | furosemide + placebo | 8.74 | | |
| | furosemide + Meloxicam | 10.8# | 1.23 | (1.01, 1.50) |
| 0-12 hours | furosemide + placebo | 10.2 | | |
| | furosemide + Meloxicam | 12.3 | NC | NC |
| 0-24 hours | furosemide + placebo | 11.4 | | |
| | furosemide + Meloxicam | 13.9# | 1.22 | (1.05, 1.42) |

* not calculated by the sponsor.
# n=18, reason was not indicated.

The results indicated that the amount of furosemide excreted in urine was 22% higher for the test treatment.

3. Pharmacodynamic

Serum and urine pharmacodynamic parameters were summarized in Tables 3 and 4, respectively.

Table 3. Summary of Pharmacodynamic data (serum)

| | Treatment | Geometric Mean | GMR | 90% CI for GMR |
|---|---|---|---|---|
| Creatinine Clearance | Furosemide + placebo | 73.0 | | |
| | furosemide + Meloxicam | 73.5 | 1.01 | (0.88, 1.15) |
| Sodium | furosemide + placebo | 139 | | |
| | furosemide + Meloxicam | 141 | 1.01 | (1.00, 1.01) |
| Potassium | furosemide + placebo | 3.95 | | |
| | furosemide + Meloxicam | 4.10 | 1.04 | (1.00, 1.08) |
| Chloride | furosemide + placebo | 104 | | |
| | furosemide + Meloxicam | 105 | 1.01 | (1.01, 1.02) |
| Uric Acid | furosemide + placebo | 0.36 | | |
| | furosemide + Meloxicam | 0.35 | 0.965 | (0.92, 1.01) |

Table 4. Summary of Pharmacodynamic Data (urine): Cumulative Urine volumes (mL)

| | Treatment | Geometric Mean | GMR | 90% CI for GMR |
|---|---|---|---|---|
| 0-4 hours | Furosemide + placebo | 1110 | | |
| | furosemide + Meloxicam | 1261 | NC* | NC |
| 0-8 hours | furosemide + placebo | 1482 | | |
| | furosemide + Meloxicam | 1506 | 1.02 | (0.933, 1.11) |
| 0-12 hours | furosemide + placebo | 1632 | | |
| | furosemide + Meloxicam | 1624 | NC | NC |
| 0-24 hours | furosemide + placebo | 1974 | | |
| | furosemide + Meloxicam | 2035 | 1.03 | (0.945, 1.13) |

The results indicated that meloxicam did not affect the pharmacodynamics of furosemide when given concomitantly.

**Conclusion:**

There is no pharmacodynamic interaction between daily dose of 40 mg furosemide and 15mg meloxicam. However, while the AUCss of furosemide was not affected by meloxicam, the Cmax and urine excretion of furosemide increased by 20% when given furosemide + meloxicam compared to furosemide alone.

**Lithium**

Study 107.144: An open, controlled study in healthy volunteers to evaluate the influence of the concomitant administration of 15 mg oral meloxicam on the steady state plasma pharmacokinetics and renal clearance of lithium (Report U95-2241)

Close clinical and pharmacokinetic monitoring is required due to the low therapeutic margin of lithium and its salts. Plasma concentrations ranging from 0.4 to 1.0 mM/L measured 12 hours after the last dose are usually required for therapeutic efficacy.

Intoxication may occur at plasma concentrations above 1.0 mM/L. An increase in lithium levels has been observed with concomitantly administratered NSAIDs, antipsychotic drugs, diuretics and theophylline. An increase of up to 40% was reported for both piroxicam and tenidap accompanied by marked clinical signs and symptoms of lithium intoxication. Therefore, this study was conducted to investigate the interaction between lithium and meloxicam.

Under the condition of this study, plasma concentrations of 0.3 to 0.7 mMoL/L were intended to be achieved and maintained by an individualized dosage regimen that was steered by monitoring of the morning pre-dosing lithium levels. This goal was set for the concomitant treatment with meloxicam, which was expected to increase rather than decrease the levels of lithium. To minimize the risk for the volunteers, stabilization on lithium was done with concomitant meloxicam treatment. Thus after termination of meloxicam treatment a decrease in lithium plasma concentration was expected.

In this multiple-dose study, lithium tablets were dosed for a total of 22 days in 16 healthy male volunteers. Subjects took one lithium acetate tablet per day on Days 1 and 2, one tablet (q12h) on Days 3-5 and two tablets (q12h) on Days 6 and 7. Then the dosage was titrated as discussed below on Days 7-9 to a final dosage maintained until Day 22. For the first 14 days, a meloxicam 15 mg capsule was taken concomitantly in the morning by all subjects, then omitted for the remaining eight days. Pharmacokinetics were assessed on Days 14 and 22.

Prior to steady-state, plasma lithium concentrations were monitored by daily morning predose concentrations, and the dosage was titrated during Days 7-9 to maintain plasma concentrations between 0.3 and 0.7 mM. Since the expected interaction would increase lithium levels, the study design and titration were provided to limit the exposure of subjects to toxic levels of lithium. Medications were taken after breakfast (lithium and meloxicam) and dinner (lithium) with 150 mL water. From Day 10 through 22, the final titration resulted in no change for eight subjects and reduction from two to 1.5 tablets (q12h) for the other eight subjects (doses switched to 1.5 tablets at Day 9 the latest).

A 12-hour steady-state concentration-time profile for lithium and meloxicam was taken on Day 14 after the final dose of meloxicam. A second 24-hour lithium concentration-time profile was obtained on Day 22 maintaining the same lithium dose as before under steady-state conditions. Urine samples were obtained to assess renal lithium clearance. Plasma and urine samples were analyzed for lithium using atomic absorption spectroscopy. Meloxicam was analyzed by a HPLC/UV procedure. Pharmacokinetic parameters were estimated using noncompartmental procedures.

**Results:**

All 16 subjects completed the study. Mean lithium concentrations are illustrated in Figure 1. Summary statistics of lithium pharmacokinetic parameters are listed in Table 1.

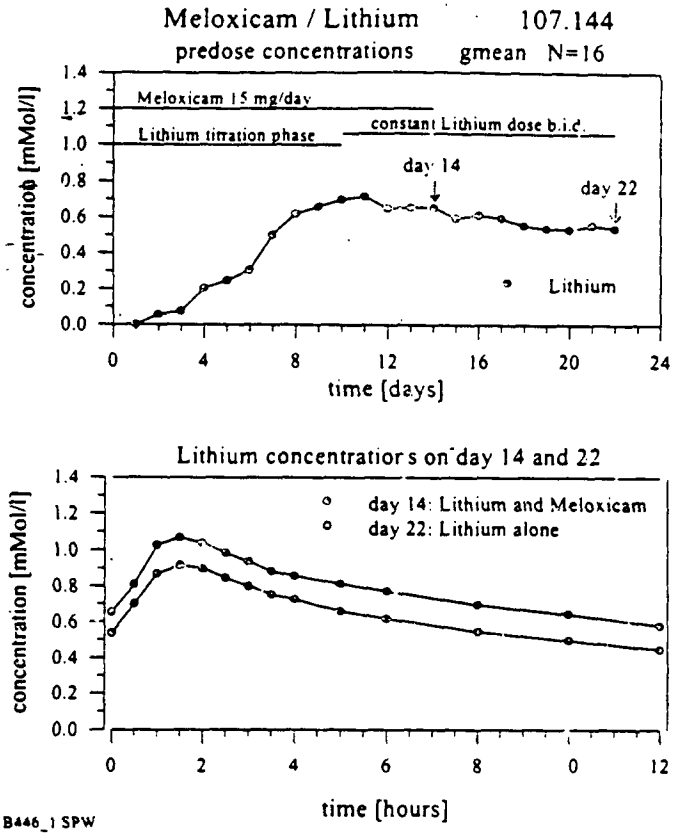



Figure 1. Geometric mean lithium plasma concentrations after multiple lithium (tablets, Day 1-22) and meloxicam (capsules, Day 1-14) doses in 16 healthy male volunteers

Table 1. Summary Statistics of PK parameters (plasma) of lithium

| | Treatment | Geometric Mean | GMR | 90% CI for GMR |
|---|---|---|---|---|
| $AUC_{ss}$ (mMol-hr/ml) | Lithium | 7.75 | | |
| | Lithium + Meloxicam | 9.40 | 1.21 | (1.15, 1.28) |
| $C_{max,ss}$ (mMol/L) | Lithium | 0.97 | | |
| | Lithium + Meloxicam | 1.12 | 1.16 | (1.09, 1.23) |
| $C_{predose,ss}$ (mMol/L) | Lithium | 0.54 | | |
| | Lithium + Meloxicam | 0.65 | 1.21 | (1.13, 1.30) |
| $C_{min,ss}$ (mMol/L) | Lithium | 0.35 | | |
| | Lithium + Meloxicam | 0.56 | 1.60 | (1.48, 1.72) |

The results showed that concomitant meloxicam administration resulted in 21% higher predose lithium concentrations and $AUC_{ss}$, and $C_{max,ss}$ values were 16% higher. An even bigger difference between $C_{min,ss}$ values was observed (60%). The sponsor indicated that this is probably because $C_{min,ss}$ is very sensitive to the time of blood sample. Since no sampling time deviation on Day 24 was reported, the reviewer can not comment on the above statement. However, the reviewer agrees with the sponsor that $C_{predose,ss}$ is a better estimate of the effect of meloxicam on lithium pharmacokinetics since it is consistent with the $C_{predose,ss}$ values on previous days and also the comparison of $AUC_{ss}$ values.

The sponsor also compared the effect of other NSAIDs on lithium pharmacokinetics:

Table 2. Percent increase in mean serum or plasma concentration of lithium when lithium was co-administered with selected NSAIDs.

| Medication | Dose | Subjects | % increase | Reference |
|---|---|---|---|---|
| Ibuprofen | 600 mg t.i.d. | patients, n=9 | 34% | R94-1360 |
| Diclofenac | 50 mg t.i.d. | healthy volunteers, n=5 | 26% | R94-1454 |
| Indomethacin | 50 mg t.i.d. | healthy volunteers, n=4 | 30% | R94-1456 |
| Indomethacin | 50 mg t.i.d. | patients, n=3 | 59% | R94-1456 |
| Indomethacin | 50 mg t.i.d. | healthy volunteers, n=5 | 40% | R94-1453 |
| Naproxen | 750 mg q.d. | patients, n=7 | 16% | R94-1450 |

Meloxicam levels were compared with those from other studies. The mean predose level in this study (0.998 µg/mL) is very close to those obtained from study 107.64 (1.05 µg/mL), study 107.74 (1.06 µg/mL), and study 107.82 (0.82 µg/mL). Levels at 2, 4, 8 6 and 12 hours are also similar. Therefore, concomitant dosing of lithium did not alter meloxicam pharmacokinetics.

Concomitant meloxicam and lithium administration was well tolerated.

**Conclusion:**

Concomitant meloxicam administration resulted in 21% higher predose lithium concentrations and $AUC_{ss}$ values. The $Cmax_{ss}$ values were increased by 16%. Thus, lithium plasma concentrations should be closely monitored in the case that meloxicam is additionally administered in the same subject.

**Overall Summary of Drug Interaction studies.**

Drug-drug interaction with meloxicam has been studied for 8 drugs. In general the study design features of the protocols was acceptable, however, it appears that most of these studies were done originally for the European approval of meloxicam and have in them the characteristics of European trials. Specifically the dose of meloxicam used (15 and 30 mg) is higher than the clinical dose studied in the U.S. (7.5 mg) and reflects the dosing and pattern of use of meloxicam in Europe. Most studies were conducted only in male subjects and the studies themselves are relatively old studies (some date back to 1989). Finally, in some of the trials, non-U.S. marketed drugs are used, such as in the digoxin study where β-acetyldigoxin tablets (Novodigal, Germany) was used. Despite these "deviations" from the U.S. norm, the drug-interaction studies are acceptable.

At a dose of 4 g three times daily, cholestyramine decreased the meloxicam AUC in healthy male subjects receiving 30 mg meloxicam IV injection by 34%. This suggests the existence of a recirculation of meloxicam in the gastrointestinal tract.

An interaction between meloxicam and aspirin at full anti-inflammatory dose was demonstrated by an increase in Cmax and AUC values of meloxicam by 24% and 10%.

The pharmacokinetic and pharmacodynamic interactions between meloxicam and furosemide were studied in both healthy volunteers and patients with compensated chronic cardiac failure (CCF). In healthy volunteers, meloxicam 15 mg daily at steady-state did not significantly affect the pharmacokinetics and pharmacodynamics of furosemide. However, slight decrease in furosemide Cmax (10%), and potassium and phosphate urinary excretion (20%) were observed. In patients with CCF, there is no pharmacodynamic interaction between daily dose of 40 mg furosemide and 15mg meloxicam. However, while the $AUC_{ss}$ of furosemide was not affected by meloxicam, the Cmax and urine excretion of furosemide increased by 20% when given furosemide + meloxicam compared to furosemide alone. The effect of furosemide on meloxicam was not studied.

Concomitant meloxicam administration resulted in 21% higher predose lithium concentrations and $AUC_{ss}$ values. The $Cmax_{ss}$ values were increased by 16%. Thus, lithium plasma concentrations should be closely monitored in the case that meloxicam is additionally administered in the same subject.

There is no pharmacokinetic interaction between a 15 mg IV dose of methotrexate and 15 mg oral dose of meloxicam in RA patients.

Meloxicam pharmacokinetics at 30 mg dose level was not affected by cimetidine.

In healthy volunteers, multiple doses of 15 mg meloxicam did not affect steady-state pharmacokinetics of digoxin, and steady-state pharmacokinetics and pharmacodynamics of warfarin.

/S/

8/25/99

Dan Wang
Division of Pharmaceutical Evaluation III

FT initialed by D. Bashaw, Pharm.D. 8/25/99

cc:

HFD-550(Lewin)
HFD-880(Division file)
HFD-880(Bashaw)
HFD-880(Wang)
HFD-850(Mira Millison, Drug, Chron Files)
HFD-205(FOI)
HFD-344(Viswanathan)
CDR: Attn: Barbara Murphy

# Clinical Pharmacology/Biopharmaceutics Review

| | | |
|---|---|---|
| NDA: | 20-938 | SUBMISSION DATE: 12/16/99 |
| PRODUCT: | MOBIC®<br>(Meloxicam) | |
| SPONSOR: | Boehringer Ingelheim<br>Pharmaceuticals, Inc.<br>Ridgefield, CT 06877 | REVIEWER: Veneeta Tandon, Ph.D. |

## Filing Review

*Class*: NSAID of the oxicam class
*Dosage form*: Tablets
*Dose*: 7.5 to 15 mg once a day
*Indication*: relief of signs and symptoms of oesteoarthritis.
*Marketing history*: Approved in over 70 countries for treatment of OA, RA, ankylosing spondylitis, available as tablets, capsules, ampules (for injection) and suppositories.

*Formulation:*

| *Component* | *mg/tablet* |
|---|---|
| Meloxicam,USP | 7.5 |
| Sodium citrate dihydrate,NF | |
| Lactose monohydrate,NF | |
| Microcrystaline cellulose,NF | |
| Povidone,USP | |
| Colloidal silicon dioxide,NF | |
| Crospovidone,NF | |
| Magenesium stearate,USP | |
| Total | 180.0 |

*PK Studies:*

Most PK studies were done in with capsule dosage form. Bioequivalence studies have been done as bridging studies between the capsule and tablet dosage forms.

*Types and numbers of studies*:
Total number = 48

| Type of study | Number submitted | Number intended to review |
|---|---|---|
| Metabolism | 3 | 3 |
| Single/multiple dose PK | 11 | ~4 |
| Dose proportionality | 7 | 4 |
| Gender effect | 2 | 2 |
| Food effect | 3 | 3 |
| Drug Interaction | 10 | 10 |
| PK in patients | 8 | ~4 |
| Renal study | 2 | 2 |
| Hepatic study | 1 | 1 |
| Bioequivalence | 4 | 4 (total 37) |

## NDA Review Issues

The package has many deficiencies that make the material difficult to review. All the data could be there but is not easily located. The NDA does have the type and kind of studies required to assess the pharmacokinetics of meloxicam. However, there are several reviewabilty issues, such as:

1. The studies in the PK section are not arranged in a logical manner. For example, Volume 1.55 has a couple metabolism studies, one protein binding study, one drug interaction study and a report on assay methodology. Other metabolism and drug interaction action studies and protein binding reports are scattered all over the volumes (1.55 through 1.99). Some of these studies are not even mentioned in the Tabular Summary of Studies (TSS) on page 30 of Volume 1.53. For example Report U 89-0756 is not mentioned in the TSS, if the reviewer reviews studies according to the table, it is very likely that such reports may be overlooked, if the studies are reviewed according to the sequential volumes, the reviewer does not find any logical order of review.
2. The study numbers and report numbers are very different for each study. For example Study # 107.116 has a report number U95-2126. All study #'s have three decimal points after 107. (i.e. 107.xxx). It is much easier to relate to a study # rather than a report number, which is more complex. If the tabs in the volumes were based on study #'s, rather than report numbers, it would be much easier to relate to a study.
3. There are different analytical validation reports for all the studies as shown on page 94 of volume 1.53, where the tabular summary for the analytical validation report is based on the study #, but in the tabs of the various volumes, there are written as report #'s with the Uxx-xxx nomenclature. From the summary it is very difficult to know which report relates to which study# and also the location of an assay validation report for a particular study is difficult to find in a volume. The quality of the assay

validation is the first thing a reviewer will like to see before giving any validity to the PK data submitted.

**Additional Request**

1. Electronic version of the individual study summary of the "Human Pharmacokinetics section" of the NDA, preferably in MS Word format (ie. Summary in Vol 1.53).

/S/

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

Team Leader: E. Dennis Bashaw, Pharm. D. /S/ 2/10/97