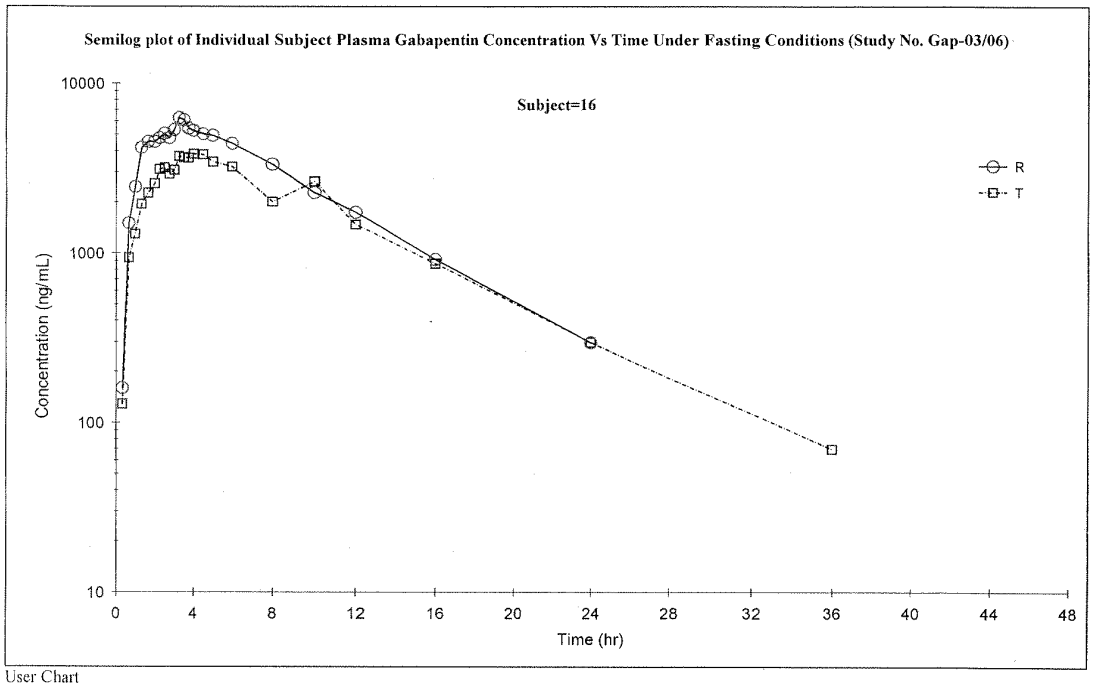
## FIGURE 49

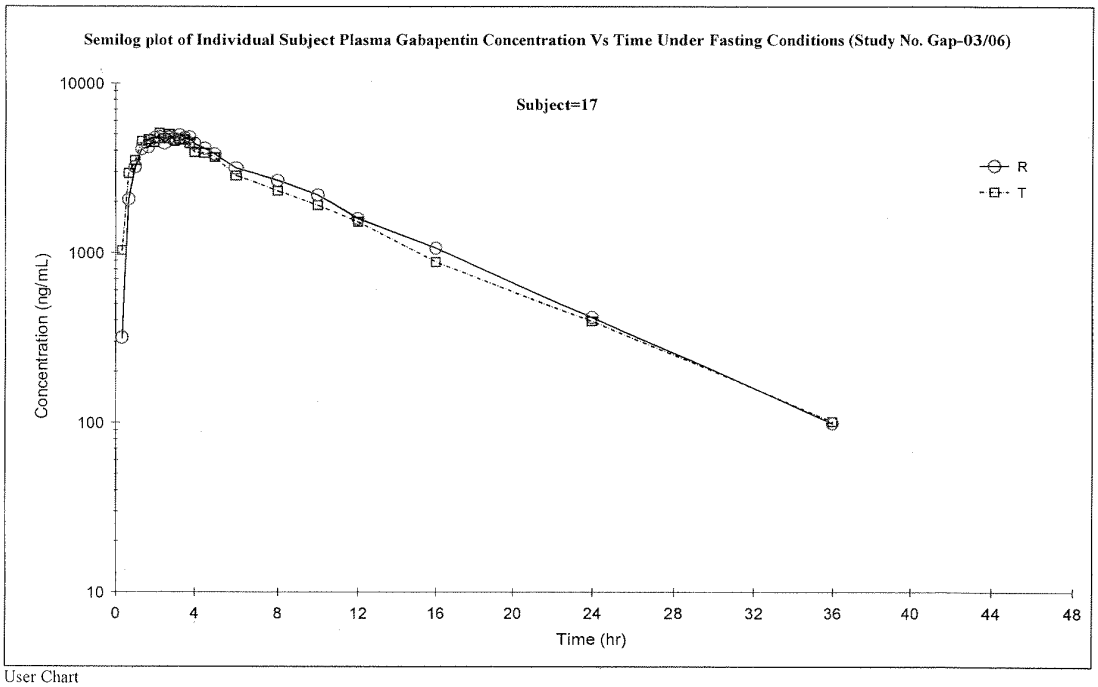



User Chart
H:\CPD-BE\Gabapentin\Gap 0306\Individual semilog plots.pco (19-Apr-2007)

## Comparative Evaluation of Pharmacokinetic Parameters of Gabapentin (Subject 16)

| Parameter | Reference (R) | Test (T) |
|---|---|---|
| $T_{max}$ (hr) | 3.25 | 4.00 |
| $C_{max}$ (ng/mL) | 6264.05 | 3835.45 |
| $AUC_{0\rightarrow t}$ (hr*ng/mL) | 52960.86 | 41807.70 |
| No.of points used for $k_{el}$ calculation | 4 | 4 |
| $k_{el}$ (1/hr) | 0.1463 | 0.1272 |
| $k_{el}$ start (hr) | 10.00 | 12.00 |
| $k_{el}$ end (hr) | 24.00 | 36.00 |
| $t_{1/2}$ (hr) | 4.74 | 5.45 |
| $AUC_{0\rightarrow\infty}$ (hr*ng/mL) | 54988.48 | 42354.98 |
| AUC % Extrapolation | 3.69 | 1.29 |
| Rsq | 0.9993 | 0.9994 |

## FIGURE 50

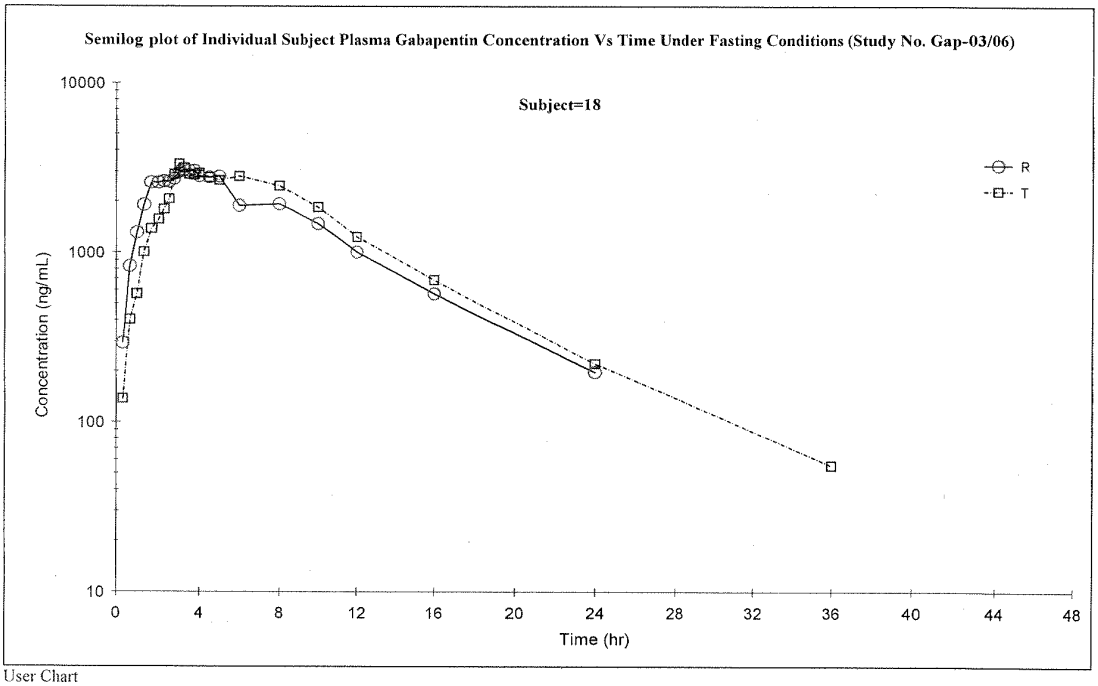



User Chart
H:\CPD-BE\Gabapentin\Gap 0306\Individual semilog plots.pco (19-Apr-2007)

## Comparative Evaluation of Pharmacokinetic Parameters of Gabapentin (Subject 17)

| Parameter | Reference (R) | Test (T) |
|---|---|---|
| $T_{max}$ (hr) | 3.25 | 2.25 |
| $C_{max}$ (ng/mL) | 4941.53 | 5067.66 |
| $AUC_{0\rightarrow t}$ (hr*ng/mL) | 51248.88 | 48386.64 |
| No.of points used for $k_{el}$ calculation | 3 | 7 |
| $k_{el}$ (1/hr) | 0.1189 | 0.1117 |
| $k_{el}$ start (hr) | 16.00 | 6.00 |
| $k_{el}$ end (hr) | 36.00 | 36.00 |
| $t_{1/2}$ (hr) | 5.83 | 6.20 |
| $AUC_{0\rightarrow\infty}$ (hr*ng/mL) | 52080.70 | 49291.53 |
| AUC % Extrapolation | 1.60 | 1.84 |
| Rsq | 1.0000 | 0.9992 |

## FIGURE 51

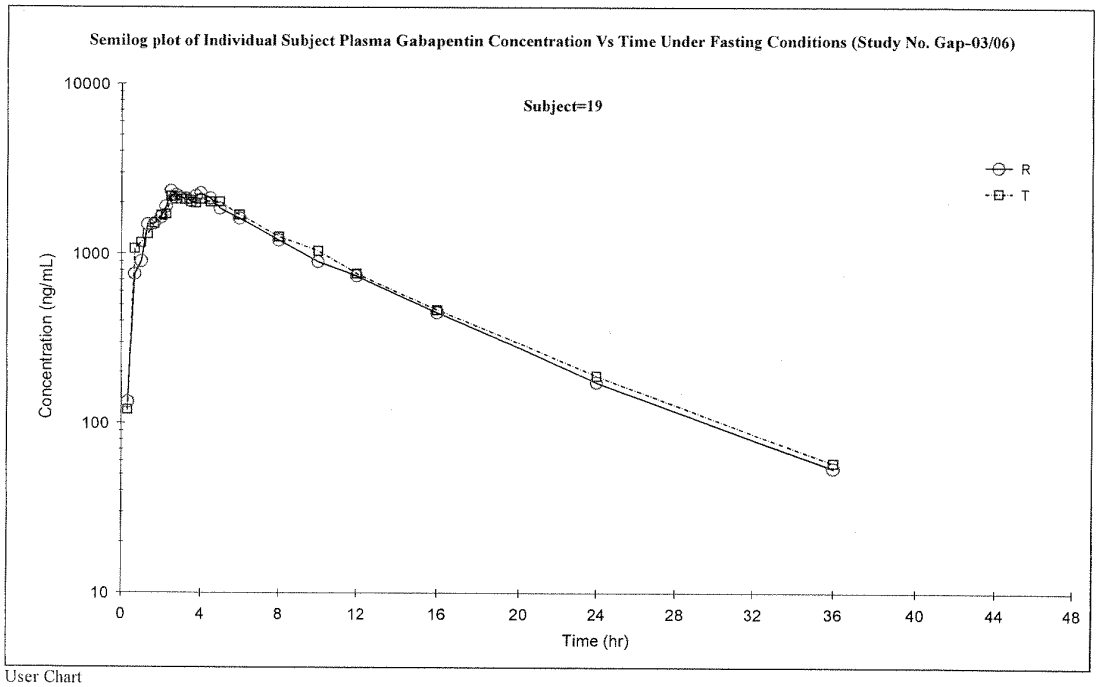



User Chart
H:\CPD-BE\Gabapentin\Gap 0306\Individual semilog plots.pco (19-Apr-2007)

## Comparative Evaluation of Pharmacokinetic Parameters of Gabapentin (Subject 18)

| Parameter | Reference (R) | Test (T) |
|---|---|---|
| $T_{max}$ (hr) | 3.25 | 3.00 |
| $C_{max}$ (ng/mL) | 3064.24 | 3318.56 |
| $AUC_{0\rightarrow t}$ (hr*ng/mL) | 29420.34 | 33965.40 |
| No.of points used for $k_{el}$ calculation | 3 | 4 |
| $k_{el}$ (1/hr) | 0.1354 | 0.1292 |
| $k_{el}$ start (hr) | 12.00 | 12.00 |
| $k_{el}$ end (hr) | 24.00 | 36.00 |
| $t_{1/2}$ (hr) | 5.12 | 5.36 |
| $AUC_{0\rightarrow\infty}$ (hr*ng/mL) | 30872.89 | 34392.08 |
| AUC % Extrapolation | 4.70 | 1.24 |
| Rsq | 0.9998 | 0.9968 |

## FIGURE 52




User Chart
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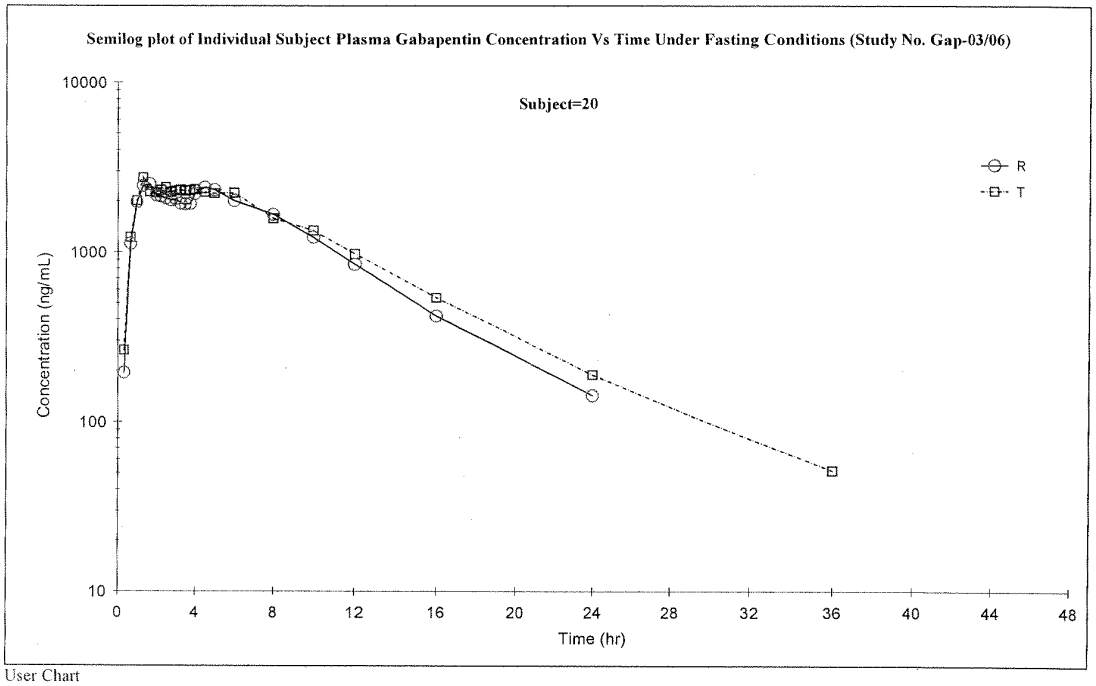
### Comparative Evaluation of Pharmacokinetic Parameters of Gabapentin (Subject 19)

| Parameter | Reference (R) | Test (T) |
|---|---|---|
| $T_{max}$ (hr) | 2.50 | 2.50 |
| $C_{max}$ (ng/mL) | 2338.43 | 2177.32 |
| $AUC_{0\rightarrow t}$ (hr*ng/mL) | 22708.03 | 23553.31 |
| No.of points used for $k_{el}$ calculation | 6 | 3 |
| $k_{el}$ (1/hr) | 0.1109 | 0.1037 |
| $k_{el}$ start (hr) | 8.00 | 16.00 |
| $k_{el}$ end (hr) | 36.00 | 36.00 |
| $t_{1/2}$ (hr) | 6.25 | 6.68 |
| $AUC_{0\rightarrow\infty}$ (hr*ng/mL) | 23196.56 | 24114.33 |
| AUC % Extrapolation | 2.11 | 2.33 |
| Rsq | 0.9973 | 0.9987 |

## FIGURE 53




User Chart
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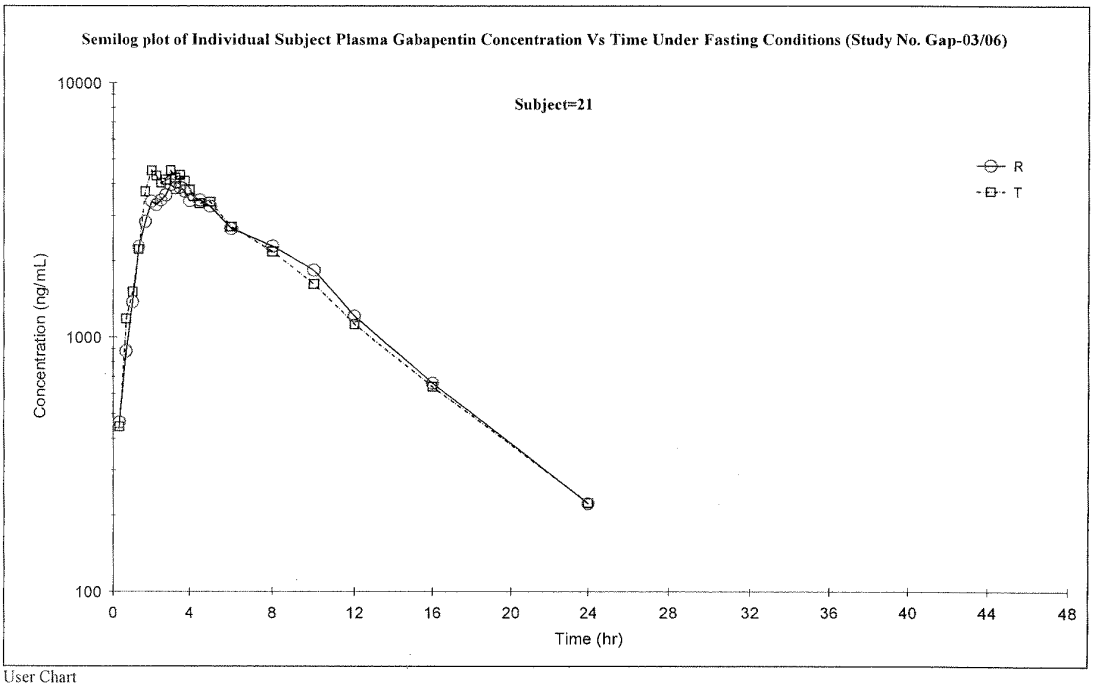
## Comparative Evaluation of Pharmacokinetic Parameters of Gabapentin (Subject 20)

| Parameter | Reference (R) | Test (T) |
|---|---|---|
| $T_{max}$ (hr) | 1.67 | 1.33 |
| $C_{max}$ (ng/mL) | 2518.32 | 2748.73 |
| $AUC_{0\rightarrow t}$ (hr*ng/mL) | 25069.10 | 28702.74 |
| No.of points used for $k_{el}$ calculation | 8 | 8 |
| $k_{el}$ (1/hr) | 0.1490 | 0.1258 |
| $k_{el}$ start (hr) | 4.50 | 5.00 |
| $k_{el}$ end (hr) | 24.00 | 36.00 |
| $t_{1/2}$ (hr) | 4.65 | 5.51 |
| $AUC_{0\rightarrow\infty}$ (hr*ng/mL) | 26025.21 | 29110.46 |
| AUC % Extrapolation | 3.67 | 1.40 |
| Rsq | 0.9958 | 0.9964 |

## FIGURE 54




User Chart
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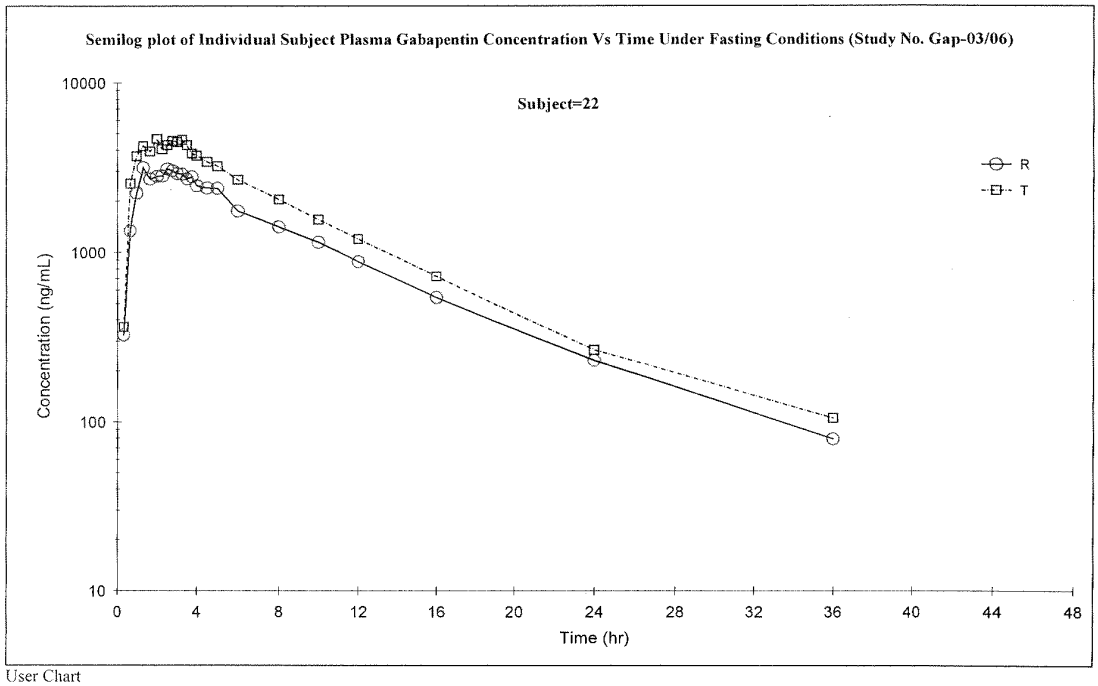
## Comparative Evaluation of Pharmacokinetic Parameters of Gabapentin (Subject 21)

| Parameter | Reference (R) | Test (T) |
|---|---|---|
| $T_{max}$ (hr) | 3.00 | 3.00 |
| $C_{max}$ (ng/mL) | 3976.07 | 4521.43 |
| $AUC_{0\rightarrow t}$ (hr*ng/mL) | 36272.48 | 37199.25 |
| No.of points used for $k_{el}$ calculation | 3 | 3 |
| $k_{el}$ (1/hr) | 0.1409 | 0.1343 |
| $k_{el}$ start (hr) | 12.00 | 12.00 |
| $k_{el}$ end (hr) | 24.00 | 24.00 |
| $t_{1/2}$ (hr) | 4.92 | 5.16 |
| $AUC_{0\rightarrow\infty}$ (hr*ng/mL) | 37846.24 | 38860.85 |
| AUC % Extrapolation | 4.16 | 4.28 |
| Rsq | 0.9992 | 0.9996 |

## FIGURE 55




User Chart
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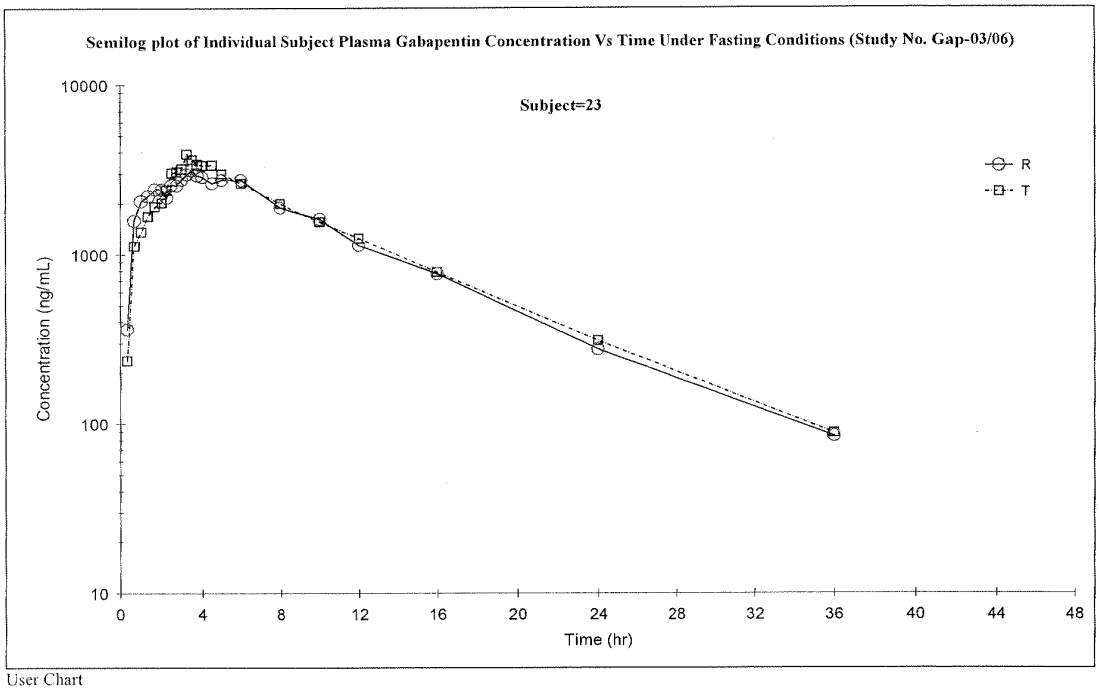
## Comparative Evaluation of Pharmacokinetic Parameters of Gabapentin (Subject 22)

| Parameter | Reference (R) | Test (T) |
|---|---|---|
| $T_{max}$ (hr) | 1.33 | 2.00 |
| $C_{max}$ (ng/mL) | 3144.05 | 4655.77 |
| $AUC_{0\rightarrow t}$ (hr*ng/mL) | 29358.81 | 41598.72 |
| No.of points used for $k_{el}$ calculation | 7 | 11 |
| $k_{el}$ (1/hr) | 0.1047 | 0.1158 |
| $k_{el}$ start (hr) | 6.00 | 3.75 |
| $k_{el}$ end (hr) | 36.00 | 36.00 |
| $t_{1/2}$ (hr) | 6.62 | 5.99 |
| $AUC_{0\rightarrow\infty}$ (hr*ng/mL) | 30109.24 | 42500.72 |
| AUC % Extrapolation | 2.49 | 2.12 |
| Rsq | 0.9962 | 0.9874 |

## FIGURE 56




User Chart
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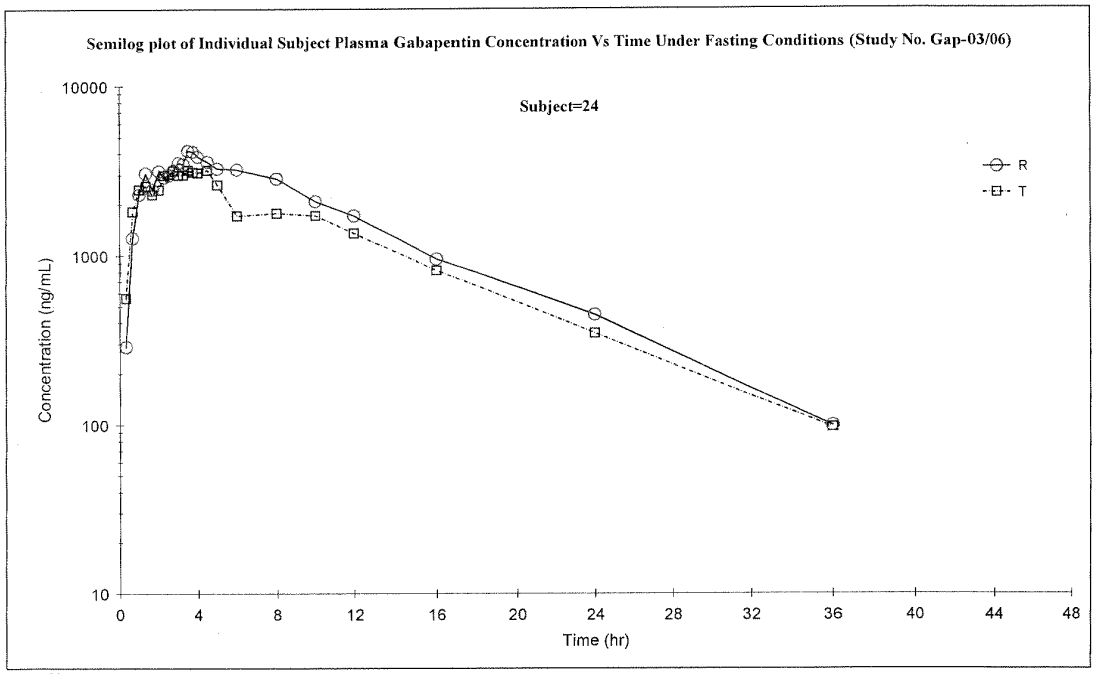
## Comparative Evaluation of Pharmacokinetic Parameters of Gabapentin (Subject 23)

| Parameter | Reference (R) | Test (T) |
|---|---|---|
| $T_{max}$ (hr) | 3.50 | 3.25 |
| $C_{max}$ (ng/mL) | 3141.15 | 3899.40 |
| $AUC_{0\rightarrow t}$ (hr*ng/mL) | 35134.55 | 36548.34 |
| No.of points used for $k_{el}$ calculation | 12 | 6 |
| $k_{el}$ (1/hr) | 0.1132 | 0.1117 |
| $k_{el}$ start (hr) | 3.50 | 8.00 |
| $k_{el}$ end (hr) | 36.00 | 36.00 |
| $t_{1/2}$ (hr) | 6.12 | 6.21 |
| $AUC_{0\rightarrow\infty}$ (hr*ng/mL) | 35878.43 | 37334.17 |
| AUC % Extrapolation | 2.07 | 2.10 |
| Rsq | 0.9960 | 0.9994 |

## FIGURE 57




User Chart
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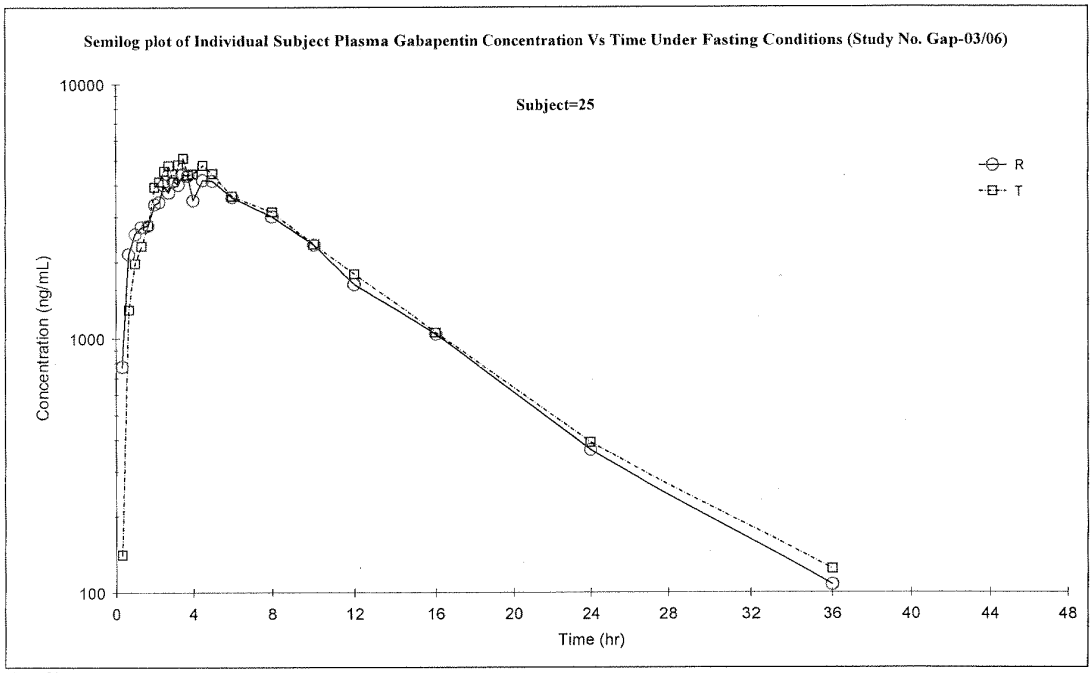
## Comparative Evaluation of Pharmacokinetic Parameters of Gabapentin (Subject 24)

| Parameter | Reference (R) | Test (T) |
|---|---|---|
| $T_{max}$ (hr) | 3.50 | 3.50 |
| $C_{max}$ (ng/mL) | 4161.31 | 3201.07 |
| $AUC_{0\rightarrow t}$ (hr*ng/mL) | 46302.36 | 36501.72 |
| No.of points used for $k_{el}$ calculation | 7 | 3 |
| $k_{el}$ (1/hr) | 0.1170 | 0.1067 |
| $k_{el}$ start (hr) | 6.00 | 16.00 |
| $k_{el}$ end (hr) | 36.00 | 36.00 |
| $t_{1/2}$ (hr) | 5.93 | 6.50 |
| $AUC_{0\rightarrow\infty}$ (hr*ng/mL) | 47141.43 | 37400.35 |
| AUC % Extrapolation | 1.78 | 2.40 |
| Rsq | 0.9976 | 1.0000 |

## FIGURE 58




User Chart
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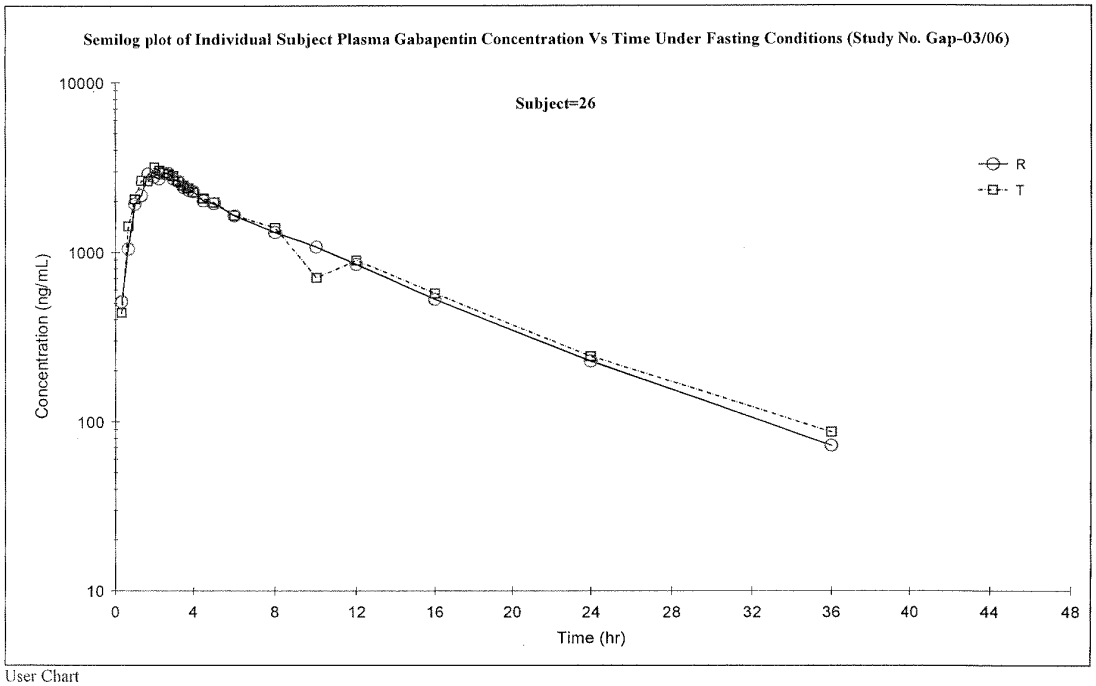
## Comparative Evaluation of Pharmacokinetic Parameters of Gabapentin (Subject 25)

| Parameter | Reference (R) | Test (T) |
|---|---|---|
| $T_{max}$ (hr) | 3.50 | 3.50 |
| $C_{max}$ (ng/mL) | 4417.93 | 5103.36 |
| $AUC_{0\rightarrow t}$ (hr*ng/mL) | 49659.60 | 52065.65 |
| No.of points used for $k_{el}$ calculation | 9 | 12 |
| $k_{el}$ (1/hr) | 0.1198 | 0.1168 |
| $k_{el}$ start (hr) | 4.50 | 3.50 |
| $k_{el}$ end (hr) | 36.00 | 36.00 |
| $t_{1/2}$ (hr) | 5.79 | 5.94 |
| $AUC_{0\rightarrow\infty}$ (hr*ng/mL) | 50556.50 | 53124.19 |
| AUC % Extrapolation | 1.77 | 1.99 |
| Rsq | 0.9969 | 0.9953 |

## FIGURE 59




User Chart
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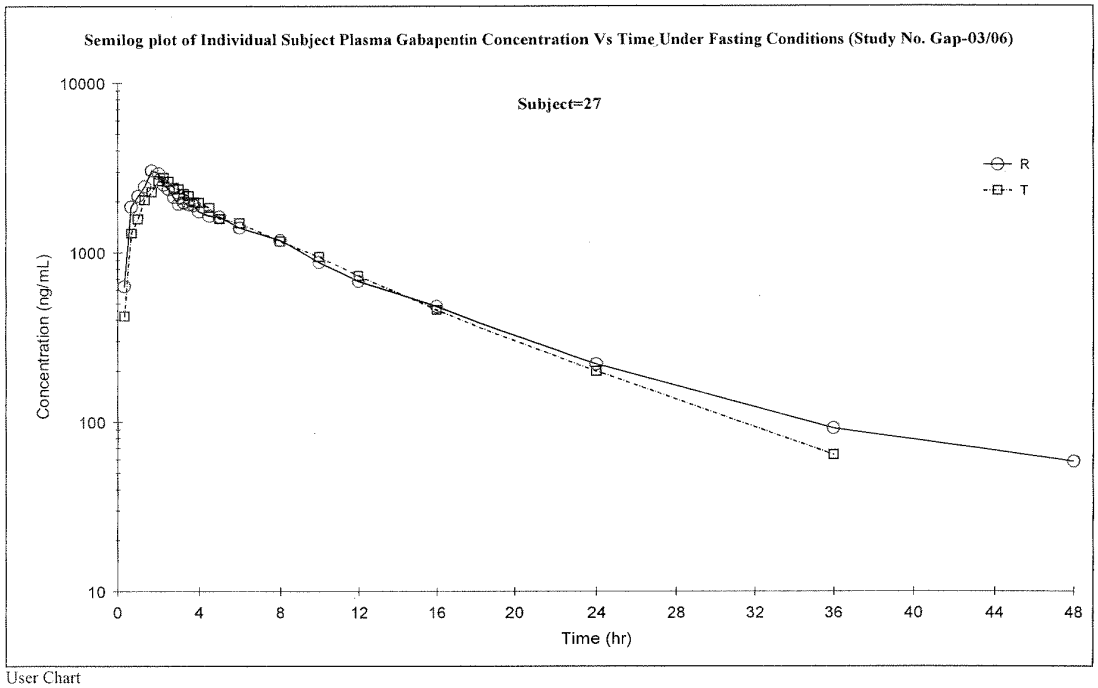
## Comparative Evaluation of Pharmacokinetic Parameters of Gabapentin (Subject 26)

| Parameter | Reference (R) | Test (T) |
|---|---|---|
| $T_{max}$ (hr) | 2.50 | 2.00 |
| $C_{max}$ (ng/mL) | 2930.54 | 3165.86 |
| $AUC_{0\rightarrow t}$ (hr*ng/mL) | 27210.78 | 27809.34 |
| No.of points used for $k_{el}$ calculation | 3 | 4 |
| $k_{el}$ (1/hr) | 0.0992 | 0.0971 |
| $k_{el}$ start (hr) | 16.00 | 12.00 |
| $k_{el}$ end (hr) | 36.00 | 36.00 |
| $t_{1/2}$ (hr) | 6.99 | 7.14 |
| $AUC_{0\rightarrow\infty}$ (hr*ng/mL) | 27934.01 | 28697.11 |
| AUC % Extrapolation | 2.59 | 3.09 |
| Rsq | 0.9993 | 0.9959 |

## FIGURE 60




User Chart
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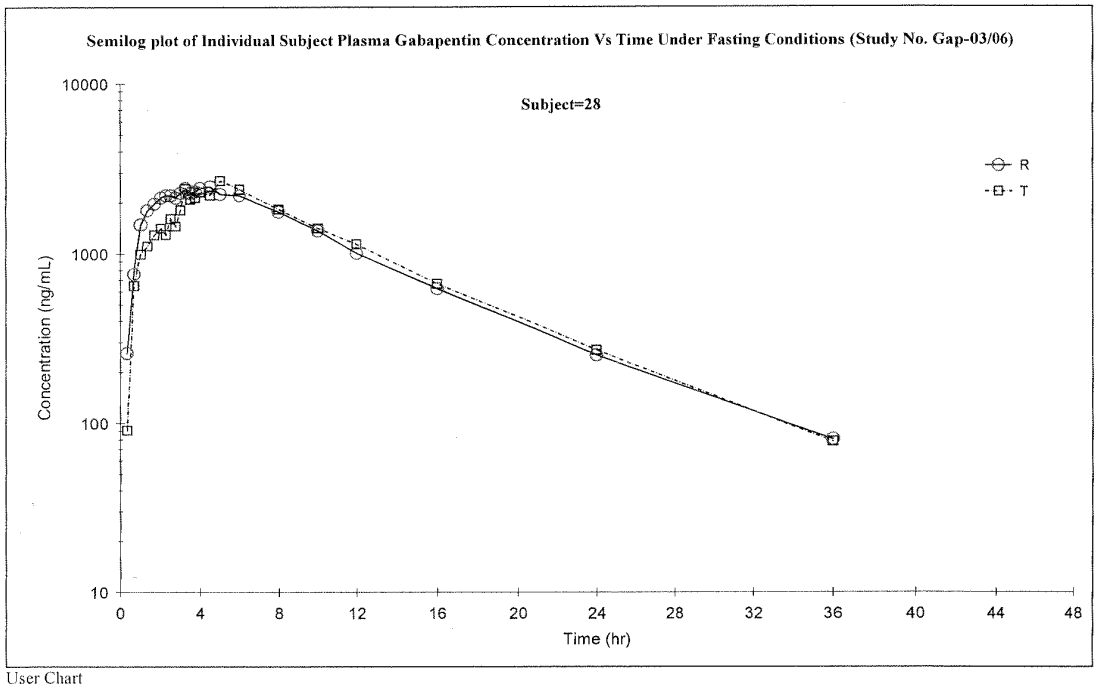
## Comparative Evaluation of Pharmacokinetic Parameters of Gabapentin (Subject 27)

| Parameter | Reference (R) | Test (T) |
|---|---|---|
| $T_{max}$ (hr) | 1.67 | 2.25 |
| $C_{max}$ (ng/mL) | 3046.88 | 2771.24 |
| $AUC_{0\rightarrow t}$ (hr*ng/mL) | 25341.96 | 24013.97 |
| No.of points used for $k_{el}$ calculation | 16 | 3 |
| $k_{el}$ (1/hr) | 0.0853 | 0.0982 |
| $k_{el}$ start (hr) | 2.75 | 16.00 |
| $k_{el}$ end (hr) | 48.00 | 36.00 |
| $t_{1/2}$ (hr) | 8.13 | 7.06 |
| $AUC_{0\rightarrow\infty}$ (hr*ng/mL) | 26022.12 | 24662.79 |
| AUC % Extrapolation | 2.61 | 2.63 |
| Rsq | 0.9761 | 0.9993 |

## FIGURE 61




User Chart
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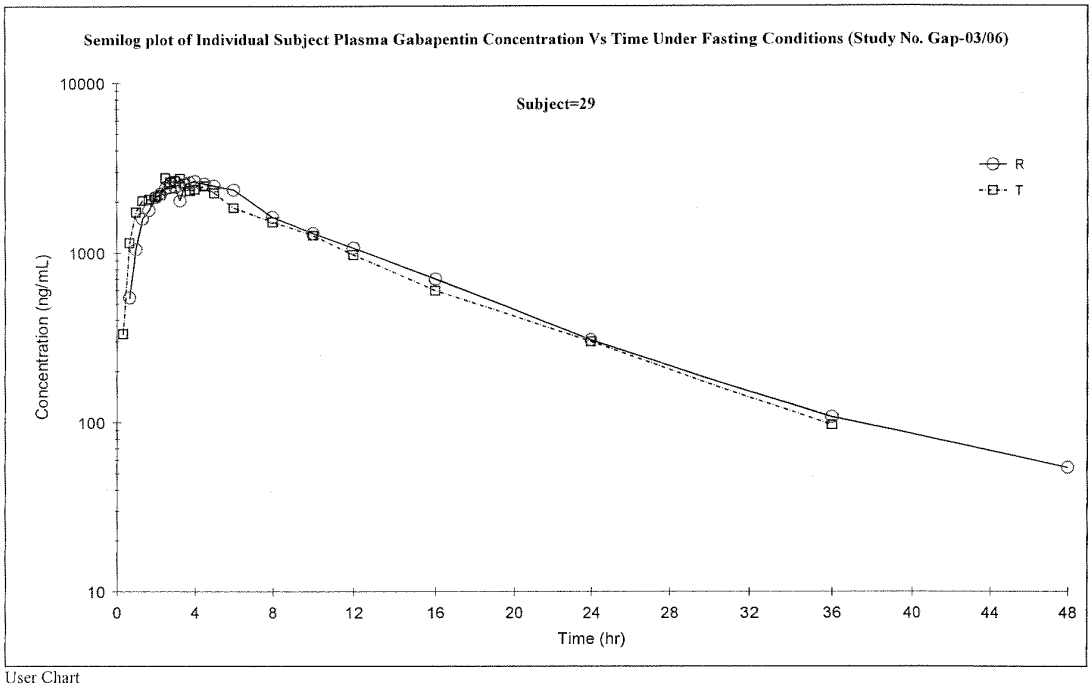
## Comparative Evaluation of Pharmacokinetic Parameters of Gabapentin (Subject 28)

| Parameter | Reference (R) | Test (T) |
|---|---|---|
| $T_{max}$ (hr) | 4.50 | 5.00 |
| $C_{max}$ (ng/mL) | 2484.96 | 2688.66 |
| $AUC_{0\rightarrow t}$ (hr*ng/mL) | 29796.28 | 29592.13 |
| No.of points used for $k_{el}$ calculation | 9 | 3 |
| $k_{el}$ (1/hr) | 0.1115 | 0.1071 |
| $k_{el}$ start (hr) | 4.50 | 16.00 |
| $k_{el}$ end (hr) | 36.00 | 36.00 |
| $t_{1/2}$ (hr) | 6.22 | 6.47 |
| $AUC_{0\rightarrow\infty}$ (hr*ng/mL) | 30512.50 | 30315.96 |
| AUC % Extrapolation | 2.35 | 2.39 |
| Rsq | 0.9964 | 0.9994 |

## FIGURE 62




User Chart
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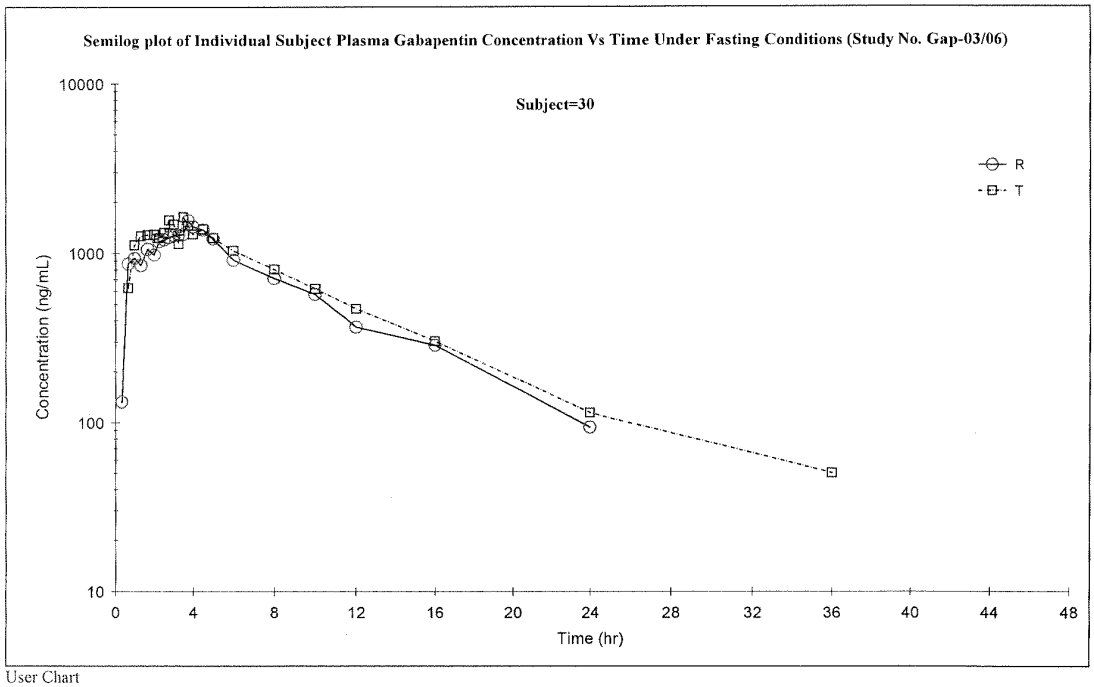
## Comparative Evaluation of Pharmacokinetic Parameters of Gabapentin (Subject 29)

| Parameter | Reference (R) | Test (T) |
|---|---|---|
| $T_{max}$ (hr) | 4.00 | 2.50 |
| $C_{max}$ (ng/mL) | 2639.00 | 2767.38 |
| $AUC_{0\rightarrow t}$ (hr*ng/mL) | 31942.24 | 29681.42 |
| No.of points used for $k_{el}$ calculation | 7 | 3 |
| $k_{el}$ (1/hr) | 0.0873 | 0.0915 |
| $k_{el}$ start (hr) | 8.00 | 16.00 |
| $k_{el}$ end (hr) | 48.00 | 36.00 |
| $t_{1/2}$ (hr) | 7.94 | 7.57 |
| $AUC_{0\rightarrow\infty}$ (hr*ng/mL) | 32558.53 | 30728.74 |
| AUC % Extrapolation | 1.89 | 3.41 |
| Rsq | 0.9892 | 0.9994 |

## FIGURE 63




User Chart
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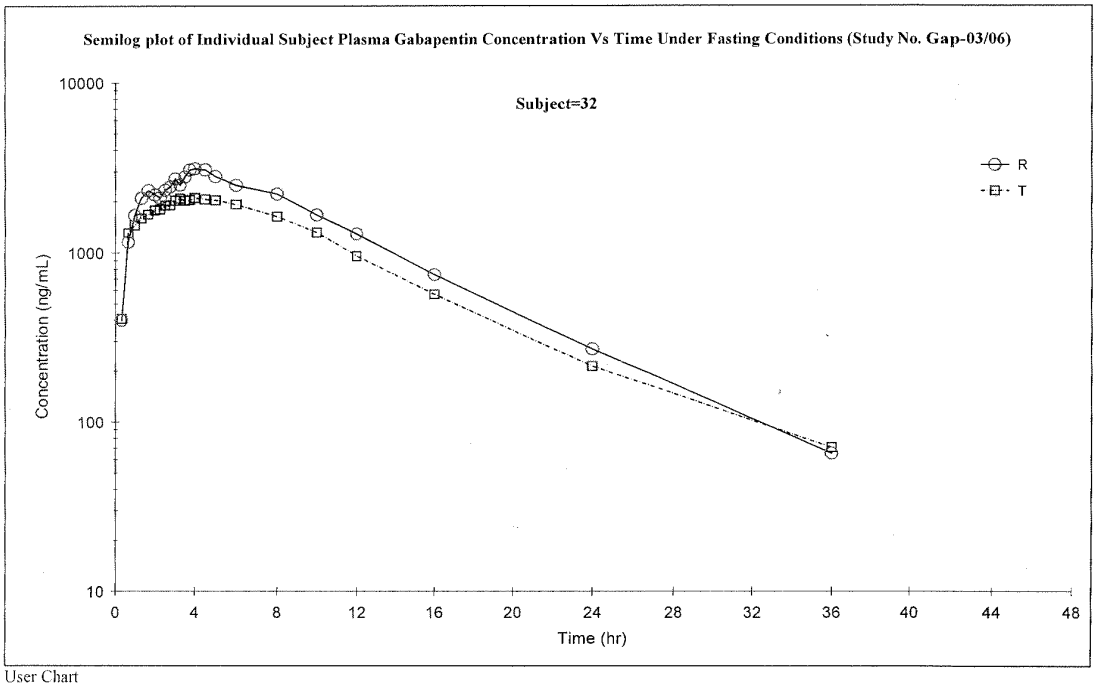
## Comparative Evaluation of Pharmacokinetic Parameters of Gabapentin (Subject 30)

| Parameter | Reference (R) | Test (T) |
|---|---|---|
| $T_{max}$ (hr) | 3.75 | 3.50 |
| $C_{max}$ (ng/mL) | 1556.16 | 1634.49 |
| $AUC_{0\rightarrow t}$ (hr*ng/mL) | 13039.34 | 15372.53 |
| No.of points used for $k_{el}$ calculation | 6 | 11 |
| $k_{el}$ (1/hr) | 0.1249 | 0.1086 |
| $k_{el}$ start (hr) | 6.00 | 3.75 |
| $k_{el}$ end (hr) | 24.00 | 36.00 |
| $t_{1/2}$ (hr) | 5.55 | 6.38 |
| $AUC_{0\rightarrow\infty}$ (hr*ng/mL) | 13786.75 | 15832.72 |
| AUC % Extrapolation | 5.42 | 2.91 |
| Rsq | 0.9895 | 0.9843 |

## FIGURE 64

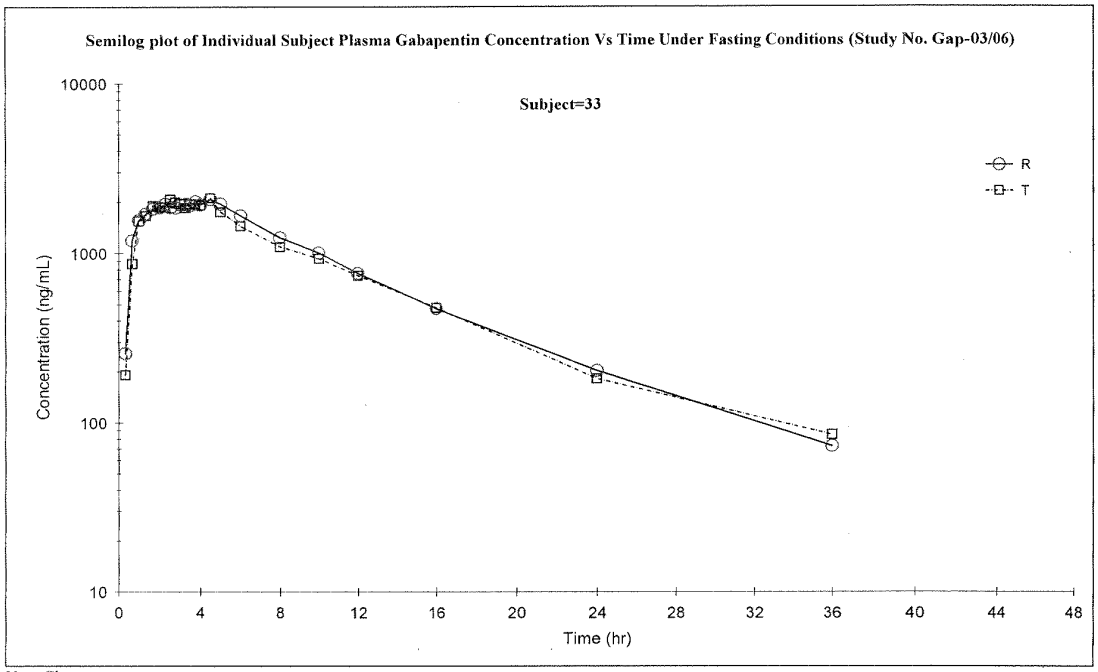



User Chart
H:\CPD-BE\Gabapentin\Gap 0306\Individual semilog plots.pco (19-Apr-2007)

## Comparative Evaluation of Pharmacokinetic Parameters of Gabapentin (Subject 32)

| Parameter | Reference (R) | Test (T) |
|---|---|---|
| $T_{max}$ (hr) | 4.00 | 4.00 |
| $C_{max}$ (ng/mL) | 3121.47 | 2099.78 |
| $AUC_{0\rightarrow t}$ (hr*ng/mL) | 35345.61 | 27020.49 |
| No.of points used for $k_{el}$ calculation | 3 | 9 |
| $k_{el}$ (1/hr) | 0.1216 | 0.1123 |
| $k_{el}$ start (hr) | 16.00 | 4.50 |
| $k_{el}$ end (hr) | 36.00 | 36.00 |
| $t_{1/2}$ (hr) | 5.70 | 6.17 |
| $AUC_{0\rightarrow\infty}$ (hr*ng/mL) | 35878.33 | 27644.89 |
| AUC % Extrapolation | 1.48 | 2.26 |
| Rsq | 0.9997 | 0.9947 |

## FIGURE 65

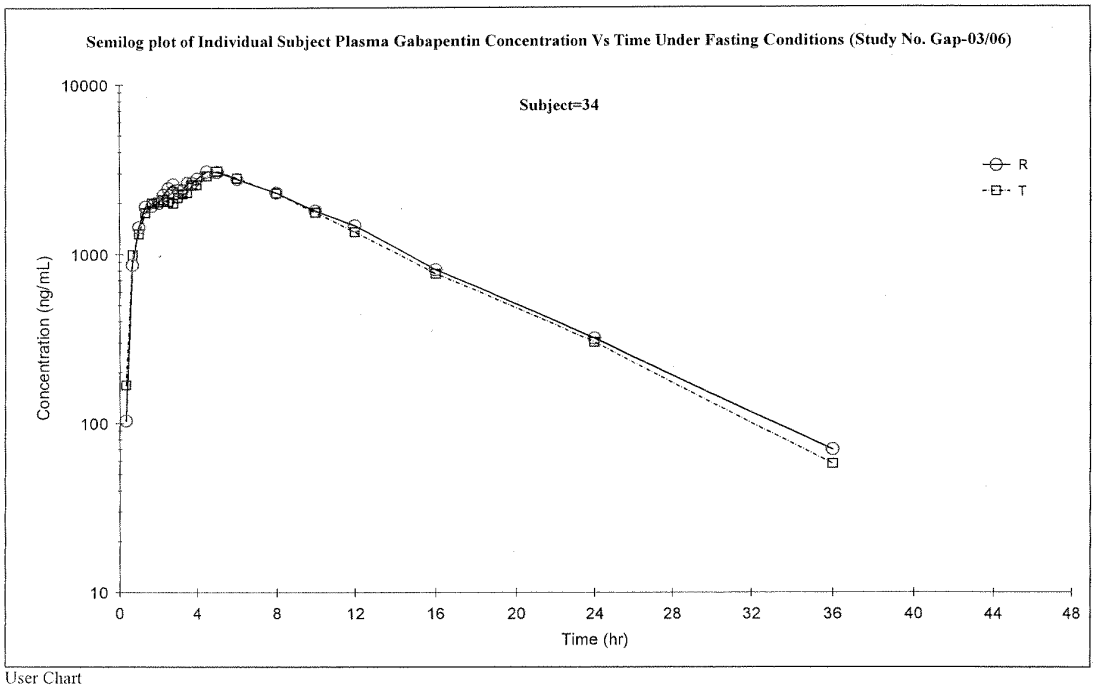



User Chart
H:\CPD-BE\Gabapentin\Gap 0306\Individual semilog plots.pco (19-Apr-2007)

## Comparative Evaluation of Pharmacokinetic Parameters of Gabapentin (Subject 33)

| Parameter | Reference (R) | Test (T) |
|---|---|---|
| $T_{max}$ (hr) | 4.50 | 4.50 |
| $C_{max}$ (ng/mL) | 2079.60 | 2112.90 |
| $AUC_{0\rightarrow t}$ (hr*ng/mL) | 23826.79 | 22657.73 |
| No.of points used for $k_{el}$ calculation | 3 | 7 |
| $k_{el}$ (1/hr) | 0.0929 | 0.0967 |
| $k_{el}$ start (hr) | 16.00 | 6.00 |
| $k_{el}$ end (hr) | 36.00 | 36.00 |
| $t_{1/2}$ (hr) | 7.46 | 7.17 |
| $AUC_{0\rightarrow\infty}$ (hr*ng/mL) | 24606.03 | 23532.53 |
| AUC % Extrapolation | 3.17 | 3.72 |
| Rsq | 0.9965 | 0.9852 |

## FIGURE 66

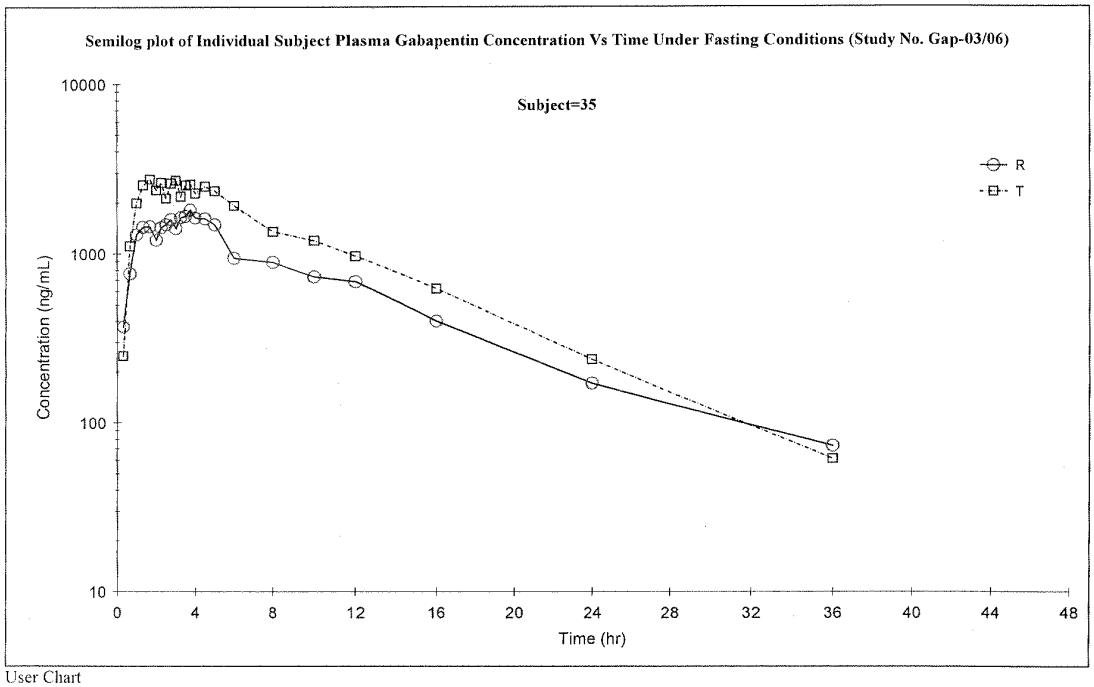



User Chart
H:\CPD-BE\Gabapentin\Gap 0306\Individual semilog plots.pco (19-Apr-2007)

## Comparative Evaluation of Pharmacokinetic Parameters of Gabapentin (Subject 34)

| Parameter | Reference (R) | Test (T) |
|---|---|---|
| $T_{max}$ (hr) | 4.50 | 5.00 |
| $C_{max}$ (ng/mL) | 3066.72 | 3076.88 |
| $AUC_{0\rightarrow t}$ (hr*ng/mL) | 36980.44 | 35470.61 |
| No.of points used for $k_{el}$ calculation | 6 | 7 |
| $k_{el}$ (1/hr) | 0.1252 | 0.1298 |
| $k_{el}$ start (hr) | 8.00 | 6.00 |
| $k_{el}$ end (hr) | 36.00 | 36.00 |
| $t_{1/2}$ (hr) | 5.54 | 5.34 |
| $AUC_{0\rightarrow\infty}$ (hr*ng/mL) | 37535.17 | 35912.02 |
| AUC % Extrapolation | 1.48 | 1.23 |
| Rsq | 0.9994 | 0.9992 |

## FIGURE 67




User Chart
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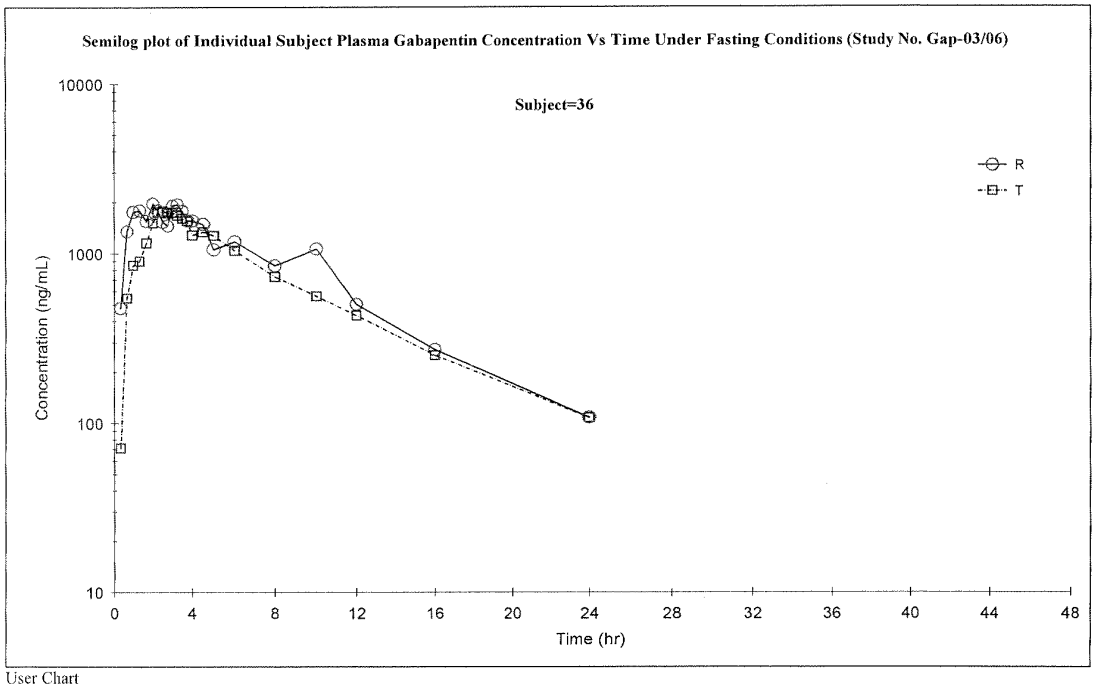
## Comparative Evaluation of Pharmacokinetic Parameters of Gabapentin (Subject 35)

| Parameter | Reference (R) | Test (T) |
|---|---|---|
| $T_{max}$ (hr) | 3.75 | 1.67 |
| $C_{max}$ (ng/mL) | 1816.44 | 2746.74 |
| $AUC_{0\rightarrow t}$ (hr*ng/mL) | 18647.47 | 29062.24 |
| No.of points used for $k_{el}$ calculation | 7 | 5 |
| $k_{el}$ (1/hr) | 0.0906 | 0.1150 |
| $k_{el}$ start (hr) | 6.00 | 10.00 |
| $k_{el}$ end (hr) | 36.00 | 36.00 |
| $t_{1/2}$ (hr) | 7.65 | 6.03 |
| $AUC_{0\rightarrow\infty}$ (hr*ng/mL) | 19450.35 | 29592.72 |
| AUC % Extrapolation | 4.13 | 1.79 |
| Rsq | 0.9890 | 0.9998 |

## FIGURE 68




User Chart
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## Comparative Evaluation of Pharmacokinetic Parameters of Gabapentin (Subject 36)

| Parameter | Reference (R) | Test (T) |
|---|---|---|
| $T_{max}$ (hr) | 2.00 | 2.50 |
| $C_{max}$ (ng/mL) | 1962.39 | 1774.46 |
| $AUC_{0\rightarrow t}$ (hr*ng/mL) | 17141.86 | 14047.61 |
| No.of points used for $k_{el}$ calculation | 3 | 5 |
| $k_{el}$ (1/hr) | 0.1265 | 0.1200 |
| $k_{el}$ start (hr) | 12.00 | 8.00 |
| $k_{el}$ end (hr) | 24.00 | 24.00 |
| $t_{1/2}$ (hr) | 5.48 | 5.78 |
| $AUC_{0\rightarrow\infty}$ (hr*ng/mL) | 17992.12 | 14940.73 |
| AUC % Extrapolation | 4.73 | 5.98 |
| Rsq | 0.9944 | 0.9965 |

# INSTITUTIONAL REVIEW BOARD (Savior- IRB)

**Savior-IRB-409/06**
**Date: October 25th, 2006**



To

The Principal Investigator
Clinical Pharmacology Department
APL Research Centre
Survey No.313, Bachupally Village
Quthubullapur Mandal
R.R. District – 500 072

**Sub: Decision of Savior-IRB for approval on BE research with Study No. Gap-03/06**

**Ref: Your Letter No. CPD/1067/06 dated October 24th, 2006 and other relevant documents.**

Dear Sir,

With reference to your above mentioned letter and after reviewing the enclosed final Protocol and Informed Consent documents, IRB is pleased to grant approval for conducting the study titled, **"An open label, randomized, two treatment, two sequence, two period, cross-over, single-dose comparative oral bioavailability study of Gabapentin 400 mg capsules (Test), manufactured by Aurobindo Pharma Ltd., India and Neurontin 400 mg capsules (Reference), marketing authorization holder Parke Davis, UK, in 36 healthy, adult, male, human subjects under fasting conditions."** as per ICH-GCP/GLP guidelines.

Sincerely yours,

SAVIOR INSTITUTIONAL REVIEW BOARD Date 25/10/06

**Chairman**
**Savior-IRB**


Plot No. G-2, Nagasai Nivas, Ameerpet, Hyderabad - 500 038. A.P. INDIA. Phone : 040-66777654

# STUDY PROTOCOL

**An open label, randomized, two treatment, two sequence, two period, cross-over, single-dose comparative oral bioavailability study of Gabapentin 400 mg capsules (Test), manufactured by Aurobindo Pharma Ltd., India and Neurontin 400 mg capsules (Reference), marketing authorization holder Parke Davis, UK, in 36 healthy, adult, male, human subjects under fasting conditions.**

**Study No. Gap-03/06**
**Version: Final**

**Date of initiation: 11th October 2006**

**Date of Finalization: 24th October 2006**

Reference (R) : Neurontin 400 mg capsules, each capsule contains 400 mg of Gabapentin, marketing authorization holder Parke Davis, Lambert Court, Chestnut Avenue, Eastleigh, Hampshire, SO53 3ZQ, UK.

Test (T) : Gabapentin 400 mg capsules, each capsule contains 400 mg of Gabapentin, manufactured by Aurobindo Pharma Ltd., India.

**Clinical Pharmacology Department**
**APL Research Centre**
**Survey No. 313, Bachupally Village**
**Quthubullapur Mandal**
**Hyderabad– 500 072**
**India**

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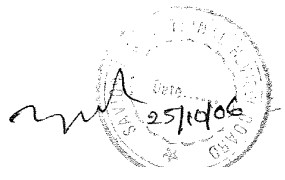
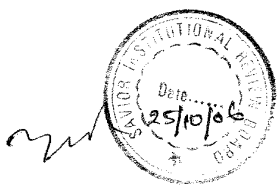
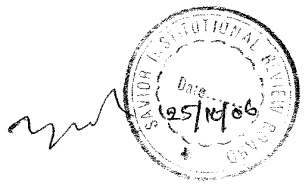




## 1.0 ABBREVIATIONS

| | | |
|---|---|---|
| AE | : | Adverse Event |
| ANOVA | : | Analysis of Variance |
| APL-CPD | : | Aurobindo Pharma Limited – Clinical Pharmacology Department |
| Approx. | : | Approximately |
| AUC | : | Area Under the Curve |
| BE | : | Bioequivalence |
| BMI | : | Body Mass Index |
| CoA | : | Certificate of Analysis |
| CPK | : | Creatine Phospho Kinase |
| CUE | : | Complete Urine Examination |
| CV | : | Coefficient of variation |
| ECG | : | Electro Cardiogram |
| EDTA | : | Ethylene Diamine Tetra Aceticacid |
| ERO | : | Expedited Review Officer |
| Exp. | : | Expiry |
| Extrap | : | Extrapolation |
| FRD | : | Formulation Research Department |
| GCP | : | Good Clinical Practice |
| Gap | : | Gabapentin |
| GLM | : | General Linear Model |
| HBs(Ag) | : | Hepatitis B surface antigen |
| HCV | : | Hepatitis C Virus |
| HIV | : | Human Immunodeficiency Virus |
| ICF | : | Informed Consent Form |
| ICH | : | International Conference on Harmonization |
| IRB | : | Institutional Review Board |
| Kcal | : | Kilocalories |
| LFT | : | Liver Function Test |
| L/h | : | Litres per hour |
| LOQ | : | Limit Of Quantification |



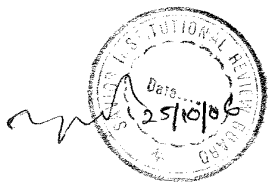


| | | |
|---|---|---|
| LSM | : | Least Square Mean |
| Ltd. | : | Limited |
| MA | : | Marketing Authorization |
| Mfg. | : | Manufacturing |
| mL | : | milliliter |
| OTC | : | Over-the-counter |
| PA | : | Posterior-Anterior View |
| QAD | : | Quality Assurance Department |
| R | : | Reference Product |
| RAD | : | Regulatory Affairs Department |
| RPR | : | Rapid Plasma Reagin |
| RFT | : | Renal Function Tests |
| RCF | : | Relative Centrifugal Force |
| RBC | : | Red Blood Corpuscles |
| SAE | : | Serious Adverse Event |
| SGOT | : | Serum Glutamate Oxaloacetate Transaminase |
| SGPT | : | Serum Glutamate Pyruvate Transaminase |
| SOP | : | Standard Operating Procedure |
| SAS | : | Statistical Analysis System |
| T | : | Test Product |
| UK | : | United Kingdom |
| WBC | : | White Blood Corpuscles |
| XX | : | Current Version Number of SOP |
| $\gamma$ – GT | : | Gamma Glutamyl Transpeptidase |

## 2.0 PROTOCOL SUMMARY

| | |
|---|---|
| **Study Title** | An open label, randomized, two treatment, two sequence, two period, cross-over, single-dose comparative oral bioavailability study of Gabapentin 400 mg capsules (Test), manufactured by Aurobindo Pharma Ltd., India and Neurontin 400 mg capsules (Reference), marketing authorization holder Parke Davis, UK, in 36 healthy, adult, male, human subjects under fasting conditions. |
| **Study Objectives** | To compare the rate and extent of absorption of Gabapentin 400 mg capsules (Test) of Aurobindo Pharma Ltd., India, with that of Neurontin 400 mg capsules (Reference) marketing authorization holder Parke Davis, UK, when given in equal doses of single oral dose containing 400 mg of Gabapentin in 36 healthy, adult, male, human subjects under fasting conditions.<br>To monitor the adverse events and ensure the safety of the subjects. |
| **Study Design** | An open label, randomized, two-treatment, two-sequence, two-period, crossover, single-dose, comparative oral bioavailability study in 36 healthy, adult, male, human subjects under fasting conditions. |
| **Sample size** | 36 healthy, adult, male, human subjects. |
| **Study treatments** | Reference (R) : Neurontin 400 mg capsules, each capsule contains 400 mg of Gabapentin.<br>Batch. No : 0132124 Exp. Date : 11/2007<br>M.A holder : Parke Davis, Lambert Court, Chestnut Avenue, Eastleigh, Hampshire, SO53 3ZQ, UK.<br>Test (T) : Gabapentin 400 mg capsules, each capsule contains 400 mg of Gabapentin.<br>Batch. No : GN4006001<br>Mfg. Date : 08/2006 Exp.Date: 07/2008<br>Mfg. By : Aurobindo Pharma Ltd., India. |
| **Introduction** | Gabapentin is an antiepileptic drug. Gabapentin was formed by the addition of a cyclohexyl group to gamma-aminobutyric acid (GABA), which allowed this form of GABA to cross the blood-brain barrier. Gabapentin is indicated as adjunctive therapy for the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy. Gabapentin is contraindicated in patients who have demonstrated hypersensitivity to the drug or to any of the components of the formulation. |





| | |
|---|---|
| **Screening** | Volunteers aged from 18 to 50 years with a body mass index (BMI) within 19-26 $kg/m^2$ will be selected according to the inclusion and exclusion criteria. They will be healthy according to physical examination (including vital signs) and normal laboratory test results {(hematology, biochemistry, urinalysis, 12-lead ECG and X-ray (PA view)} including negative HIV, Hepatitis B, Hepatitis C and RPR tests.<br>Drugs of abuse (Benzodiazepines, Opioids, Amphetamines, Cannabinoids, Cocaines and Barbiturates) in urine will be tested during the day of check-in for Period-I & II. |
| **Dose** | A single oral dose of 400 mg x 1 capsule of reference (R) or test (T) product will be administered as per the randomization schedule witnessed by any alternative study personnel in the presence of quality assurance personnel. Subjects will receive the alternate treatment in the subsequent period following crossover with the following treatment sequence i.e. either R–T or T–R. Subjects will be dosed with 240 mL of drinking water. |
| **Dietary Plan** | Subjects will be provided standard meal (dinner) consisting of approx.1000 kcal during the day of check-in (Day-0).<br>Subjects will be required to fast over night (at least 10.0 hours) before dosing and a minimum of four hours thereafter. Post dose meal on Dosing Day (Day–1) consisting of approx. 2400 kcal as per the meal plan (divided into lunch- approx. 1000 kcal., snacks- approx. 400 kcal., and dinner- approx. 1000 kcal.) will be provided at 4.0 hours 30 minutes (lunch), 8.0 hours 15 minutes (snacks) and 13 hours (dinner) respectively, whereas the meal on next day of dosing (Day-2) consisting of approx. 2800 Kcal {(divided into breakfast-approx. 400 kcal., lunch-approx. 1000 kcal., snacks-approx. 400 kcal., and dinner consisting of approx. 1000 kcal) will be provided at 24 hours 30 minutes, 28 hours 30 minutes, 32 hours 30 minutes and 37.0 hours post-dose respectively}. The meal plans will be provided by the dietician.<br>During clinical residence, the meal plans will be kept identical for both the periods. Information on the standardized meal, quantity and time will be recorded on the relevant raw data forms.<br>Drinking water will not be permitted one hour before dosing and until one hour post-dose, at other times drinking water will be permitted *ad libitum*. |
| **Sampling Schedules** | Blood samples 1 x 6 mL will be collected in prelabelled vacutainer tubes containing potassium EDTA during each period. The venous blood samples will be withdrawn at pre-dose (0.0) and at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.25, 2.5, 2.75, 3.0, 3.25, 3.5, 3.75, 4.0, 4.5, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0 and 48.0 hours post dose. |



| | |
|---|---|
| **Blood loss** | For each subject the total number of blood draws will be 50 (25 x 2 for 2 periods) The total volume of blood withdrawn will be 358 mL. (8 mL for screening, 42 mL discarded heparinised blood, 300 mL for both the periods and 8 mL for post study laboratory tests at the end of Period-II). |
| **Safety Assessment** | In each period, vital signs monitoring will be done at the time of volunteer check-in, pre-dose and at 1.0, 3.0, 12.0, 24.0, 36.0 and 48.0 hours post-dose. Adverse event monitoring (subject well being questionnaire) will be done at 2.0, 5.0 and 8.0 hours post-dose and if any adverse events are observed by either clinical staff or reported by subjects at times other than scheduled times will be recorded. |
| **Washout Period** | There will be a washout period of at least 07 days between each treatment schedule. |
| **Clinical Residence** | At least 10 hours 30 minutes before dosing and until the 48.0 hours post dose in each period. |
| **Post-study Lab Investigations** | 8 mL of blood will be collected for post-study laboratory investigations (Hematology ("absolute eosinophil count" test in post-study lab investigations if the subject's eosinophil count more than 6 % in post study results), LFT and RFT) and 12-lead ECG will also be done at the end of period–II or at any stage after the dosing if the subject is withdrawn or dropped from the study for any reason. |
| **Bioanalytical Method and Analytical Procedure** | Gabapentin will be estimated in plasma using a validated method developed at the bioanalytical unit of APL Research Centre. Reanalysis will be performed as per the SOP No: APL-CPD-423-XX of the bioanalytical unit. |
| **Pharmacokinetic Parameters and Analysis** | $T_{max}$, $C_{max}$, $AUC_{0-t}$, $AUC_{0-\infty}$, $k_{el}$ and $T_{1/2}$ will be determined from the plasma Gabapentin data using WinNonlin version 5.0.1 |
| **Statistical Analysis** | Summary statistics, ANOVA, 90% confidence interval and Ratio Analysis and intra subject variability will be calculated using SAS® 9.1.3 version. |
| **Ethical Considerations** | The study will be carried out as per the ICH-GCP guidelines and principles of Declaration of Helsinki. Protocol and ICF document approval will be taken from the IRB before initiation of the study, except for volunteer screening. |
| **Summary and Final Report** | Summary and final report will be prepared having clinical, bioanalytical, pharmacokinetic and statistical data subjected to Quality Audit. |
| **Archives** | Raw data and reports will be archived at the CPD with controlled access for 15 years. |

## 3.0 INVESTIGATOR'S DECLARATION

Study Title: An open label, randomized, two treatment, two sequence, two period, cross-over, single-dose comparative oral bioavailability study of Gabapentin 400 mg capsules (Test), manufactured by Aurobindo Pharma Ltd., India and Neurontin 400 mg capsules (Reference), marketing authorization holder Parke Davis, UK, in 36 healthy, adult, male, human subjects under fasting conditions.

We, the undersigned, declare that we have read and understood this protocol and hereby agree to conduct the study in accordance with all requirements regarding the obligations of investigators and all other pertinent requirements of the ICH 'Guideline for Good Clinical Practice' and 'Good Laboratory Practice'. We further agree to ensure that all associates assisting in the conduct of study are informed regarding their obligations.

We agree to comply with all relevant Standard Operating Procedures (SOPs) required for the conduct of this study and would document any significant deviation occurring during the study.

| | |
|---|---|
| **Dr. Nitin Kulkarni**<br>**Clinical Investigator** | 24/10/06<br>**Date** |
| **Mr. M. Nagesh**<br>**Bioanalytical Investigator** | 24.10.06<br>**Date** |
| **Mr. H. L.V. Ravi Kiran**<br>**Pharmacokinetic Investigator** | 24/10/06<br>**Date** |
| **Mr. J. Balaji**<br>**Bio-Statistical Investigator** | 24/10/06<br>**Date** |
| **Dr. A. T. Bapuji**<br>**Principal Investigator** | 24/10/06<br>**Date** |



## 4.0 CONTACT PERSONNEL

**Principal Investigator**

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Quthubullapur Mandal
Hyderabad-500072
India

Telephone: 91-40-23040261,
91-40-23040262
Mobile No: 9848732447

**Clinical Investigator:**

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Clinical Pharmacology Department
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2nd & 3rd Floor of Mirra Multispeciality
Hospital, Alluri Sitaramaraju Nagar
Opp. J.P.N.Nagar Colony, Miyapur
Hyderabad-500050
India.

Telephone: 91-40-23045809,
91-40-23045709

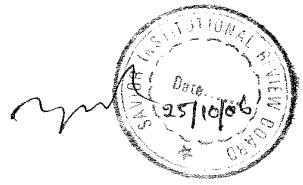
**Chairman Savior-IRB :**

Name : Justice Y.V. Narayana (Retd.)

Address : Address: Flat No: 402, Pooja's Pride
Plot No: 75, Srinagar Colony
Hyderabad-500073, India

Telephone: 91-40-23743173.





## 5.0 FACILITIES

5.1 Clinical Unit
Clinical Pharmacology Department
APL Research Centre
Plot Nos. 33 – 35
2nd and 3rd Floor, Mirra Multi-Speciality Hospital
Alluri Sitaramaraju Nagar, Opp. J.P.N.Nagar Colony, Miyapur
Hyderabad – 500050, India.

5.2 Clinical laboratory services
Clinical Pharmacology Department
APL Research Centre
Plot Nos. 33 – 35
2nd Floor, Mirra Multi-Speciality Hospital
Alluri Sitaramaraju Nagar,
Opp. J.P.N.Nagar Colony,
Miyapur, Hyderabad – 50050,
India.

5.3 Bioanalytical Unit
Clinical Pharmacology Department
APL Research Centre
Survey No. 313
Bachupally Village
Quthubullapur Mandal
Hyderabad – 500072, India.

5.4 Pharmacokinetic & Biostatistical Unit
Clinical Pharmacology Department
APL Research Centre
Survey No. 313,
Bachupally Village
Quthubullapur Mandal
Hyderabad – 500072, India.

5.5 Biomedical Waste
SembRamky Environmental Management Pvt. Ltd.
6-3-1089/G/10 & 11, Gulmohar Avenue
Rajbhavan Road, Somajiguda
Hyderabad, India.

**Note:** Clinical laboratory Investigations will be done in an accredited laboratory, whenever necessary, as a standby to in house facility. X-ray will be performed at the Radiological unit of the Mirra Multi-speciality hospital.

## 6.0 INTRODUCTION AND INFORMATION ON REFERENCE PRODUCT

### 6.1 Background Information

The present study is undertaken to compare the rate and extent of absorption of Gabapentin 400 mg capsules of Aurobindo Pharma Ltd., India with that of Neurontin 400 mg capsules of Parke Davis, UK, when both are given as a single oral dose under fasting conditions.

### 6.2 Pharmacology

Gabapentin is an antiepileptic drug. This drug is available in capsules (100 mg, 300 mg, and 400 mg), tablets (600 mg and 800 mg) and oral solutions (250 mg/5 mL).

The mechanism by which gabapentin exerts its anticonvulsant action is unknown, gabapentin prevents seizures as do other marketed anticonvulsants. Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but it does not modify $GABA_A$ or $GABA_B$ radioligand binding, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation. Furthermore, gabapentin did not alter the cellular uptake of dopamine, noradrenaline, or serotonin.

### 6.3 Pharmacokinetics

Mean plasma gabapentin concentrations (Cmax) occurred approximately 3 hours (Tmax) following single oral doses of gabapentin regardless of dose size or formulation. Mean Tmax values following multiple dose administration were approximately 1 hour shorter than the values following single-dose administration.

Mean Cmax and AUC values increased with increasing dose; however, the increase was less than dose proportional. Deviation from linearity was very slight up to 600 mg for both parameters and thus should be minimal at doses of 300 mg to 400 mg three times daily where the anti-epileptic effect generally occurs.

Plasma gabapentin concentration-time profiles were similar between gabapentin solution and capsule formulations following single doses of 300 and 400 mg. Absolute bioavailability of a 300 mg oral dose of gabapentin was approximately 60%. At doses of 300 mg and 400 mg, gabapentin bioavailability was unchanged following multiple-dose administration.

Based on results of bioavailability studies performed with gabapentin tablets, the 600 and 800 mg tablets are bioequivalent to marketed gabapentin Capsules. The 600 mg tablets were found to be bioequivalent to 2 x 300 mg marketed capsules based on similar rate and extent of drug absorption. Likewise, 800 mg tablets were found to be bioequivalent to 2 x 400 mg marketed capsules based on a similar rate and extent of drug absorption.

The presence of food did not influence the bioavailability of gabapentin.

Gabapentin is not metabolised in humans and does not induce hepatic mixed function oxidase enzymes. Gabapentin elimination from plasma following IV administration was best described by linear pharmacokinetics. Elimination half-life

(T½) of gabapentin ranged from 5 to 7 hours. Gabapentin elimination parameters, apparent plasma T½ and renal clearance ($CL_R$) were independent of dose and remained unchanged following repeated administration. Renal clearance was the sole elimination pathway for gabapentin. Since gabapentin is not metabolised in humans, the amount of drug recovered in urine is indicative of gabapentin bioavailability. Following a single 200 mg oral dose of [$C_{14}$] gabapentin recovery of radioactivity was essentially complete with approximately 80% and 20% of the dose recovered in urine and faeces, respectively.

As renal function (as determined by creatinine clearance) decreases with increasing age, gabapentin oral clearance, renal clearance and elimination-rate constant decrease proportionally. Clearance of gabapentin based on body weight in children above 4 years of age is similar to that in adults.

The results of a single-dose, two-way crossover, comparative bioavailability study in the fasted state comparing Gabapentin 600 mg tablets and 2 x 300 mg Gabapentin capsules are summarized below.

| Parameter | Gabapentin | | | | % Ratio of Geometric Means |
|---|---|---|---|---|---|
| | 600 mg tablets | | 2 X 300 mg capsules | | |
| | Arithmetic (CV%) | Geometric | Arithmetic (CV%) | Geometric | |
| | Mean values from measured data | | | | |
| $AUC_T$ (µg.hr/mL) | 51.3 (31.8) | 48.9 | 46.8 (28.4) | 45.2 | 108 |
| $AUC_I$ (µg.hr/mL) | 52.5 (30.2) | 50.4 | 47.7 (27.1) | 46.1 | 109 |
| Cmax (µg/mL) | 4.94 (30.9) | 4.71 | 4.48 (25.9) | 4.35 | 108 |
| Tmax (hr) | 3.2 (27.3) | -- | 3.5 (34.1) | -- | --- |
| $T_{1/2}$ (hr) | 15.6 (88.2) | -- | 15.4 (90.5) | -- | --- |

## 6.4 Interactions

Morphine: In a study involving healthy volunteers (N=12), when a 60-mg controlled-release morphine capsule was administered 2 hours prior to a 600-mg gabapentin capsule, mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine. Morphine pharmacokinetic parameter values were not affected by administration of gabapentin 2 hours after morphine. The magnitude of interaction at other doses of gabapentin and /or morphine is not known.

Gabapentin may be used in combination with other anti-epileptic drugs without concern for alteration of the plasma concentrations of gabapentin or serum concentrations of other anti-epileptic drugs.

There is no interaction between gabapentin and phenytoin, valproic acid, carbamazepine or phenobarbitone. Gabapentin steady-state pharmacokinetics are

similar for healthy subjects and patients with epilepsy receiving anti-epileptic agents.

Gabapentin and an aluminium and magnesium containing antacid when given at the same time, gabapentin 's bioavailability was reduced by up to 24%. It is recommended that gabapentin is taken about two hours following any such antacid administration. The slight decrease in renal excretion of gabapentin observed when co-administered with cimetidine is not expected to be of clinical importance.

Renal excretion of gabapentin is unaltered by probenecid. Food has no effect on gabapentin pharmacokinetics.

Because false positive readings were reported with the Ames N-Multistix SG® dipstick test when gabapentin was added to other anticonvulsant drugs, the more specific sulphosalicylic acid precipitation procedure is recommended to determine urinary protein

## 6.5 Adverse Reactions

**Neuropathic Pain:** Based on placebo-controlled studies, the most common possible side-effects (>1/10) associated with treating neuropathic pain with Gabapentin are: dizziness and somnolence.

Common possible side-effects (between 1/10 and 1/100) are: diarrhoea, dry mouth, peripheral oedema, weight gain, abnormal gait, amnesia, ataxia, abnormal thinking, rash and amblyopia.

Uncommon possible side-effects (between 1/100 and 1/1000) are: accidental injury, asthenia, back pain, constipation, flatulence, nausea, confusion, hypesthesia, vertigo, dyspnea and pharyngitis.

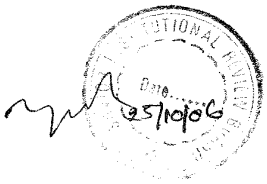
**Epilepsy (Adults):** Since Gabapentin has most often been administered in combination with other anti-epileptic agents, it is not possible to determine which agents, if any are associated with adverse events. However, based on placebo-controlled, double blind studies, the most common possible side-effects (>1/10) are: somnolence and dizziness.

Common possible side-effects (between 1/10 and 1/100) are: ataxia, fatigue, nystagmus, tremor, diplopia, amblyopia, abnormal vision most often described as a visual disturbance, dysarthria, amnesia, asthenia, paraesthesia, arthralgia, purpura, dyspepsia, anxiety, weight increase, urinary tract infection and pharyngitis.

Uncommon possible side-effects (between 1/100 and 1/1000) are: leucopenia, nervousness, rhinitis and male sexual dysfunction (impotence).

As with the other AEDs there have been rare reports of urinary incontinence, pancreatitis, elevated liver function tests, erythema multiforme and Stevens Johnson Syndrome where a causal relationship to treatment has not been established. Rarely confusion, depression, emotional lability, hostility, abnormal thinking and psychoses/hallucinations have been reported. Blood glucose fluctuations in patients with diabetes, myalgia, headache, nausea and/or vomiting have also been reported.





**Additional Post-Marketing Adverse Events:** Additional post-marketing adverse events (associated with treating epilepsy and/or neuropathic pain) include acute kidney failure, allergic reaction including urticaria, alopecia, angioedema, chest pain, hepatitis, jaundice, hallucinations, movement disorders such as choreoathetosis, dyskinesia and dystonia, palpitation, thrombocytopenia, and tinnitus.
Adverse events following the abrupt discontinuation of gabapentin have also been reported. The most frequently reported events are anxiety, insomnia, nausea, pain and sweating.

## 6.6 Warnings and Precautions

Although there is no evidence of rebound seizures with Gabapentin, abrupt withdrawal of anticonvulsant agents in epileptic patients may precipitate status epilepticus. When, in the judgement of the clinician, there is a need for dose reduction, discontinuation or substitution of alternative anticonvulsant medication, this should be done gradually over a minimum of one week.

Gabapentin is not generally considered effective in the treatment of absence seizures. Patients who require concomitant treatment with morphine may experience increases in gabapentin concentrations. Patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately.

Patients taking Gabapentin can be the subject of mood and behavioural disturbances. Such reports have been noted in patients on Gabapentin although a causal link has not been established.

Caution is recommended in patients with a history of psychotic illness. On commencing Gabapentin therapy, psychotic episodes have been reported in some patients with, and rarely without, a history of psychotic illness. Most of these events resolved when Gabapentin was discontinued or the dosage was reduced.

## 6.7 Contra-Indications

Gabapentin is contra-indicated in patients who are hypersensitive to Gabapentin or to the product's components.

## 6.8 Dosage and administration

**Neuropathic Pain: Adults (over the age of 18)**

Gabapentin should be titrated to a maximum dose of 1800 mg per day. Titration to an effective dose can progress rapidly and can be accomplished over a few days by administering 300 mg once a day on day 1, 300 mg twice a day on day 2 and 300 mg three times a day on day 3, as described in Table 1.

**Table 1: DOSING CHART - INITIAL TITRATION**

| Dose | Day 1 | Day 2 | Day 3 |
|---|---|---|---|
| 900 mg | 300 mg<br>once a day | 300 mg<br>two times a day | 300 mg<br>three times a day |



Thereafter, the dose can be increased using increments of 300 mg per day given in three divided doses to a maximum of 1800 mg per day. It is not necessary to divide the doses equally when titrating Gabapentin.

It is not necessary to monitor Gabapentin plasma concentrations to optimise Gabapentin therapy. The maximum time between doses in a three times daily schedule should not exceed 12 hours. Gabapentin may be given orally with or without food.

If Gabapentin is discontinued, or the dose reduced or substituted with an alternative medication, this should be done gradually over a minimum of one week.

Gabapentin Titration Pack: The Gabapentin Titration Pack is available for the convenience of prescribers, for the treatment of neuropathic pain. The titration pack contains all capsules and tablets required to reach 1800 mg per day, over 15 days of treatment, with 1800 mg per day reached on day 13. It starts with 1 x 300 mg capsule on day one and finishes with 3 x 600 mg tablets on days 13-15, carefully packed in sequence to ensure correct usage.

**Epilepsy: Adults and Children aged over 12**

The anti-epileptic effect of Gabapentin generally occurs at 900 to 1200 mg/day. It is not necessary to monitor Gabapentin plasma concentrations to optimise Gabapentin therapy.

Titration to an effective dose can progress rapidly and can be accomplished over a few days by administering 300 mg once a day on day 1, 300 mg twice day on day 2 and 300 mg three times a day on day 3, as described in Table 1.

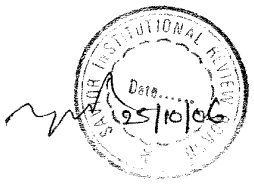
Thereafter, the dose can be increased using increments of 300 mg per day given in three equally divided doses to a maximum dose of 2400 mg per day. The maximum time between doses in a three times daily schedule should not exceed 12 hours. Gabapentin may be given orally with or without food.
If Gabapentin is discontinued and/or an alternate anticonvulsant medication is added to the therapy, this should be done gradually over a minimum of one week.

## 6.9 Indications

**Neuropathic Pain:** Neurontin is indicated for the treatment of neuropathic pain.

**Epilepsy (Adults and children over 12 years of age):** Neurontin is an anti-epileptic drug indicated as add-on therapy for partial seizures and partial seizures with secondary generalisation in patients who have not achieved satisfactory control with or who are intolerant to standard anticonvulsants used alone or in combination





## 7.0 STUDY OBJECTIVES

To compare the rate and extent of absorption of Gabapentin 400 mg capsules (Test) of Aurobindo Pharma Ltd., India, with that of Neurontin 400 mg capsules (Reference) marketing authorization holder Parke Davis, UK, when given in equal doses of single oral dose containing 400 mg of Gabapentin in 36 healthy, adult, male, human subjects under fasting conditions.

To monitor the adverse events and ensure the safety of the subjects.

## 8.0 STUDY DESIGN

### 8.1 Title

An open label, randomized, two-treatment, two-sequence, two-period, crossover, single-dose, comparative oral bioavailability study in 36 healthy, adult, male, human subjects under fasting conditions.

### 8.2 Study treatments

**Reference and test products for the study are:**

Reference (R) : Neurontin 400 mg capsules, each capsule contains 400 mg of Gabapentin.
Batch. No : 0132124 Exp. Date : 11/2007
M.A holder : Parke Davis, Lambert Court, Chestnut Avenue, Eastleigh, Hampshire, SO53 3ZQ, UK.
Test (T) : Gabapentin 400 mg capsules, each capsule contains 400 mg of Gabapentin.
Batch. No : GN4006001
Mfg. Date : 08/2006 Exp.Date: 07/2008
Mfg. By : Aurobindo Pharma Ltd., India.

### 8.3 Randomization

The order of receiving the test and reference products for each subject during the two periods of the study will be determined according to randomization schedule (generated using SAS version 9.1.3). The randomization will be balanced and the code will be kept under controlled access. The personnel involved in dispensing of study drugs will be accountable for ensuring compliance to randomization schedule.

### 8.4 Number of subjects

Sufficient number of healthy, adult, male, human volunteers will be screened with volunteer's consent to enroll 36 subjects for the study.

### 8.5 Drug administration

A single oral dose of reference (R) or test (T) product will be administered, based on randomization along with 240 mL water.

### 8.6 Dietary Plan

Subjects will be provided standard meal (dinner) consisting of approx.1000 Kcal during the day of check-in (Day-0).

Subjects will be required to fast over night (at least 10.0 hours) before dosing and a minimum of four hours thereafter. Post dose meal on Dosing Day (Day–1) consisting of approx. 2400 kcal as per the meal plan. Whereas the meal on next day of dosing (Day-2) consisting of approx. 2800 kcal.

During clinical residence, the meal plans will be kept identical for both the periods.

### 8.7 Sampling schedule

In each period a total of 25 blood samples (6 mL each) will be collected in a pre-labeled vacutainer tubes containing potassium EDTA.

The blood samples will be collected prior to administration of dose in each period pre-dose (0.0) and at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.25, 2.5, 2.75, 3.0, 3.25, 3.5, 3.75, 4.0, 4.5, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0 and 48.0 hours post dose.

For each subject the total volume of blood withdrawn will be 358 mL.

### 8.8 Safety monitoring

#### 8.8.1 Vital signs

In each period, vital signs monitoring will be done in sitting posture (except respiration rate which will be taken in supine position) at the time of check-in, pre-dose (0.0) and at 1.0, 3.0, 12.0, 24.0, 36.0 and 48.0 hours post-dose.

#### 8.8.2 Adverse event monitoring

Adverse event monitoring (subject well being questionnaire) will be done at 2.0, 5.0 and 8.0 hours post-dose and if any adverse events are observed by either clinical staff or reported by subjects at times other than scheduled times will be recorded.

### 8.9 Washout Period

At least 07 days washout period will be observed between each treatment schedule.

### 8.10 Clinical residence

Subjects will be admitted and housed in the Clinical Pharmacology Unit (CPU) from at least 10 hours 30 minutes before dosing and until the 48.0 hours post dose in each period.

### 8.11 Analytical method

Gabapentin will be estimated in plasma using a validated method developed at the Bioanalytical unit of APL Research Centre.

## 9.0 STUDY RESTRICTIONS

- Subjects will be instructed not to smoke from atleast 48 hours before check-in and till completion of the study.
- Ensure that the subjects should refrain from using any medicines (either prescription or over-the-counter drugs) particularly two weeks before the first administration of study medication. Instruct the subject to refrain for the same till the entire duration of the study.
- Subjects will be instructed to abstain from alcohol and xanthine containing food and beverages, (chocolates, tea, coffee or cola drinks) cigarettes and tobacco products, for atleast 48 hours prior to check-in, for each period.
- Subjects will be required to fast over night (at least 10.0 hours) before dosing and a minimum of four hours thereafter. Drinking water will not be permitted one hour before dosing and until one hour post-dose.
- Subjects will be instructed not to consume grape fruit (mosumbi/sweet lime) juice within the 48 hours prior to check-in.
- Subjects will be dosed while in sitting posture and will be instructed to remain seated or ambulatory for first two hours following the drug administration. However postural change of the subjects can be allowed for performing scheduled vitals. Thereafter, the subjects will be allowed to engage only in normal activities while avoiding severe physical exertion. In case of adverse events/medical emergency, subject is allowed to lay down on the right side and those subjects will be revaluated to find out whether they can be continued in the study.

## 10.0 CLINICAL PROCEDURES

### 10.1 Subject Selection

#### 10.1.1 Eligibility Assessment

For the purpose of this study the following eligibility assessments will be carried out before enrolment of any volunteer into the study.

### 10.1.2 Screening

The screening will be carried out after taking a written informed consent for screening from volunteers and will include the following:

- Demographic data including sex, date of birth, height and weight, BMI, history of smoking, history of intake of abusive/recreational drugs, history of alcohol consumption, history of blood donation, history of participation in a drug research study.
- Medical history including present complaints (if any), relevant past medical history, family history, history of any allergy to food, drugs, animals and treatment history.
- Complete physical examination including vital signs (Blood Pressure, Pulse rate, Oral temperature and Respiratory rate) and Systemic examination.
- 12-lead ECG for heart rate, rhythm and specific finding (if any).
- Chest X-ray (PA view).

### 10.1.3 Clinical laboratory tests

- Hematology–RBC count, Platelet count, Hemoglobin, Total and differential WBC count.
- Blood grouping & Rh typing and bleeding time.
- Biochemistry – Fasting blood glucose, serum sodium, potassium, chloride, calcium, phosphorous and total cholesterol.
- Hepatic profile – SGOT, SGPT, & Total Bilirubin, Alkaline Phosphatase, γ – GT, total protein and albumin.
- Renal profile – serum creatinine, serum urea and serum uric acid.
- Urine – Complete Urine Examination, which include physical, bio-chemical and microscopic examination.
- Drugs of abuse (Benzodiazepines, Opioids, Amphetamines, Cannabinoids Cocaines and Barbiturates) on the day of check-in for Period I and Period II.
- Screening for infectious diseases – HIV 1 & 2, HBs(Ag), HCV and RPR.

### 10.1.4 Inclusion Criteria

Subjects must fulfill the following criteria to be considered for inclusion into this study.

- Healthy males within the age range of 18 to 50 years.
- A body mass index within 19-26 $kg/m^2$.
- Given written informed consent to participate in the study.
- Absence of disease markers of HIV 1 & 2, hepatitis B & C virus and RPR.

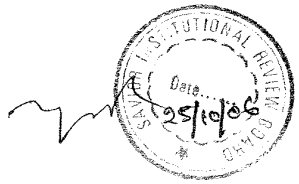
- Absence of significant disease or clinically significant abnormal laboratory values on laboratory evaluation, medical history and physical examination during the screening.
- A normal 12-lead ECG.
- A normal chest X-ray (PA view).
- No history or no evidence of hypersensitivity to Gabapentin.
- No history of significant systemic diseases.
- No history of psychiatric disorders.
- No donation of blood (one unit or 350 mL) within 56 days prior to receiving the first dose of study medication.
- No history of addiction to any recreational drug or drug dependence.
- No participation in any clinical study within the past 56 days.
- No receipt of any prescription drugs or over-the-counter drugs (e.g.: Cold preparations, and antacid preparations vitamins and natural products used for therapeutic benefits), within two weeks prior to receiving the first dose of study medication.
- No history of dehydration from diarrhea, vomiting or any other reason within a period of 24 hours prior to the study.
- No family history of neurological disorders.
- Not consumed alcohol and xanthine containing food and beverages, (chocolates, tea, coffee or cola drinks) cigarettes and tobacco products, for atleast 48 hours, prior to check-in.
- Not consumed grape fruit (mosumbi/sweet lime) juice within the 48 hours prior to check-in.
- Negative results for drugs of abuse (Benzodiazepines, Cocaines, Opioids, Amphetamines, Cannabinoids and Barbiturates) in urine during the day of check-in for period I and period II.
- Comprehension of the nature and purpose of the study and compliance with the requirement of the entire protocol.

### 10.1.5 Exclusion Criteria

The subjects will be excluded based on the following criteria.

- History of seizures.
- History of alcohol consumption for more than two units/day (1 unit = 30 ml of spirit/or 1 pint of beer), or having consumed alcohol within 48 hours prior to check-in.
- High caffeine (more than 5 cups of coffee or tea/day) or tobacco (more than 9 cigarettes/beedies/cigars per day) consumption.
- History of difficulty with donating blood or difficulty in accessibility of veins in left or right arm.





- Receipt of any prescription drugs or over-the-counter (OTC) drugs (e.g.: Cold preparations, and antacid preparations vitamins and natural products used for therapeutic benefits) within two week prior to receiving the first dose of study medication.
- An unusual or abnormal diet, for whatever reason e.g. because of fasting due to religious reasons.

### 10.2 Withdrawal Criteria

Subjects may be withdrawn from the study by the Clinical Investigator/attending Physician for any of the following reasons during the course of the study:

- If the subject suffers from significant illness.
- After dosing, if the subject vomits, at or before 2 times the median $T_{max}$ of Gabapentin.
- If the subject requires unacceptable concomitant medications.
- If the subject has entered the study in violation of the inclusion and the exclusion criteria.
- If the subject is found to be non co-operative.
- If the subject decides to voluntarily withdraw from the study.

**Note:**

Any subject withdrawals will be reported for:

Reasons for withdrawal (if any).

Clinical assessment of the subject will be done at the time of withdrawal/on discretion of attending physician/Clinical Investigator, if a subject is withdrawn during the study.

#### 10.2.1 Criteria for withdrawing subjects from Bio-analysis

- Samples from subject withdrawn / dropped out will not be analyzed.

### 10.3 Drug Receipt, Accountability and Storage

An adequate number of drug products for administration and sample retention purpose along with the COA and *in-vitro* dissolution data, will be received by the Clinical Investigator or his designate from the concerned person of FRD/RAD through Principal Investigator or his designate. The drug products will be stored in the pharmacy under prescribed storage conditions and will be logged-in the Drug Accountability Log Book.

### 10.4 Drug Dispensing

The Pharmacist will use required number of drug products for dispensing in to the drug-dispensing containers as unit doses based on total number of study subjects to conduct each period, witnessed by Clinical Investigator/ Physician/ Co-Investigator, in the presence of Quality Assurance personnel. The remaining drug products will be stored in their original container as retention samples. The drug dispensing procedure will be carried out as per SOP. No: APL-CPD-216-XX.

The drug dispensing containers used for dispensing will be properly labeled for the study number, period number, subject number, treatment, date of dispensing, date of drug administration and the initials of the persons involve in dispensing and dosing as per the SOP No. APL-CPD-214-XX.

### 10.5 Dosing and Treatment

The Clinical Investigator/Physician will verify the treatment as per the randomization schedule. A single oral dose of 400 mg x 1 capsule of reference (R) or test (T) product will be administered along with 240 mL water as per the randomization schedule witnessed by any alternative study personnel in the presence of quality assurance personnel. Subjects will receive the alternate treatment in the subsequent period after crossover with the following treatment sequence i.e. either R-T or T-R. The drug administration procedure will be carried out as per the SOP. No: APL-CPD-217-XX. Compliance for dosing after dose administration will be assessed by examination of the oral cavity by trained study personnel.

### 10.6 Dietary Plan

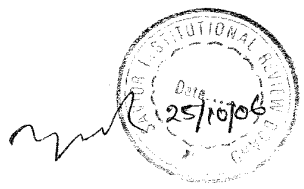
Subjects will be provided standard meal (dinner) consisting of approx.1000 K.cal during the day of check-in (Day-0).

Subjects will be required to fast over night (at least 10.0 hours) before dosing and a minimum of four hours thereafter. Post dose meal on Dosing Day (Day–1) consisting of approx. 2400 kcal as per the meal plan (divided into lunch- approx. 1000 kcal., snacks- approx. 400 kcal., and dinner- approx. 1000 kcal.) will be provided at 4.0 hours 30 minutes (lunch), 8.0 hours 15 minutes (snacks) and 13 hours (dinner) respectively, whereas the meal on next day of dosing (Day-2) consisting of approx. 2800 Kcal {(divided into breakfast-approx. 400 kcal., lunch-approx. 1000 kcal., snacks-approx. 400 kcal., and dinner consisting of approx. 1000 kcal) will be provided at 24 hours 30 minutes, 28 hours 30 minutes, 32 hours 30 minutes and 37.0 hours post-dose respectively}. The meal plans will be provided by the dietician.

During clinical residence, the meal plans will be kept identical for two periods. Information on the standardized meal, quantity and time will be recorded on the relevant raw data forms.

Drinking water will not be permitted one hour before dosing and until one hour post-dose, at other times drinking water will be permitted *ad libitum.*





## 10.7 Sampling

### 10.7.1 Blood Sampling Schedule

A total of 25 blood samples (6 mL each) in each period will be collected in a pre-labeled vacutainer tubes containing potassium EDTA. The blood samples will be collected prior to administration of dose in each period pre-dose (0.0) and at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.25, 2.5, 2.75, 3.0, 3.25, 3.5, 3.75, 4.0, 4.5, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0 and 48.0 hours after administration of each product. The actual collection time of each blood sample will be recorded. Time deviations will be noted as protocol deviations.

For each subject the total number of blood draws will be 50 (25 x 2 for 2 periods). For each subject the total volume of blood withdrawn will be 358 mL. (8 mL for screening, 42 mL discarded heparinised blood, 300 mL for both the periods and 8 mL for post study laboratory tests at the end of Period-II).

### 10.7.2 Blood Sampling Procedure

Samples will be collected through an indwelling cannula placed in a forearm vein. The pre-dose samples will be collected prior to drug dosing. The post-dose samples will be collected within 2 minutes of the scheduled time where the end time of collection to the nearest minute would be recorded. Time deviations more than 2 minutes of actual blood collection time will be recorded as protocol deviations.

Intravenous indwelling cannula would be kept in place up to 12 hours post dose by injecting adequate amount but not more than 1 ml of 5 IU/mL of heparin in normal saline solution during the collection of multiple samples. In such a case, the blood sample would be collected after discarding the first 1 mL of heparinised blood from the tubing. Blood may also be withdrawn by a fresh clean venipuncture either by using sterile syringe and needle or disposable sterilized needle and vacutainer if the cannula is blocked.

If the blood sample collection time coincides with the other study events like vitals, subject well-being questionnaire and meal, the sequence of the events would be followed as: blood sample collection followed by vitals, subject well-being questionnaire and meal.

### 10.7.3 Handling of Blood Samples

Each blood sample will be collected into a pre-labeled vacutainer tube containing potassium EDTA. The samples collected at each time point will be centrifuged (at 2500 RCF and 4°C for 10 minutes) to separate plasma, immediately after receiving the blood samples from all the subjects. The separated plasma samples will then be transferred to deep freezer maintained below –20°C in pre-labeled tubes for temporary storage up to 4.0 hours and finally transferred to or directly to deep freezer maintained below -70°C for storage until analysis. Separated plasma samples of the subjects will be transferred from Clinical Unit to Bio analytical Unit as per the SOP No: APL-CPD-228-XX.



### 10.8 Admission and Stay

Subjects will be admitted and housed in the clinical facility at least 10 hours 30 minutes before the administration of the dose during each period of the study. They will be discharged 48.0 hours post dose, if not suffering from any adverse events. In case of any adverse events, the subjects will be kept under observation until recovery.

### 10.9 SAFETY ASSESSMENT

Safety assessments would be carried out at the time of screening, subject check-in, during the course of the study and subject check-out.

Detailed medical examination including medical history, physical and systemic examination, vital signs, Chest X-ray (PA view), 12-lead ECG and laboratory tests (as per Section 10.1.3 `Clinical Laboratory Tests') would be carried out at the time of screening to exclude any clinically significant medical condition that may interfere or likely to interfere with the pharmacokinetics of the drug.

#### 10.9.1 Vital Signs

In each period, vital signs monitoring will be done in sitting posture (except respiration rate which will be taken in supine position) at the time of check-in, pre dose and at 1.0, 3.0, 12.0, 24.0, 36.0 and 48.0 hours post-dose.

#### 10.9.2 Adverse event monitoring

Adverse event monitoring (subject well being questionnaire) will be done at 2.0, 5.0 and 8.0 hours post-dose and if any adverse events are observed by either clinical staff or reported by subjects at times other than scheduled times will be recorded.

#### 10.9.3 Handling and Reporting of Adverse Events

During the course of the study, subjects will be monitored for any adverse event, which will be recorded in the appropriate raw data forms. The subjects would be required to inform the attending personnel or physician of any adverse event that may occur during the time of their stay at the clinical facility. The attending physician/staff nurse may also enquire about any adverse events that may occur during the course of the study while monitoring the vital parameters. A medically qualified designate will be available round the clock during the time of housing at the clinical facility/or on phone. All drug and/or study related adverse events will be treated by the attending physician either at Clinical Unit, CPD or Mirra Multispeciality Hospital or tertiary Hospital at no extra cost to the subject as per SOP No.s: APL-CPD-222-XX and APL-CPD-245-XX.

Any adverse event observed shall be recorded and appropriately treated. The IRB shall be informed of the adverse event in the next convened meeting or through the clinical review report. The serious adverse events shall be informed as per the section 10.9.4.

The severity of adverse events will be graded on a three-point scale as follows.

Mild: Discomfort noticed but no disruption of normal daily activity.
Moderate: Discomfort sufficient to reduce or affect normal daily activity
Severe: Inability to work or perform normal daily activity

All clinically important abnormal laboratory results occurring during the study should be revaluated at adequate time intervals until they return to baseline values, to an acceptable level according to the clinical investigator or until a diagnosis that explains said changes is made.
The criteria to determine whether an abnormal test result should be reported as an adverse event are the following:

- When the test result is accompanied by an associated symptom
- When the test result requires an additional diagnostic examination or medical/surgical intervention.
- When the test result leads to a change in the study drug dose or study discontinuation, introduction of a significant concomitant drug treatment or other therapy.
- When the test results leads to any of the outcomes included in the definition of serious adverse event
- When the test result is considered as an adverse event by the Clinical investigator.

**Relationship to Investigational Product:**

The assessment of the relationship of an adverse event to the administration of study drug (Remote/conditional, possible, probable, definite, none/doubtful) will be assessed according to the SOP No: APL-CPD-222-XX.

- Remote: The event was most probably produced by other factors such as the patient's clinical state, therapeutic intervention or concomitant therapy and does not follow a known response pattern to the trial product.
- Possible: The event follows a reasonable temporal sequence from the time of product administration and/or follows a known response pattern to the trial product but could have been produced by other factors such as the patient's clinical state, therapeutic intervention or concomitant therapy.
- Probable: The event follows a reasonable temporal sequence from the time of product administration and/or follows a known response pattern to the trial product and could not have been produced by other factors such as the patient's clinical state, therapeutic intervention or concomitant therapy.
- Definite: The event follows a reasonable temporal sequence from the time of product administration and/or follows a known response pattern to the trial product and could not have been produced by other factors such as the patient's clinical state, therapeutic intervention or concomitant therapy and either occurs immediately following trial product administration, or improves on stopping the product or there is a positive reaction at the application site.
- Not related: The event is clearly related to other factors such as the patient's clinical state, therapeutic intervention or concomitant therapy.

### 10.9.4 Immediately reportable adverse events

Any adverse event that is serious will be reported on telephone or fax to the IRB with in one working day of occurrence. Such reports will be followed by detailed description with full follow-up report later (with in 7 days), which will include copies of hospital case reports and other documents where ever applicable.

All adverse events shall be evaluated for duration, severity, action taken, date and time of resolution and association with the study treatment. The study may be suspended or terminated depending on the seriousness of the adverse event.

**Note:**
Adverse Drug Reactions (ADR) are all noxious and unintended responses to a medicinal product related to any dose.
An adverse event (AE) is any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product. This can include any unfavourable and unintended signs (such as rash or enlarged liver), or symptoms (such as nausea or chest pain), an abnormal laboratory finding (including blood tests) or a disease temporarily associated with the use of the study medication.
A Serious Adverse Event (SAE) or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability / incapacity.
- Results in a congenital anomaly / birth defect.

Unexpected Adverse Event: Any adverse drug experience, the specificity or severity of which is not consistent with the package insert for marketed products.

### 10.9.5 Concomitant Medication and Treatment

The attending physician or the Clinical Investigator shall decide whether to continue with the subject in case the subject requires concomitant non-study medications during the study or the washout period. The decision will be based on the following:

- If there is likelihood of pharmacokinetic interactions with other non-study medications given during the course of the study.
- Depending on the time and duration of non-study medications.

### 10.9.6 Post-study Evaluation

**Post study medical examination**

Post study medical examination will be done at the end of the study or at any stage after the dosing if the subject is withdrawn or dropped from the study for any reason /on discretion of attending Physician/ Clinical Investigator. Whenever necessary, expert medical opinion will be taken and recorded.

**Post-study Lab Investigations**

At the end of period-II, 12-lead ECG and laboratory tests [Hematology ("absolute eosinophil count" test in post-study lab investigations if the subject's eosinophil count more than 6 % in post study results), RFT and LFT] will be done or at any stage after the dosing if the subject is withdrawn or dropped from the study for any reason /on discretion of attending Physician/ Clinical Investigator. Whenever necessary, expert medical opinion will be taken and recorded.

## 11.0 BIOANALYTICAL PROCEDURE AND SAMPLE ANALYSIS

### 11.1 Sample analysis

Samples will be assayed for plasma Gabapentin using a validated method developed at the bioanalytical unit of APL Research Centre. All samples from each subject will be analysed on the same standard curve. Quality control samples will be distributed through each batch of study samples assayed as per SOP No: APL-CPD-422-XX. The analysts will not have access to the randomization schedule, which is used for drug dispensing.

### 11.2 Procedure for Re-analysis

Repeat analysis for analytical anomalies will be performed wherever required as per repeat analysis SOP No: APL-CPD-423-XX. Both initial and repeat analysis concentrations will be reported in the table form.

### 11.3 Recording and Reporting of Data on Drug Levels

Analytical results will be presented in tabular form in the bioanalytical report. Additionally, accuracy, precision and linearity data for each standard curve and all quality control samples will be presented.

## 12.0 DATA ANALYSIS

### 12.1 Data Entry

Subject-wise, period-wise generated concentration-time data of plasma Gabapentin levels will be transferred electronically from bioanalytical unit to Pharmacokinetic & Biostatistical unit for pharmacokinetic and statistical analysis as per the SOP No: APL-CPD-109-XX of CPD, Aurobindo Pharma Ltd.

### 12.2 Pharmacokinetic Parameters and Analysis

Pharmacokinetic parameters for plasma Gabapentin will be evaluated with WinNonlin software version 5.0.1. If necessary, an unequal number of subjects per sequence will be used for PK and statistical analysis. Pharmacokinetic parameters for plasma Gabapentin will be calculated as follows:

| | |
|---|---|
| $C_{max}$ | Maximum measured plasma concentration over the time span specified. |
| $AUC_{0-t}$ | The area under the plasma concentration versus time curve, from time 0 to the last measurable concentration, as calculated by the linear trapezoidal method. |
| $AUC_{0-\infty}$ | The area under the plasma concentration versus time curve from time 0 to time infinity. $AUC_{0-\infty}$ is calculated as the sum of the $AUC_{0-t}$ plus the ratio of the last measurable plasma concentration ($C_t$) to the elimination rate constant $k_{el}$. $AUC_{0-\infty} = AUC_{0-t} + C_t / k_{el}$. |
| AUC %Extrap | The % extrapolation calculated as, $\frac{AUC_{0-\infty} - AUC_{0-t}}{AUC_{0-\infty}} * 100$ |
| $T_{max}$ | Time of the maximum measured plasma concentration. If the maximum value occurs at more than one time point, $T_{max}$ is defined as the first time point with this value. |
| $k_{el}$ | Apparent first order elimination rate constant calculated from a semi-log plot of plasma concentration versus time point. The parameter will be calculated by linear square regression analysis using the last 3 (or more) non-zero plasma concentrations. |
| $T_{1/2}$ | The elimination or terminal half-life will be calculated as 0.693 /$k_{el}$. |

If predose concentration is less than or equal to 5% of $C_{max}$ value in any subject, that subject data will be included in all pharmacokinetic calculations without any adjustments. If the predose value is greater than 5% of $C_{max}$, that subject will be dropped for pharmacokinetic calculations.

### 12.3 Statistical Analysis

Statistical analysis will be performed on pharmacokinetic data of samples assayed and quantified for Gabapentin using the SAS® software version 9.1.3. If a pharmacokinetic parameter cannot be determined for one period, the corresponding subject will be excluded for that particular statistical comparison.

#### 12.3.1 Summary Statistics

Mean, standard deviations and coefficients of variation will be calculated for the demographic variables like age, height, weight and BMI, plasma concentrations at each individual time point as well as for the pharmacokinetic parameters ($C_{max}$, $T_{max}$, $AUC_{0-t}$, $AUC_{0-\infty}$, $k_{el}$ and $T_{½}$) for Gabapentin and in addition, following statistical information will be provided for $AUC_{0-t}$, $AUC_{0-\infty}$, $C_{max}$ for Gabapentin:

i) Geometric Mean
ii) Arithmetic Mean

iii) Ratios of Mean
iv) 90% Confidence Intervals

### 12.3.2 Analysis of Variance (ANOVA)

The Lntransformed pharmacokinetic parameters ($C_{max}$, $AUC_{0-t}$ and $AUC_{0-\infty}$) will be statistically analysed using General Linear Model (PROC GLM) of SAS® software. The factors included in this model will be the treatment received, the period at which it is given along with the sequence in which each treatment being received and the subject effect (nested within the sequence). The sequence effect will be tested using the subject nested within sequence mean square from the ANOVA as the error term. Each analysis of variance will include calculation of least square mean (LSM). Two one-sided test at 5% level of significance will be used to compare the average values of pharmacokinetic parameters determined after administration of test and reference products.

### 12.3.3 Confidence Intervals and Ratio Analysis

90% confidence intervals for the exponential of the difference between the test and the reference products will be calculated for the Lntransformed parameters ($C_{max}$, $AUC_{0-t}$ and $AUC_{0-\infty}$). The confidence intervals will be expressed as percentages relative to the LSM of the reference treatments.

Ratio of means of each test and reference formulation will be calculated for untransformed pharmacokinetic parameters $C_{max}$, $AUC_{0-t}$ and $AUC_{0-\infty}$. The geometric means will be reported for the ln-transformed parameters.
The test product is considered as bioequivalent to the reference if the 90% CI of these parameters fall within the acceptance range of 80-125%.

### 12.3.4 Intra Subject Variability

Intra subject variability for the Gabapentin subject plasma data will be calculated and reported.

## 13.0 DATA MANAGEMENT

### 13.1 Documentation

Entire data, except the analytical data, lab investigation reports and other tests generated during conduct of the study will be directly recorded in raw data forms as per the related SOPs of APL-CPD. Results of lab investigations and other tests will be transcribed into laboratory report format as per SOP No. APL-CPD-315-XX. Clinical raw data consisting of medical history, physical examination and clinical laboratory case report forms, adverse reaction documentation and actual clock times of dosing and sample collection will be provided.

The included bioanalytical raw data will consist chromatograms of all subjects and the forms filled for recording the study related activities. The computer-generated chromatograms will also be treated as bioanalytical raw data. The statistical raw data containing the WinNonlin and SAS output will also be provided. Raw data

will be completed by the study personnel and checked by the respective group leaders wherever applicable.

All clinical raw data related to the study will be in the custody of Clinical Investigator or his designate and analytical raw data in the custody of Bioanalytical investigator or his designate until archiving.

### 13.2 Accessibility

Accessibility of the raw data will be limited to the IRB, QAD and the regulatory agencies for scheduled inspection and audits.

## 14.0 REGULATORY REQUIREMENTS AND ETHICAL CONSIDERATIONS

### 14.1 Basic principles

This study will be carried out as per the ICH, `Guidance for Good Clinical Practices (GCP)' and the principles of Declaration of Helsinki.

### 14.2 Institutional Review Board

The IRB shall review the protocol and the informed consent form for this study and no study specific procedures will be carried out until a written approval is obtained from the IRB except for medical screening of volunteer to record their health status.

### 14.3 Informed Consent

Approval from IRB will be taken for informed consent documents (English and relevant translations) before initiation of the study. Informed consent documents will be made in a language understandable by volunteers. Informed consent will be obtained as per SOP No.APL-CPD-207-XX.

### 14.4 Subject Compensation

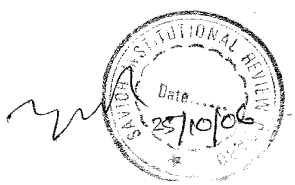
The subjects will be suitably compensated for their participation in the study, as per the SOP No. APL-CPD-230-XX, titled, 'Compensation for volunteers/subjects for clinical study'.

### 14.5 Protocol Amendments and Approval from IRB

Any change or addition to this protocol requires a written protocol amendment. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, must be approved by Investigator and IRB (Chairman/ERO) before implementation.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of the subjects included in the study. If an immediate change to the protocol is felt necessary by the investigator and is implemented for safety reasons, the IRB will be notified within 10 working days. Amendments affecting only administrative aspects of the study will not require formal protocol amendments or IRB approval but the IRB will be kept informed of such administrative changes in the next convened meeting.





### 14.6 Study Deviations

Study will be conducted in accordance with the Protocol, SOPs (Standard Operating Procedures) and regulatory requirements. Deviations (if any), at any stage of the study will be recorded promptly and corrective action will be taken. All clinical study deviations will be informed to the IRB through the clinical review report or in the next convened meeting.

### 14.7 Study Termination

The Principal Investigator/Clinical Investigator reserves the right to terminate the study at any time for safety reasons or in the best interest of the subject's welfare. The IRB can also cancel the study for major ethical violations. The subjects would be briefed on the reasons for the termination and compensated adequately.

### 14.8 Confidentiality of the Data

The data identifying study subject's name will be kept confidential and will be accessible only to concerned study personnel, quality assurance department, and if necessary, to the IRB and regulatory agencies.

### 14.9 Publication Policy

Publication of the results of the study, whether in whole or in part, shall be within the sole and absolute discretion of Director APL-Research Centre.

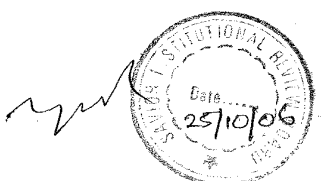
## 15.0 SUMMARY AND FINAL REPORTS

Clinical report, bioanalytical report (including chromatograms of 20% of subjects serially selected) and biostatistical report will be prepared giving details of each operation conducted. The summary report will also be prepared which will contain main points of the clinical, bioanalytical, biostatistical report and pharmacokinetic data, figures and tables of mean and individual subject plasma concentrations and pharmacokinetic profiles. Copies of the protocol, informed consent document and letter of approval from the IRB and randomization schedule will be appended to the summary report.

## 16.0 QUALITY ASSURANCE AUDITS

The actual conduct of the study during the various phases and the raw data generated during the course of the study will be liable for inspection and quality audit for conformance to this protocol and all the governing APL-CPD SOPs by Head-Quality Assurance department or his designate. An audit schedule will be drawn prior to the study. Audit reports will be issued. After corrective actions have been taken and reviewed, QA authentication statement will be issued, which is included in the study report.





## 17.0 ARCHIVES

A representative sample of the test and reference drug products used in the study will be archived. Electronic copies (if generated) or else the paper copies of the entire raw data (Including chromatograms, SAS, WinNonlin outputs, PK data, forms filled both in the clinical and bioanalytical sections, medical screening records, X-ray reports and clinical investigations reports) generated during the study along with a copy of the protocol, informed consent form and its amendments, audit reports, IRB Correspondence will be archived in APL-CPD for a period of 15 years.

## 18.0 BIOWASTE DISPOSAL

All the biowaste generated during the clinical and analytical phases of the study will be managed as per the SOP No.APL-CPD-113-XX.

## 19.0 REFERENCES

19.1 http://emc.medicines.org.uk/emc/industry/default.asp?page=displaydoc.asp&documentid=17095
19.2 Medical Economic Company Inc, Physician's Desk Reference, 60th Edition, 2006, P.2498-2503.
19.3 Churchill Livingstone, Therapeutic Drugs, 2nd Edition, P:G1-G3.
19.4 The Complete Drug Reference, Martindale, 33rd Edition , P: 350-351.
19.5 http://www.pfizer.com/pfizer/download/uspi_neurontin.pdf
19.6 http://www.pfizer.ca/english/our%20products/prescription%20pharmaceuticals/default.asp?s=1&id=10&doc=enmonograph
19.7 http://www.vapbm.org/criteria/Gabapentin.pdf
19.8 http://www.medsafe.govt.nz/Profs/Datasheet/n/Neurontincap.htm
19.9 http://www.fda.gov/cder/foi/nda/2002/21-397.pdf_Neurontin_BioPharmr.pdf

## 20.0 LIST OF APPENDICES

Appendix – 1 Study Flowchart (CLINICAL)

Appendix – 2 Event Schedule

Appendix – 3 Blood Sampling Schedule

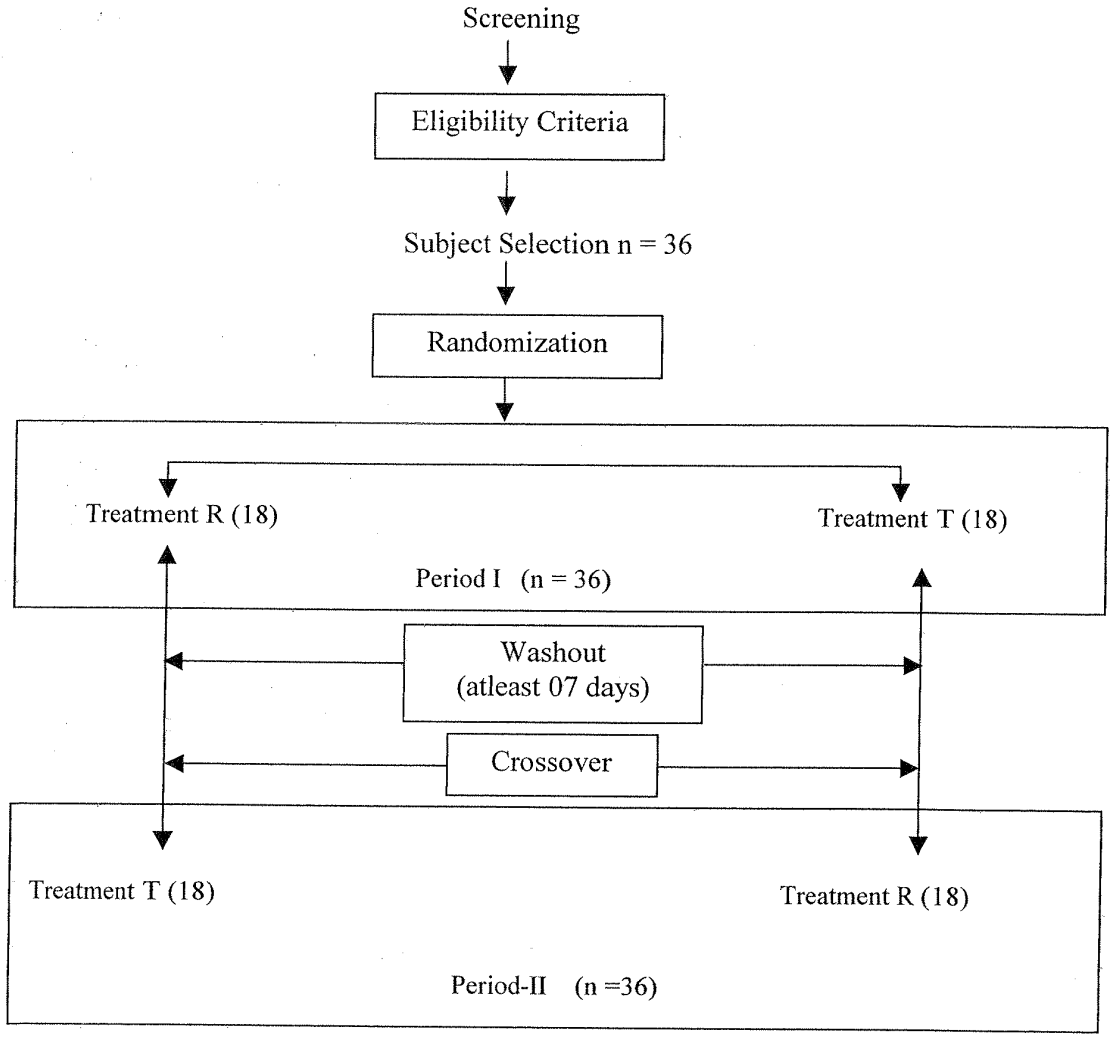
Appendix – 4 Investigator CVs

Appendix – 5 Normal Values for Laboratory Investigations

Appendix – 6 Declaration of Helsinki

Appendix – 7 Informed Consent Document

## APPENDIX – 1
## STUDY FLOW CHART (CLINICAL)




n - Number of subjects
R - Reference Product
T - Test Product

**APPENDIX – 2**

**EVENT SCHEDULE**

| Sl.No | Requirement | | Screening | Period-I | | | Period-II | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Check-in | Dosing Day | Check-out | Check-in | Dosing Day | Check-out |
| 1 | (*)Informed consent | | ✓ | ✓ | | | | | |
| 2 | Demographics | | ✓ | | | | | | |
| 3 | Medical history | | ✓ | | | | | | |
| 4 | **Medical examination** | General and systemic examination | ✓ | | | | | | |
| | | #Vitals | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | ECG (12 lead) | ✓ | | | | | | ✓ |
| | | Chest X-ray (PA view) | ✓ | | | | | | |
| | | Post medical examination | | | | | | | ✓ |
| 5 | Subject well being questionnaire | | | | ✓ | | | ✓ | |
| 6 | **Clinical laboratory tests** | Hematology: RBC count, hemoglobin, Total & differential WBC count & platelets count and absolute eosinophil count***. | ✓ | | | | | | ✓ |
| | | Blood grouping & Rh typing and bleeding time | ✓ | | | | | | |
| | | LFT: SGOT, SGPT, Total bilirubin , alkaline phosphatase, and γ – GT, total protein and albumin. | ✓ | | | | | | ✓ |
| | | Serum electrolytes:{serum sodium, potassium & chloride} serum calcium and phosphorous. | ✓ | | | | | | |
| | | Blood glucose (Fasting), Total Serum cholesterol | ✓ | | | | | | |
| | | RFT: serum creatinine, serum urea and serum uric acid. | ✓ | | | | | | ✓ |
| | | (**) CUE | ✓ | | | | | | |
| | | Drugs of abuse in urine: {benzodiazepine, opioids, amphetamines, cannabinoids, cocaines & barbiturates} | | ✓ | | | ✓ | | |
| | | Screening for infectious diseases: {HIV 1 & 2, HBs(Ag), HCV and RPR} | ✓ | | | | | | |

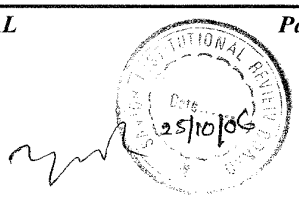
(*)Informed consent procedure would be obtained as per Sop no. APL-CPD- 207-XX

(**) CUE (Complete Urine Examination), which includes physical, bio-chemical and microscopic examination.

***Perform this "absolute eosinophil count" test in post-study lab investigations if the subject's eosinophil count is more than 6 % in post study results.

# Vitals will also be done at the time of 36.0 & 48.0 hrs post dose of both period I and II.





## APPENDIX- 3
## BLOOD SAMPLING SCHEDULE

| Sample No. | Sampling Time (hours) | Clock Time (hours)** |
|---|---|---|
| 1 | 0.0 (pre-dose) | 07.00 am |
| - | Dosing | 08.00 am |
| 2 | 0.33 | 08.20 am |
| 3 | 0.67 | 08.40 am |
| 4 | 1.0 | 09.00 am |
| 5 | 1.33 | 09.20 am |
| 6 | 1.67 | 09.40 am |
| 7 | 2.0 | 10.00 am |
| 8 | 2.25 | 10.15 am |
| 9 | 2.5 | 10.30 am |
| 10 | 2.75 | 10.45 am |
| 11 | 3.0 | 11.00 am |
| 12 | 3.25 | 11.15 am |
| 13 | 3.5 | 11.30 am |
| 14 | 3.75 | 11.45 am |
| 15 | 4.0 | 12.00 Noon |
| 16 | 4.5 | 12.30 pm |
| 17 | 5.0 | 1.00 pm |
| 18 | 6.0 | 2.00 pm |
| 19 | 8.0 | 4.00 pm |
| 20 | 10.0 | 6.00 pm |
| 21 | 12.0 | 8.00 pm |
| 22 | 16.0 | 12.00 Midnight |
| 23 | 24.0 | 8.00 am |
| 24 | 36.0 | 8.00 pm |
| 25 | 48.0 | 8.00 am |

** Clock time may change depending upon the time of drug administration
0.33- 48.0 hours represents post dose sampling.



## APPENDIX – 4

## CURRICULUM VITAE

**NAME:** Dr.Nitin Kulkarni

**EDUCATIONAL QUALIFICATIONS**

M.B.B.S.

**PROFESSIONAL WORK EXPERIENCE**

- Presently working as Clinical Investigator in Clinical Unit of Clinical Pharmacology Department of APL Research Center, Hyderabad since May 2004.
- Worked as a Physician and Medical Investigator in Vimta Labs, Hyderabad from April 2002 to May 2004.
- Worked in Sai Vani Hospital, Domalguda, Hyderabad from July 2001 to March 2002.
- Worked in CDR Hospital, Hyderaguda, Hyderabad from October 1998 to June 2001.

04 years of research experience covering Bioavailability, Bioequivalence studies.

As a Medical Investigator in Vimta Labs, conducted more than 75 Bioequivalence/ Bioavailability studies, which included screening and selection of healthy volunteers, preparation of related SOP's, preparation of protocols, conducting IRB meetings, managing adverse events, monitoring of other study related procedures as per GCP/GLP requirements and preparation of clinical reports.

Exposure in overall study conduct/management of around 200-250 Bioequivalence/ Bioavailability studies as per GCP/GLP requirements, submitted to various regulatory agencies.

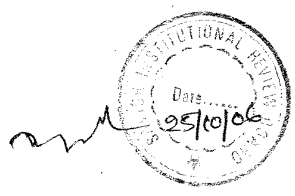
Experienced in preparation of related SOP's, study protocols/ICF documents and clinical reports.

Training on Good Clinical Practise (in-house) as per ICH-GCP requirements through self-acquaintance and group discussions.

Attended various Workshops and Seminars on Investigators and GCP.

Signature: Nitin

Date: 01/05/06



## Appendix-4

# CURRICULUM VITAE

Name: **MEDA NAGESH**

## EDUCATIONAL QUALIFICATIONS

Master of Pharmacy in Pharmacology, U.C.P.S., under Kakatiya University, Warangal, INDIA. (1997-1999).

## PROFESSIONAL WORK EXPERIENCE

⇒ Presently, working as scientist, Clinical Pharmacology Department (Bioanalytical), APL Research Centre, Hyderabad, INDIA (October2004 till date).

⇒ Worked as Research Scientist, Drug development division (Bioanalytical), at Ranbaxy Research Laboratories, Gurgaon, INDIA (March 2004 to September2004).

⇒ Worked as R&D Executive, Pharmacokinetics division (Bioanalytical) at Sun Pharma Advanced research Centre, Baroda, INDIA (January 2002 to February 2004).

⇒ Worked as Officer at DRL Generics, Biopharmaceutics division, Hyderabad, INDIA (August 2001 to December 2001).

⇒ Worked as Research Assistant, Pharmacokinetics division (Bioanalytical) at Sun Pharma Advanced research Centre, Baroda, INDIA (October 1999 to July 2001).

Having more than 6 years of research experience in bioanalytical area covering Bioavaialabilty (drug discovery and Development) and Bioequivalence studies.

Experienced in developing and validating bioanalytical methods, analysis of biostudy samples, preparation of SOPs and bioanalytical reports.

Signature: Nagesh

Date: 01.08.2006

Date 25/10/06

Appendix-IV

# CURRICULUM VITAE

**NAME: H.L.V. Ravi Kiran**

**EDUCATIONAL QUALIFICATIONS:** Master of Pharmacy in Pharmacology, Department of Pharmaceutical Sciences, Andhra University, Visakhapatnam, Andhra Pradesh, India. (2000 - 2002).

**CURRENT JOB:** Working as Research Associate-IV, Pharmacokinetic and Biostatistics Department, APL Research center, Hyderabad, India (November 2004 to till date).

**CURRENT JOB PROFILE:** Leading the Pharmacokinetic & Biostatistics Department for successful completion of Protocol Design, Pharmacokinetic & Statistical Analysis for Bioequivalence studies for various regulated markets.

**PROFESSIONAL WORK EXPERIENCE**

- Worked as a Clinical Research Associate, Vimta Labs Ltd, Hyderabad, India (August, 2002 to November 2004).
- Worked as a Study Coordinator for about 150 Bioequivalence studies done at Vimta for submitting to various regulatory bodies.
- Experienced in preparation of protocols, ICF documents, reports and management of Institutional Review Board Issues.
- Experienced Good exposure in preparation of SOPs as per ICH GCP Guidelines.
- Experienced in monitoring the clinical studies as per ICH GCP Guidelines.
- Having a profound knowledge on GCP, GLP and attended several training sessions, workshops and seminars on GCP and GLP.
- Exposed to various internal and external audits of sponsors and various regulatory authorities.
- Having 4 years research experience covering Bioavailability, Bioequivalence studies.

Signature: Ravi Kiran

Date: 10/08/06

SAVI INSTITUTIONAL REVIEW BOARD Date 25/10/06

# Appendix-4

**NAME:** J.BALAJI

**EDUCATIONAL QUALIFICATION:**

M.Sc ( STATISTICS ), University College Of Science, Osmania University, Hyderabad.

**PROFESSIONAL WORK EXPERIENCE:**

Presently working as Trainee Research Associate in Bio-statistics Department, Clinical Pharmacology Department, APL Research Centre, Hyderabad from October 2005.

Worked as Research Executive in Market Research Department for Innovative Research Services, Mumbai from May 2005 – September 2005.

Signature:
(J.Balaji)

Date: 01/05/06

25/10/06

# Appendix-4
# Curriculum vitae

**Name:** Dr A.T. Bapuji

**Educational Qualifications:** M.Pharm, PhD (Pharmaceutical Medicine)

**Current Job:** Head, Bioanalytical, Clinical Pharmacology Department, APL Research center, Hyderabad.INDIA

**Current Job Profile:**
(Oct2004-Present)

Leading the Department and a team of Bioanalytical scientists, Pharmacokinetists and statistician in successful completion of Bioanalytical projects for Bioequivalence studies for various regulated markets.

**Previous Job Profile:**
(Dec 1993-Oct 2004)
**Group leader,**
Ranbaxy Research Laboratories, Gurgaon, Haryana, India

Led a group of Bioanalytical scientists in successful completion of more than 400 BA/BE studies for US-FDA and other regulated Markets for various formulations

Expertise in Development and validation of Bioanalytical methods

Established the Bioanalytical Laboratory to the highest GLP standards in various capacities.

Expertise in GLPs/GCPs and various regulatory standards.

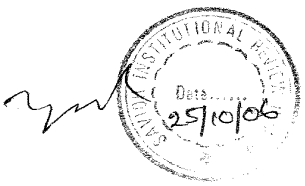
Proficiency in design and development of protocols for various types dosage forms

Extensive experience in Pharmacokinetic and statistical evaluations.

Handled various software for data analysis and data interpretation.

Hands on Experience as a laboratory manager and expertise on various advanced analytical instrumentation for quantitation.

Signature: A T Bapuji Date: 18.09.06



## APPENDIX – V
## NORMAL VALUES FOR LAB INVESTIGATIONS



| Sl.No | TESTS | METHOD | NORMAL RANGE |
|---|---|---|---|
| **A. HAEMATOLOGY** | | | |
| 1. | Haemoglobin | Cell Counter and Microscopic examination | Males – 13.0 -18.0 gm% |
| 2. | Red Blood cells | | Males – 4.5 - 5.9 mill /cumm |
| 3. | White Blood cells | | 4000 – 11000 /cumm |
| 4. | Differential Count | | |
| a. | Neutrophils | Microscopic Examination | 40 – 75 % |
| b. | Lymphocytes | | 20 – 45 % |
| c. | Eosinophils | | 1 – 6 % |
| d. | Monocytes | | 2 – 10 % |
| e. | Basophils | | 0 – 1 % |
| f. | Absolute Eosinophils Count | | 40-440 Cells / cumm |
| 5. | Platelet Count | Cell counter | 1.5 - 4.4 lakhs/cumm |
| 6. | Blood grouping | Agglutination | -- |
| 7. | Rh Typing | Agglutination | -- |
| 8. | Bleeding time | Duke's | 1 – 5 minutes |
| **B. IMMUNOLOGY** | | | |
| 1. | HIV 1 & 2 | Elisa | Negative |
| 2. | RPR | Agglutination | Non-reactive |
| 3. | Anti HCV | Elisa | Negative |
| 4. | HBsAg | Elisa | Negative |
| **C. BIOCHEMISTRY (VITALAB SELECTRA-E ANALYSER)** | | | |
| 1. | RBS/PPBS/FBS | GOD – POD | 60-160 / upto160 / 60-110 mg/dL |
| 2. | Serum Calcium | Arsenazo – III | 9.0 – 11.0 mg/dL |
| 3. | Serum Phosphorous | Phosphomolybdate UV | 2.3 – 4.7 mg/dL |
| 4. | Serum Cholesterol | CHOD – PAP | < 240 mg/dL |
| 5. | Serum Triglycerides | Enzymatic | 10 – 190 mg/dL |
| 6. | **Electrolytes** | | |
| a. | Serum Sodium | Ion select electrode | 136 – 155 mmol/L |
| b. | Serum Potassium | | 3.5 – 5.5 mmol/L |
| c. | Serum Chloride | | 96 - 106 mmol/L |
| 7. | Serum Amylase | UV Kinetic | < 220 IU/L |
| **D. HEPATIC PROFILE** | | | |
| 1. | SGOT | UV Kinetic | 0 – 35 IU/L |
| 2. | SGPT | UV Kinetic | 0 – 35 IU/L |
| 3. | Alkaline Phosphotase | PNPP | 80 – 306 IU/L |
| 4. | Total Bilirubin | Jendrassik and Grof | 0.1 – 1.2 mg/dL |
| 5. | Direct Bilirubin | Jendrassik and Grof | <0.3 mg/dL |
| 6. | Indirect Bilirubin | -- | -- |
| 7. | Gamma GT | Kinetic | 11 – 50 IU/L |
| 8. | Total Protein | Biuret | 5.5 – 8.0 g/dL |
| 9. | Albumin | Bromcresolgreen | 3.5 – 5.5 g/dL |

12/09/06
Dr. CH. SRINIVASA RAO
PATHOLOGIST

Date 25/10/06

| Sl.No | TESTS | METHOD | NORMAL RANGE |
|---|---|---|---|
| **E. RENAL PROFILE** | | | |
| 1. | Serum uric acid | Uricase | 2.5 – 8.0 mg/dL |
| 2 . | Serum Creatinine | Jaffe Kinetic | 0.6 – 1.5 mg/dL |
| 3 | Blood Urea | Urease - GLDH | 15 - 45 mg/dL |
| **F. BIOCHEMISTRY(DADE BEHRING ANALYSER)** | | | |
| 1. | Fasting Glucose | Hexokinase | 70 -110 mg/dL |
| 2. | Urea | Urease | 15-39 mg/dL |
| 3. | Creatinine | Jaffe Kinetic | 0.8-1.3 mg/dL |
| 4. | Uric Acid | Uricase | 3.5-7.2 mg/dL |
| 5. | Calcium | OCPC | 8.5-10.1 mg/dL |
| 6. | Phosphorous | Phosphomolybdate | 2.5-4.9 mg/dL |
| 7. | Total Cholesterol | CHOD-PAP | < = 200 mg/dL |
| 8. | Total Bilirubin | Jendrassik and Grof | < = 1.0 mg/dL |
| 9. | SGOT (AST) | IFCC | 15-37 U/L |
| 10. | SGPT (ALT) | IFCC | 30-65 U/L |
| 11. | Alkaline Phosphatase | PNPP-AMP | 50-136 U/L |
| 12. | Gamma GT | IFCC-Enzymatic | 15-85 U/L |
| 13. | Total Protein | Biuret | 6.4-8.2 g/dL |
| 14. | Albumin | Bromocresol Purple | 3.4-5.0 g/dL |
| 15. | Triglyceride | Enzymatic | 0-150 mg/dL |
| 16 | Amylase | UVKinetic/ CNP G3 | 25-115 U/L |
| 17 | CreatinePhosphokinase(CPK) | UVEnzymatic | 35-232 U/L |
| **IMT(Integrated Multisensor Technology) Electrolytes** | | | |
| 17. | Sodium | IntegratedMultisensor Technology | 136 – 145 mmol/L |
| 18. | Potassium | | 3.5 – 5.1 mmol /L |
| 19. | Chloride | | 98 – 107 mmol /L |
| **G. COMPLETE URINE EXAMINATION** | | | |
| **1.** | **Physical Examination** | | |
| a. | Colour | | Yellow / Pale Yellow |
| b. | Appearance | | Clear / Slightly Turbid |
| c. | Deposit | | Nil |
| d. | $P^H$ | Dip strip | 4.6 – 8.0 |
| e. | Specific gravity | | 1.001 – 1.035 |
| **2.** | **Chemical Examination** | | |
| a. | Proteins | Dip strip | Negative |
| b. | Glucose | | Negative |
| c. | Ketones | | Negative |
| d. | Bilirubin | | Negative |
| e. | Urobilinogen | | Negative |
| f. | Nitrite | | Negative |
| g. | Blood | | Negative |
| **3.** | **Microscopic Examination** | | |
| a. | Pus Cells | Microscopic | 0 –5 / hpf |
| b. | Red Blood Cells | | Nil |
| c. | Epithelial Cells | | 0 –5 / hpf |

12/09/06

Dr. CH. SRINIVASARAO

PATHOLOGIST

INSTITUTIONAL REVIEW BOARD

Date 25/10/06

| Sl.No | TESTS | METHOD | NORMAL RANGE |
|---|---|---|---|
| d. | Casts | | Nil |
| e. | Crystals | | Nil |
| **H. DRUGS OF ABUSE IN URINE** | | | |
| 1. | Benzodiazepines | Immuno chromatographic assay | Negative |
| 2. | Opioids | | Negative |
| 3. | Amphetamines | | Negative |
| 4. | Barbiturates | | Negative |
| 5. | Cannabinoids | | Negative |
| 6. | Cocaine | | Negative |

**Note:**

1. **Normal range and method for all parameters change as per the specifications of the kit used for performing the tests.**

2. **Method is subject to change as per the availability of the kit.**

3. **Appendix –V was taken from Annexure-VII, SOP NO: APL-CPD-315-05 (Reporting of the Test Results)**

19/09/06
Dr. CH. SRINIVASA RAO
PATHOLOGIST.

INSTITUTIONAL REVIEW BOARD
Date 25/10/06

# APPENDIX-6
# Declaration Of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
**Ethical Principles for Medical Research Involving Human Subjects**
Adopted by the 18th WMA General Assembly,
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly,
Washington 2002
Note of Clarification on Paragraph 30 added by the WMA General Assembly,
Tokyo 2004

## A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

## B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on hum an beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects

with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

## C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.1

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.2

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

1 Note of clarification on paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

2 **Note of clarification on paragraph 30 of the WMA Declaration of Helsinki**

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

9.10.2004

| Volunteer Reg. No.: APL - | Subject No.: S - |
|---|---|

## Appendix-7
## Informed Consent Document

Title: An open label, randomized, two treatment, two sequence, two period, cross-over, single-dose comparative oral bioavailability study of Gabapentin 400 mg capsules (Test), manufactured by Aurobindo Pharma Ltd., India and Neurontin 400 mg capsules (Reference), marketing authorization holder Parke Davis, UK, in 36 healthy, adult, male, human subjects under fasting conditions.

Volunteers Name: _____ _____ _____
(First Name) (Last Name) (Surname)

Date of Birth: _____(dd/mm/yy)

Age: _____ (completed years)

Address: _____

_____

Telephone No.: _____

Dear Subject,

You are being asked to take part in the above mentioned research study.

It is important to read carefully and understand the information given in this document before agreeing to participate in the current study. All clarifications and questions must be discussed during the oral presentation of this document. You must sign and date this document and submit to us for our records. A photocopy of the same will be given to you for your future reference.

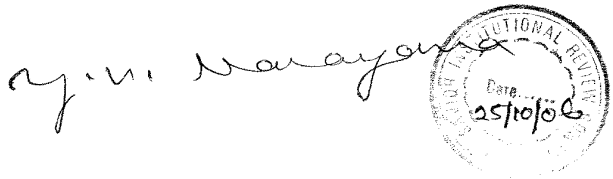
The purpose of this document is to clearly state the procedures of the study and to ensure that you enter the study only after knowing all relevant facts about it. The informed consent document describes the purpose of the study, possible benefits, risks or discomfort, alternative treatment and confidentiality. It also bears the declaration of your voluntary participation in the study.

The informed consent is not a contract and you can withdraw from the study at anytime, at your own will.

Volunteer Signature _____ Date _____

Signature of the Clinical Investigator /Physician : _____ Date : _____





| Volunteer Reg. No.: APL - | Subject No.: S - |
|---|---|

## 1.0 Introduction

Gabapentin belongs to a class of drugs called anticonvulsants. Gabapentin affects chemicals and nerves in the body that are involved in the cause of seizures and some types of pain. They are used to treat seizures (epilepsy) and herpes zoster (shingles). This medicine is also used to manage a condition called postherpetic neuralgia (pain after "shingles").

## 2. 0 What is the nature of the study?

This study involves research. Bioavailability/Bioequivalence studies are conducted to compare the rate and extent of absorption of two different formulations. In this study, we are comparing the test formulation Gabapentin 400 mg capsules manufactured by Aurobindo Pharma Ltd., India with that of the established & marketed reference formulation for Gabapentin 400 mg capsules in regulated market (Europe) under the brand name of Neurontin 400 mg capsules in 36 healthy, adult, human subjects under fasting conditions. You are likely to be one of the 36 healthy, adult, male human subjects, who will participate in this study.

## 3.0 What is the purpose of the research?

Gabapentin is indicated for the treatment of epilepsy and this drug sold in various regulated markets (countries) under different brand names. Aurobindo Pharma Ltd., India, has manufactured same strength of Gabapentin capsules and would like to sell in Europe. In order to achieve this Aurobindo Pharma Ltd., India, has designed a research study in human beings to show that equivalent amount of Gabapentin is present in blood when either capsules manufactured by Aurobindo Pharma Ltd., India or reference capsules of Parke Davis, UK, are given to same human being at different time under fasting conditions.

## 4.0 Description of the study

### 4.1 What are the Inclusion Criteria?

You will be `eligible' to participate in the study only when you satisfy all of the following criteria:

4.1.1 You are male within the age group of 18 to 50 years.

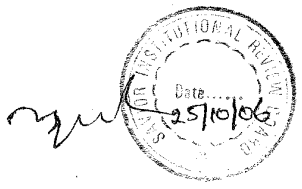
4.1.2 You have a body mass index between 19 to 26 kg/m$^2$.

4.1.3 You are willing to provide written informed consent to participate in the study.

4.1.4 You have no diseases as HIV, Hepatitis virus and Syphilis.

Volunteer Signature : _____ Date: _____





| Volunteer Reg. No.: APL - | Subject No.: S - |
|---|---|

4.1.5 You have no significant disease or no clinically significant abnormality in laboratory test results, medical history or physical examination during screening.

4.1.6 You have normal 12 lead ECG.

4.1.7 You have a normal chest X-ray (PA view).

4.1.8 You are compliant with requirements of the entire protocol.

4.1.9 You have no history of hypersensitivity to Gabapentin.

4.1.10 You have no history of significant systemic disease.

4.1.11 You have no history of psychiatric disorders.

4.1.12 You have no history of addiction to any recreational drug or drug dependence.

4.1.13 You have not donated blood (one unit or 350 mL) within 56 days prior to receiving the first dose of study medication.

4.1.14 You have not participated in any clinical study within the past 56 days.

4.1.15 You have not received any prescription drugs or over-the-counter (OTC) drugs (e.g.: Cold preparations, and antacid preparations vitamins and natural products used for therapeutic benefits), within the two weeks prior to receiving the first dose of study medication.

4.1.16 You have no history of dehydration from diarrhoea, vomiting or any other reason within a period of 24 hours prior to the study.

4.1.17 You have no family history of neurological disorders.

4.1.18 You have not taken alcohol, cigarettes, tobacco products and any form of xanthine (chocolates, tea, coffee or cola drinks) containing food and beverages at least 48 hours prior to check-in.

4.1.19 You have negative results for drugs of abuse (barbiturates, benzodiazepines, opioids, amphetamines, cocaines and cannabinoids) in urine during the day of check in for Period I and Period II.

4.1.20 You have not taken grape fruit (mosumbi/sweet lime) juice within the 48 hours prior to check-in for Period I and Period II.

**4.2 What are the Exclusion Criteria?**

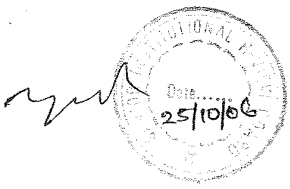
You will be `ineligible' to participate in this study if you satisfy any one of the following criteria

4.2.1 If you have history of seizures.

4.2.2 If you have history of alcohol consumption for more than two units/day (1 unit = 30 ml of spirit/or 1 pint of beer), or having consumed alcohol within 48 hours prior to check-in.

Volunteer Signature : _____ Date: _____





| Volunteer Reg. No.: APL - | Subject No.: S - |
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4.2.3 If you consume more than 5 cups of coffee or tea/day or tobacco (more than 9 cigarettes/ beedies/ cigars/day).

4.2.4 If you have history of difficulty with donating blood or if you have difficulty in accessibility of veins in left or right arm.

4.2.5 If you have taken an unusual or abnormal diet, for whatever reason e.g. because of fasting due to religious reasons.

**4.3. What is Study Procedure?**

4.3.1 You had undergone various screening tests which include medical examination, blood tests, urine tests, tests for infectious diseases (HIV 1 & 2, hepatitis B & C virus and Syphilis), Chest X-ray (PA view) and 12-lead ECG at the time of screening, for which you had given 8 mL of blood and approximately 20-25 mL of urine for various screening tests.

4.3.2 You will be eligible for admission into the study only after you satisfy all the laboratory tests, medical examination, and study protocol requirements.

4.3.3 Study will be in two periods. In each of the two periods you will be required to check in at APL-CPD centre at least 10 hours 30 minutes before the administration of dose i.e. the previous evening to Day –1 (day of drug administration).

4.3.4 Urine tests for drugs of abuse (Barbiturates, Benzodiazepines, Opioids, Amphetamines, Cocaines and Cannabinoids) will be conducted during the day of check-in for period-I & II, for which you are requested to give approximately 20-25 mL of urine sample in both the periods.

4.3.5 Eligibility criteria, which include vitals, will be done at the time of check-in, of each period.

4.3.6 Thirty six (36) subjects will be involved in the study along with you.

4.3.7 You will be required to stay at clinical Unit, CPD, APL Research Centre, Mirra Multispeciality Hospital, Plot Nos. 33-35, Alluri Sitaramaraju Colony, Opp. J. P. N. Nagar Colony, Miyapur, Hyderabad-500050 for two periods i.e. Period I and Period II.

4.3.8 In Period I you will receive either Reference (R) (Neurontin 400 mg capsule, marketing authorization holder Parke Davis, UK) or Test (T) (Gabapentin 400 mg capsule, manufactured by Aurobindo Pharma Ltd., India). The order in which you will receive study medication will be will be randomly determined.

4.3.9 There will be a wash out period of at least 07 days between the two periods.

4.3.10 In Period-II you will receive the alternate medication (if you have received Reference R in Period-I, you will receive Test T in Period-II and vice-versa).

Volunteer Signature : _____ Date: _____



25/10/06

| Volunteer Reg. No.: APL - | Subject No.: S - |
|---|---|

4.3.11 In each period, after an overnight fast of at least 10 hours you will receive, orally, either Reference (R) or Test (T) with 240 mL of water.

4.3.12 In each period, after completion of high fat break fast, you will receive, orally, either Reference (R) or Test (T) with 240 mL of water.

4.3.13 Your drug dosing will be in sitting posture and you will be instructed to remain seated or ambulatory for the first 2.0 hours following drug administration. Thereafter you will be allowed to engage only in normal activities while avoiding severe physical exertion.

4.3.14 A post dose standardized meal consisting of approx. 2400 kcal as per the meal plan, will be provided at 4.0 hours 30 minutes (lunch consisting of approx. 1000 kcal), 8 hours 15 minutes (snacks consisting of approx. 400 kcal) and 13.0 hours (Dinner consisting of approx. 1000 kcal) respectively, whereas the meal on next day of dosing (Day-2) consisting of approx. 2800 kcal {(divided into breakfast-approx. 400 kcal., lunch-approx. 1000 kcal., snacks-approx. 400 kcal., and dinner consisting of approx. 1000 kcal) will be provided at 24 hours 30 minutes, 28 hours 30 minutes, 32 hours 30 minutes and 37.0 hours post-dose respectively} where as the dinner (consisting of approx.1000 kcal) will be provided during the day of check-in. The meal plans will be provided by the dietician.

4.3.15 Vital signs monitoring will be done in sitting posture (except respiration rate which will be taken in supine position) at the time of check-in, pre-dose and at 1.0, 3.0, 12.0, 24.0, 36.0 and 48.0 hours post-dose in each period.

4.3.16 Adverse event monitoring (subject well being questionnaire) will be done at 2.0, 5.0 and 8.0 hours post-dose in each period.

4.3.17 In case the mealtime coincides with the sample collection time, vitals and Subject well being questionnaire, the sequence of events would be followed as: Blood sampling, vitals, Subject well being questionnaire and meals.

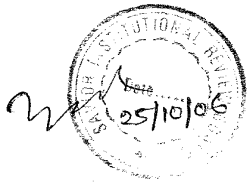
4.3.18 Blood samples will be collected during each period. Blood samples will be collected through an indwelling cannula (small plastic tube) placed in a forearm vein. First blood sample (pre-dose) will be collected before drug administration.

4.3.19 Intravenous indwelling cannula would be kept in place upto 12 hours post dose by injecting 1 mL of 5 IU/mL of heparin (a substance normally present in human body) in normal saline solution to prevent blood clotting and facilitate blood sample collection.

4.3.20 Blood samples will be collected at pre dose (0.0) and at 0.33 (20 minutes), 0.67 (40 minutes), 1.0 (1 hour), 1.33 (1 hour 20 minutes), 1.67 (1 hour 40 minutes), 2.0 (2 hours), 2.25 (2 hours 15 minutes), 2.5 (2 hours 30 minutes), 2.75 (2 hours 45 minutes), 3.0 ( 3 hours), 3.25 ( 3 hours 15 minutes), 3.5 ( 3 hours 30 minutes), 3.75 ( 3 hours 45 minutes), 4.0, 4.5, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0 and 48.0 hours post dose.

Volunteer Signature : _____ Date: _____





4.3.21 At every time point 6 mL of blood will be collected.

4.3.22 At the discretion of the attending Physician / Clinical Investigator blood may also be withdrawn by a fresh clean vein puncture using a disposable sterilized needle and vacutainer whenever cannula is blocked.

4.3.23 Combining two periods, the total number of blood samples collected will be 50 (25x2). The total volume of blood withdrawn will be 358 mL, including 8 mL for screening, 42 mL discarded blood prior to collection through the venous cannula, 300 mL for two periods and 8 mL for post-study lab investigations (at the end of period II).

4.3.24 All the adverse events would be treated by the attending physician either at Clinical Unit, CPD or Mirra Multispeciality Hospital or tertiary Hospital at no cost to you.

4.3.25 You will be discharged at the end of 48.0 hours post dose, sample collection of the study, if you are in good health and not suffering from any adverse events. In case of any adverse events, you will be given proper medical care and kept under observation until recovery.

4.3.26 Your approximate duration of stay at Clinical Unit, CPD would be approximately 65.0 hours for each period.

4.3.27 You will be informed in the event of new information that may be relevant to take decision regarding your participation in the study.

4.3.28 At the end of the period-II, 8 mL blood will be taken for the blood tests (Hematology ("absolute eosinophil count" test in post-study lab investigations if the subject's eosinophil count is more than 6 % in post study results), LFT and RFT), 12-lead ECG will be done.

4.3.29 In case if you are withdrawn/drop out from study by any reason (before completion of the study and after the dosing in period-I) safety assessments mentioned in section: 4.3.28 will also be done.

**4.4. What are the study restrictions?**

4.4.1 You should not smoke for atleast 48 hours before check-in and till completion of the study.

4.4.2 You should refrain from using any medicines (either prescription or over-the-counter drugs) particularly two weeks before the first administration of study medication and till completion of the study.

4.4.3 You should abstain from alcohol and xanthine containing food and beverages, (chocolates, tea, coffee or cola drinks) cigarettes and tobacco products, for atleast 48 hours prior to check-in, for each period and during the in-house stay.

Volunteer Signature : _____ Date: _____



Date 25/10/06

| Volunteer Reg. No.: APL - | Subject No.: S - |
|---|---|

4.4.4 You should not consume grape fruit (mosumbi/sweet lime) juice within the 48 hours prior to check-in, for each period.

4.4.5 You are required to fast over night (at least 10.0 hours) before dosing and a minimum of four hours thereafter.

4.4.6 Drinking water will not be permitted one hour before dosing and until one hour post-dose.

4.4.7 You will be dosed while in sitting posture and you should remain seated or ambulatory for first two hours (except for respiration rate during vitals) following the drug administration. Thereafter, you will be allowed to engage only in normal activities while avoiding severe physical exertion.

**4.5. What are the administrative requirements?**

4.5.1 Please follow the study procedures as explained by the staff.

4.5.2 Please always wear ID cards issued to you.

4.5.3 Kindly sleep according to the sleep call.

4.5.4 Please follow the procedures explained during dosing.

4.5.5 Please be in sitting position or be ambulant for 2 hours after dosing.

4.5.6 Please be available at the blood collection room at the scheduled time.

4.5.7 Please co-operate with the phlebotomists at the time of sample drawing.

4.5.8 Please come for ambulatory visits at the scheduled time mentioned to you, if any.

4.5.9 Immediately report to the staff (nurse/custodian/doctors) in case of any discomfort.

4.5.10 Please consume fully the given fixed quantity of standardized food during your in-house stay and do not share your food with others.

4.5.11 In case of any emergency, while you are in toilet , please press the emergency calling bell.

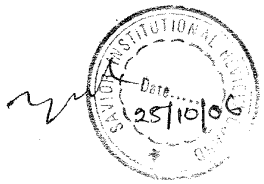
**5.0 What are the risks of the study?**

Gabapentin is already marketed in many countries including India for the last several years. Generally, it is well-tolerated drug. However, side effects are known to occur in few people. These side effects are reported to occur on long terms use of drug.

We anticipate that there will be no serious side effects if one capsule (test drug) or one relative reference capsule is administered to the healthy human subject. This is only our assessment but mild side effects can occur.

Volunteer Signature : _____ Date: _____





| Volunteer Reg. No.: APL - | Subject No.: S - |
|---|---|

Dizziness (reeling of head), somnolence (sleepiness), diarrhoea (loose stools), dry mouth, peripheral oedema (outside serous fluid accumulation), weight gain, abnormal gait (abnormal pattern of walking), amnesia (lack or loss of memory), ataxia (irregularity of muscular action), abnormal thinking, rash, amblyopia (dimness of vision), accidental injury, asthenia (weakness or loss of strength), back pain, constipation (condition in which bowel evacuations occur infrequently), flatulence (excessive production of gases in the stomach or intestine), nausea (feeling of vomiting), confusion, hyperesthesia (increased sensitivity to stimulation), vertigo (a sensation of dizziness and falling), dyspnea (difficult or labored respiration), pharyngitis (inflammation of pharynx), fatigue (tiredness or exhaustion of strength), nystagmus (oscillatory movement of the eye ball), tremors (Involuntary trembling), diplopia (the perception of two images of a single object or double vision), abnormal vision, dysarthria (difficulty in articulation), asthenia (weakness or loss of strength), paraesthesia (spontaneously occurring abnormal tingling sensations like burning / tickling / prickling), arthralgia (Pain in joints), purpura (small purple haemorrhagic spots on the skin and mucous membranes), dyspepsia (indigestion), anxiety (feeling of tension), weight increase, urinary tract infections, leucopenia (reduction in the number of white blood cells), nervousness ( excessive excitability), rhinitis (inflammation of nose), impotence (Loss of strength, especially copulative), urinary incontinence, pancreatitis (inflammation of pancreas), elevated liver function tests, erythema multiforme (desquamation, ulceration and necrosis of the skin and mucous membranes which occur after the use of some drugs), Stevens Johnson Syndrome (a severe form of allergic reaction appear on the palms of the hands and soles of the feet.), confusion, depression ( decrease in functional activity), emotional lability, abnormal thinking, hallucinations (perception of a sense without stimulation, especially noticed in some mental disorders), blood glucose fluctuations in patients with diabetes, myalgia (pain in muscles), headache, nausea and/or vomiting have also been reported.

**Additional Post-Marketing Adverse Events:** acute kidney failure, urticaria (an itchy skin reactions characterized by red margins), alopecia (loss of hair), chest pain, hepatitis (inflammation of liver), jaundice (yellow discoloration of skin and eyes), movement disorders such as choreoathetosis, dyskinesia (impairment in the ability to control movements characterized by lack of coordination.), dystonia (Impairment of muscle tone), palpitation (Sensation of rapid heartbeats), thrombocytopenia (reduction in the number of platelets in the blood), and tinnitus (noises in the ear).

Adverse events following the abrupt discontinuation of gabapentin are anxiety (feeling of tension), insomnia (Inability to fall asleep / lack of adequate sleep), nausea (feeling of vomiting), pain and sweating.

The procedure of taking blood may cause local discomfort, bruising, swelling and rarely a local infection, at the site of cannula insertion and dizziness.

Volunteer Signature : _____ Date: _____



| Volunteer Reg. No.: APL - | Subject No.: S - |
|---|---|

**6.0 Are there benefits for taking part in the study?**

This is a research oriented clinical study. You will not have any direct benefits from the study. Since you do not require treatment with any of the study drug medications, you are unlikely to be benefited by taking these medications. By participating in this study you will get a free medical check-up, plus your probable satisfaction of serving the interest of drug research. You will also be informed about your health status.

**7.0 What about confidentiality?**

Your study data will be kept confidential.

The following organizations may monitor this study/related records and data for quality assurance and data analysis:

- Concerned regulatory authority (like ANVISA- Brazil, US-FDA / UK-MHRA/ DCGI).
- Designated personnel / Investigator: QAD/CPD of APL RC.
- Members of Savior Institutional Review Board.

Accessible reports will however not disclose any information that reveals the identity of any specific volunteer.

**8.0 What is the financial compensation?**

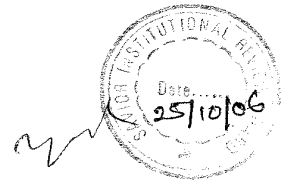
You will be compensated for your time, effort, transportation and inconveniences caused during your voluntary participation in the study. For this study, a total compensation of Rs. 3,705/- (Three thousand seven hundred and five rupees only) will be paid.

In case of premature withdrawal/drop-out from the study you will be entitled to the following compensation.

| **Reasons of withdrawal/dropout from the study** | Compensation |
|---|---|
| You are withdrawn from the study on medical decision, for your health interest or in case of any adverse events by the Clinical Investigator/attending Physician. | Full payment |
| After initiation of the study (check-in in Period –I), you dropout on your own free will and/or are absent for further phases of the study. | Proportionate participation payment. |

Volunteer Signature : _____ Date: _____





| Volunteer Reg. No.: APL - | Subject No.: S - |
|---|---|

| | |
|---|---|
| You are withdrawn from the study by the Clinical Investigator/ attending Physician at any time after check-in in Period-I due to violation of the requirements of the study and Indiscipline. | Proportionate participation payment. |

In case of any disputes pertaining to payments, you may approach the Savior-IRB and the decision of the Savior-IRB will be binding on you as well as Aurobindo Pharma Ltd., India.

**9.0 What will be the compensation for Adverse Events?**

You will be treated completely either at Clinical Unit, CPD, or Mirra Multispeciality Hospital or any other tertiary Hospital for any adverse events encountered during your stay at clinical unit, CPD with out any cost to you. In case of any serious mishap, justifiable compensation as decided by Savior-IRB or as per the insurance policy, will be paid.

**10.0 What about my nature of participation?**

Your participation in this study is voluntary. You are free to participate and refuse to volunteer for this study. Your refusal to participate or withdrawal will involve no penalty or loss of benefits to which you would otherwise be entitled and will not effect your selection for any future studies. If you decide to voluntarily withdraw from this study, the Clinical Investigator/attending Physician will promptly discuss with you the best means of orderly termination from this study. We assure you that your relations with APL-CPD or its staff will not be affected even if you prematurely withdraw from the study at your own free will with / without stating any reason.

**11.0 What are my rights as I participate?**

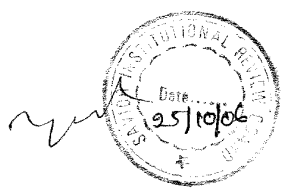
Your rights as a research volunteer and your safety will be protected by the Savior Institutional Review Board, and APL-CPD will also assure the integrity, safety, rights and confidentiality of the study volunteers. You have right to withdraw from the study at any time during your voluntary participation in the study.

**12.0 What is expected from me?**

You are requested to co-operate with the Clinical Unit, CPD staff. On arrival you and your baggage will be searched. Your personal belongings will be checked at the time of check-in during each period of the study. During your participation in this study you are expected to abide by the rules of the Clinical Unit, CPD and maintain discipline during the course of stay for the study. You will be required to follow all the study and administrative requirements of the study.

Volunteer Signature : _____ Date: _____





| Volunteer Reg. No.: APL - | Subject No.: S - |
|---|---|

**13.0 What are the circumstances under which your participation will be terminated without your consent by the investigator?**

13.1 In case of adverse events for your safety.
13.2 Non co-operative and does not follow the protocol.
13.3 If it is discovered that, you have withheld some vital information pertaining to your past medical history.
13.4 If you vomit soon after the drug administration (As decided by the clinical investigator/Physician).

**14.0 What is the additional cost that may result to you if you participate?**

You will be not required to pay any additional cost to APL–CPD for your participation. All your conveyance, boarding and lodging will be looked after by APL- CPD. In addition, compensation as per SOP No. APL-CPD-230-XX will be given.

**15.0 Whom do I call if I have a question or problem?**

During the entire study period, you are free to obtain further information on any issue or subject. In case of any urgent questions related to the study need advice, you may contact the following personnel at APL-CPD.

- Dr. A. T. Bapuji, Mobile No. :9848732447
- Dr. Nitin Kulkarni, Mobile No. :9866625222

**Address:**
Clinical Unit
APL-CPD
Mirra Multispeciality Hospital
2nd and 3rd Floor
Plot no: 33,34,35,Alluri Sitaramaraju Colony
Opp.J.P.N.Nagar Colony, Miyapur
Hyderabad-500050. Tel: 91-40-23045809 / 91-40-23045709

**If you have questions regarding your rights as human volunteer, you are free to call the Chairman of Savior-IRB:**

Justice Y.V. Narayana (Retd.)
Chairman (Savior- IRB)
Address: Flat No: 402 Pooja's Pride
Plot No: 75, Srinagar Colony
Hyderabad-500 073.
Tel: 91-40-23743173.

Volunteer Signature : _____ Date: _____



25/10/06

| Volunteer Reg. No.: APL - | Subject No.: S - |
|---|---|

## Volunteer Informed Consent Declaration Form

**Title of the Study**: An open label, randomized, two treatment, two sequence, two period, cross-over, single-dose comparative oral bioavailability study of Gabapentin 400 mg capsules (Test), manufactured by Aurobindo Pharma Ltd., India and Neurontin 400 mg capsules (Reference), marketing authorization holder Parke Davis, UK, in 36 healthy, adult, male, human subjects under fasting conditions.

**Study Number: Gap-03/06**

**Declaration**:
I hereby declare that:

1. I have read the text of the Informed Consent Document and have had enough time to thoroughly familiarize myself with it and understand the contents of it after the presentation of the study. I have had an opportunity to ask questions which have been answered to my satisfaction.
2. I understand that the study involves research.
3. I understand the nature and purpose of the study.
4. I have understood all the study related procedures.
5. My participation is voluntary.
6. I have the right to withdraw from the study at any time.
7. I understand the potential risks and benefits of the study.
8. I know that there is no direct medical benefit to me if I participate in this study except free medical checkup.
9. I have not withheld any information regarding my medical history.
10. I understand that I can be withdrawn from the study at any time without my consent to protect my health or for violating the study requirements.
11. I will comply with all administrative requirements of APL-CPD while conducting the study.
12. I will be compensated for my time, effort, transportation and inconveniences caused during my voluntary participation in the study.
13. In case of mishap, justifiable compensation as decided by Savior-IRB board will be made available to me.

Volunteer Signature : _____ Date: _____



| Volunteer Reg. No.: APL - | Subject No.: S - |
|---|---|

14. All drug and / or study related adverse events will be attended by APL-CPD at no cost to me.
15. In case of any study related questions or emergencies or my rights as a subject / volunteer, I can contact any one of the people mentioned on the previous page.
16. My signature/thumb impression confirms my consent for the participation in the study.
17. This consent is based on the information provided to me.
18. I have received a copy of signed ICF document.
19. I am willing to give additional blood samples for study specific tests if any and for repeat post study laboratory investigation(s) / post study safety assessment(s) (if any) as per the decision of Clinical Investigator / Physician.

| | |
|---|---|
| Volunteer's Name: | Impartial Witness's Name: |
| Signature/Thumb:<br><br>Date: | Impartial Witness's Address:<br><br>Signature: Date: |

**Note:** Witnessing Informed Consent document is only applicable for illiterate Volunteers.

Consent Obtained By: _____

'Signature of the Clinical Investigator /Physician : _____ Date : _____

కార్యకర్త నమోదు నెం: APL - ☐ స్వచ్ఛంద ముగా పాల్గొను వ్యక్తి నెం: S - ☐

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అనుబంధ ము - 7

## పిపేచనాపూర్వక అంగీ కార పత్రం

**అధ్యయనం పేరు:** భారతదేశంలోని అరబిందో ఫార్మా లిమిటెడ్ వారు తయారు చేసిన గాబాపెన్‌టిన్ 400 మి.గ్రా., పరీక్ష కాప్సూల్స్‌కు మరియు యుకె లోని పార్క్ డెపిస్, వారు మార్కెటింగ్ అధికార ము కలిగియున్న న్యూరాన్‌టిన్ 400 మి.గ్రా., రిఫరెన్స్ కాప్సూల్స్‌కు, పోలికతోకూడిన జీవతుల్యతాధ్యయనం. ఆరోగ్యవంతులైన, వయోజనులైన 36 మగ వ్యక్తులకు, మందు పేరు తెలిపి, యాధృచ్ఛిక ముగా, రెండు సార్లు వరుసగా, రెండు సమయాలలో ఒకదాని తరువాత ఒకటిగ ఒక మోతాదు మందును సిరాహోర పరిస్థితులలో ఇస్తారు.

కార్యకర్త పేరు: ..... ..... .....
మొదటి పేరు చివరి పేరు ఇంటి పేరు

జన్మదిన తేది: ..... (దిన ము /నెల /సంవత్సరం)

వయస్సు : ..... ..... (సిండిన సంవత్సరాలలో)

చిరునామా: .....
.....

ఫోన్ నెం: .....

ప్రియమైన కార్యకర్త,

మీమ్మల్నిపైన పేర్కొనబడిన పరిశోధనాధ్యాయములో పాల్గొనవలసినదిగా కోరుచున్నాము.

ప్రస్తుత అధ్యయన ములో పాల్గొనటానికి అంగీకారాన్నితెలిపే ముందు, మీరు ఈ పత్ర ములో ఇచ్చినటువంటి సమాచారాన్ని శ్రుణ్ణంగా చదివి మరియు అర్థం చేసుకోవట ము చాలా ముఖ్య ము. ఈ పత్ర ము గురించి మౌఖిక ముగా తెలియజేయునపుడే మీరు అన్ని వివరణలు మరియు ప్రశ్నలు చర్చించాలి. మీరు ఈ పత్ర మును సంతక ము చేసి మరియు తేది వేసి మరియు మా భద్రపరచు సమాచారనిమిత్తమై మాకు ఇవ్వవలెను. భవిష్యత్తులో మీ గుర్తు కోసం ఈ పత్ర ము యొక్క నకలు ప్రతి మీకు ఇవ్వబడుతుంది.

కార్యకర్త సంతక ము ..... తేది.....

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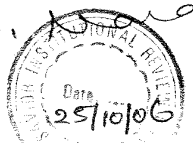


కార్యకర్త నమోదు నెం: APL - [ ]  స్వచ్ఛంద ముగా పాల్గొను వ్యక్తి నెం: S - [ ]

ఈ పత్ర ము యొక్క ముఖ్య ఉద్దేశ్య ము ఏమన గా ఈ అధ్యయన మున కు సంబంధించిన విధానాలను గురించి మీకు క్షుణ్ణంగా తెలియజేయుట కొర కు మరియు ఈ అధ్యయన మున కు సంబంధించిన అన్ని కీలకాంశ ములు తెలిసిన తర్వాతనే మీరు ఈ అధ్యయన ములోకి ప్రవేశించినారని నిశ్చయ పరుచుట కు. పిపేచనాపూర్వక అంగీకార పత్ర ము అధ్యయన ఉద్దేశ్య మును, సాధ్య మగు ప్రయోజనాలను, ప్రమాదాలను లేదా అసౌకర్యాలను, ప్రత్నామ్యాయ చికిత్స మరియు రహస్యతను గురించి వివరిస్తుంది. ఈ పత్ర ము మీరు అధ్యయన ములో స్వచ్ఛంద ముగా పాల్గొను మీ ధ్రువీకరణను తెలుపుతుంది.

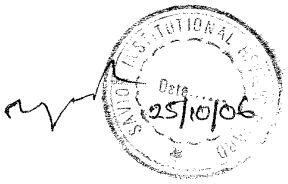
పిపేచనాపూర్వక అంగీకారం అనునది ఒక ఒప్పంద ము/ఒడంబడిక కాదు మరియు మీరు ఏ సమయ ములోనైనా అధ్యయన ములో పాల్గొనకుండా మీ ఇష్ట ప్రకార ము వైదొలగవచ్చును.

కార్యకర్త సంతకము: ..... తేది.....

క్లినికల్ పరిశోధకుని / వైద్యుని సంతకం..... తేది.....

కార్యకర్త సంతకము ..... తేది.....





కార్యకర్త నమోదు నెం: APL - [ ] స్వచ్ఛందముగా పాల్గొను వ్యక్తి నెం: S - [ ]

1. పరిచయం:

గాబాపెన్‌టిన్ అను ఈ మందు యాంటికన్‌వల్సంట్స్ అను తరగతికి చెందినది. గాబాపెన్‌టిన్ అను ఈ మందు శరీరములో ఫిట్స్, మూర్ఛలు ను పుట్టించు కొన్ని రసాయనాలను మరియు నాడుల మీద పని చేయును. ఈ మందును తీవ్ర మూర్ఛ లలో మరియు సలుపు/నొప్పి పేడి మంట వాపు తో కూడిన బొబ్బలు (హెర్పస్ జోస్టర్) ను చికిత్స చేయుటలో వాడుదురు. దీనిని హెర్పస్ జోస్టర్ తర్వాత వచ్చు నరాల నొప్పిని (మజ్జాతంతు వేదన) / ఒకటి లేక పెక్కునాడుల వేదన తగ్గించుటలో కూడ వాడుదురు.

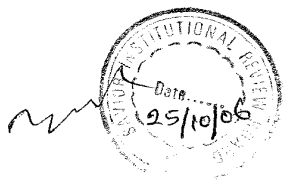
2. ఈ అధ్యయన ము యొక్క స్వభావ ము ఏమిటి?

ఈ అధ్యయనము పరిశోధనతో కూడినది. రెండు వేర్వేరు ఫార్ములేషన్స్ (ఒకే మందు యొక్క రెండు వేర్వేరు రూపాంతరములు) యొక్క శోషణ ప్రక్రియ ఒక నిర్ణీత సమయములో ఎంత పరిమాణములో జరుగునో పోల్చుటకొరకు జీవతుల్యతాధ్యయనములను చేయుదురు. ఈ అధ్యయనములో, మేము భారతదేశములోని అరబిందో ఫార్మా లిమిటెడ్ వారిచే తయారుచేయబడిన గాబాపెన్‌టిన్ 400 మి.గ్రా., కాప్సూల్స్‌కు ఇప్పటికే తయరుచేయబడి & నియంత్రిత/ చట్టపరమైన మార్కెట్ (యుకె)లో న్యూరాన్‌టిన్ అనే బ్రాండ్ పేరుతో లభ్యమగుచున్న గాబాపెన్‌టిన్ 400 మి.గ్రా., కాప్సూల్స్‌తో 36 మంది ఆరోగ్యవంతులైన, వయోజనులైన, మగ వ్యక్తులకు నిరాహార పరిస్థితులలో పోల్చుచున్నాము. ఈ అధ్యయనములో స్వచ్ఛందముగా పాల్గొను 36 మంది ఆరోగ్యవంతులైన, వయోజనులైన, మగ వ్యక్తులలో మీరు కూడ ఒకరు.

3. ఈ పరిశోధన ఉద్దేశ్యమేమిటి?

గాబాపెన్‌టిన్ మందును మూర్ఛ వ్యాధులలో / ఫిట్స్‌ను చికిత్స చేయుటలో వాడుదురు మరియు ఈ మందును పిపిధ చట్టపరమైన/ నియంత్రిత మార్కెట్ల (దేశముల)లో పిపిధ బ్రాండ్ పేరులతో అమ్ముచున్నారు. అరబిందో ఫార్మా లిమిటెడ్, భారతదేశము, కూడా గాబాపెన్‌టిన్ కాప్సూల్స్‌ను నియంత్రిత మార్కెట్ (యుకె) లో ప్రవేశపెట్టుటకు (అమ్ముట కొరకు) తయారుచేసినది. ఇలా చేయుట కొరకు అరబిందో ఫార్మా లిమిటెడ్, భారతదేశము, ఒక పరిశోధనాత్మక అధ్యయనమును మానవుల్లో చేయుటకు రూపకల్పన చేసినది. ఈ అధ్యయనములో అరబిందో ఫార్మా లిమిటెడ్, భారతదేశము, తయారుచేసిన గాబాపెన్‌టిన్ కాప్సూల్స్‌ను లేదా పార్క్ డెపిస్, యుకె వారు తయారు చేసిన రిఫరెన్స్ కాప్సూల్స్‌ను ఒకే మానవునికి వేరువేరు కాలంలో నిరాహార పరిస్థితులలో ఇచ్చిన యెడల వాటి పరిమాణము రక్తములో సమానమేమో చూస్తారు.





4. అధ్యయనం గూర్చి వివరము:

4.1 ఈ అధ్యయనంలో పాల్గొనటానికి నిర్దేశిత ప్రమాణములు:

క్రింద సూచించిన ప్రమాణాలన్నిటిని మీరు సంతృప్తిపరచగలిగినట్లైతేనే మీరు ఈ అధ్యయనములో పాల్గొనుటకు అర్హులు.

4.1.1 మీరు 18 నుంచి 50 ఏళ్ళ మధ్య వయస్సు గల మగ వారై ఉండాలి.

4.1.2 మీ శరీర బరువు సూచిక 19-26 కె.జి/ మీ$^2$ మధ్యలోనే ఉండవలెను.

4.1.3 ఈ అధ్యయనంలో పాల్గొనాలంటే మీరు లిఖిత పూర్వక అంగీకారాన్ని తెలపటానికి సంసిద్ధంగా ఉండాలి.

4.1.4 మీకు హెచ్.ఐ.వి, హెపటైటిస్ బైరస్ మరియు సిఫిలిస్ వ్యాధులుండరాదు.

4.1.5 మీకు పరీక్ష (స్క్రీనింగ్) చేసినపుడు లాబొరేటరీ పరీక్షలయందు, మీ వైద్య చరిత్రలోగాని లేదా శారీరక పరీక్షల్లోగాని వైద్యపరమైన పేర్కొనదగిన అసాధారణ పరిణామములు లేదా వ్యాధులున్నట్లు ఫలితాలు రాకూడదు.

4.1.6 మీకు 12 లీడ్ ఇ.సి.జి సాధారణంగానే ఉండాలి.

4.1.7 మీకు ఛాతీ ఎక్స్ రే (పి ఏ దృశ్యము) సాధారణంగానే ఉండాలి.

4.1.8 మీరు ప్రోటోకాల్‌లో పేర్కొన్న అవసరాలకు అనుగుణంగా (లక్షణాలన్నీ) ఉండాలి.

4.1.9 గాబాపెన్‌టిన్ కాప్సూల్స్ కు అతి సున్నితంగా స్పందించే గుణం మీకు ఉండరాదు.

4.1.10 మీకు శరీర అంతర భాగాలకు సంబంధించి పేర్కొనదగిన వ్యాధుల చరిత్ర ఉండరాదు.

4.1.11 మీరు మానసిక రుగ్మతల చరిత్ర లేని వారై ఉండాలి.

4.1.12 మీరు ఉత్తేజితం చేసే మత్తు మందులకు, మాదక ద్రవ్యాలకు అలవాటుపడిన లేదా ఆధారపడిన చరిత్ర లేని వారై ఉండాలి.

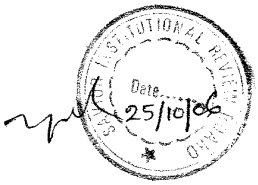
4.1.13 ఈ అధ్యయనంలో మొదటి మోతాదు మందును తీసుకొనే 56 రోజుల లోపు మీరు రక్తదానం (ఒక యూనిట్ లేదా 350 మి.లీ.) చేయని వారై ఉండాలి.

4.1.14 మీరు గత 56 రోజులు లోపు ఏ క్లినికల్ అధ్యయనములోను పాల్గొనని వారై ఉండాలి.

4.1.15 అధ్యయనంలో మొదటి మోతాదు మందును తీసికొనే రెండు వారాలలోపు మీరు డాక్టరు రాసిన ఏ మందూ లేదా డాక్టరు రాసివ్వని మందులను [ఉదాహరణకు: జలుబు మరియు కడుపు నందు మంటను తగ్గించేందుకు ఉపయోగించే పి, పిటమినులు మరియు అయుర్వేదిక్ మందులు (జబ్బును తగ్గించేందుకు వాడబడునపి)] వాడని వారై ఉండాలి.

కార్యకర్త సంతకము ..... తేది.....





4.1.16 అధ్యయనానికి 24 గంటల ముందు అతిసార వ్యాధి, వాంతులు లేదా ఏ ఇతర కారణ ము చేత కాని మీరు నిర్జలీకరణకు గురై ఉండరాదు.

4.1.17 మీరు నరాల సంబంధిత అపవ్యవస్థ కలిగిన కుటుంబ చరిత్ర లేనివారై ఉండాలి.

4.1.18 మీరు మందు మోతాదు తీసుకునే (చెక్-ఇన్) సమయమునకు 48 గంటల ముందు నుంచి మద్యం, సిగరెట్లు, పొగాకుతో తయరుచేసిన ఉత్పత్తులు మరియు గ్జాంతీన్ కలిగిన ఏ ఆహార ము మరియు పానీయాలను (చాక్లెట్లు, టీ, కాఫీ లేదా కోలా పానీయములు) స్వీకరించని వారై ఉండాలి.

4.1.19 మీరు అధ్యయన ములోని పీరియడ్-1 మరియు పీరియడ్-2లోని చెక్-ఇన్ సమయములయందు మూత్ర ములో అబ్యూజ్ డ్రగ్స్ (బర్బిట్యురేట్స్, బెంజొడియజెపిన్స్, ఒపియొఇడ్స్, అంఫెటమైన్స్, కొకైన్స్ మరియు కన్నబినొఇడ్స్) కనుగొనుటకు నిర్వహించు నిర్ధారణ పరీక్షలయందు ప్రతికూల పలితాలు వచ్చిన వారై ఉండాలి.

4.1.20 మీరు అధ్యయన ములోని పీరియడ్-1 మరియు పీరియడ్-2 లోని చెక్-ఇన్ సమయమునకు ముందుగా 48 గంటల లోపు ద్రాక్ష రసం (మూసంబి/ తీయని నిమ్మరసం) త్రాగని వారై ఉండాలి.

**4.2 ఈ అధ్యయనంలో మీరు పాల్గొనటానికి వీలుకాని ప్రమాణ ములు:**
క్రింద సూచించిన ప్రమాణ ములలో ఏ ఒక్క ప్రమాణమునైనను సంతృప్తిపరిచినా మీరు ఈ అధ్యయన ములో పాల్గొనుటకు అనర్హులు.

4.2.1 మీరు ఫిట్స్/మూర్ఛ రోగ చరిత్ర కలిగిన వారైతే అనర్హులు.

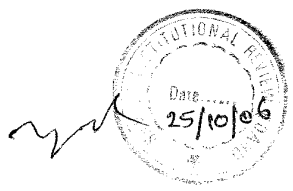
4.2.2 మీరు రోజుకు రెండు యూనిట్ల కన్నా ఎక్కువ మద్యమును తీసుకొను చరిత్ర కలిగినా (1 యూనిట్ మద్యం= 30 మి. లీ. స్పిరిట్ లేదా 1 పింట్ బీర్) లేదా అధ్యయన ప్రారంభ ము (చెక్-ఇన్)నకు 48 గంటలలోపు మద్యం తీసుకున్నవారైనా అనర్హులు.

4.2.3 మీరు రోజుకు అయిదు కప్పులకు మించి కాఫీ లేదా టీ త్రాగినా లేదా రోజుకు తొమ్మిదికి మించి పొగాకు ఉత్పత్తులను (సిగరెట్లు/ బీడీలు/ చుట్టలు) త్రాగినా అనర్హులు.

4.2.4 మీరు రక్తదానం చేయుటలో అసౌకర్యానికి గురియగు చరిత్ర కలిగినవారైనా లేదా మీకు ఎడమ లేదా కుడి చేతులలో రక్తనాళ ములు దొరుకుటలో ఇబ్బందులు కలిగినా అనర్హులు.

4.2.5 మీరు ఏ కారణం చేతనైనా, అలవాటులేని లేదా అసాధారణమైన ఆహారం తీసుకున్నా అనర్హులు.
ఉదా: మతపరమైన కారణాల వలన మీరు ఉపవాసం ఉన్నచో





4.3 అధ్యయనం నిర్వహించే విధానం:

4.3.1 మీరు వివిధ ప్రాథమిక పరీక్షలు అంటే డాక్టరుచే పరీక్ష, రక్తపరీక్షలు, మూత్రపరీక్షలు, అంటువ్యాధులకు సంబంధించిన పరీక్షలు [హెచ్ఐవి 1&2, హెపటైటిస్ B&C మరియు సిఫిలిస్], ఛాతి ఎక్స్‌రే (పిఎ దృశ్యము) మరియు 12 లీడ్ ఇ.సి.జి స్క్రీనింగ్ సమయంలో చేయించుకొనుట కొరకు ప్రాథమిక పరీక్షల కొరకు 8 మి.లీ. రక్తము మరియు మూత్ర పరీక్షల కొరకు సుమారు 20-25 మి.లీ. మూత్రం ఇచ్చియున్నారు.

4.3.2 మీరు లాబొరేటరి పరీక్షలు, వైద్య పరీక్ష మరియు ఈ అధ్యయనం ప్రోటోకాల్‌లోని అన్ని ఆవశ్యకతలకు అనుగుణంగా సంతృప్తికరంగా ఉంటేనే మీరు అధ్యయనంలో పాల్గొనడానికి అర్హులగుదురు.

4.3.3 అధ్యయనం రెండుసార్లు జరుగుతుంది. మీరు ప్రతి పీరియడ్‌లో మందు మోతాదు తీసుకుంటానికి 10 గంటల 30 నిమిషముల ముందుగా అంటే మందు మోతాదు తీసుకొనే ముందురోజు సాయంత్రం ఎపిఎల్ - సిపిడి కేంద్రానికి రావలసి ఉంటుంది.

4.3.4 మీకు అధ్యయనం కొరకు ప్రతిపీరియడ్‌లోని (పీరియడ్-1 & పీరియడ్-2) చెక్ - ఇన్ సమయములో, మూత్రములో కొన్ని రకాల అబ్యూజ్ డ్రగ్సును (బర్బిట్యురేట్స్, బెంజొడియజెపిన్స్, ఒపియొఇడ్స్, అంఫెటమైన్స్, కొకైన్స్ మరియు కన్నబినొఇడ్స్) కనుగొనుటకు మూత్ర పరీక్షలు నిర్వహించెదరు. మీరు అబ్యూజ్డ్ డ్రగ్స్ పరీక్షల కొరకు సుమారు 20-25 మి.లీ. మూత్రం ఇవ్వవలసి ఉంటుంది.

4.3.5 అధ్యయనంలో పాల్గొనటానికి కావలసిన అర్హతలలో భాగముగా, ప్రాణావశ్యకమైన పరీక్షలు కలిపి ప్రతీ పీరియడ్ నందు చెక్-ఇన్ అప్పుడు చేయుదురు.

4.3.6 ఈ అధ్యయనంలో మీతో కలిపి ముప్పై ఆరు (36) మంది స్వచ్ఛందముగా పాల్గొను వ్యక్తులు పాల్గొంటారు.

4.3.7 మీరు మొదటిసారి (పీరియడ్ 1) మరియు రెండోసారి (పీరియడ్ 2) కూడా క్లినికల్ యూనిట్, సిపిడి, ఏపిఎల్ పరిశోధన కేంద్రము, మిర్యాలగూడా స్పెషాలిటీ హాస్పిటల్, ప్లాట్ నెం.33-35, అల్లూరి సీతారామరాజు కాలనీ, జె.పి.ఎన్.నగర్ కాలనీ ఎదురుగా, మియాపూర్, హైదరాబాద్-500050 లో ఉండవలసి ఉంటుంది.

4.3.8 మీరు మొదటిసారి రిఫరెన్స్ R (న్యూరాన్‌టిన్ 400 మి.గ్రా., కాప్సూల్, యుకె లోని పార్క్ డెపిస్, వారు మార్కెటింగ్ అధికారము కలిగియున్నది) లేదా టెస్ట్ T (గాబాపెన్‌టిన్ 400 మి.గ్రా., కాప్సూల్, అరబిందోఫార్మా లిమిటెడ్, ఇండియా, వారు తయారు చేసినది)గాని తీసుకుంటారు. అధ్యయనంలో మందును ఇచ్చే క్రమాన్ని యాధృచ్ఛికముగా నిర్ణయిస్తారు.

కార్యకర్త సంతకము ..... తేది.....



4.3.9 మొదటి మోతాదు తీసుకున్న తరువాత కనీసము 07 రోజులు పూర్తయిన పిమ్మట రెండో మోతాదు ఇవ్వటం జరుగుతుంది.

4.3.10 పీరియడ్ 2 లో మీకు ప్రత్నామ్యాయ మందు ఇవ్వబడుతుంది (ఒకవేళ మీరు పీరియడ్ 1లో రిఫరెన్స్ Rను తీసుకుంటే, మీరు టెస్ట్ Tని పీరియడ్ 2 లో తీసుకుంటారు మరియు ఆ విధముగా రెండవసారి అంతకు ముందు తీసుకోని మందును ఇవ్వటము జరుగుతుంది).

4.3.11 మీరు ప్రతి పీరియడ్ లోను సుమారు పది గంటలపాటు నిరాహారంగా ఉన్న తరువాత రిఫరెన్స్ (R) లేదా టెస్ట్ (T) మందును 240 మి.లీ. నీటితో నోటిద్వారా తీసుకోవాలి.

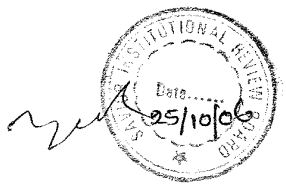
4.3.12 మీరు ప్రతి పీరియడ్ లోను మాత్ర వేసుకున్నాక 4 గంటలపాటు నిరాహారముగా ఉండవలెను.

4.3.13 మీకు కూర్చొన్న స్థితిలో ఉన్నపుడు మందు ఇవ్వబడును మరియు మీరు మందును తీసుకున్న 2 గంటలలో ఆలాగే కూర్చోని ఉండవలెను లేదా మందును తీసుకున్న 2 గంటలలో నడవవచ్చును. అప్పటినుంచి, మీకు అధిక శారీరక శ్రమ లేని సాధారణ కార్యక్రమములలో/పనులలో పాల్గొనుటకు అనుమతివ్వబడును.

4.3.14 మాత్రను వేసుకున్న తరువాత ఆహార నిపుణుడు సూచించిన విధముగా మొదటిరోజు (మాత్రను తీసుకున్న రోజు) సుమారు 2400 కి.కేలరీలు ఆహారాన్ని క్రింద చెప్పబడిన విధంగా ఇస్తారు. మాత్రను వేసుకున్న 04 గంటల 30 నిమిషములకు (మధ్యాహ్నభోజనము -సుమారు 1000 కి.కేలరీలు) మరియు 08గంటల 15 నిమిషములకు (స్నాక్స్ - సుమారు 400కి.కేలరీలు)మరియు 13గంటలకు (డిన్నర్ - సుమారు 1000కి.కేలరీలు) ఇవ్వబడుతుంది. మాత్ర వేసుకొన్న రెండవ రోజు సుమారు 2800 కి.కేలరీల ఆహారాన్ని క్రింద చెప్పబడిన విధంగా ఇస్తారు. మాత్ర వేసుకున్న 24 గంటల 30 నిమిషాలకు (బ్రేక్ ఫాస్ట్ - సుమారు 400 కి.కేలరీలు), 28 గంటల 30 నిమిషాలకు (మధ్యాహ్నభోజనము -సుమారు 1000 కి.కేలరీలు), 32 గంటల 30 నిమిషాలకు (స్నాక్స్ - సుమారు 400 కి.కేలరీలు) మరియు 37 గంటలకు (డిన్నర్- సుమారు 1000కి.కేలరీలు) ఇవ్వబడుతుంది. మాత్రను తీసుకునే ముందురోజు రాత్రి డిన్నర్ (సుమారు 1000 కి.కేలరీలు) ఇవ్వబడుతుంది.

4.3.15 చెక్-ఇన్ సమయమందు ప్రాణావశ్యకమైన పరీక్షలు కూర్చున్న స్థితిలో ఉన్నప్పుడు (శ్వాసక్రియ సంబంధిత పరీక్షలు మాత్రము పెల్లికల/పెన్ను మీద పడుకున్నప్పుడు చేయుదురు) మందు ఇచ్చే ముందర మరియు మందు ఇచ్చిన తరువాత వరుసగా 1.0, 3.0, 12.0, 24.0, 36.0 మరియు 48.0 గంటలప్పుడు చేయుదురు.





4.3.16 మందు యొక్క పరిణామములు (స్వచ్ఛంద ముగా పాల్గొను వ్యక్తి యొక్క క్షేమము తెలుసుకొనుటకై ఉపయోగించు ప్రశ్నా పత్రము), మందు ఇచ్చిన తరువాత వరుసగా 2.0, 5.0 మరియు 8.0 గంటలప్పుడు తెలుసుకొంటారు.

4.3.17 భోజన సమయం, పరీక్ష సమయం (అంటే ప్రాణావశ్యకమైన పరీక్షలు), స్వచ్ఛంద ముగా పాల్గొను వ్యక్తి యొక్క క్షేమము ఉద్దేశించి అడిగే ప్రశ్నలు మరియు రక్తనమూనా తీసుకొనే సమయము ఒకేసారి అయితే మొదట రక్తనమూనా తీసుకుంటారు. తరువాత ప్రాణావశ్యకమైన పరీక్షలు, సబ్జక్ట్ యొక్క క్షేమము ఉద్దేశించి అడిగే ప్రశ్నలు మరియు భోజన ప్రక్రియలు చెప్పబడిన క్రమములో ఒకదాని తరువాత మరొకటి ఉంటాయి.

4.3.18 ప్రతి పీరియడ్ లోను రక్తనమూనాలను సేకరిస్తారు. రక్తనమూనాలను ముంజేతి రక్తనాళము నుంచి చిన్న ప్లాస్టిక్ ట్యూబు ద్వారా స్వీకరిస్తారు. మందు వేసే ముందు కూడా రక్తనమూనా సేకరిస్తారు.

4.3.19 రక్త సేకరణ ప్రక్రియ సులభతరము చేయుటకు మరియు రక్తం గడ్డ కట్టకుండా నివారించడానికి 1.0 మి.లీ. (5 IU/mL) హెపారిన్ (ఇది మానవ శరీరంలో సామాన్యంగా ఉంటుంది)ను ఉప్పు నీటి ద్రావణంలో ముంజేతికి ఉన్న చిన్న ప్లాస్టిక్ ట్యూబు ద్వారా ఇంజెక్ట్ చేసి మందును వేసుకొన్న 12.0 గంటల వరకు అలాగే ఉంచడం జరుగుతుంది.

4.3.20 మందును వేసుకొనక ముందు (0.0) మరియు మందును వేసుకున్న తరువాత వరుసగా 0.33 (20 నిమిషములు), 0.67 (40 నిమిషములు), 1.0 (1 గంట), 1.33 (1 గంట 20 నిమిషములు), 1.67 (1 గంట 40 నిమిషములు), 2.0 (2 గంటలు), 2.25 (2 గంటల 15 నిమిషములు), 2.5 (2 గంటల 30 నిమిషములు), 2.75 (2 గంటల 45 నిమిషములు), 3.0(3 గంటలు), 3.25(3 గంటల 15 నిమిషములు), 3.5 (3 గంటల 30 నిమిషములు), 3.75 (3 గంటల 45 నిమిషములు), 4.0, 4.5, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0 మరియు 48.0 గంటలకు రక్తనమూనాలు తీసుకుంటారు.

4.3.21 రక్తనమూనా సేకరించు ప్రతిసారి 6 మి.లీ. రక్తం తీసుకుంటారు.

4.3.22 ప్లాస్టిక్ ట్యూబులో రక్తం గడ్డకట్టినచో క్లినికల్ పరిశోధకులు లేదా డాక్టరు సూచిస్తే మరో రక్తనాళము నుంచి కూడా డిస్పోజబుల్ స్టెరిలైజ్డ్ సూది మరియు వాక్యుటైనర్ ఉపయోగించి రక్తనమూనా సేకరిస్తారు.

4.3.23 మొత్తం మీద రెండు పీరియడ్‌లు కలిపి 50 (25x2) రక్తనమూనాలు తీస్తారు. స్క్రీనింగ్ లో తీసిన 8 మి.లీ. నమూనా, మందు వదిలిపేసిన 42 మి.లీ., రక్తం (ప్రతిసారి 1 మి. లీ.) మరియు అధ్యయనంలో రెండు పీరియడ్‌లోనూ తీసిన 300 మి.లీ. మరియు పీరియడ్ 2 అధ్యయనం అనంతరం ల్యాబ్ పరీక్షలకు 8 మి.లీ. కలిపి నమూనాగా సేకరించిన రక్తం మొత్తం 358 మి.లీ. మించదు.

4.3.24 మందు మరియు/లేదా అధ్యయనమునకు సంబంధించి వచ్చే అన్ని అవాంచనీయ పరిణామములకు క్లినికల్ యూనిట్, సిపిడి లోని డాక్టరు కాని లేదా మిర్రా మల్టి స్పెషాలిటి ఆసుపత్రిలో కాని లేదా దగ్గరలో ఉన్న తగిన ఆసుపత్రిలో కాని చికిత్స చేయడం జరుగుతుంది. దీని కోసం మీరు ఖర్చు పెట్టనవసరం లేదు.

4.3.25 మీరు ఆరోగ్యంగా, ప్రతికూల పరిస్థితులకు లోనుకాకుండా ఉన్నట్లయితే అధ్యయనం పూర్తయిన తరువాత (మందు ఇచ్చిన 48.0 గంటల తరువాత) ఇంటికి పంపివేస్తారు. ఒకవేళ ప్రతికూల పరిస్థితులు ఉంటే, మీకు తగిన వైద్య చికిత్స చేసి, కోలుకునే వరకూ అబ్జర్వేషన్ లో ఉంచడం జరుగుతుంది.

4.3.26 మీరు ప్రతిపీరియడ్‌లోను క్లినికల్ యూనిట్, సిపిడికేంద్రంలో సుమారు 65.0 గంటలపాటు ఉండవలసి ఉంటుంది.

4.3.27 మీరు అధ్యయనములో పాల్గొనుటకై తీసుకొను నిర్ణయమును ప్రభావితం చేయు సమాచారమైనా, అధ్యయమునకు సంబంధించి ఏ నూతన సమాచారమైనను మీకు తెలుపగలము.

4.3.28 పీరియడ్ 2 లో చివరి రక్తనమూనా తీసుకొన్న తరువాత, 8 మి.లీ. రక్తం, రక్తపరీక్ష { హెమటలాజి(ఒకవేళ అధ్యయనం అనంతరం, పరీక్షలో పాల్గొన్న వ్యక్తికి ఇసినోఫిల్ పరీక్ష లో 6% కన్నా ఎక్కువగా ఉన్నచో సంపూర్ణ ఇసినోఫిల్ పరీక్ష ను చేయుదురు), ఆర్.ఎఫ్.టి మరియు ఎల్.ఎఫ్.టి} కొరకు ఇవ్వవలసి యుండును మరియు 12 లీడ్ ఇ.సి.జి పరీక్షలు పీరియడ్ 2 చివరిలో చేయుదురు.

4.3.29 మీరు ఏ కారణం చేతనైనగాని పీరియడ్ 1 లో మందు ను వేసుకున్న తర్వాత నుంచి అధ్యయనం పూర్తి అవ్వటానికి ముందుగా, అధ్యయనం నుంచి తీసివేయబడినచో లేదా తొలగినచో మీకు సెక్షన్ 4.3.28 లో చెప్పబడిన పరీక్షలు ఉంటాయి.

**4.4. అధ్యయమునకు సంభందించిన నిబంధనలు ఏమిటి?**

4.4.1 మీరు అధ్యయన సమయానికి కనీసము 48 గంటల ముందు నుండి మరియు అధ్యయనము పూర్తయ్యే వరకు ధూమపానము చేయకూడదు.



Date 25/10/06

4.4.2 మీరు ప్రత్యేకించి మొదటి అధ్యయన మందును తీసుకునే రెండు వారాల ముందు ఏ పిధమైన మందులను (వైద్యుడు సూచించిన/వ్రాసిన మందులు గాని లేదా వైద్యుడు సూచించని/వ్రాయని మందులనుగాని) తీసుకోని ఉండకూడదు. అధ్యయన ములో స్వచ్ఛంద ముగా పాల్గొను వ్యక్తి అధ్యయన ము పూర్తయ్యే వరకు ఈ నిబంధనకు లోబడి ఉండాలి.

4.4.3 మీరు కనీసము అధ్యయన సమయము (చెక్-ఇన్)నకు 48 గంటల ముందుగా, ప్రతి పీరియడ్‌లోను మరియు క్లినిక్‌లో ఉన్న సమయమందు మద్యపానము మరియు గ్జాంతిన్ కలిగిన ఆహార ము మరియు పానీయములు (చాక్లెట్లు, టీ, కాఫీ లేదా కోలా పానీయములు), సిగరెట్లు మరియు పొగాకు ఉత్పత్తులు తీసుకోకుండా ఉండవలెను.

4.4.4 మీరు ప్రతి పీరియడ్ లోని చెక్-ఇన్ సమయమునకు ముందు 48 గంటల ముందుగా ద్రాక్ష రసము (మూసంబి/తీయని నిమ్మ రసము) తీసుకోని ఉండరాదు.

4.4.5 మీరు మందును తీసుకునే ముందు రాత్రి (కనీసము 10 గంటలు) మరియు మందు తీసుకున్న అనంతర ము కనీసము 4 గంటల వరకు నిరాహార ముగా ఉండవలెను.

4.4.6 మందు తీసుకోవటానికి 1 గంట ముందు మరియు మందు తీసుకున్న తరువాత 1 గంట వరకు త్రాగు నీరు తీసుకొనుటకు అనుమతివ్వబడదు.

4.4.7 మీకు కూర్చొన్న స్థితిలో ఉన్నపుడు మందు ఇవ్వబడును మరియు మీరు మందును తీసుకున్న 2 గంటలలో ఆలాగే కూర్చోని ఉండవలెను లేదా మందును తీసుకున్న 2 గంటలలో నడవవచ్చును. అప్పటినుంచి, మీకు అధిక శారీరక శ్రమ లేని సాధారణ కార్యక్రమములలో/పనులలో పాల్గొనుటకు అనుమతివ్వబడును.

**4.5 పరిపాలనా సంభంధిత ఆవశ్యకతలు ఏమిటి?**

4.5.1 దయచేసి సిబ్బంది పివరించిన అధ్యయన పద్ధతులను పాటించండి.

4.5.2 దయచేసి ఎల్లప్పుడూ మీకు ఇవ్వబడిన గుర్తింపు కార్డులను ధరించండి.

4.5.3 దయచేసి నిద్ర సమయాలకనుగుణ ముగా నిద్రకు ఉపక్రమించండి.

4.5.4 దయచేసి మందు మోతాదు తీసుకొనుటలో పివరించబడిన పద్ధతులను పాటించండి.

4.5.5 దయచేసి మందు మోతాదు తీసుకున్న తర్వాత 2 గంటల వరకు కూర్చున్న స్థితిలో లేదా నడుస్తూ ఉండండి.

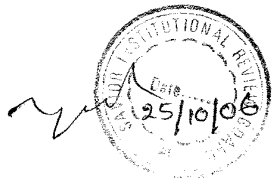
4.5.6 దయచేసి ప్రణాళిక (నిర్ణయించబడిన) సమయానికి రక్తసేకరణ గది వద్ద అందుబాటులో ఉండండి.

4.5.7 దయచేసి రక్తనమూనా సేకరణ సమయమందు ఫ్లీబోటామిస్ట్‌లతో సహకరించండి.

4.5.8 దయచేసి మీకు చెప్పబడిన ప్రణాళికా సమయములకు అంబులేటరి పిజిట్స్‌కు రండి.

కార్యకర్త సంతకము ..... తేది.....





4.5.9 ఏ పిదమైన అసౌకర్యము కలిగినా వెంటనే సిబ్బంది (నర్స్/కన్సోడియన్/వైద్యులు)కి ఫిర్యాదు చేయండి.

4.5.10 దయచేసి క్లినిక్‌లో ఉన్న సమయమందు స్థిర పరిమాణములో మీకు ఇవ్వబడిన ప్రమాణీకరించిన ఆహార మును పూర్తిగా తినవలెను మరియు ఇతరులతో మీ ఆహార మును పంచుకొనకూడదు.

4.5.11 మీరు మరుగుదొడ్డిని ఉపయోగించునపుడు, ఏ అత్యవసర పరిస్థితులలోనయినా పిలుపు గంటను మోగించండి.

## 5. అధ్యయనంలో ప్రమాదాలే మిటి?

గాబాపెన్‌టిన్ కాప్యూల్స్ భారతదేశంలోను మరియు ఇతర దేశములలో గత కొన్నేళ్ళుగా మార్కెట్‌లో లభ్యమగుచున్నది. సాధారణముగా ఈ మందు బాగుగా సహింపబడును. ఏది ఏమైనా, ఈ మందు వలన కొద్ది మంది మనుష్యులలో అనవసర పలితాలు సంభవించును. ఈ పలితాలు దీర్ఘకాలికముగా వాడుట చేత సంభవించునని పేర్కొనబడినవి.

ఒక పరీక్ష కాప్యూల్‌ను లేదా సంబంధిత రిఫరెన్స్ కాప్యూల్‌ను ఆరోగ్యవంతమైన మానవునికి ఇచ్చినచో ఏమి తీవ్రమైన పలితాలు ఉండవని మేము ముందుగా ఊహించుచున్నాము. ఇది మా ఊహింపు మాత్రమే, అయితే అంతగా తీవ్రము కాని ఇతర పలితాలు కలుగవచ్చు.

తల తిరుగుచున్నట్లు అనిపించడం, నిద్ర వచ్చినట్లుగా ఉండుట/నిద్రా వస్థ/ నిద్ర మత్తు, అతిసార వ్యాధి/ విరోచనములు / బేదులు, నోరు పొడిగా ఉండుట, పరధీయ ఒళ్ళు వాపు, బరువు పెరుగుట, అసాధారణమైన నడక రీతి, జ్ఞాపకశక్తి తగ్గుట,మతి మరుపు, కండరాల చర్యలలో అస్థిరత, అసాధారణమైన ఆలోచన, దద్దుర్లు, దృష్టిలో మాంద్యము, యాదృచ్ఛికంగా శారీరకవోసి కలుగుట, శక్తిని కోల్పోవుట / బలహీనముగా ఉండుట / నీరసముగా ఉండుట, వెన్ను నొప్పి, మలబద్ధకం, కడుపు ఉబ్బరము, వాంతి భ్రమ, తిక మక పడటం, ఎక్కువ చురుకుదనము, సూక్ష్మ గ్రాహ్యత ఎక్కువ స్థాయిలో ఉండుట, తల లేదా ఒళ్ళు తిరిగుట, పరిసరము తను చుట్టూ తిరుగుతున్నట్లు ఉండుట లేదా పరిసరములో తను గుండ్రంగా తిరుగుతున్నట్లు ఉండుట, శ్వాస పీల్చడంలో ఇబ్బందులు, గొంతులో వాపుదల లేదా కందుట, అలసట/బడలిక, అసంకల్పితంగా, వేగంగా ఒక రీతిలో కంటి గ్రుడ్డు కదులుట, వణుకు, ఒకేవస్తువురెండుగా కనపడుట, అసాధారణమైన దృష్టి, ఉచ్చారణ యందు కష్టము, శక్తిని కోల్పోవుట / బలహీనముగా ఉండుట / నీరసముగా ఉండుట, చక్కిలిగిలి పెట్టినట్లు (సూదులతో పొడిచినట్లు ఉండుట), కీళ్ళ నొప్పులు, చర్మం మీద రక్తం గూడు కట్టిన మచ్చలు, అజీర్ణము, వ్యాకులత/ఆత్రుత, బరువు పెరుగుట, మూత్ర వ్యవస్థ, మూత్ర పిసర్జనకు సంబందించిన వ్యాధులు, గొంతులో వాపుదల లేదా కందుట, రక్తములో తెల్ల రక్త కణాలు సంఖ్య తక్కువుగా ఉండుట, కంగారు పడటం / ఆందోళన వ్యక్త పరచు ప్రవర్తన, సంభోగ దుర్బలత్వము / బలహీనత, పాంక్రియాస్ లో వాపుదల/ క్లోమములో నొప్పి, కాలేయ పిధి పరీక్షలు విపరీతమగుట, మందులు వాడిన తర్వాత కల్గు పర్యవసానము / చర్మము మరియు శ్లేష్మపొరల మీద చీరుకొని పోయి వ్రణములు, అలర్జి ప్రతి చర్యలవలన వచ్చు ఒక తీవ్ర తరమైన దద్దుర్లు (ఈ అలర్జి

చర్యలు అర చేతుల మీద మరియు కాళ్ల పాదాల మీద వచ్చును), తిక మక పడటం, సిరుత్సాహపడుట / మానసికంగా క్రుంగి పోవుట, కలవరపడుట, ఉద్వేగ ము, విభ్రమ ము(ముఖ్యముగా కొన్ని మానసిక పరిణామములో ప్రేరేపణ లేకుండానే 'ంద్రియజ్ఞాన ము కలుగుట), రక్తములో చక్కెర శాతము ఎక్కువుగా ఉండుట, కండరాల నొప్పి, తల నొప్పి, వాంతి భ్రమ, వాంతి.

**మార్కెటింగ్ తర్వాత వచ్చిన ఇతర పరిణామాలు:** మూత్రపిండాలు సరిగా పనిచేయక పోవడం, చర్మములోని దద్దుర్లు, జుట్టు ఊడిపోవుట, రొమ్ము నొప్పి, కాలేయము వాపు, పచ్చ కామెర్లు, చలన ము లేకపోవుట, కండరబిగువులో లోపం, గుండె దడ, రక్తములో ప్లేట్ లెట్స్ సంఖ్య తగ్గుట, చెవిలో గంటల శబ్ద ము రావడం.

వ్యాకులత/ఆత్రుత, నిద్ర లేమి రోగం, వాంతి భ్రమ, నొప్పి, చెమట పట్టుట మొదలగు పరిణామాలవల్ల గాబాపెన్‌టిన్ తీసుకోవడం ఆపివేయడమైనది.

ముంచేతికి ఉంచిన ట్యూబు ద్వారా రక్తము తీసుకోవటం అనే పద్ధతి వలన తల తిరుగుచున్నట్లు అనిపించడం మరియు ట్యూబు ఉంచిన ప్రదేశ ములో జీల, వాపు, అసౌకర్యము మరియు ఇన్‌ఫెక్షన్ కలుగవచ్చు.

## 6. అధ్యయనంలో పాలుపంచుకొనడం వలన ఏమైనా ప్రయోజనాలున్నాయా?

ఇది పరిశోధనతో కూడిన క్లినికల్ అధ్యయన ము. అధ్యయనం వల్ల మీకు ప్రత్యక్ష ప్రయోజనం ఉండదు. అధ్యయనంలో ఇచ్చే మందుల చికిత్స మీకు అవసరం లేదు కనుక ఈమందుల వల్ల మీకు ప్రయోజనం ఉండదు. ఈ అధ్యయనంలో పాల్గొనటం ద్వారా ఉచితంగా వైద్య పరీక్ష చేయించుకొనవచ్చు. మందుల పరిశోధనకు తోడ్పడ్డామనే సంతృప్తి మీకు లభిస్తుంది. మీ ఆరోగ్య పరిస్థితి గురించి మీకు తెలుస్తుంది.

## 7. రహస్యతను గురించి ఏమిటి?

అధ్యయనంలో సేకరించిన మీ వైద్య సమాచారాలను రహస్యంగా ఉంచుతారు.
అధ్యయనానికి సంబంధించిన సమాచారాలను నాణ్యతా హామీ కోసం, సమాచార విశ్లేషణ కోసం క్రింది సంస్థలు పరిశీలించవచ్చు.

- సంబంధిత నియంత్రణాధికారులు (ఉదా: బ్రెజిల్-ఎనిపిసా/ యుయస్-ఎఫ్‌డిఎ/ యు.కె-ఎం.హెచ్.ఆర్.ఎ / డి.సి.జి.ఐ.)
- అధ్యయన రూపకల్పన సభ్యులు/ పరిశోధకుడు: క్యూఏడి/ ఏపిఎల్ ఆర్‌సి -సిపిడి
- సేపియర్ ఐఆర్‌బి సభ్యులు.

అందుబాటులో ఉండే ఫలితాలలో ఏ నిర్దిష్ట కార్యకర్తను గుర్తించే సమాచారం ఉండదు.



Date 25/10/06

## 8. ఆర్థిక పరిహారం ఎంత?

మీరు స్వచ్ఛందంగా అధ్యయనంలో పాల్గొన్నందుకు, మీరు వెచ్చించిన కాలానికి, అధ్యయనంలో పాల్గొనడానికి ప్రయత్నించినందుకు, రవాణా ఖర్చులకు మరియు మీకు కలిగిన అసౌకర్యానికి ఆర్థిక పరిహారం ఇవ్వబడుతుంది. ఈ అధ్యయనానికి మీకు రూ.3,705/- (మూడువేల ఏడు వందల ఐదు రూ పాయలు) చెల్లించటం జరుగుతుంది.

అధ్యయనం ముగియకుండా మీరు వైదొలగితే క్రింది విధంగా పరిహారం ఉంటుంది.

| అధ్యయనం నుంచి వైదొలగే/ తొలగించినందుకు కారణాలు | పరిహారం |
|---|---|
| క్లినికల్ పరిశోధకుడు/అధ్యయన సమయంలో ఉండే వైద్యుడు మీ ఆరోగ్యం దృష్ట్యా లేదా ప్రతికూల సంఘటనల దృష్ట్యా అధ్యయనం నుంచి తొలగించాలని తీసుకునే వైద్య పరమైన నిర్ణయం | పూర్తిగా చెల్లింపు ఉంటుంది |
| అధ్యయనం మొదలైన తరువాత (పీరియడ్-1 లో చెక్-ఇన్ తర్వాత) మీరు ఐచ్ఛికంగా వైదొలగినపుడు మరియు/ లేదా అధ్యయనంలోని ఇతర దశలకు రానందుకు. | పాల్గొన్న నిష్పత్తికి బకాయిలు. |
| పీరియడ్-1 లో చెక్-ఇన్ తర్వాత, ఏ సమయములోనైనా మీరు అధ్యయనానికి కావలసిన అంశాలను అతిక్రమించి నందుకు, మరియు క్రమశిక్షణా రాహిత్యానికిగాను, క్లినికల్ పరిశోధకుడు / అధ్యయన సమయంలో ఉండే వైద్యుడు మిమ్మల్ని అధ్యయనం నుంచి తొలగించవచ్చు. | పాల్గొన్న నిష్పత్తికి బకాయిలు. |

చెల్లింపులకు సంబంధించిన ఏ వివాదములకైనా, మీరు సేపియర్- ఐఆర్‌బిని సంప్రదించవచ్చును మరియు సేపియర్- ఐఆర్‌బి యొక్క నిర్ణయం మీకు అలాగే అరబిందో ఫార్మా లిమిటెడ్, ఇండియా వారికి కూడా వర్తిస్తుంది.

## 9. అవాంఛనీయ పరిణామములకు పరిహార మేమిటి?

క్లినికల్ యూనిట్, సిపిడి లో ఉన్నపుడు ఎదురయ్యే అవాంఛనీయ పరిణామములకు క్లినికల్ యూనిట్, సిపిడి లేదా మిర్రా హాస్పిటల్ గాని లేదా దగ్గరలో ఉన్న ఏ సూపర్ స్పెషాలిటీ హాస్పిటల్ లో గాని, మీకు ఖర్చు లేకుండా వైద్యం చేయడం జరుగుతుంది. తీవ్ర ప్రమాదం సంభవించినపుడు సేపియర్- ఐఆర్‌బి సభ్యులు నిర్ణయించిన ప్రకారం లేదా భీమా పాలసీ నిర్ధారించిన నిరపరాధ పరిహారం చెల్లించడం జరుగుతుంది.

కార్యకర్త సంతకము ..... తేది.....

**10. ఈ అధ్యయన ములో నేను పాలుపంచుకోవడ ము ఏ పిధమైనది?**

మీరు ఈ అధ్యయన ములో స్వచ్ఛంద ముగా పాల్గొనుచున్నారు. మీరు ఈ అధ్యయన ములో పాల్గొనుటకు మరియు పాల్గొనకుండా తిరస్కరించుటకు మీకు పూర్తి స్వేచ్ఛ ఉంది. మీరు ఈ అధ్యయన ములో పాల్గొనుటకు తిరస్కరించినా మరియు ఈ అధ్యయన ము నుండి పైదొలిగినా ఏ పిధమైన జరిమానాకాని లేదా మీకు లభించు ప్రయోజన ములను కోల్పోవట ముకాని జరుగదు మరియు భపిష్యత్తు అధ్యయన ములలో మీరు పాల్గొనుటకు ఏ పిధమైన ఆటంక ములు ఉండవు. మీరు ఈ అధ్యయనం నుంచి పైదొలగాలనుకుంటే, అధ్యయనం డాక్టరు / క్లినికల్పరిశోధకుడు మీతో చర్చించి అధ్యయనం నుంచి సక్రమంగా తొలిగిపోయే మార్గాన్ని మీకు పివరిస్తారు. మీ అంతట మీరు కారణ ము చెప్పి / కారణ ము చెప్పకుండాను అధ్యయన ము మధ్యలో నుండి పైదొలిగిన పరిస్థితులోకూడా, ఎపిఎల్ - సిపిడితో లేక దాని సిబ్బందితో కాని మీ సంబంధ ములు చెడిపోవని హామీ ఇస్తున్నాము.

**11. అధ్యయనంలో పాల్గొంటున్నపుడు నా హక్కు లేమిటి?**

పరిశోధనలో స్వచ్ఛంద ముగా పాల్గొను వ్యక్తిగా మీహక్కులను మరియు మీ భద్రతను సేపియర్- ఐఆర్బి కాపాడుతుంది, మరియు ఎపిఎల్ - సిపిడి కూడా అధ్యయన కార్యకర్తలగా మీ సమగ్ర భద్రత, హక్కులు, రహస్యాలను కాపాడతామని హామీ ఇస్తుంది. అధ్యయన ములో స్వచ్ఛంద ముగా పాల్గొను ఒక వ్యక్తిగా మీరు ఏ సమయములోనైనా అధ్యయన ము నుండి పైదొలుగుటకు మీకు హక్కు ఉన్నది.

**12. నా నుంచి ఏమి ఆశిస్తున్నారు ?**

మీరు క్లినికల్ యూనిట్, సిపిడి సిబ్బందితో సహకరించాలని మనపి చేస్తున్నాము. మీరు క్లినికల్ యూనిట్కు రాగానే మిమ్మల్ని మరియు మీ సామానును సోదా చేస్తారు. మీ వ్యక్తిగత వస్తువులను అధ్యయన ములోని పతి పీరియడ్ లోను చెక్-ఇన్ సమయమందు తనిఖీ చేస్తారు. ఈ అధ్యయన ములో పాల్గొను సమయములో మీరు క్లినికల్ యూనిట్, సిపిడి నియమములను పాటిస్తారని మరియు అధ్యయన ము పూర్తయ్యేవరకు మీరు ఉండే సమయములో క్రమశిక్షణను పాటిస్తారని ఆశిస్తున్నాము. మీరు ఈ అధ్యయన సంబంధిత మరియు పరిపాలనా సంబంధిత ఆవశ్యకతలను కూడా పాటించవలెను.

**13. మీ అంగీకారం లేకుండా, అధ్యయనం నుంచి పరిశోధకుడు మిమ్మల్ని తొలగించే పరిస్థితులేమిటి?**

13.1 తీసుకున్న మందుకు పతికూల పరిణామ ములు సంభపించినపుడు.

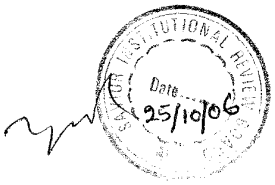
13.2 సహకరించనపుడు మరియు పోటోకాల్ ను పాటించనపుడు.

13.3 మీ పాణావశ్యక సమాచారాన్ని తెలియజేయు ఏదైనా మీ పూర్వ చరిత్రను మీరు ఉద్దేశపూర్వక ముగా దాచిపెట్టారని తెలుసుకున్నప్పుడు.

13.4 మీకు మందును తీసుకొన్న కొంచెం సేపటికే వాంతి అయినచో (క్లినికల్ పరిశోధకుడు నిర్ణయించిన పకార ము).

కార్యకర్త సంతకము ..... తేది.....





**14. మీరు పాల్గొంటే, అదనంగా మీకు అయ్యే ఖర్చు ఏమిటి?**

అధ్యయనంలో పాలుపంచుకున్నందుకు, మీరు ఏవిధమైన పైకము ఎపిఎల్-సిపిడికి చెల్లించనవసరం లేదు. మీరు క్లినికల్ యూనిట్‌కు రావలసినప్పుడు వాటికయ్యే ఖర్చులు, మీరు క్లినికల్ యునిట్ లో ఉన్నప్పుడు మీకు వసతులు మరియు భోజనము మొదలగున్నవి ఎపిఎల్-సిపిడి చూసుకుంటుంది.

**15. నేనేదైనా అడగాలనుకున్నప్పుడు లేదా సమస్య వచ్చినపుడు నేనెవరిని సంప్రదించాలి?**

అధ్యయనం జరుగుతున్నంత కాలం, మీరు స్వేచ్ఛగా అధ్యయనానికి సంబంధించిన మరికొంత సమాచారాన్ని ఏ విషయముపైనను పొందవచ్చును. అధ్యయనానికి సంబంధించి ఏ అత్యవసర ప్రశ్నలకైనా సలహాలు (సమాధానాలు) పొందవలసివస్తే క్రింద సూచించిన ఎపిఎల్-సిపిడి సిబ్బందిని సంప్రదించవచ్చు.

- డాక్టరు ఎ. టి. బాపూజి, మొబైల్ నంబర్ : 9848732447
- డాక్టరు సితిన్ కులకర్ణి, మొబైల్ నంబర్ : 9866625222

<u>చిరునామా :</u>
క్లినికల్ యూనిట్,
అరబిందో ఫార్మా లి మిటెడ్ (సిపిడి)
మిర్రా మల్టీస్పెషాలిటీ హాస్పిటల్
2 వ మరియు 3 వ ఫ్లోర్
ప్లాట్ నెం. 33, 34, 35, అల్లూరి సీతారామరాజు కాలనీ,
జె.పి. ఎన్‌నగర్ కాలనీ ఎదురుగా,
మియాపూర్, హైదరాబాద్-500 050.
టెలిఫోన్: 91-40-23045809/ 91-40-23045709.

**మానవ కార్యకర్తగా మీ హక్కులను గురించి ప్రశ్నలుంటే సేపియర్-ఐఆర్‌బి చైర్మన్ ను మీరు సంప్రదించవచ్చు.**

జస్టిస్ పి.పి.నారాయణ (రిటైర్డ్)
చైర్మన్ (సేపియర్ - ఐఆర్‌బి)

చిరునామా : ప్లాట్‌నెం. 402, పూజా'స్ ప్రయిడ్,
ప్లాట్ నెం. 75, శ్రీనగర్ కాలనీ, హైదరాబాద్-500073.
టెలిఫోన్: 91-40-23743173



25/10/06

కార్యకర్త నమోదు నెం: APL - ☐ స్వచ్ఛందముగా పాల్గొను వ్యక్తి నెం: S - ☐

## అధ్యయనంలో స్వచ్ఛందముగా పాల్గొను వ్యక్తి పిపేచనాపూర్వక అంగీకారాన్ని తెలియచేయుచున్న పత్రం

**అధ్యయనం పేరు:** భారతదేశంలోని అరబిందో ఫార్మా లిమిటెడ్ వారు తయారు చేసిన గాబాపెన్‌టిన్ 400 మి.గ్రా., పరీక్ష కాప్స్యూల్స్‌కు మరియు యుకె లోని ఫార్క్ డెపిస్, వారు మార్కెటింగ్ అధికారము కలిగియున్న న్యూరాన్‌టిన్ 400 మి.గ్రా., రిఫరెన్స్ కాప్స్యూల్స్‌కు, పోలికతోకూడిన జీవతుల్యతాధ్యయనం. ఆరోగ్యవంతులైన, వయోజనులైన 36 మగ వ్యక్తులకు, మందు పేరు తెలిపి, యాధృచ్ఛికముగా, రెండు సార్లు వరుసగా, రెండు సమయాలలో ఒకదాని తరువాత ఒకటిగ ఒక మోతాదు మందును నిరాహార పరిస్థితులలో ఇస్తారు.

**అధ్యయన ము నెం: జిఎపి-03/06**

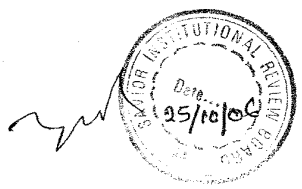
**ప్రకటన:**

**నేను ప్రకటించునది ఏమనగా :-**

1. నేను పిపేచనాపూర్వక అంగీకార పత్రాన్ని చదివాను మరియు అధ్యయనము గురించి మౌఖికముగా చెప్పిన తరువాత దానిలోని విషయాలను సావకాశంగా అవగాహన చేసుకోవటానికి,సమగ్రంగా అర్థము చేసుకోవటానికి తగినంత సమయము లభించినది.నాకు అధ్యయనానికి సంబంధించిన ప్రశ్నలు అడగటానికి అవకాశము, వాటికి సంతృప్తికరమైన సమాధానాలు లభించాయి.
2. ఈ అధ్యయనము పరిశోధన తో కూడినది అని అర్థము చేసుకున్నాను.
3. ఈ అధ్యయనము యొక్క స్వభావాన్ని మరియు ఉద్దేశమును అర్థము చేసుకున్నాను.
4. ఈ అధ్యయనము నకు సంబంధించిన అన్ని విధానాలను అర్థము చేసుకున్నాను.
5. నేను స్వచ్ఛంధముగా అధ్యయనములో పాల్గొంటున్నాను.
6. ఏ సమయంలోనైనా అధ్యయనం నుంచి తొలగిపోయే హక్కు నాకు ఉంది.
7. ఈ అధ్యయనం వల్ల కలుగ బోయే ప్రమాదాలు మరియు ప్రయోజనములు అర్థము చేసుకున్నాను.
8. ఈ అధ్యయనంలో పాల్గొనడం వల్ల నాకు ఉచిత వైద్య పరీక్షలు తప్ప ప్రత్యక్షంగా వైద్యపరమైన ప్రయోజనంలేదని నాకు తెలుసు.
9. నా వైద్య చరిత్రకు సంభంధించి ఏ సమాచారాన్ని నేను దాచలేదు.
10. నా ఆరోగ్యాన్ని పరిరక్షించటానికి లేదా అధ్యయన అవసరాలను ఉల్లంగించుట చేతగాని, అధ్యయనం నుంచి నన్ను ఏ సమయంలోనైనా నా అనుమతి లేకుండా తొలగించవచ్చును.
11. నేను ఈ అధ్యయనము జరుగు సమయములో ఎపిఎల్-సిపిడి యొక్క అన్ని పరిపాలనా సంబంధిత ఆవశ్యకతలకు అనుగుణముగా ఉండగలను.
12. నేను స్వచ్ఛంధముగా ఈ అధ్యయనములో పాల్గొనటము వలన నేను వెచ్చించే సమయానికి, నా ప్రయత్నానికి, నా రవాణా ఖర్చులకు గాను మరియు నాకు కలుగు ఇబ్బందులకు తగిన పరిహారము చెల్లించటము జరుగుతుంది.

కార్యకర్త సంతకము ..... తేది.....





13. ఏదైనా ప్రమాదం సంభవించినపుడు, సేపియర్-ఐఆర్‌బి బోర్డు నిర్ణయించిన నిరపరాధ ఆర్థిక పరిహారం నాకు లభిస్తుంది.
14. మందు మరియు/ లేదా అధ్యయన సంబంధిత అవాంచనీయ పరిణామములకు నాకు ఖర్చు లేకుండా ఎపిఎల్-సిపిడి చికిత్స చేయిస్తుంది.
15. ఏమైనా అధ్యయన సంబంధిత ప్రశ్నలు వేయాలనుకున్నపుడు లేదా అత్యవసర పరిస్థితులలో లేదా అధ్యయనంలో స్వచ్ఛంద ముగా పాల్గొను వ్యక్తిగా నా హక్కుల కొరకు ముందు పుటలలో సూచించిన వ్యక్తులను సంప్రదించవచ్చు.
16. అధ్యయనంలో పాల్గొనటానికి అంగీకారాన్ని తెలుపుతున్నట్లుగా నా సంతకం లేదా వేలి ముద్ర నిర్ధారిస్తుంది.
17. నాకు తెలిసిన సమాచారాన్ని ఆధారం చేసుకుని ఈ అంగీకార పత్రము రూపొందించబడినది.
18. సంతకముతో కూడిన పిపేచనాపూర్వక అంగీకార పత్రం యొక్క ఒక ప్రతిని నేను తీసుకున్నాను.
19. క్లినికల్ పరిశోధకుడు/వైద్యుడు నిర్ణయించిన ప్రకారము, అధ్యయనము చివరలో ఒకవేళ కొన్ని లాబొరేటరి పరీక్షలు మరలా చేయవలసి వస్తే అధ్యయన అనంతరము నిర్భయత్వ మదింపు (లు) (ఒకవేళ) చేయవలసి వస్తే, వీటి కొరకు కావలసిన రక్త నమూనాలను ఇవ్వడానికి నేను అంగీకరిస్తున్నాను.

| | |
|---|---|
| కార్యకర్త పేరు: | పక్షపాతంలేని సాక్షి పేరు:<br>పక్షపాతంలేని సాక్షి చిరునామా: |
| కార్యకర్త సంతకం / వేలి ముద్ర:<br><br>తేది: | సంతకం: తేది: |

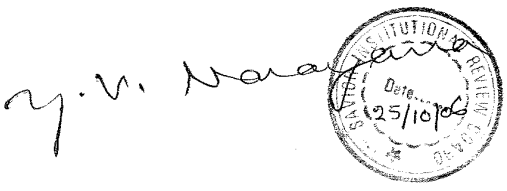
గమనిక: పక్షపాతంలేని సాక్షి సంతకం నిరక్షరాశ్యులైన కార్యకర్తకు మాత్రమే సంభందించినది.

అంగీకారాన్ని తీసుకున్నవారు: ..... ...

క్లినికల్ పరిశోధకుని / వైద్యుని సంతకం..... తేది.....

కార్యకర్త సంతకము ..... తేది.....





CLINICAL PHARMACOLOGY DEPARTMENT

UNIT: BIOSTATISTICS

RANDOMIZATION SCHEDULE

Study no.: Gap-03/06

Test Drug (T) : Gabapentin 400 mg capsules, each capsule contains 400 mg of Gabapentin, manufactured by Aurobindo Pharma Ltd., India.

Batch no. : GN4006001;Mfg Date: 08/2006; Exp. Date: 07/2008

Reference Drug (R) : Neurontin 400 mg capsules, each capsule contains 400 mg of Gabapentin, marketing authorization holder: Parke Davis, Lambert Court, Chestnut Avenue, Eastleigh, Hampshire, SO53 3ZQ, UK.

Batch no. : 0132124;Mfg Date: Not Available; Exp. Date: 11/2007

| Subject ID | Sequence | Period I | Period II |
|---|---|---|---|
| 01 | 2 | T | R |
| 02 | 1 | R | T |
| 03 | 2 | T | R |
| 04 | 1 | R | T |
| 05 | 1 | R | T |
| 06 | 2 | T | R |
| 07 | 1 | R | T |
| 08 | 2 | T | R |
| 09 | 1 | R | T |
| 10 | 2 | T | R |
| 11 | 1 | R | T |
| 12 | 2 | T | R |
| 13 | 2 | T | R |
| 14 | 1 | R | T |
| 15 | 2 | T | R |
| 16 | 1 | R | T |
| 17 | 1 | R | T |

J Balaji 20/11/06

Prepared by: J.Balaji (Biostatistician, APLRC-CPD)

20/11/06

Approved by: Dr.A.T.Bapuji (Principal Investigator, APLRC-CPD)

CLINICAL PHARMACOLOGY DEPARTMENT

UNIT: BIOSTATISTICS

RANDOMIZATION SCHEDULE

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Batch no. : 0132124;Mfg Date: Not Available; Exp. Date: 11/2007

| Subject ID | Sequence | Period I | Period II |
|---|---|---|---|
| 18 | 2 | T | R |
| 19 | 2 | T | R |
| 20 | 1 | R | T |
| 21 | 2 | T | R |
| 22 | 1 | R | T |
| 23 | 1 | R | T |
| 24 | 2 | T | R |
| 25 | 1 | R | T |
| 26 | 2 | T | R |
| 27 | 1 | R | T |
| 28 | 2 | T | R |
| 29 | 1 | R | T |
| 30 | 2 | T | R |
| 31 | 2 | T | R |
| 32 | 1 | R | T |
| 33 | 1 | R | T |
| 34 | 2 | T | R |

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Approved by: Dr.A.T.Bapuji (Principal Investigator, APLRC-CPD)

CLINICAL PHARMACOLOGY DEPARTMENT

UNIT: BIOSTATISTICS

RANDOMIZATION SCHEDULE

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Batch no. : 0132124;Mfg Date: Not Available; Exp. Date: 11/2007

| Subject ID | Sequence | Period I | Period II |
|---|---|---|---|
| 35 | 2 | T | R |
| 36 | 1 | R | T |

J. Balaji 20/11/06

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20/11/06

Approved by: Dr.A.T.Bapuji (Principal Investigator, APLRC-CPD)