Synopsis – Study 10403

Title of Study A double-blind, randomised, placebo-controlled, parallel-group, phase III study evaluating the efficacy and safety of gaboxadol 5 mg and 10 mg daily in elderly outpatients with primary insomnia
Investigators 62 investigators in 8 countries *Signatory investigator* – Jan Hedner, Professor, MD, University of Gothenburg, Gothenburg, Sweden
Study Centres 62 centres – 6 in Belgium, 10 in Canada, 7 in Finland, 6 in France, 12 in Germany, 7 in Norway, 5 in Sweden, and 9 in the United Kingdom
Publications None (as of the date of this report)
Study Period *First patient first visit* – 4 May 2004 *Last patient last visit* – 4 November 2005
Objectives • *Primary objective:* – to compare the hypnotic efficacy of gaboxadol 5 mg (GBX05) and 10 mg (GBX10) daily with that of placebo (PBO) over a 4-week treatment period in a population of elderly outpatients suffering from primary insomnia • *Secondary objectives*: – to compare the safety of GBX05 and GBX10 with that of PBO over a 4-week treatment period in a population of elderly outpatients suffering from primary insomnia – to evaluate rebound insomnia and withdrawal effects during a 1-week, double-blind, placebo-controlled run-out period
Methodology • Multinational, multi-centre, randomised, double-blind, parallel-group, placebo-controlled, fixed-dose study of gaboxadol in elderly patients with primary insomnia. • The study consisted of the following phases/periods: – Screening Phase – 1-week single-blind PBO run-in period – Core Phase – 4-week double-blind treatment period with either PBO, GBX05, or GBX10 – Run-out Phase – 1-week double-blind run-out period. Patients who had received gaboxadol (GBX) in the Core Phase received either GBX (at the same dose as that in the Core Phase) or PBO (GBX05-GBX05 or GBX05-PBO, and GBX10-GBX10 or GBX10-PBO) and patients who had received placebo in the Core Phase continued on PBO (PBO-PBO). – Safety Follow-up Phase – 4-week safety follow-up period

Number of Patients Planned and Analysed

- 505 were planned for enrolment: approximately 170 in each of the three treatment groups
- Patient disposition is tabulated below:

	PBO		GBX05		GBX10		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients randomised	175		186		180		541	
Patients treated (all-patients-treated set (APTS)):	175		186		178		539	
Patients completed	145	(83)	157	(84)	148	(83)	450	(83)
Patients withdrawn	30	(17)	29	(16)	30	(17)	89	(17)
Primary reason for withdrawal:								
Adverse event(s)	6	(3.4)	1	(0.5)	11	(6.2)	18	(3.3)
Lack of efficacy	12	(6.9)	17	(9.1)	8	(4.5)	37	(6.9)
Analysis sets:								
APTS	175		186		178		539	
Full-analysis set (FAS)	174		185		176		535	
Per-protocol Set (PPS)	172		181		168		521	

Diagnosis and Main Inclusion Criteria

Female and male outpatients with a primary diagnosis of primary insomnia according to DSM-IV-TR™ criteria, who:

- had a subjective time to sleep onset (sTSO) ≥45 minutes and a subjective total sleep time (sTST) <6.0 hours
- were aged ≥65 years
- were otherwise healthy in the opinion of the investigator

Investigational Product, Dose and Mode of Administration, Batch Number

Gaboxadol – 5 mg/day or 10 mg/day before bedtime; encapsulated tablets or hard gelatin capsules, orally:

- hydrochloride formulation, 5 mg encapsulated tablets, batch No. PD1458/R817
- hydrochloride formulation, 10 mg encapsulated tablets, batch No. PD1459/R820
- monohydrate formulation, 5 mg capsules, batch No. 0928 DFC 002 B 001
- monohydrate formulation, 10 mg capsules, batch No. 0928 DFC 002 C 001

Duration of Treatment

5 weeks of double-blind placebo-controlled treatment: 4 weeks of double-blind treatment in the Core Phase followed by 1 week of double-blind treatment in the Run-out Phase

Reference Therapy, Dose and Mode of Administration, Batch Number

Placebo – once daily before bedtime; orally; encapsulated tablets, batch No. PD1457/R819; hard gelatin capsules, batch No. P 0928 DFC 001 P 001

Criteria for Evaluation – Efficacy

- Sleep parameters – subjective daily assessments based on the morning questionnaire (using an electronic diary):
  - total sleep time (sTST)
  - time to sleep onset (sTSO)
  - freshness upon awakening (sFRESH)
  - number of awakenings per night (sNAW)
  - wakefulness after sleep onset (sWASO)
  - quality of sleep (sQUAL)
  - presence/absence of premature awakening (sPAWK)
  - estimated amount of premature awakening (sEAWK; how much earlier the premature awakening occurred)
- Daytime performance – subjective daily assessments based on the evening questionnaire (using an electronic diary):
  - daytime energy (sENERGY)
  - daytime relaxedness (sRELAX)
  - daytime tiredness (sTIRED)
  - daytime ability to function (sFUNCTION)
  - daily subjective number of naps (sNNAPS)
  - daily subjective mean nap duration (sNAPDUR)
- Weekly assessments:
  - Clinical Global Impression – Severity of Illness (CGI-S) and Clinical Global Impression – Global Improvement (CGI-I) scores
  - Profile of Mood States (POMS) total and subscale scores
  - Quality of Life – 36-item Short-Form Health Survey (SF-36) subscale scores

Criteria for Evaluation – Safety

- Adverse events (AEs), clinical safety laboratory tests, vital signs, weight, electrocardiograms (ECGs), and physical examinations
- Withdrawal effects (based on the Withdrawal Symptom Questionnaire [WSQ])
- Rebound insomnia (based on sTST and sTSO)

Statistical Methods

- The following analysis sets were used:
  - *all-patients-treated set* (APTS) – all randomised patients who took at least one dose of double-blind IMP
  - *full-analysis set* (FAS) – all patients in the APTS who had at least one valid baseline and post-baseline assessment of an efficacy variable
  - *per-protocol set* (PPS) – all patients in the FAS who had no major protocol deviations
- All efficacy analyses were conducted on the FAS; supplementary analyses were conducted on the PPS. All safety analyses were conducted on the APTS.
- Weekly means of sleep parameters and of daytime performance were based on the daily assessments. Based on the individual weekly means (sTSTm, sTSOm, and so on), mean values for the treatment groups were calculated.
- A formal testing strategy was established to adjust for multiplicity; the strategy involves a multi-step combination of Hochberg's procedure and a closed-testing procedure with two stages:
  - Stage 1 – the following hypotheses (primary) were considered:
    - H11: sTSTm – no difference between GBX10 and PBO at Week 1
    - H12: sTSOm – no difference between GBX10 and PBO at Week 1
  - To account for multiplicity related to the Stage 1 hypothesis, Hochberg's procedure was used.
  - Stage 2 – if at least one of the Stage 1 hypotheses was positive, then the Stage 2 hypotheses (secondary) were evaluated at the 5% level, again applying Hochberg's procedure:
    - H21: sTSTm – no difference between GBX10 and PBO at Week 4
    - H22: sTSOm – no difference between GBX10 and PBO at Week 4
    - H23: sFRESHm – no difference between GBX10 and PBO at Week 1
    - H24: sENERGYm – no difference between GBX10 and PBO at Week 1
  - Only hypotheses that were rejected after multiplicity adjustment (that is, those hypotheses that were positive for GBX10) were tested at the 5% level for GBX05, using a closed-test procedure. Furthermore, the secondary Stage 2 hypotheses for GBX05 were not evaluated at the 5% level if none of the primary Stage 1 hypotheses for GBX05 were positive.
- The statistical analyses were based on the FAS and observed cases (OC) at Weeks 1 to 4, and primarily used a longitudinal data analysis (LDA) model with an unstructured covariance matrix and Week, CCentre (grouped centres), and Treatment group as factors and the baseline value of the parameter as a covariate; the interaction terms Baseline value*Week and Treatment *Week were included. The 95% confidence limits for the estimated treatment differences were calculated.
- Based on the estimates obtained from the LDA model, the separate hypotheses in the testing strategy described above were tested. For analyses in the testing strategy, the LDA model was also applied to the PPS.
- Analyses outside the testing strategy were performed on an exploratory basis; for these analyses, *statistical significance* implies nominal p-values <0.05.
- For sTSO and sWASO, all analyses were performed on log-transformed data and repeated using non-transformed data.

Statistical Methods – continued

- To assess the validity of the assumptions and the robustness of the results, the following analyses were performed for sTSTm and log_sTSOm at Week 1 (that is, for the parameters in Stage 1 of the testing strategy; for completeness, the analyses were also performed for sTSOm and at Week 4): ANCOVA, based on the FAS using OC, and using worst observation carried forward (WOCF), non-parametric analyses, and rank analyses. In addition, an LDA model (FAS, OC) was used to estimate the treatment effect for Weeks 1 to 4 combined, corresponding to a summary statistics approach.
- The influence of covariates (CCentre, country, parameter baseline value, sex, age, weight, body mass index (BMI), lean body mass (LBM), Zung-A total score, and Zung-D total score) was studied by adding terms to the ANCOVA model (FAS, OC) as specified in the SAP; covariate analyses were performed at the 10% level of significance.
- The overall incidence of adverse events, as well as the incidences of adverse events by SOC and preferred term, were compared between treatment groups using Fisher's exact test.
- The time to first occurrence of certain adverse events (dizziness, headache, nausea, and somnolence) was analysed using Kaplan-Meier plots, log-rank tests, and the Cox model.
- For GBX05 and GBX10, exploratory logistic regression analyses were performed for the following adverse events in the Core Phase: dizziness, headache, nausea, and somnolence. Each of the covariates sex, age, weight, LBM, and creatinine clearance were included as univariate covariates. In addition, a multivariate model simultaneously including sex, age, LBM, and CrCL was fitted.
- Absolute values and changes from screening/baseline to the last assessment in clinical safety laboratory tests, vital signs, weight/BMI, and ECG parameters were summarised using descriptive techniques. Values outside the reference range, as well as potentially clinically significant (PCS) values, were flagged and tabulated.
- Analysis of withdrawal symptoms was based on the WSQ. The total scores per day are presented, using descriptive statistics. The Withdrawal Signal Effect (reflects whether three or more items were new, or had worsened, for a patient) was further analysed using χ^2-tests and pairwise comparisons of treatment groups. Each active treatment group was compared with its corresponding PBO group.
- To evaluate rebound insomnia, descriptive analyses comparing sTSTm or sTSOm at baseline, at Week 4, and at Week 5 for all three treatment groups were performed. Changes in sTSTm and sTSOm during the Run-out phase were evaluated using a standard ANCOVA for sTSTm and sTSOm at Week 5, comparing the GBX05-GBX05 group to the GBX05-PBO group, and the GBX10-GBX10 group to the GBX10-PBO group.
- For the first 3 days in the Run-out Phase, descriptive day-by-day analyses of sTST and sTSO were performed, comparing the mean daily sTST and sTSO values to the baseline mean values for patients entering the Run-out Phase.
- Patients were categorised as having rebound insomnia, if their sTST or sTSO value after the first night in the Run-out Phase was worse than their worst assessment in the Screening Phase (worst case baseline). In addition, analyses were performed using the mean sTST and mean sTSO during the Screening Phase as baseline (mean baseline). Each active treatment group (patients randomised to that treatment group at baseline who were subsequently randomised to PBO after Week 4) was compared to the overall PBO group (patients who took PBO during the entire study), using Fisher's exact test.

Demography of Study Population

- In all three treatment groups, the ratio of women to men was approximately 2:1, the mean age was approximately 71 years, and the vast majority of patients were Caucasian (>98%). There were no clinically relevant differences in height, weight, BMI, or LBM between the treatment groups for either women or men.
- At baseline, the patients slept approximately 4.5 hours (sTSTm) and had a time to sleep onset of approximately 110 minutes (sTSOm). Furthermore, the patients had approximately 2.5 awakenings per night (sNAWm), with a total duration of approximately 2 hours (sWASOm).

Efficacy Results

- Based on the testing strategy (focusing on efficacy at Weeks 1 and 4), both GBX05 and GBX10 improved sleep maintenance (sTSTm), sleep induction (sTSOm), freshness upon awakening (sFRESHm), and daytime energy (sENERGYm).
- The mean baseline value and the mean changes from baseline (FAS, OC, LDA) for each of the sleep parameters, for the daytime performance variables, and for the CGI scales are summarised below:

Efficacy Variable	Treatment Group	Baseline	Mean Change from Baseline at[a]			
			Week 1	Week 2	Week 3	Week 4
Sleep Parameter						
sTSTm (min)	PBO	268	24.6	33.2	33.5	32.3
	GBX05	264	41.9**	48.4**	54.3***	52.5**
	GBX10	277	44.6***	47.2*	45.9*	56.4***
sTSOm (min)[b]	PBO	109	-17.5	-26.4	-26.5	-26.6
	GBX05	113	-30.6*	-33.1	-35.5	-38.0**
	GBX10	104	-30.2*	-34.5	-34.2	-42.3**
sFRESHm (points)	PBO	41	4.1	5.5	6.0	5.6
	GBX05	42	9.4***	10.5***	10.9***	12.3***
	GBX10	42	9.9***	9.8**	10.8***	12.7***
sQUALm (points)	PBO	39	5.7	7.3	8.4	7.8
	GBX05	40	11.8***	11.6**	13.3***	14.4***
	GBX10	38	12.1***	12.7***	13.5***	16.0***
sNAWm (n)	PBO	2.3	-0.5	-0.5	-0.6	-0.6
	GBX05	2.5	-0.5	-0.5	-0.6	-0.7
	GBX10	2.5	-0.5	-0.6	-0.6	-0.6
sWASOm (min)[b]	PBO	114	-14.1	-21.2	-24.6	-27.4
	GBX05	115	-19.9	-29.8	-36.2	-38.7*
	GBX10	118	-30.1*	-36.1**	-33.6*	-38.5*
Daytime Performance						
sENERGYm (points)	PBO	48	1.3	2.5	2.6	2.0
	GBX05	49	5.5**	5.4*	7.8***	7.6***
	GBX10	46	5.9***	6.6**	5.8*	8.5***
sRELAXm (points)	PBO	51	1.0	2.9	3.2	2.4
	GBX05	52	5.8***	5.6	8.5***	8.3***
	GBX10	47	7.3***	8.0***	7.5**	9.3***
sTIREDm (points)	PBO	47	-0.4	0.9	1.1	0.5
	GBX05	47	5.7***	4.8*	6.9***	7.0***
	GBX10	43	6.3***	6.0**	5.0*	7.0***
sFUNCTIONm (points)	PBO	57	-0.2	0.1	0.6	0.2
	GBX05	57	3.4**	3.2*	5.1**	5.0**
	GBX10	53	5.1***	4.4**	4.3*	5.9***
CGI						
CGI-S (points)	PBO	3.7	-0.4	-0.4	-0.5	-0.5
	GBX05	3.6	-0.5*	-0.7**	-0.7*	-0.8*
	GBX10	3.8	-0.5	-0.6**	-0.7*	-0.9**
CGI-I (points)	PBO		3.7	3.6	3.5	3.5
	GBX05		3.4**	3.3**	3.3*	3.3**
	GBX10		3.4**	3.3**	3.2**	3.2***

*p ≤0.05, **p ≤0.01, ***p ≤0.001 *versus* PBO

a For CGI-I: mean scores at Weeks 1, 2, 3, and 4

b Baseline values and mean changes from baseline are based on non-transformed values (FAS, OC, LDA); statistical significance is based on log-transformed values (FAS, OC, LDA).

Efficacy Results – continued

- Throughout the Core Phase, GBX05 and GBX10 were statistically significantly more effective than PBO in improving sTSTm: on average, patients in the GBX05 group slept 15 to 21 minutes longer than patients in the PBO group, and patients in the GBX10 group slept 12 to 24 minutes longer than patients in the PBO group.
- Throughout the Core Phase, patients fell asleep faster in the GBX groups than in the PBO group: on average, patients fell asleep 7 to 13 minutes faster in the GBX05 group than in the PBO group and 8 to 16 minutes faster in the GBX10 group than in the PBO group. These improvements in sTSOm were statistically significant at Weeks 1 and 4.
- Patients felt more refreshed upon awakening in the GBX groups than in the PBO group: on average, the improvements in sFRESHm were 5 to 7 points in the GBX05 group and 4 to 7 points in the GBX10 group. These improvements were statistically significant throughout the Core Phase.
- Patients had a higher subjective quality of sleep in the GBX groups than in the PBO group: on average, the improvements in sQUALm were 4 to 7 points in the GBX05 group and 5 to 8 points in the GBX10 group. These improvements were statistically significant throughout the Core Phase.
- Throughout the Core Phase, in all three treatment groups, the mean number of awakenings per night decreased by approximately 0.6 from baseline, with no statistically significant differences between either of the GBX groups and the PBO group.
- Patients had less wakefulness after sleep onset in the GBX groups than in the PBO group: on average, the improvements in sWASOm were 6 to 12 minutes in the GBX05 group and 9 to 16 minutes in the GBX10 group. These improvements were statistically significant at Week 4 in the GBX05 group and throughout the Core Phase in the GBX10 group.
- In general, the differences between each of the GBX groups and the PBO group with respect to the presence or absence of subjective premature awakening (sPAWKm) were not statistically significant. Premature awakening (sEAWK) occurred later in the GBX groups than in the PBO group; the differences relative to the PBO group were statistically significant throughout the Core Phase in the GBX05 group and at Week 4 in the GBX10 group.
- Throughout the Core Phase, patients had more daytime energy (sENERGYm), felt more relaxed (sRELAXm), were less tired (sTIREDm), and were more able to function (sFUNCTIONm) in the GBX groups than in the PBO group:
  - sENERGYm improved, on average, 3 to 6 points in the GBX05 group and 3 to 7 points in the GBX10 group; these improvements were statistically significant throughout the Core Phase.
  - sRELAXm improved, on average, 3 to 6 points in the GBX05 group and 4 to 7 points in the GBX10 group; these improvements were statistically significant throughout the Core Phase (except for the GBX05 group at Week 2).
  - sTIREDm improved, on average, 4 to 7 points in both the GBX05 and GBX10 groups; these improvements were statistically significant throughout the Core Phase.
  - sFUNCTIONm improved, on average, 3 to 5 points in the GBX05 group and 4 to 6 points in the GBX10 group; these improvements were statistically significant throughout the Core Phase.
- For both sNNAPSm and sNAPDURm, the mean changes from baseline were small in all three treatment groups and there were no statistically significant differences between either of the GBX groups and the PBO group.
- The improvements in the mean CGI-S scores, all of which were in favour of GBX05 and GBX10, were statistically significant throughout the Core Phase in the GBX05 group and at Weeks 2, 3, and 4 in the GBX10 group.
- The mean CGI-I scores were statistically significantly better in the GBX05 and GBX10 groups than in the PBO group throughout the Core Phase.
- The improvements in the POMS total scores, all of which were in favour of GBX05 and GBX10, were statistically significant at Weeks 1 and 3 (and for GBX10, also at Week 2).

Efficacy Results – continued

- The improvements in the POMS subscale scores, all but one of which were in favour of GBX05 and GBX10, were statistically significant at some time points; for the *fatigue* subscale, the improvements in the GBX groups were statistically significant throughout the Core Phase (except for the GBX05 group at Week 2).
- There were statistically significantly greater improvements in the GBX05 and GBX10 groups than in the PBO group in the SF-36 subscales *vitality* at Weeks 2 and 4 and in *role – emotional* at Week 4. In addition, there were statistically significantly greater improvements in the GBX05 group than in the PBO group in *social functioning* at Week 4 and in *role – physical* at Weeks 2 and 4.

Safety Results

- The adverse event incidence for the entire study is summarised below:

	PBO		GBX05		GBX10	
	n	(%)	n	(%)	n	(%)
Patients who died	0	(0.0)	0	(0.0)	0	(0.0)
Patients with serious AEs (SAEs)	0	(0.0)	1	(0.5)	2	(1.1)
Patients with AEs	79	(45)	75	(40)	78	(44)
Total number of AEs	159		140		183	

n = number of patients; % = percentage of patients within treatment group

- During the Core Phase, approximately 40% of the patients in each of the three treatment groups had one or more adverse events.
- The proportion of patients who had adverse events considered *related* to treatment was slightly, but not statistically significantly, higher in the GBX10 group (31%) than in the GBX05 (19%) and the PBO (23%) groups.
- The proportion of patients who withdrew due to adverse events was also slightly, but not statistically significantly, higher in the GBX10 group (6%) than in the GBX05 (1%) and the PBO (3%) groups.
- There was a difference in the distribution and nature of adverse events in the GBX10 group, compared to those in the GBX05 and PBO groups. Adverse events belonging to the *nervous system* SOC had a statistically significantly higher incidence in the GBX10 group than in the PBO group. This statistically significant difference was also found in men, but there was no statistically significant difference in women. Adverse events in the remaining SOCs were essentially equally distributed in all three treatment groups.
- In the GBX10 group, dizziness (8%), headache (7%), and nausea (6%) were the adverse events with the highest incidences in the Core Phase. In the GBX05 group, headache (8%) and back pain (4%) were the adverse events with the highest incidences, whereas in the PBO group, headache (6%), nausea (5%), dry mouth (3%) and nasopharyngitis (3%) were the adverse events with the highest incidences. Dizziness had a statistically significantly higher incidence in the GBX10 group (8%) than in the PBO group (2%). A similar and statistically significant difference was seen in women; in men, the incidence of dizziness was not statistically significantly different between the GBX10 and PBO groups.
- Most of the adverse events had an onset within the first weeks, lasted less than a week, and were generally *mild* or *moderate*.
- One case of depression was reported in the PBO group, but none in the GBX05 or GBX10 groups.
- In the Core Phase, the incidence of falls was 2% (3 patients) in the GBX10 group, whereas no patients had falls in the GBX05 and PBO groups. One patient in the GBX05-GBX05 group fell in the Run-out Phase. In none of the cases was dizziness reported prior to the fall.
- In all three treatment groups, the overall incidence of adverse events was similar across age, body weight, and LBM categories.
- An exploratory statistical analysis did not find any influence of 5 selected covariates (sex, age, body weight, LBM, and creatinine clearance) on the incidences of dizziness, headache, nausea, or somnolence.

Safety Results – continued

- During the Run-out Phase, no difference in the overall incidence of adverse events was seen between treatment groups and there was no indication of any specific adverse event related to run-out. During the Run-out Phase, less than 15% of the patients in any treatment group had adverse events. During the Safety Follow-up Phase, less than 2% of the patients in any treatment group had adverse events.
- Two patients (1 in the GBX05 group and 1 in the GBX10 group) had SAEs during the Core Phase, and 1 SAE was reported during the Safety Follow-up Phase (GBX10-PBO), but none of the SAEs were considered *related* to IMP.
- The incidence of symptoms possibly relevant for abuse was low, albeit slightly higher in the GBX10 group (5%) than in the PBO group (1%). No symptom occurred in more than 2 patients (1%) in any treatment group.
- There were no clinically relevant changes within treatment groups, or differences between treatment groups, in clinical laboratory values, vital signs, weight changes, or ECGs.
- Neither the pooled nor the day-by-day analysis for Days 1 to 3 in the Run-out Phase indicated a statistically significantly higher proportion of patients with withdrawal signals in the GBX05-PBO group than in the GBX05-GBX05 group; or in the GBX10-PBO than in the GBX10-GBX10 group.
- There was no overall rebound effect. However, transient rebound insomnia based on sTST was observed on Day 1 after discontinuation of GBX10 treatment using one of the baseline definitions (mean baseline). Rebound insomnia based on sTSO was not observed.

Conclusions

- GBX10 and GBX05 are more effective than PBO in the treatment of primary (chronic) insomnia in the elderly, as demonstrated using the pre-defined testing strategy focusing on efficacy at Weeks 1 and 4: patients in the GBX groups have a greater increase in total sleep time (sTSTm) and a greater decrease in time to sleep onset (sTSOm); patients in the GBX groups also feel more refreshed upon awakening (sFRESHm) and have more daytime energy (sENERGYm).
- Exploratory analyses suggest that patients treated with GBX05 and GBX10 improve more than patients treated with PBO; that is, gaboxadol-treated patients have a consistently greater improvement in the quality of sleep (sQUALm) and a consistently greater improvement in the daytime performance variables sRELAXm, sTIREDm, and sFUNCTIONm. There is insufficient evidence to suggest an effect of gaboxadol treatment on the number of awakenings per night (sNAWm), but there is an apparent decrease in the wakefulness after sleep onset (sWASOm) upon treatment with GBX10.
- There is no overall rebound after discontinuation of gaboxadol treatment, but transient rebound insomnia cannot be excluded in a few cases.
- GBX10 and GBX05 are generally safe and well tolerated in the elderly.
- The adverse events with the highest incidence during gaboxadol treatment are dizziness, headache, and nausea.
- There is no evidence to suggest an abuse potential with gaboxadol treatment, when specifically analysing symptoms possibly relevant for abuse.
- There is no evidence of withdrawal symptoms and no new adverse events are observed after discontinuation of 4 weeks of gaboxadol treatment.

Date of the Report

9 February 2007

This study was conducted in compliance with the principles of *Good Clinical Practice*.