2 SYNOPSIS

Name of company/sponsor: SmithKline Beecham	Individual study table referring to part of the dossier:	(For National Authority use only)
Name of drug product: Deroxat®	Volume:	
Name of active ingredient: Paroxetine	Page: 1	

Study title:	Randomized, multicenter, double-blind, comparison study of the efficacy and safety of Deroxat® (paroxetine) and Anafranil® (clomipramine) in the treatment of unipolar major depression in [adolescent] patients 12 to 20 years of age.
Investigators:	- Dr. xxxxxxxxxxxxx, coordinator, xxxxxxxxx, Paris - 38 investigators - psychiatrists and child psychiatrists, hospital practitioners, private practitioners or PMC practitioners.
Study centers:	39 centers, including 23 hospitals, throughout France
Publications (references):	-
Studied period (years): 1997 - 1998 Date of first enrollment: March 17, 1997 Date of last enrollment: December 21, 1998 Date of last visit: April 28, 1999	Clinical development phase: III
Study objectives:	Comparison of the efficacy and safety of Deroxat® (paroxetine) and Anafranil® (clomipramine) in the treatment of unipolar major depression in adolescents 12 to 20 years of age.
Methodology:	Phase III, randomized, multicenter, double-blind, controlled, double placebo study versus clomipramine in two parallel groups stratified by age bracket, for 56 days (to a maximum of 168 days), with direct individual benefit.
Number of patients (planned and analyzed):	150 patients planned, 121 analyzed.
Diagnosis and main criteria for inclusion:	• Patients from 12 to 20 years of age; • Unipolar major depression, defined according to the DSM-IV criteria; • MADRS score ≥ 24 at the selection visit. This score had to still be $\underline{\geq}$ 24 at the enrollment visit and was not to have decreased by more than 20% since selection.
Test product: dose and mode of administration, batch number:	• Deroxat® 20-mg tablet, - 1st period of 21 days = 20 mg of Deroxat® (one tablet in the morning), - 2nd period of 35 days = 20 or 40 mg of Deroxat® (one or two tablets in the morning). - After D56 until D168 maximum: the treatment was either continued at the same dosage, modified, or discontinued, depending on the response. • Oral route • Deroxat® = lots 427 and 620, Placebo = lactose 25612 • Expiration date: lot 427: 08/05/1998; lot 620: 01/12/2000

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Duration of treatment: *(for both treatments)*	• Efficacy evaluation = up to 56 days. It involved all of the patients, including those whose treatment was extended up to 168 days. • Safety evaluation = up to 168 days.
Reference therapy: dose and mode of administration, batch number:	Anafranil® 75-mg tablet 1st period of 21 days = 75 mg of Anafranil® (1 tablet in the evening) 2nd period of 35 days = 75 or 150 mg of Anafranil® (1 or 2 tablets in the evening) After D56 until D168 maximum, the treatment was either continued at the same dosage, modified, or discontinued, depending on the response Oral route Anafranil® = lot: T6023; placebo = lactose 256121 Expiration dates: lot T6023: March 2001; lot T7061: 10/01/2002
Criteria for evaluation EFFICACY	- PRIMARY CRITERION: • number of complete responders: improvement in the MADRS score by at least 50% compared with the baseline score at the enrollment visit. • Clinical Global Impression (CGI) at D56 - SECONDARY CRITERIA: • MADRS scales from the enrollment visit to D56 and upon discontinuation of treatment. • HSCL-58 self-report at D21, D56, and until discontinuation of treatment. • GAF questionnaire from enrollment to D56, at each visit, if applicable at D168. • number of treatment failures in both groups. • number of non-responders in both groups.
SAFETY	Evaluation and comparison of Deroxat® and Anafranil®, by recording Intercurrent Events.
Statistical methods	- N was calculated for [an] expected difference of 25% between the 2 treatments, with stratification according to age bracket, or 120 evaluable patients - Two-tailed tests with α = 5% and power = 80% - Evaluation of efficacy over 56 days and of safety over a maximum of 168 days. - Tests used = qualitative variables: chi-squared test quantitative variables: Student's t test or Wilcoxon rank-sum test, logistic regression and ANOVA for repeated measurements
EFFICACY RESULTS	- The number of complete responders on D56 was greater in the Deroxat® group than in the Anafranil® group (p=0.06 for the ITT population, p=0.01 for the per protocol population). - The improvement in the MADRS score was greater in the Deroxat® group, which was demonstrated by logistic analysis (p=0.026). Similarly, the analysis of variance revealed a greater decrease in the MADRS over time in the Deroxat® group (p=0.003). - The patients' condition improved (psychological, social, and occupational functioning) in both groups, but with no significant difference between the two (GAF). - The percentages of global improvement of the disease were comparable in the two groups (CGI).

SAFETY RESULTS	- Emergent intercurrent events: 97 patients presented with 314 events; their incidence was in keeping with the known characteristics of the two study treatments. - Serious intercurrent events: 22 patients presented with 32 serious intercurrent events. No statistically significant difference was observed between the two treatment groups (p=0.47). - Among all of these events, 67 were deemed severe by the investigator, and no significant difference between the two treatment groups was observed. Nor was there any difference between the two treatment groups with respect to the number of discontinuations of treatment related to an intercurrent event. The intercurrent events related to Deroxat® were fewer than those associated with Anafranil® (p=0.03) in bracket 2, except for the events that were described as severe by the investigator, for which the distribution between the two groups was equivalent.
CONCLUSION	- This study therefore demonstrated that the efficacy of Deroxat® is at least equivalent to that of Anafranil® for treating unipolar major depression in young subjects (12 to 20 years of age), and that the safety profile of Deroxat® is in keeping with the product's characteristics.
Date of the report:	MARCH 24, 2000