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Sponsor/company:	sanofi-aventis	ClinialTrials.gov Identifier:	NCT00385411
Generic drug name:	Valproic Acid and Sodium Valproate	Study Code:	VAPOP_L_8971
		Date:	02 October 2009

Title of the study:	Therapeutic follow-up observational study and population kinetics ancillary study of valproate microgranules (Micropakine® SR) in patients aged between 6 months and 15 years suffering from epilepsy. VAPOP Study		
Investigator(s):	Dr. Catherine CHIRON (Hôpital Necker-Enfants Malades) Pr Olivier DULAC (Hôpital Necker-Enfants Malades) Dr Mathilde CHIPAUX (Hôpital Necker-Enfants Malades)		
Study center(s):	Hôpital Necker-Enfants Malades, Paris (clinical study)		
Publications (reference):	NA		
Study period: ate first patient enrolled: 14 March 2006 Date last patient completed: 20 October 2008		Phase of development: Phase IV	
Objectives:	**Primary objective:** Therapeutic follow-up study: - To evaluate the clinical and biological safety of valproate administered in the form of microgranules, under usual prescribing conditions, with clinical follow-up and individual dosage adjustment, using plasma concentrations of valproate and concomitant antiepileptic medications, as well as laboratory tests. **Secondary objectives:** Population kinetics ancillary study: - To estimate the population pharmacokinetic parameters of valproate administered in the form of Micropakine® SR 0.33 mg under the recommended therapeutic conditions. - To evaluate the influence of age, weight, gender and concomitant antiepileptic medications on the pharmacokinetics of Micropakine® SR 0.33 mg. - To analyze the relationship between plasma concentrations and adverse events for Micropakine® SR 0.33 mg and the main concomitant medications, with the objective of better defining the conditions of use of Micropakine® SR 0.33 mg and of these concomitant medications, and to highlight possible warnings for use to prevent adverse events. - To investigate the influence of genetic profiles on the pharmacokinetics of sodium valproate / valproic acid		
Methodology:	An open-label, single center, observational, safety study. A population pharmacokinetics study.		
Number of patients:	Planned: 80	Randomized: NA	Treated: 81

Evaluated:	Efficacy/Pharmacodynamics: NA	Safety: 81	Pharmacokinetics: 80
Diagnosis and criteria for inclusion:	6 months to 15 years of age, presenting with any type of epilepsy, receiving valproate at time of inclusion in the form of Micropakine® SR from 20 to 30 mg/kg/d, taken orally b.i.d. (although one patient was included who was receiving the treatment o.d.) and no more than three other antiepileptic agents (a treatment with a benzodiazepine antiepileptic taken daily or as needed more than twice / week, should be considered as an antiepileptic treatment), followed by pediatricians or neuropediatricians in hospital practice, whose consent form has been signed by the parents or the holders of parental authority and, if possible, by the child him- or herself and whose parents or legal guardian do not present any linguistic or cultural obstacles to the proper understanding of the study.		
Investigational product: Dose: Administration:	Micropakine® SR 0.33 mg (valproate) 20 to 30 mg/kg/d 20 to 30 mg/kg/d PO		
Duration of treatment: Not applicable (usual patient's prescription)	Duration of observation: from a minimum of 2 months and a maximum of 6 months		
Reference therapy: Dose: Administration:	NA NA NA		
Criteria for evaluation:			
Efficacy Or Pharmacodynamics:	NA		
Safety:	Adverse events reported by the patient or noted by the investigator; clinical, neurological, mental status assessments, behavioural disorders and number/type of seizures, hematology and blood chemistry.		
Pharmacokinetics:	Pharmacokinetic parameters and covariates able to explain the variability in the pharmacokinetic parameters of valproate.		
Pharmacokinetic sampling times and bioanalytical methods:	The 3 blood samples corresponding to the 3 planned times of sampling were the following: one blood sample drawn just before the morning dose of VPA, one blood sample drawn between 1 and 5 hours after the morning dose of VPA and one blood sample drawn between 5 and 8 hours after the morning dose of VPA.		

Statistical methods:	There was a descriptive analysis of the safety parameters for the safety population. For each parameter and related analysis, the number of missing data was indicated. The qualitative variables were described by size and percentage. The quantitative variables were described by the mean, standard deviation, median, minimum and maximum. Population pharmacokinetics study: The pharmacokinetics data (doses administered, exact dates and times of the last administration of medication and of the blood sample, corresponding measured values of valproate concentrations, individual covariates) were analyzed according to the population approach with the NONMEM software. Since height, age, body surface area and body weight were highly correlated, the covariate that produced the highest decrease in the objective function during the "forward" step was retained in the final model, and the 3 others were then not tested in the backward step. This analysis was performed for the ITT and the PP populations.
Summary:	A total of 81 patients were included in the study: 43 (53.1%) patients were male and 38 (46.9%) were female, the mean (SD) age was 5.9 (3.8) years, the mean (SD) weight was 22.6 (11.0) kg, the mean (SD) height was 113.5 (22.8) cm, the BMI was 16.6 (3.1) kg/m^2 . The first seizure took place 0.5 to 15 years before the inclusion, with a mean (SD) of 4.2 (3.9) years. The most frequent syndromes were generalized epilepsy (n=20, 24.7%), partial epilepsy (n=14, 17.3%) and severe myoclonic epilepsy in infancy (n=11, 13.6%). A total of 20 patients (24.7%) of the patients presented other types of syndromes. A majority of etiologies were idiopathic (n=38, 46.9% of the patients). 44.4% of the patients (n=36) presented other concomitant diseases. Four patients were withdrawn from the study: One patient (male / 2 year-old) was excluded from the ITT and the PP population for protocol violation: a suspension of Micropakine® SR administration decided by the parents; the patient did not provided evaluable PK data. One patient (male / 8 year-old) withdrew his consent. Two patients (female / 6 year-old and male / 1 year-old) were lost to follow-up.

Efficacy results or Pharmacodynamic results:	NA
Safety results:	36 patients (44.4%) presented at least one AE during the study; the most frequent AE were not related to treatment, as they were infections. Only 11 patients (13.6%) presented AE considered related to treatment; the each of the most frequent AE related to treatment (tremor and aggressive behavior) only affected 3 out of 81 patients (3.7%). All AE were mild to moderate in intensity, except one severe AE: one subject presented a severe prolonged epileptic seizure (30 minutes), which was not related to treatment. In all, 6 patients presented serious adverse events (SAE), none of which was related to treatment.There was no death, no adverse event that led to premature withdrawal from the study. The follow-up of biological safety and of the clinical, neurological and mental status examination between the inclusion and visit V2 showed no relevant change. The number (%) of patients presenting seizures since the previous visit was similar at V1 and V2 (32 patients (40.5%) at V1 and 28 patients (35.9%) at V2) but the median number of seizures per month decreased from 30.0 to 10.0 seizures per month from V1 to V2. The number (%) of patients presenting seizures since the previous visit was the similar: 32 patients (40.5%) at V1 and 28 patients (35.9%) at V2, and the median number of seizures per month decreased from 30.0 to 10.0 seizures per month from V1 to V2. Similarly, the number (%) of patients presenting the same type of seizures since the previous visit was the same: 27 patients (87.1%) at V1 and 27 patients (96.4%) at V2. In the case of patients presenting seizures of a different type since the previous assessment, the apparition of clonic and tonico-clonic seizures was more frequent at V2 compared to V1 (45.5% new patients versus 22.7%), but there were fewer new patients with tonic seizures at V2 compared to V1 (9.1% versus 18.2) and fewer new patients with partial seizures without secondary generalization (4.5% versus 13.6%).
Pharmacokinetic results:	VPA pharmacokinetics were well described by a one compartment model with first-order absorption and elimination and an exponential residual error. Apparent clearance was related to body weight by an allometric model with an exponent 0.44. The other covariates (sex, comedication, creatinin clearance) had no influence on the VPA kinetics. Mean population estimates (% interindividual variability) were 0.25L/h (27.7%) for CL/F, 5.42L (77%) for V/F and 0.44 h^{-1} for Ka. The interindividual variability of Ka could not be estimated. The model was validated by visual predictive checks and was found to accurately predict the concentrations of VPA in this population. Monte Carlo simulations showed that a 10mg/kg twice daily (BID) regimen would achieve the 50-100 mg/L target concentration interval with a probability of 70%.
Date of report:	11-June-2009