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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NA
		Study Code:	L_8752
Generic drug name:	Drotaverine	**Date:**	12/Dec/2007

Title of Study: Comparative efficacy and tolerability of drotaverine 80mg and ibuprofen 400mg in patients with primary dysmenorrhea – Protocol L-8752 DOROTA

Investigator: Professor Romuald DEBSKI

Study centres: 11 centres in Poland

Studies period (years): 2004 (date of first enrolment: 16 March 2004) (date of last patient completed: 18 November 2004)	**Phase of development:** III

Objective:

To show that drotaverine 80mg is at least as effective and as well-tolerated as ibuprofen 400mg in the treatment of primary dysmenorrhea.

Methodology:

Multicentre, randomised, double-blind, double-dummy, non inferiority, phase III study conducted in two parallel group

Number of patients:

- Planned: 320 (160 per group)
- Included (Randomised) : 323 (drotaverine: 161; ibuprofen: 162)
- Treated: 317 (drotaverine: 157; ibuprofen; 160)

Diagnosis and main criteria for inclusion:

Women suffering from primary dysmenorrhea.
Women aged between 18 and 35 years.
History of at least 6 months dysmenorrhea with presence of moderate to severe pain in each of the last 3 cycles.
With regular menstrual cycles (25-35 days)
Using an adequate barrier contraception method with a negative pregnancy test before randomization
Able and willing to give a written informed consent

Test product: drotaverine 80mg.

Dose: 3 tablets / day
Mode of administration: 1 tablet of drotaverine 80mg + 1 tablet of ibuprofen matched placebo x 3 / day

Reference therapy: ibuprofen 400mg

Dose: 3 tablets / day
Mode of administration: 1 tablet of ibuprofen 400mg + 1 tablet of drotaverine matched placebo x 3 / day

Duration of treatment: 3 whole days (i.e. 9 intakes for the whole treatment period)	**Duration of observation:** 1 cycle

Criteria for evaluations:

Efficacy:

- *Primary criteria*:
  Pain intensity rated by patients on a 4-point categorical scale (0=none, 1=mild, 2=moderate, 3=severe) at baseline and 0.5, 1, 2, 3, 4, 5 and 6 hours after the first intake.
  Analysed variable: the weighted sum of pain intensity differences over the 6-hour assessment period (SPID-6).
- *Secondary criteria*:
  - Pain intensity differences from baseline at each time point after the first intake.
  - Rate ratio of patients requiring rescue medication.
  - Rate ratio of responders (pain intensity within one hour after the first intake equal to 0 (none) or 1 (mild) without using any rescue or forbidden medication during the treatment period).
  - Patient's overall global assessment of efficacy (excellent, good, fair, poor) at the end of the treatment period.

Safety:

- Adverse events reported by the patient/ or noted by the investigator.
- Vital signs (blood pressure and heart rate) measured at each visit.
- Patient's overall global assessment of tolerability (excellent, good, fair, poor) at the end of the treatment period.

Statistical methods:

Efficacy:

Primary analysis performed in PP population and supportive analysis in mITT population.

Primary criterion: the statistical test of non-inferiority related to the primary efficacy analysis of the SPID-6 was one-sided and was conducted at a significance level of alpha = 5% using the appropriate two-sided 90% confidence intervals for the difference (drotaverine – ibuprofen) between treatment groups. A covariance analysis adjusted on the pain intensity at baseline was performed to derive this confidence interval. The upper limit of this interval was used in order to test the non-inferiority hypothesis: if it was lower than 0.228 the conclusion was that the efficacy of drotaverine 80mg was not inferior to that of ibuprofen 400mg.

Safety: analysis performed in safety population (treated patients)

Other than primary criterion comparisons between groups:

- Chi-square test (or Fisher exact test if at least one of the expected count is less than 5) for qualitative data.
- Student t test for normally distributed quantitative variables.
- Wilcoxon rank sum test for ordinal data or not normally distributed quantitative variables.

Normality was assessed using Shapiro Wilk test.

Results:

Primary Efficacy criterium in PP population (main analysis)

PP population	**Drotaverine 80 mg (N=145)**	**Ibuprofen 400 mg (N=145)**	**Total (N=290)**
Value of SPID-6			
N	145	145	290
Missing data	0	0	0
Mean	**-1.0**	**-1.4**	-1.2
Standard deviation	0.99	0.87	0.96
Minimum	-3.0	-2.9	-3.0
Median	-1.0	-1.6	-1.3
Maximum	1.0	1.0	1.0

Between groups comparison (covariance analysis adjusted on the pain intensity at baseline)	Difference (1) 90%CI (2)	**0.40 ± 0.10** **[0.23;0.57]**

(1) : Estimate and standard error of the estimate of the adjusted difference of change between the two groups
(2) : Parametric 90% confidence interval of the estimate of the adjusted difference (drotaverine - ibuprofen) between the two groups .

The upper limit of the 90% CI was superior to 0.228 (the non inferiority margin) then the non-inferiority of drotaverine 80mg compared to ibuprofen 400mg was not demonstrated.

Primary Efficacy criterium in mITT population (supportive analysis)

mITT population	**Drotaverine 80 mg (N=153)**	**Ibuprofen 400 mg (N=156)**	**Total (N=309)**
Value of SPID-6			
N	153	156	309
Missing data	0	0	0
Mean	**-1.0**	**-1.4**	-1.2
Standard deviation	0.99	0.86	0.95
Minimum	-3.0	-2.9	-3.0
Median	-1.0	-1.6	-1.3
Maximum	1.0	1.0	1.0
Between groups comparison (covariance analysis adjusted on the pain intensity at baseline)	Difference (1) 90%CI (2)	**0.40 ± 0.10** **[0.24;0.56]**	

(1) : Estimate and standard error of the estimate of the adjusted difference of change between the two groups
(2) : Parametric 90% confidence interval of the estimate of the adjusted difference (drotaverine - ibuprofen) between the two groups .

The upper limit of the 90% CI was superior to 0.228 then the non-inferiority of drotaverine 80mg compared to ibuprofen 400mg was not demonstrated.

Results:

Secondary efficacy criteria

Secondary efficacy criteria	**PP population**		**MITT population**	
	drotaverine 80mg (N=145)	**ibuprofen 400mg (N=145)**	**drotaverine 80mg (N=153)**	**ibuprofen 400mg (N=156)**
rate ratio of patients requiring rescue medication	29.0%	11.7% p<0.001	32.0%	13.5% p<0.001
rate ratio of responders	26.9%	45.5% p<0.001	26.1%	44.2% p<0.001
patient's overall assessment: excellent or good	42.7%	71% p<0.001	41.8%	68.6% p<0.001

Safety

Out of the 317 patients included in the safety analysis, 27 patients (17.2%) in the drotaverine 80mg group and 29 patients (18.1%) in the ibuprofen 400mg group reported at least one treatment emergent adverse event (TEAE). These events were considered to be possibly related to the study treatment by the investigator in 21 patients in each group (drotaverine 80mg: 13.4%; ibuprofen 400mg: 13.1%). They led to study discontinuation in 1 patient (0.6%) in each group.
No serious adverse event was reported.

The most frequent adverse events were gastro-intestinal disorders reported by 12 patients (7.6%) in the drotaverine 80mg group and 17 patients (10.6%) in the ibuprofen 400mg group and considered to be possibly related to the study treatment in 10 patients (6.4%) in the drotaverine 80mg group and 15 patients (9.4%) in the ibuprofen 400mg group.
Out of the other possibly-related events, nervous system disorders were experienced by 7 patients (4.5%) in drotaverine 80mg group and 6 patients (3.8%) in ibuprofen 400mg group, ear and labyrinth disorders by 6 patients (3.8%) in drotaverine 80mg group and 3 patients (1.9%) in ibuprofen 400mg group and menorrhagia by 2 patients (1.3%) in each group.

Regarding vital signs no clinically relevant changes were observed in both groups.

Although the patient's global assessment of the tolerability was significantly better (p=0.02) with ibuprofen 400mg (excellent or good: 86.8%) than with drotaverin 80mg (excellent or good: 78.4%), no relevant difference between the both groups was observed for frequency, nature, intensity and causality of the reported adverse events. As many of the last ones belonged to possible symptoms of dysmenorrhea, the assessment of safety may have been matched with that of efficacy by the patients.

Date of report: 5 May 2006