2 SYNOPSIS

Name of Company: Istituto Luso Farmaco D'Italia S.p.A.	**TABULAR FORMAT**	**(For National Authority Use only)**	
Name of Finished Product: N.A.	**REFERRING TO PART OF THE DOSSIER**		
Name of active substance(s):	**Volume:**		
Frovatriptan 2.5 mg + Dexketoprofen 37.5 mg Frovatriptan 2.5 mg + Dexketoprofen 25 mg Frovatriptan 2.5 mg + placebo	**Page:**		

Title of the study:
Comparison between frovatriptan plus different treatment regimens of dexketoprofen (25 mg and 37.5 mg) and frovatriptan alone in the acute treatment of migraine without aura and migraine with aura attacks.

Study Centres and Principal Investigator(s):

[redacted]

SYNOPSIS (cont.)

Name of Company: Istituto Luso Farmaco D'Italia S,p.A.	**TABULAR FORMAT**		**(For National Authority Use only)**
3333Name of Finished Product: N.A.	**REFERRING TO PART OF THE DOSSIER**	5.3	
Name of active substance(s):	**Volume:**		
Frovatriptan 2.5 mg + Dexketoprofen 37.5 mg Frovatriptan 2.5 mg + Dexketoprofen 25 mg Frovatriptan 2.5 mg + placebo	**Page:**		
Study Centres and Principal Investigator(s) (cont.d): [redacted]			
Publication (reference):			
Studied period (years): **2009-2010**	**Date of first enrolment:** **Date last visit completed:**	**31JUL09** **12APR10**	**Phase of development:** **III**

Objectives:
Objectives of this study were to assess possible superiority of frovatriptan plus dexketoprofen over frovatriptan alone in the acute treatment of migraine attacks, and to compare safety of treatments under study

Methodology:
Multicenter, randomized, double-blind, over encapsulation, active controlled, three parallel groups, phase III study.

Number of subjects (planned and analysed):
A total of three-hundred subjects have been planned to be randomised in 25 Italian clinical sites. A total of 321 subjects were screened and 314 randomised. Out of them, 281 had migraine attack within one month from randomisation, as per protocol and thus, entered in the statistical analyses.

Diagnosis and main criteria for inclusion:
Male and female subjects, 18-65 years old able to comply with study procedure and willingness to participate (signature of informed consent at screening visit), presenting diagnosis of migraine with or without aura, meeting the criteria issued by the International Headache Society in 2001 (*appendix 3 of the study protocol*), frequency of 1 to 6 migraine attacks per month for at least 6 months prior to start of the study. Females of childbearing potential had to have a prior to enrolment negative pregnancy test and use adequate contraceptive protection for all study duration (from the moment they have signed their informed consent, at V-1, until the end of the follow-up period).

0004

Name of Company: Istituto Luso Farmaco D'Italia S.p.A.	**TABULAR FORMAT**		**(For National Authority Use only)**
Name of Finished Product: N.A.	**REFERRING TO PART OF THE DOSSIER**	5.3	
Name of active substance(s):	**Volume:**		
Frovatriptan 2.5 mg + Dexketoprofen 37.5 mg Frovatriptan 2.5 mg + Dexketoprofen 25 mg Frovatriptan 2.5 mg + placebo	**Page:**		

Diagnosis and main criteria for inclusion (cont.d):

Moreover, subjects had not to meet any of the following exclusion criteria: diagnosis of typical aura with non-migraine headache, typical aura without headache, basilar migraine, hemiplegic migraine, opthalmoplegic migraine, coexistence of other headache types, in addition to migraine with aura or migraine without aura; history of drug abuse in acute migraine attacks treatment (subjects taking drugs to treat acute migraine attacks for 10 or more days a month); use of prophylactic migraine attacks therapy in case dose had not been stable for at least three months before V0 (in case of stable dose, it had to remain the same for all study duration); use of antipsychotics or antidepressant drugs (unless they were taken as prophylaxis of migraine attacks) within the three months prior to V0; concomitant use of ergotamine-derived (including methysergide), St John's Wort (Hypericum perforatum), monoamine-oxidase inhibitors, NSAIDs (COX-2 inhibitors), oral corticosteroid, warfarin or other coumarins, selective serotonin reuptake inhibitors, antiaggregant agents such as aspirin, heparin, lithium, methotrexate, idantoine and sulphonamides; alcohol/drug abuse or dependence (*appendix 4 of the study protocol*) in accordance to DSM-IV criteria; allergy to IMP or similar drugs or hypersensitivity to any ingredient of the trial drug composition; anamnesis of myocardial infarction, ischemic heart disease, coronary vasospasm, peripheral vascular disease, signs or symptoms suggesting ischemic heart disease, severe or moderately severe hypertension, or non controlled mild hypertension, previous cerebrovascular accident (CVA) or transient ischemic attack (TIA), risk of coronary disease, including hard smoking or nicotine substitute treatment, without a preliminary cardiovascular evaluation; familiar galactose intolerance, with lactase deficit or glucose-galactose malabsorption, liver pathology (AST or ALT >3 times greater than normal upper limit or total serum bilirubin >1.5 times greater than normal upper limit), renal insufficiency (serum creatinine >200 Omol/L or 2 mg/dL); previous hypersensitivity reactions to NSAIDs (e.g., asthma, broncospasm, acute rhinitis, nasal polyp, urticaria, or angioneurotic oedema); active peptic ulcer/bleeding or positive anamnesis for peptic ulcer/bleeding or chronic dyspepsia; history of gastrointestinal bleeding or perforation related to NSAIDs therapies; presence of gastrointestinal bleeding or other active bleeding, or blood coagulation diseases; Crohn's disease or ulcerous colitis, bronchial asthma, severe cardiac failure, bleeding diathesis or other coagulation disturbances, hemopoietic impairment, systemic lupus erythematosus or connective system pathologies; pregnancy or breast feeding; concurrent involvement in another investigational study or participation within 6 months prior to the start of this study (V0).

Test product, dose, mode of administration, batch N°:

Frovatriptan 2.5 mg film coated tablets over-encapsulated in DBAA capsules suitable to keep the blinding + 3 dexketoprofen 12.5 mg tablets over-encapsulated in DBAA capsules suitable to keep the blinding, manufactured by A. Menarini MMLS – Firenze, to be taken only once, at the migraine headache onset with an adequate amount of water. Each dose consisted of two capsules, one red and one white to be taken together.
Batch: CTE0926; Expiry date: FEB2012 (Frovadex capsules); Batch: CTE0918; Expiry date: FEB2011 (dexketoprofen 37.5mg capsules)

Test product, dose, mode of administration, batch N°:

Frovatriptan 2.5 mg film coated tablets over-encapsulated in DBAA capsules suitable to keep the blinding + 2 dexketoprofen 12.5 mg tablets over-encapsulated in DBAA capsules suitable to keep the blinding, manufactured by A. Menarini MMLS – Firenze, to be taken only once, at the migraine headache onset with an adequate amount of water. Each dose consisted of two capsules, one red and one white, to be taken together.
Batch: CTE0926; Expiry date: FEB2012 (Frovadex capsules); Batch: CTE0915; Expiry date: FEB2011 (dexketoprofen 25mg capsules)

Reference therapy, dose, mode of administration, batch N°:

Frovatriptan 2.5 mg film coated tablets over-encapsulated in DBAA capsules suitable to keep the blinding + 1 placebo tablet over-encapsulated in DBAA capsules suitable to keep the blinding, manufactured by A. Menarini MMLS – Firenze, to be taken only once, at the migraine headache onset with an adequate amount of water. Each dose consisted of two capsules, one red and one white to be taken together.
Batch: CTE0926; Expiry date: FEB2012 (Frovadex capsules); Batch: CTE0915; Expiry date: FEB2011 (placebo capsules)

SYNOPSIS (cont.)

Name of Company: Istituto Luso Farmaco D'Italia S.p.A.	**TABULAR FORMAT**		**(For National Authority Use only)**
Name of Finished Product: N.A.	**REFERRING TO PART OF THE DOSSIER**	5.3	
Name of active substance(s):	**Volume:**		
Frovatriptan 2.5 mg + Dexketoprofen 37.5 mg Frovatriptan 2.5 mg + Dexketoprofen 25 mg Frovatriptan 2.5 mg + placebo	**Page:**		

Criteria for evaluation (efficacy):

- Percentage of subjects pain-free at 2 hours, before any rescue medication (primary end-point);
- Percentage of subjects pain-free at 1 hour and 4 hours, before any rescue medication;
- Sustained pain-free (percentage of subjects pain-free within 2 hours with no use of rescue medication or recurrence within 48 hours);
- Percentage of subjects with a decrease in headache from severe or moderate to mild or none within 2 hours (headache relief);
- Percentage of subjects with a decrease in headache from severe or moderate to mild or none at 1 hour, at 2 hours and at 4 hours;
- Time to meaningful relief, defined subjectively by the subject;
- Speed of onset of action evaluated by comparing pain intensity at 60, 90 120 and 240 min;
- Percentage of subjects taking rescue medication;
- Subjects' preference for treatments;
- Percentage of subjects with resolution of nausea, vomiting, photophobia, phonophobia and osmophobia;
- Incidence of recurrence: percentage of subjects pain-free within 2 hours after treatment and recurrence of headache within 48 hours from treatment
- Percentage of subjects pain free at 24 hours, before any rescue medicationPercentage of subjects pain-free within 2 hours with no use of rescue medication or recurrence within 24 hours (Sustained pain-free at 24 hours).
- Percentage of subjects with meaningful relief within 30 minutes
- Time to recurrence

Criteria for evaluation (safety):

AEs, physical examination, vital signs.

Statistical methods:

The statistical analysis had been performed using SAS® version 9.2. Classic summary statistics (n, mean, median, standard deviation, coefficient of variation (%), min, and max) had been produced for quantitative variables while the qualitative information was summarized by means of frequency tables. Primary variable was assessed by Mantel-Haenszel chi-square statistic using 3 x 2 contingency tables for tests of association and 2 x 2 contingency tables for comparisons between treatments (e.g. frovatriptan plus dexketoprofen (high dose) versus frovatriptan alone) was used to compare. The Kaplan-Meier method was used to analyze the time to meaningful relief, defined subjectively by the subject and the groups were compared using the two sided log-rank test. All others secondary parameters were assessed in the same way as primary variable (Mantel-Haenszel chi-square statistic and contingency tables).

The primary and all secondary parameters, were assessed on all the following identified additional subpopulation:

- Per Protocol (PP) population that includes all subjects from the FAS population without any major protocol violation;
- Menstruating women population that includes all female subjects who had a migraine attack 2 days before or 3 days after menstrual cycle;
- Treated before or after 30 minutes – populations that include the subjects who took treatment before 30 minutes from migraine onset and after 30 minutes from migraine onset;
- Treated before or after 60 minutes – populations that include the subjects who took treatment before 60 minutes from migraine onset and after 60 minutes from migraine onset.

Name of Company: Istituto Luso Farmaco D'Italia S,p.A.	**TABULAR FORMAT**		**(For National Authority Use only)**
Name of Finished Product: N.A.	**REFERRING TO PART OF THE DOSSIER**	5.3	
Name of active substance(s):	**Volume:**		
Frovatriptan 2.5 mg + Dexketoprofen 37.5 mg Frovatriptan 2.5 mg + Dexketoprofen 25 mg Frovatriptan 2.5 mg + placebo	**Page:**		

Results:

The analysis of the primary efficacy variable (i.e. pain free at two hours since the migraine attack without intake of any rescue medication) showed that both the combination therapies, at the dose of 25 mg and 37.5 mg of dexketoprofen plus frovatriptan 2.5 mg, are efficacious and well tolerated and more efficacious than frovatriptan 2.5 mg alone. Substantially, this result is confirmed in the other identified subpopulation, in particular considering PP and menstruating women populations. In the other subpopulation, the trend of efficacy is the same, even if statistically significances are not always achieved due to the small number of subjects considered. Statistically significant difference among treatments, has been obtained in the treated after 30 minutes population and not in the treated before 30 minutes one and this result is likely due to the presence of dexketoprofen that presents a short T_{max} and a quick onset of action.

The same efficacy profile has been shown after 4 hours for all analysed populations and, particularly, in treated after 30 and 60 minutes and in menstruating women populations, where the pain is likely to reach more severe intensity, while, after one hour, no statistically significant differences among groups could be found, even if, from a clinical point of view, combinations are always much better than frovatriptan alone in the all considered subpopulations with, as mean, twice the percentage of subjects pain free at 1 hour in the combination groups compared with the group treated only with Frovatriptan.

Considering percentage of subjects pain free within two hours and without recurrence or rescue medication within 48 hours, no differences among treatments were found in any of the studied populations, however, in all studies sub populations, number of pain free subjects is about 10% more in the groups treated with combinations respect to that in the group treated with frovatriptan only.

Again, the two combinations are statistically significant better than frovatriptan alone, in relieving headache within two hours in the FAS populations and almost all other considered subpopulations. Considering the subpopulation treated before and after 30 and 60 minutes, once again a statistically significant difference was found only in the treated after 60 minutes population.

Quite similar results were obtained considering percentage of subjects with headache relief at 1, 2 and 4 hours with better results at 4 hours. This results can be related to time to meaningful relief that does not change in a statistically significant way among treatments groups except, once again, and confirming the major effectiveness of combinations when given late respect to migraine onset, in the treated after 30 and 60 minutes populations, however combinations appear, from a clinical point of view, always more effective than frovatriptan alone also in obtaining meaningful relief of headache.

As concern the speed of onset, that considers percentages of subjects with decrease of one point in headache intensity at 60, 90, 120 and 240 minutes, combinations are statistically significant better than frovatriptan alone at 1, 1.5 and 2 hours but not at 4 hours. This result is substantially confirmed in all analysed subpopulations apart, again, for the treated after 60 minutes population in which difference among treatments is statistically significant also after 4 hours.

Considering the use of rescue medications, treatments are statistically different only in the FAS population, however, in all analysed subpopulation, the use of rescue medication is significantly lower in the groups treated with the associations frovatriptan plus dexketoprofen respect to the group treated with frovatriptan only.

No differences were found, among the three treatment groups, as concerns frequency and time to recurrence, meaningful relief at 30 minutes, percentages of subjects pain-free at 2 hours with recurrence within 48 hours, and subjects pain-free at 24 hours while, for other considered secondary variables some differences were found, in particular, concerning subjects' preference for treatment in all studied sub-populations, favourable to combinations, resolution of phonophobia in PP population (where frovatriptan alone resulted better than combination with dexketoprofen 37.5 mg), resolution of osmophobia where overall among treatments difference was found in treated after 30 minutes population, and sustained pain free at 24 hours in FAS, PP, treated after 30 minutes and treated before 60 minutes populations.

Name of Company: Istituto Luso Farmaco D'Italia S.p.A.	**TABULAR FORMAT**		**(For National Authority Use only)**
Name of Finished Product: N.A.	**REFERRING TO PART OF THE DOSSIER**	5.3	
Name of active substance(s):	**Volume:**		
Frovatriptan 2.5 mg + Dexketoprofen 37.5 mg Frovatriptan 2.5 mg + Dexketoprofen 25 mg Frovatriptan 2.5 mg + placebo	**Page:**		

Results (cont.d):
Worthy of note, in the MW population clinically significant differences between frovatriptan 2.5 mg plus dexketoprofen 25 mg and frovatriptan 2.5 mg plus dexketoprofen 37.5 mg was found for that concerns primary variable and most of the secondary (i.e. pain free at 4 hours, headache relief within 2 hours, speed of relief onset, sustained pain free) in favour of the higher dose combination.
The safety results showed that all study treatments are safe and well tolerated and the rate of occurrence of adverse events related to treatment was low (mainly involving gastrointestinal system for subjects treated with combination therapies) and the 2 serious AE were not related.

Moreover, the subjects treated with the associations of frovatriptan plus dexketoprofen showed a lower use of rescue medication respect to those treated with frovatriptan alone, helping to prevent painkillers abuse, frequently present in migraine patients.

Conclusions:
In conclusion, the results of the study indicate that administration of a combination therapy based on frovatriptan and dexketoprofen, combining different mechanisms of action, is more effective than frovatriptan alone, while maintaining a comparable safety profile.
The association, at both doses of dexketoprofen, showed a better efficacy respect to monotherapy in all assessed end-points, and, where the difference did not reach statistically significant levels, a clear trend in favour of two associations is obtained.
This better efficacy is found on one hand in terms of higher levels of pain free and pain relief achieved and on the other hand in terms of faster onset of action (see results about pain free at one and two hours, pain relief at one and two hours, mean time to meaningful relief, speed of onset of action).
Between the two doses of dexketoprofen tested in combination with frovatriptan 2.5 mg, that equal to 37.5 mg, showed the best results particularly in two categories of persons, i.e in those who received the treatment belatedly respect to the onset of pain, over 30 or 60 minutes after migraine onset of, and women who treated a migraine attack related to the menstrual cycle. These cases are those where the pain is likely to reach higher levels of severity, and where it is possible to well recognize a proportional relationship between efficacy and anti-inflammatory dosage.

Date of the report: final version, 26/11/2010

0008