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Name of Finished Product: Droxidopa	**Volume:**	
Name of Active Ingredient(s): L-threo-3,4-dihydroxyphenylserine (L-threo-DOPS)	**Page:**	

Methodology:

This was a Phase II, multi-center, randomized, double-blind, placebo-controlled, dose-response, factorial 12 arm parallel group study to be completed in approximately 120 patients. Inclusion was based on a clinical diagnosis of fibromyalgia as defined by the 1990 American College of Rheumatology (ACR) criteria and a score of between 20 mm and 90 mm on the Visual Analog Scale for Pain (VAS-P) section of the SF-MPQ at screening and baseline visits. Patients taking pregabalin prior to enrollment were required to discontinue its use three weeks prior to other screening procedures and for the duration of the study (upon appropriate written consent). Following a 4 to-10 day screening and baseline period, eligible patients were randomized and entered a nine-week treatment period comprised of one week of dose titration and eight weeks of treatment at a fixed dose, followed by a four-week safety follow-up period. The first 52 patients were randomized to one of 12 treatment groups (droxidopa monotherapy 200, 400, or 600mg TID, carbidopa monotherapy 25 or 50mg TID, droxidopa/carbidopa therapy 200/25, 400/25, 600/25, 200/50, 400/50 or 600/50mg TID, or placebo TID). Based on recommendation by the study Data Monitoring Committee (DMC), following the second interim analysis, the remaining 68 patients were randomized to one of the following 7 treatment groups: droxidopa monotherapy (600mg) TID, carbidopa monotherapy (50mg) TID, droxidopa/carbidopa therapy (400/25, 200/50, 400/50 or 600/50mg) TID, or placebo TID.

During the treatment period, patients underwent the following evaluations: pain assessment (using SF-MPQ) at each visit, evaluation of fibromyalgia symptoms by completion of the Patient Global Impression of Change (PGI-C), Fibromyalgia Impact Questionnaire (FIQ), 20-item Multidimensional Fatigue Inventory (MFI-20), Jenkins' Sleep Problem scale (JSP), as well as dolorimetry and tender point count) at each visit; evaluation of depression using the Hamilton depression scale (HAM-D) after three, five and nine weeks of treatment (or early discontinuation); and quality of life assessment using the 36-item short form questionnaire (SF-36) after the completion of the nine-week treatment or at early discontinuation.

Safety was assessed by the frequency of adverse events, vital signs and changes in concomitant medications at each visit, as well as changes from baseline values for routine clinical laboratory parameters (haematology, chemistry, and urinalysis), 12-lead electrocardiogram (ECG), serum pregnancy testing for women of childbearing potential at end of treatment (EOT). Safety follow-up for changes in adverse events continued for 4 weeks following the last study treatment.

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Number of patients:

	D_{200} [b]	D_{400} [b]	D_{600}	PL	D_{200}/C_{25} [b]	D_{200}/C_{50}	D_{400}/C_{25}	D_{400}/C_{50}	D_{600}/C_{25} [b]	D_{600}/C_{50}	C_{25} [b]	C_{50}
Planned, n [a]	10	10	10	10	10	10	10	10	10	10	10	10
Randomized, n	5	5	15	15	5	14	15	13	3	15	4	13
ITT Population, n	4	5	15	15	5	14	14	13	3	14	4	13
Safety Population, n	4	5	15	15	5	14	14	13	3	15	4	13
Per Protocol, n	4	5	12	14	4	14	10	9	3	13	3	9
Completed, n (%)	17 (71)			8(53)	46 (73)						9 (53)	

Source: Table 14.1.1.1

[a] Planned 10 patients per 12 treatment arms, as per the original protocol, Version 1.01, dated May 23, 2008. The first 52 patients were randomized according to this schedule. Based on recommendation by the study DMC, following the second interim analysis, the remaining 68 patients were randomized to one of 7 treatment groups (instead of 12): droxidopa monotherapy (600mg) TID, carbidopa monotherapy (50mg) TID, droxidopa/carbidopa therapy (400/25, 200/50, 400/50 or 600/50mg) TID, or placebo TID.

[b] Treatment arm discontinued following the second interim analysis by the DMC.

Diagnosis and main criteria for inclusion: To be eligible for study, patients were to meet all of the inclusion criteria AND none of the exclusion criteria:

Summary of the Inclusion Criteria:

Eligible patients were males or females aged 18 years or over, with a clinical diagnosis of fibromyalgia as defined by the 1990 American College of Rheumatology (ACR) criteria. They had to provide written informed consent to participate in the study and have a score of between 20mm and 90mm on the Visual Analog Scale for Pain (VAS-P) section of the SF-MPQ at screening and baseline visits.

Summary of the Exclusion Criteria:

Patients were excluded from the study if they had any of the following: uncontrolled hypertension (defined as systolic blood pressure >160 mmHg and/or diastolic blood pressure >110 mmHg) or use of ≥2 antihypertensive medications, any significant cardiac arrhythmia, any significant systemic, hepatic, cardiac or renal illness, diabetes mellitus or insipidus, history of closed angle glaucoma, clinically relevant depression (defined as a score greater than 17 on the Hamilton Depression Scale [HAM-D]), history of known or suspected drug or substance abuse, known gastrointestinal illness or disorder that may, affect the absorption of study drug, known or suspected current malignancy or a history of cancer within 5 years prior to randomization (one year for non-melanoma, non-invasive skin cancers), a mental disorder that interfered with the diagnosis and/or with the conduct of the study (e.g. schizophrenia, major depression, dementia), clinically significant abnormalities on clinical examination or laboratory testing or a known or suspected hypersensitivity to the study medication or any of its ingredients.

Patients taking pregabalin were excluded, unless they provided written informed consent and agreed to discontinue pregabalin use 3 weeks prior to other screening procedures and for the duration of the study. Other prohibited medications at screening were tri-cyclic antidepressants and norepinephrine re-uptake inhibitors.

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Exclusion Criteria (cont'd):

Other general exclusion criteria were inability to adequately co-operate or comply with the study requirements for the duration of the study, recent (within 1 month) participation in another clinical trial with an investigational agent or previous enrollment in the study.

Gender-specific exclusion criteria included pregnancy (including plans to become pregnant), breastfeeding, and lack of or refusal to use adequate contraception for women of childbearing potential (WOCP) and sexually active males whose partner is a WOCP. Pregnancy in WOCP was ruled out by a urine pregnancy test at screening and baseline, with a confirmatory serum beta HCG pregnancy test in case the urine pregnancy test was positive.

Test product, dose and mode of administration:

Each active study medication capsule contained 200mg droxidopa. Each active supplemental study medication capsule contained 25mg carbidopa. Each daily blister foil card of study medication contained 15 capsules containing droxidopa 200mg and/or placebo and carbidopa 25mg and/or placebo. Patients were instructed to take five capsules three times a day with approximately 100mL (typically half a glass) of water.

Reference therapy, dose and mode of administration:

Matching placebo capsules contained the same ingredients as the active study medication capsules, except that droxidopa and/or carbidopa were replaced by an equivalent quantity of mannitol. Patients in the placebo group were taking the same number of capsules and according to the same schedule as patients allocated to active treatment.

Duration of treatment:

Study treatments were administered over nine weeks (one week dose titration followed by eight weeks of stable dosing), followed by a 4 week post-treatment safety follow-up period, during which no treatments were given.

Criteria for Evaluation of Efficacy:

The **primary** measure of efficacy is the change from baseline to EOT (Visit 7, week 9 or early withdrawal) in the SF-MPQ total score.

The **secondary** efficacy parameters were changes in SF-36, FIQ, PGI-C, HAM-D, JSP scale, MFI, tender point count and dolorimetry for tenderness. These parameters were used to evaluate the following:

- Overall effect of droxidopa and droxidopa/carbidopa on the quality of life (SF-36), fatigue (FIQ, PGI-C, HAM-D, JSP-S, MFI-20) as well as tender point count, and dolorimetry for tenderness;
- Dose-response relationship for droxidopa (between 200, 400, and 600mg TID), or carbidopa (25 and 50mg TID) and combinations of droxidopa/carbidopa (200/25, 200/50, 400/25, 400/50, 600/25 and 600/50mg TID) in the treatment of fibromyalgia patients;
- Clinical benefit of treatment with droxidopa (200, 400, and 600mg TID), or carbidopa (25 and 50mg TID) and combinations of droxidopa/carbidopa (200/25, 200/50, 400/25, 400/50, 600/25 and 600/50mg TID) in the treatment of fibromyalgia patients;
- Estimate the optimal dose of droxidopa and droxidopa/carbidopa for relief of fibromyalgia pain using response surface methodology.

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Criteria for Evaluation of Safety:

The safety of droxidopa and droxidopa/carbidopa treatments was evaluated based on the occurrence of treatment-emergent adverse events (TEAE) and specific evaluation of changes in blood pressure, heart rate, ECG, and laboratory findings across the study.

Statistical methods:

This was a phase II, dose-response study to establish the Proof of Concept (PoC) for droxidopa (including combinations) and to generate hypotheses which would be addressed in later confirmatory trials. The 3 x 4 factorial design was chosen to allow for both an estimation of a dose response for droxidopa (0, 200, 400 and 600mg) and the contribution of carbidopa (0, 25 and 50mg) in the treatment of the pain of fibromyalgia. The response surface methodology was applied to ascertain if an optimal dose combination exists among the monotherapies and combinations studied.

Since carbidopa is not expected to have a direct therapeutic effect, no efficacy assessment of carbidopa as a monotherapy was planned, however this analysis was ultimately done for exploratory purposes. The level of significance has been set at 0.20 for both purposes of sample size estimation and for providing evidence of a sufficient degree of separation of the compared groups.

The first 52 patients were randomized to one of 12 treatment groups: droxidopa monotherapy (200, 400, or 600 mg TID), carbidopa monotherapy (25 or 50 mg TID), droxidopa/carbidopa therapy (200/25, 400/25, 600/25, 200/50, 400/50, or 600/50 mg TID), or placebo TID.

Per the recommendation of the DMC, five treatment groups were stopped after the second interim data review. The remaining 68 of the planned 120 subjects were enrolled into one of the following seven treatment groups: droxidopa monotherapy (600 mg TID), carbidopa monotherapy (50 mg TID), droxidopa/carbidopa therapy (400/25, 200/50, 400/50, or 600/50 mg TID), or placebo TID. This change of enrollment caused the unequal allocation of patients to the treatment groups in the original 12 group (3X4) design; conditional power was not estimated for the new allocation of patients. However, because the study is considered exploratory and PoC in nature, inferential statistics were provided to support any observed data trends rather than confirm a hypothesis.

The following populations were analyzed:

- Intention-to-treat (ITT): All randomized patients who received at least one dose of study drug and had at least one post-randomization efficacy assessment were included in the modified intent-to-treat (ITT) analysis according to the treatment to which they were randomized.
- Per Protocol (PP) Population: included all randomized patients who did not have any major protocol violation (as defined in the statistical analysis plan or SAP) and were at least 80% compliant with the investigational product use. The PP population was used for sensitivity analysis of the primary efficacy endpoint.
- Safety Population: included all randomized patients who received at least one dose of study drug. Patients were included in the analysis according to the treatment they received.

  Review of protocol violations and assignment of patients to analysis populations was performed prior to unblinding, in order to minimize the potential for bias.

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Primary Efficacy Analysis:

The change from baseline in SF-MPQ pain score at EOT (Visit 7 or early withdrawal) was analyzed using an Analysis of Covariance (ANCOVA), with droxidopa and carbidopa as factors and baseline value as covariate. Since the primary objective of the study was to assess the efficacy of droxidopa alone and in combination with carbidopa in reducing fibromyalgia pain, the response from the droxidopa and combined therapy were compared with the monotherapy as well as the placebo group. These were implemented using the "estimate" statement through a General Linear Model (GLM).

Model assumptions were checked by examining the distribution of the residuals for normality, and testing the homogeneity of the variance. While the main efficacy analysis was on the ITT population, the same analysis was conducted on the PP population as a sensitivity analysis.

In addition to the ANCOVA, a response surface methodology was applied to assess the dose-response relationship for droxidopa and droxidopa/carbidopa combination, and to ascertain if an optimal dose exists among the monotherapies and combinations. In the response surface regression model, which included baseline as covariate, the dose levels of droxidopa and carbidopa were treated as continuous variables to facilitate the hypothesis tests for linear, quadratic, and cross product terms. The lack of fit test statistics was examined to ensure the model is significant. A ridge analysis was applied to determine the region in which the optimum response lies.

The statistical modeling exercise focused on the SF-MPQ overall pain score, whereas other SF-MPQ component scores (sensory, effective, and VAS-P) were presented as descriptive statistics to provide supportive information.

Secondary Efficacy Analyses:

All secondary efficacy outcomes were presented as descriptive statistics; no statistical inference was conducted.

For further details please refer to Appendix 16.1.9.

Missing Data:

There were no missing subscores for the SF-MPQ overall or for the two subscores within a visit, as any missing item (not recorded as mild, moderate, or severe) of the SF-MPQ was considered as "none" and set to zero, as per the scoring manual. If the entire SF-MPQ was "not done" at a visit, then the overall pain score and the other two subscores were set to missing

When data for the primary efficacy outcome were missing at the EOT (Visit 7 or early withdrawal), these data were estimated using the mixed model for repeated measures and the restricted maximum likelihood method, taking into consideration the unequal spaced time intervals between visits.

Data that was part of a survey tool (e.g. SF-36, FIQ, JSP) was estimated using methodology established for each instrument. If two or fewer items were missing on the JSP scale, the missing items were imputed with the average score from the non-missing items before the total score was calculated; otherwise the total score was set to missing. For the HAM-D scale, if fewer than 50% of the items were missing, data were replaced with the mean of the non-missing items from the same category (i.e. five-point or three-point scale questions). There were no imputations for missing PGI score values.

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SUMMARY OF EFFICACY RESULTS:

Primary Endpoint:

At the end of the nine-week treatment period, there was a reduction (improvement) from baseline in the mean SF-MPQ pain scores in all four treatment groups: 4.2 reduction in the droxidopa/carbidopa combination, a 4.4 point reduction in the droxidopa monotherapy groups, and a 2.7 point reduction in the placebo group. Statistical comparisons did not yield significant differences between the two droxidopa-containing treatments or between either of the droxidopa-containing regimens and carbidopa/placebo. Pre-defined sensitivity analyses of the primary efficacy variable were performed on the PP population and yielded similar results. Additional analyses indicated a 6.8 point reduction in the carbidopa monotherapy group; since this was not a planned analysis, according to the SAP, no statistical comparison was made between the carbidopa monotherapy cohort and the other treatment groups.

Comparison of the three dose levels of droxidopa (200 mg TID, 400 mg TID and 600 mg TID, which formed the pooled droxidopa monotherapy group) with placebo suggest a possible dose-response relationship, with the two low doses showing less (-1.3 points) or comparable reduction (-2.8) in SF-MPQ pain score compared to placebo (-3.0), whereas there was a greater reduction (-6.2) in the 600 mg TID group. However, these observations should be assessed with caution, due to the low and unequal number of patients in these treatment groups.

Secondary Endpoints:

None of the treatments demonstrated consistently greater improvements from baseline to EOT across the eight domains of SF-36. However, clinically significant changes (≥12.5 point increases) from baseline to EOT were observed for the Bodily Pain, Role-Physical, Role-Emotional and Social Functioning domains in the droxidopa monotherapy group. While no formal statistical comparisons were made between the groups, these changes were numerically greater compared to the corresponding increases in the droxidopa/carbidopa combination, carbidopa monotherapy and placebo groups. Consistent with quality of life assessments using the SF-36 questionnaire, droxidopa administered as monotherapy or in combination with carbidopa, resulted in a 9.7 and 9.3 point reduction in the FIQ total score from baseline to EOT, which represented a clinically important reduction of ≥14%, compared to corresponding reductions of 7.1 and 4.7 points in the carbidopa and placebo groups, respectively.

The greatest reduction (improvement) in the General Fatigue score of the MFI-20 was also observed in the combined droxidopa monotherapy group (-2.1 points compared to -0.7 to +0.5 in the other three treatment groups), the clinical relevance of this finding is uncertain. There were no meaningful changes in any of the treatment groups in PGI-C scores, HAM-D scores, tender point count and dolorimetry assessments.

There was a high rate of concomitant medication use in the study population, particularly analgesics (taken by 75% to 87% of patients in the four treatment groups), and anti-inflammatory and antirheumatic products (47% to 67%), and this had likely an impact on the efficacy assessments.

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SUMMARY OF THE SAFETY RESULTS:

The majority of patients in all four treatment groups (86%-88% in the droxidopa-containing treatment groups and 80% to 82% in the placebo and carbidopa groups) reported at least one AE during study treatment or during the four-week post-treatment follow-up period. The majority of the AEs (95% in the droxidopa/carbidopa, 87% in the droxidopa monotherapy, 92% in the carbidopa monotherapy and 95% in the placebo group) were mild to moderate in intensity. The percentage of patients with at least one severe AE was higher in the droxidopa-containing regimens (11% to 21%) compared to the placebo group (7%).

More than half of patients in all four groups (59% in the droxidopa/carbidopa combination group, 71% in the droxidopa monotherapy group, 53% in the carbidopa monotherapy group and 67% in the placebo group) experienced AEs assessed as at least possibly treatment-related by the investigators.

With the exception of nervous system disorders, which were more commonly reported in the droxidopa-containing treatment groups (47-50%) compared to placebo (33%), the distribution of adverse events by MedDRA SOC was comparable between the treatment groups. the most frequently reported AEs (rate ≥15%) in all four combined groups were headache, nausea, diarrhoea, nasopharyngitis, dizziness and vomiting. Headache, a known side effect of droxidopa, occurred at a comparable frequency in the droxidopa groups (28-29%) compared to the carbidopa and placebo groups (24% and 27%, respectively). The remaining five common AEs occurred at a somewhat higher rate in the carbidopa groups compared to the droxidopa-containing regimens or placebo.

A total of 3 patients experienced a treatment-emergent SAE; one each in the droxidopa monotherapy (migraine), carbidopa monotherapy (urinary tract infection) and placebo groups (pulmonary embolism). Adverse events led to withdrawal of 7 (6%) patients in the overall safety population, and were comparably distributed amongst the two droxidopa-containing and the carbidopa monotherapy groups.

Analysis of clinical and laboratory safety parameters revealed no clinically meaningful adverse effect of the study treatments on hematology, clinical chemistry, urinalysis, vital signs, or weight measurements.

There were no adverse changes from baseline to EOT in blood pressure (BP) measurements in any of the combined treatment groups. The greatest change was seen in those patients in the droxidopa monotherapy group, who experienced a mean increase of 2.5 mmHg in systolic BP compared to a mean decrease of 7.1 mmHg in the placebo group.