SYNOPSIS

INN : FEXOFENADINE

Study number : M016455/4074

Study title : Double-blind, parallel, randomised, placebo-controlled comparison of the efficacy and safety of fexofenadine HCl (MDL 16,455A) 120 mg once daily versus loratadine 10 mg once daily in the treatment of patients with seasonal allergic rhinitis.

CSR date : 23 October 2002

The study results and synopsis are supplied for informational purposes only.

Not all of the study results have necessarily been reviewed by the Regulatory Authorities.

The decision to prescribe and take a product should always be made on the basis of the most recent version of the product information and product package insert in the country of prescription.
STUDY SYNOPSIS

M016455/4074

TITLE
Double-blind, parallel, randomised, placebo-controlled comparison of the efficacy and safety of fexofenadine HCl (MDL 16,455A) 120 mg once daily versus loratadine 10 mg once daily in the treatment of patients with seasonal allergic rhinitis.

INVESTIGATORS, STUDY SITE
Multinational: (10 countries, 58 centres: Italy – 14 centres, Germany – 13 centres, South Africa – 8 centres, France – 6 centres, Portugal – 5 centres, Austria – 3 centres, Belgium – 3 centres, Greece – 2 centres, Poland – 2 centres, and Turkey – 2 centres).

PHASE
IIIb

INDICATION
Seasonal Allergic Rhinitis (SAR)

OBJECTIVES

Primary:
• To compare the efficacy of fexofenadine versus loratadine in seasonal allergic rhinitis by assessment of 24 hr reflective Total Symptom Scores (TSS) over the study period.

Secondary:
• To compare the efficacy of fexofenadine versus placebo by assessment of 24 hr reflective TSS over the study period.
• To compare the efficacy of loratadine versus placebo by assessment of 24 hr reflective TSS over the study period.
• To compare the efficacy of fexofenadine versus loratadine, fexofenadine versus placebo and loratadine versus placebo by assessment of the instantaneous trough TSS.
• To compare the overall study drug effectiveness by patient and physician evaluations in the three treatment groups.
• To assess the degree of severity of nasal congestion in the three treatment groups.
• To assess the degree of severity of the individual symptoms of sneezing; rhinorrhoea; itchy nose, palate and/or throat; and itchy watery, red eyes in the three treatment groups.
• To collect, analyse and compare data on the quality of life.
• To compare the incidence of adverse events in the three treatment groups.

DESIGN
Multinational, multicentre, three-armed, double-blind, parallel group, randomised, placebo-controlled (1:1:1) study. There was a placebo run-in phase of 3-7 days and a randomised treatment phase of 14 days.
POPULATION
Male and female patients aged between 12 and 75 years with a medical history of SAR for at least the previous two years. A total of 684 patients (228 patients per group) were to be recruited from a maximum of 57 centres. During the study, 58 centres enrolled patients.

TREATMENTS
Placebo was taken during a single-blind run-in period after which the patients were randomised to fexofenadine, loratadine or placebo. Patients randomised to fexofenadine took one 120 mg capsule each morning; patients randomised to loratadine took one 10 mg capsule each morning, and patients randomised to placebo took one placebo capsule each morning.

EFFICACY DATA
The primary analysis variable was the change in the average 24 hr reflective TSS during the double-blind treatment period from the average 24 hr reflective TSS during baseline. TSS was defined as the sum of the reported symptom severity scores for the following symptoms: sneezing; rhinorrhea; itchy nose, palate and/or throat; and itchy, watery, red eyes. The degree of severity was recorded each morning before taking medication reflectively for the previous 24 hours (24 hour reflective) and instantaneously for the previous hour (instantaneous trough) every day during the placebo run-in phase and during the active treatment phase. The degree of severity of nasal congestion was also recorded. The overall study drug effectiveness was assessed by the patient and by the physician.

SAFETY DATA
Safety was assessed by recording blood pressure and heart rate, and by recording adverse events reported by the patient or observed by the investigator during and after end of the treatment.

QUALITY OF LIFE DATA
Quality of life before, during and at the end of treatment was assessed using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).

STUDY DURATION AND DATES
The duration of this study was 9 months. Patient recruitment started in March 1998 and ended in November 1998.

STATISTICAL PROCEDURES
Demographic and baseline characteristics were assessed for comparability between the three treatment groups. Characteristics that were compared included age, sex, race, weight, height, years since start of SAR symptoms and baseline symptom scores. Categorical variables were compared using a Chi-squared test, and continuous variables using a Kruskal-Wallis test.

The primary efficacy variable, change in 24 hr reflective TSS, was analysed using an analysis of covariance with treatment and pooled centre as main effects, and the average baseline 24 hr reflective TSS as covariate.

The change in average instantaneous trough TSS, the change in the degree of nasal congestion, the change in individual symptom scores and the change in the total quality of life score were analysed similarly.

The patient’s and physician’s evaluation of overall effectiveness of study medication was compared using the Mantel-Haenszel test with centre as the stratification variable.
Incidence rates of treatment-emergent adverse events were summarised by treatment, system organ class, overall incidence and intensity both for all treatment-emergent adverse events and for the possibly related treatment-emergent adverse events. Patients who prematurely discontinued the study medication because of adverse events were listed. Baseline to endpoint changes in vital signs were analysed descriptively.

**INTERIM ANALYSIS**
No interim analysis was performed.

**RESULTS - STUDY PATIENTS AND CONDUCT**

A total of 698 patients were screened for entry into the study. Of the 684 patients who received single-blind placebo medication during the placebo run-in, 44 did not receive double-blind treatment. Six hundred and forty patients (fexofenadine: 217, loratadine: 208 and placebo: 215) were exposed to double-blind treatment. Twenty-nine (4.5%) exposed patients discontinued and 611 exposed patients completed the study. Two patients were excluded from the ITT analysis, leaving 638 patients (fexofenadine: 216, loratadine: 208 and placebo: 214) evaluable for the ITT analysis. Eighty-one patients were excluded from the PP analysis leaving 557 patients (fexofenadine: 189, loratadine: 181 and placebo: 187) evaluable for the PP analysis.

**RESULTS - EFFICACY**

Primary Efficacy Results

**24 hour reflective TSS**

The mean change in average 24 hr reflective TSS between the baseline and treatment periods for the fexofenadine treatment group was $-3.44$ compared to $-2.98$ and $-2.08$ for the loratadine and placebo treatment groups, respectively. Comparison of average 24 hr reflective TSS between treatment groups showed fexofenadine to be at least as effective as loratadine (95% CI: $-0.80$; $0.07$). Fexofenadine and loratadine were both shown to be more effective than placebo (p-values: fexofenadine vs placebo, <0.0001 and loratadine vs placebo, 0.0007). Point estimates and 95% confidence intervals for the mean differences between the treatment groups for the change in average 24 hr reflective TSS are summarised below.

<table>
<thead>
<tr>
<th>Treatment Comparison</th>
<th>Treatment Difference +/- SE</th>
<th>P-value</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fexofenadine vs Loratadine</td>
<td>$-0.36 +/- 0.22$</td>
<td>0.1022</td>
<td>(-0.80 ; 0.07)</td>
</tr>
<tr>
<td>Fexofenadine vs Placebo</td>
<td>$-1.12 +/- 0.22$</td>
<td>&lt;0.0001</td>
<td>(-1.56 ; -0.69)</td>
</tr>
<tr>
<td>Loratadine vs Placebo</td>
<td>$-0.76 +/- 0.22$</td>
<td>0.0007</td>
<td>(-1.20 ; -0.32)</td>
</tr>
</tbody>
</table>

P-values, means and associated standard errors from ANCOVA model containing pooled centre, treatment and baseline, unless otherwise specified

Average Baseline = The average of the non-missing scores during the placebo phase
Average Treatment = The average of the non-missing scores during the 2-week treatment phase
Secondary Efficacy Results

*Instantaneous trough TSS*

The mean change in average instantaneous trough TSS between the baseline and treatment periods for the fexofenadine treatment group was −2.84 compared to −2.41 and −1.64 for the loratadine and placebo treatment groups, respectively. Comparison of average instantaneous trough TSS between treatment groups showed fexofenadine to be at least as effective as loratadine (95% CI: −0.75; 0.11). Fexofenadine and loratadine were both shown to be more effective than placebo (p-values: fexofenadine vs placebo, <0.0001 and loratadine vs placebo, 0.0047). Point estimates and 95% confidence intervals for the mean differences between the treatment groups for the change in average instantaneous trough TSS are summarised below.

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Fexofenadine vs Loratadine</td>
<td>-0.32 +/- 0.22</td>
<td>0.1477</td>
<td>(-0.75 ;0.11</td>
</tr>
<tr>
<td>Fexofenadine vs Placebo</td>
<td>-0.94 +/- 0.22</td>
<td>&lt;0.0001</td>
<td>(-1.37 ;-0.51</td>
</tr>
<tr>
<td>Loratadine vs Placebo</td>
<td>-0.62 +/- 0.22</td>
<td>0.0047</td>
<td>(-1.06 ;-0.19</td>
</tr>
</tbody>
</table>

P-values, means and associated standard errors from ANCOVA model containing pooled centre, treatment and baseline, unless otherwise specified

Average Baseline = The average of the non-missing scores during the placebo phase
Average Treatment = The average of the non-missing scores during the 2-week treatment phase

*Nasal congestion*

The mean change in average 24 hr reflective nasal congestion score from baseline to the 2-week treatment period for the fexofenadine treatment group was −0.56 compared to −0.38 and −0.44 for the loratadine and placebo treatment groups, respectively. The confidence interval suggests that fexofenadine is superior to loratadine (p-value: 0.0351). Fexofenadine was shown to be more effective than placebo (p-value: 0.0198) but loratadine was not shown to be more effective than placebo (p-value: 0.8400). The mean change in average instantaneous trough nasal congestion score from baseline to the 2-week treatment period for the fexofenadine treatment group was −0.48 compared to −0.35 and −0.41 for the loratadine and placebo treatment groups, respectively. Fexofenadine and loratadine were not found to be more effective than placebo (p-values: fexofenadine vs placebo, 0.1558 and loratadine vs placebo, 0.9027).

*Individual symptom scores*

Both fexofenadine and loratadine showed improvement over placebo in the relief of all individual 24 hr reflective and instantaneous trough symptoms. In all cases, this improvement was highly significant. For the 24 hr reflective individual symptom of itchy, watery or red eyes fexofenadine was shown to be more effective than loratadine (p-value: 0.0232).

*Overall assessment of effectiveness*

Overall treatment success was defined as complete or marked relief. Assessment as moderate or slight relief was not regarded as treatment success. The overall treatment success according to investigators’ assessments were 45.0 %, 41.3 % and 38.8 % for the fexofenadine, loratadine and
placebo treatment groups, respectively. Overall success as assessed by patients was 48.3 %, 43.8 % and 39.8 % for the fexofenadine, loratadine and placebo treatment groups, respectively. However, these differences were not statistically significant. The results of the comparisons of investigators’ and patients’ assessments showed fexofenadine slightly more effective than loratadine.

**Rhinocconjunctivitis Quality of Life**

The mean change in overall rhinoconjunctivitis quality of life between Visit 2 and Visit 4 (LOCF used to replace missing data) for the fexofenadine treatment group was –1.26 compared to –0.97 and –0.91 for the loratadine and placebo treatment groups, respectively. Thus, the fexofenadine group exhibited a greater improvement in quality of life over the 2 weeks of active treatment than was observed in the loratadine and placebo groups. Comparison of overall rhinoconjunctivitis quality of life between treatment groups showed fexofenadine at least as effective as loratadine.

The seven individual items that made up the assessment of overall rhinoconjunctivitis quality of life were: Activities, Sleep, Non Nose/Eye Symptoms, Practical Problems, Nasal Symptoms, Eye Symptoms and Emotional. The results of the mean change from Visit 2 to Visit 4 (LOCF) showed similar results for each of the seven individual items, with fexofenadine effecting the largest change in all the areas, followed by loratadine and placebo.

**RESULTS - SAFETY**

The three treatment groups had similar adverse event profiles.

A total of 84 (13.1 %) patients reported at least one treatment-emergent adverse event. At least one treatment-emergent adverse event was reported by 33 (15.2 %) patients from the fexofenadine treatment group, 25 (12.0 %) patients from the loratadine treatment group and 26 (12.1 %) patients from the placebo treatment group.

The treatment-emergent adverse events reported most frequently (for more than 1 % of patients valid for the safety analysis) were headache (12 [1.9 %] patients) and somnolence (9 [1.4 %] patients). Five patients (2.3 %) in the fexofenadine group, four patients (1.9 %) in the loratadine group and three patients (1.4 %) in the placebo group reported treatment-emergent headaches. Somnolence was reported by four patients (1.8 %) in the fexofenadine group, by three patients (1.4 %) in the loratadine group and by two patients (0.9 %) in the placebo group. The incidence of treatment-emergent adverse events was similar for the three treatment groups.

A total of 33 (5.2 %) patients reported possibly related treatment-emergent adverse events. At least one treatment related adverse event was reported by 13 (6.0 %) patients from the fexofenadine treatment group, 11 (5.3 %) patients from the loratadine treatment group and 9 (4.2 %) patients from the placebo treatment group.

A total of ten patients experienced adverse events which led to their premature termination from the study. Three patients from the fexofenadine group, two patients from the loratadine group and five patients from the placebo group were discontinued from the study as a result of adverse events. Two of the patients in the fexofenadine group were terminated due to treatment-emergent adverse events considered to be at least possibly related to the study treatment, one due to moderate diarrhea, nausea and vomiting, one due to moderate somnolence (this patient also reported mild sinusitis not related to treatment). The other patient in the fexofenadine group who terminated due to a treatment-emergent adverse event was terminated due to severe pharyngitis not related to study medication. In the loratadine group one patient was terminated due to a moderately dry mouth possibly related to study
medication, while the other was terminated due to moderate somnolence and asthenia, both of which were probably related to study medication, even though these events started in the placebo phase. In the placebo group, three patients terminated prematurely due to probably related treatment-emergent adverse events: moderate gastrointestinal pain, moderate vertigo and nausea, and moderate somnolence, one due to an adverse event unlikely to be related to study drug, moderate asthma and one due to an adverse event not related to study drug, moderate sinusitis.

No deaths or serious adverse events were reported during the study. No clinically significant changes were observed for heart rate, systolic or diastolic blood pressure in any of the treatment groups.

The safety results indicate that the active study medication (fexofenadine and loratadine) was as well tolerated as placebo.

CONCLUSIONS

The results show that fexofenadine was at least as effective as loratadine in reducing the symptoms of seasonal allergic rhinitis as assessed by the 24 hr reflective TSS and the instantaneous trough TSS. Both fexofenadine and loratadine were observed to be more effective than placebo in relieving seasonal allergic rhinitis symptoms. These results were confirmed by the reflective nasal congestion scores, individual symptom scores and the quality of life analysis. The investigators’ and patients’ assessments of treatment success rates showed fexofenadine to be slightly more effective than loratadine, but the difference was not significant.

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