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|---|---|---|---|
| DRUG PRODUCT | H 199/18 | **Synopsis** | (FOR NATIONAL AUTHORITY USE ONLY) |
| DRUG SUBSTANCE(S) | H 199/18 capsule | REFERRING TO PART OF THE DOSSIER | |
| DOCUMENT NO. | SH-QBE-0010 | | |
| VERSION NO. | 01 | | |
| STUDY CODE | SH-QBE-0010 | | |
| DATE | 28 May, 1999 | | |

# A placebo-controlled study on the efficacy of on demand treatment with two doses of H 199/18 in maintaining control of symptoms in patients with gastroesophageal reflux disease without macroscopic esophagitis - A multicentre study

## STUDY CENTRE(S)

Multicentre study including 116 centres in the United Kingdom (UK), the Republic of Ireland and Canada.

## PUBLICATION (REFERENCE)

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## OBJECTIVES

Primary Objective:

- To compare the efficacy of on demand treatment with either H 199/18 40 mg, 20 mg or placebo over a 6-month period following initial complete resolution of heartburn, in the study SH-QBE-0009, with regard to time to discontinuation due to unwillingness to continue.

Secondary Objectives:

- To compare the efficacy of on demand treatment with either H 199/18 40 mg, 20 mg or placebo over a 6-month period with regard to time to discontinuation due to insufficient control of heartburn.
- To study the patients' dosing habits with on demand treatment.
- To evaluate the safety and tolerability of H 199/18.

## STUDY DESIGN

Double-blind, randomised, placebo controlled and parallel group designed study with H 199/18 40 mg, 20 mg or placebo.

### DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Patients with complete resolution of heartburn, defined as no heartburn during the last 7 days of the 4 week treatment in the study SH-QBE-0009, were eligible to enter this study.

### TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

H 199/18 40 mg once daily on demand, capsule, batch numbers: H1222-04-01-04, H1222-04-01-05 or H1222-04-01-06 or H 199/18 20 mg once daily on demand, capsule, batch numbers: H1189-04-01-03 or H1189-04-01-04.

### COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Placebo once daily on demand, capsule, batch numbers: H0459-06-03-05 or H0459-06-03-06.

### DURATION OF TREATMENT

Double blind on-demand treatment for six months or until study discontinuation.

### MAIN VARIABLE(S):

EFFICACY

The primary variable was time to study discontinuation due to unwillingness to continue.

Secondary variable was time to study discontinuation due to insufficient control of heartburn.

- SAFETY

Adverse events (AE), laboratory assessments and vital signs.

### STATISTICAL METHODS

For the primary variable and the secondary variable the three treatment groups were compared using Life Table methods for graphic presentation and a logrank test with stratification based on *H. pylori* (*Helicobacter pylori*) status.

Both Intention to treat (ITT) and Per protocol (PP) analyses were made for the primary variable.

Patients' dosing habits were described using descriptive statistics, frequency tables as assessed by Medical event monitoring system (MEMS®) containers.

Laboratory data was presented in terms of the number of patients with median, mean and standard deviations. A cross table showing the number of patients with values below, within, or above the normal range at baseline (visit 1 in SH-QBE-0009) versus the same classification at the last visit was provided for each laboratory variable. Graphs showing last visit values

versus the baseline values were presented for each treatment group and each laboratory variable.

## PATIENTS

| | H 199/18 40 mg | H 199/18 20 mg | Placebo | Total |
|---|---|---|---|---|
| No. planned | 260 | 260 | 130 | 650 |
| No. randomised and treated | 282 | 293 | 146 | 721 |
| Males/Females | 135/147 | 135/158 | 58/88 | 328/393 |
| Mean age (range) | 48.4 (18-80) | 48 (20-79) | 48.2 (22-76) | 48.2 (18-80) |
| No. analysed for efficacy (ITT) | 282 | 293 | 130 | 721 |
| No. analysed for safety | | | | 717 |
| No. completed | 238 | 235 | 71 | 544 |

## SUMMARY

- EFFICACY RESULTS

One hundred sixteen patients discontinued due to unwillingness to continue and of these, 92 patients discontinued the study due to insufficient control of heartburn as shown in Table 1. The logrank test showed a statistically significant difference between the active treatments and placebo in favor of H 199/18 40 mg and 20 mg. However, there was no statistical difference between the two active treatment groups. (Figure 1)

**Table 1. Number (%) of patients by outcome, ITT.**

| | H 199/18 40 mg | H 199/18 20 mg | Placebo | All |
|---|---|---|---|---|
| Total | 293(100%) | 282(100%) | 146(100%) | 721(100%) |
| Discontinued due to unwillingness to continue | | | | |
| No | 260( 89%) | 260( 92%) | 85( 58%) | 605( 84%) |
| Yes | 33( 11%) | 22( 8%) | 61( 42%) | 116( 16%) |
| Unwilling due to insufficient control of heartburn | 25( 9%) | 14( 5%) | 53( 36%) | 92( 13%) |
| Unwilling due to adverse event | 2( 1%) | 4( 1%) | 7( 5%) | 13( 2%) |
| Unwilling due to other reason | 6( 2%) | 4( 1%) | 1( 1%) | 11( 2%) |

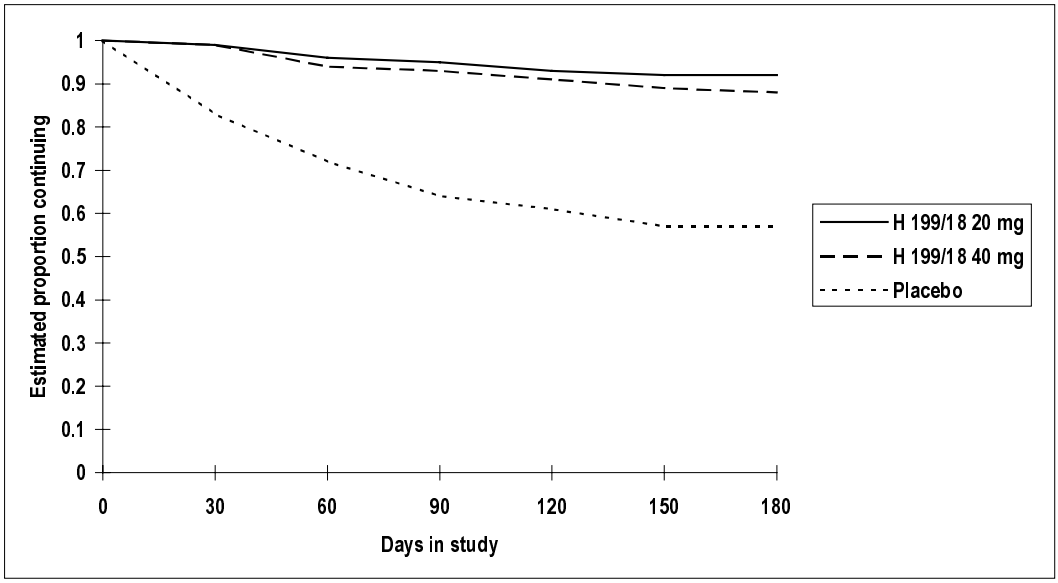


**Figure 1. Time to discontinuation due to unwillingness to continue, ITT.**

The mean number of doses of H 199/18 40 and 20 mg taken per day was 0.29 and 0.33 respectively, i.e. on average one capsule every third day.

- SAFETY RESULTS

  On-demand treatment with H 199/18 was safe and well tolerated. No specific differences between the treatment groups were seen, especially when taking into consideration the longer exposure times in the H 199/18 groups compared with the placebo group. The laboratory profiles were similar for the three treatment groups with small deviations during the study period.

## DATE OF THE REPORT

May 28, 1999