Synopsis of study report: <No. 212/2001>
Location in Module 5:

Study Code:
BY217/FHP040

Report Date:
13 December 2002

Title of the study:

Dose proportionality of roflumilast after single oral administration of 125 µg, 250 µg or 500 µg roflumilast – an open, randomized, three-period change-over study

Study center(s):

AAI Deutschland GmbH & Co KG, 89231 Neu-Ulm, Germany

Publication (reference):

n.a.

Studied period (years):

2001

Clinical phase:

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Objectives:

Primary: Dose proportionality of a single oral administration of 125 µg, 250 µg or 500 µg roflumilast as demonstrated by pharmacokinetics of roflumilast and its major metabolite roflumilast N-oxide

Secondary: Safety and tolerability

Methodology:

The study was conducted according to an open, randomized, three-period change-over design. It was planned to include 12 healthy subjects of either sex between 18 and 45 years of age.

All subjects received three tablets: single doses of orally administrated 125 µg, 250 µg and 500 µg roflumilast in the morning of Day 1 of each period in a randomized order. So in total, each subject took 125 µg + 250 µg + 500 µg = 875 µg roflumilast in the course of the study.

No. of subjects (total and for each treatment):

Twelve subjects were included in the study. All subjects received all treatments according to protocol.

Diagnosis and criteria for inclusion:

Healthy subjects of either sex, between 18 and 45 years of age (both inclusive), were included in the study.

Test product:

Roflumilast

Dose:

125 µg, 250 µg and 500 µg respectively

Mode of administration:

oral

Batch No.:

BY217-154

Duration of treatment:

Five days per period, wash-out phase of at least 10 days between the treatment periods

Reference product:

n.a.

Dose:

n.a.

Mode of administration:

n.a.

Batch No.:

n.a.

Criteria for evaluation:

The primary objective of the study was to investigate dose proportionality of a single oral administration of 125 µg, 250 µg and 500 µg roflumilast as demonstrated by pharmacokinetics of roflumilast and its major metabolite roflumilast N-oxide.

Statistical methods:

ANOVA after logarithmic transformation; point estimates and 90% confidence intervals for the respective Test/Reference ratios

SUMMARY - CONCLUSIONS

Summary:

Twelve subjects were included in the study and completed the study according to protocol. Nine subjects receiving roflumilast apprised in total 23 adverse events. Two of these events occurred after a single dose of 125 µg roflumilast, 4 of these events occurred after a single dose of 250 µg roflumilast and 17 of these events occurred after a single dose of 500 µg roflumilast. Twelve of these events were considered to be likely drug related, and 11 were considered to be unlikely drug related. The most often reported events were: headache (7 episodes with 5 mild and 2 moderate intensity in 6 subjects) and vomiting (3 episodes with 1 mild, 1 moderate and 1 severe intensity in 3 subjects). The intensity of adverse events was predominantly mild or moderate. One subject receiving a dose of 500 µg roflumilast reported eight adverse events, all of which could have been due to an intercurrent viral infection. Adverse events such as vomiting, nausea, and dizziness were reported under a dose of 500 µg roflumilast only.

No serious adverse events occurred. For hematological and clinical chemical parameters, no directed changes of the mean or median values of clinical relevance were observed. No directed changes in the mean or median values of blood pressure, pulse rate, ECG times and intervals were observed. A systematic influence on QTc values was not detected.

Conclusions:

The primary objective of the study was to investigate dose proportionality of a single oral administration of 125 µg, 250 µg and 500 µg roflumilast as demonstrated by pharmacokinetics of roflumilast and its major metabolite roflumilast N-oxide

Test/Reference ratios found for AUC(0-∞) and Cmax revealed dose proportionality between the 500 µg and the 250 µg dose for roflumilast. Point estimates and 90% confidence intervals were within the equivalence range.

There was no strict dose proportionality found for the 125 µg dose, most probably due to limitations by the lower limit of quantitation.
For roflumilast N-oxide, dose proportionality was found for both Test doses when compared to the Reference dose of 250 µg roflumilast. The point estimates for the Test/Reference ratios of the geom. means of AUC(0-∞) and Cmax for the 125 µg as well as for the 500 µg dose and their respective 90% confidence limits were inside the equivalence range.
A single dose of 125 µg or 250 µg or 500 µg roflumilast was well tolerated in 12 healthy subjects of either sex (4 male, 8 female) with regard to adverse events, vital signs, ECG parameters and laboratory values.