Synopsis of study report: 210/2001

Location in Module 5:

Study Code:

BY217/FHP033

Report Date:

10-Jun-2002

Title of the study:

Male endocrine function after single and repeated oral administration of 250 µg or 500 µg roflumilast.

Study center(s):

AAI Deutschland GmbH & Co KG, Wegenerstr. 13, D-89231 Neu-Ulm.

Publication (reference):

Not applicable

Studied period (years):

2001

Clinical phase:

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Objectives:

Primary: Male endocrine function after single and repeated oral administration of 250 µg or 500 µg roflumilast.

Secondary: Adrenal cortex function (glucocorticoid and mineralocorticoid) after single and repeated oral administration of 250 µg or 500 µg roflumilast.
Safety and tolerability.

Methodology:

A double-blind, placebo-controlled, randomized, three-period changeover design. Levels of testosterone, FSH, LH, inhibin-B, progesterone, ACTH and aldosterone, as well as concentrations of sodium and potassium were determined at the screening examination, and on study days 1 and 14 at pre-dose, and at 2h after the administration of study medication (500 µg roflumilast, 250 µg roflumilast and placebo). Cortisol levels before and after ACTH stimulation test (0.25 mg of Synacthen® intravenously) was determined in the morning of study day –7 of the first study period, and on study day 15 of each study period.

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

A total of 25 subjects were included in the study. A total of 24 per-protocol subjects for each treatment (500 µg roflumilast, 250 µg roflumilast, placebo) completed the study.

Diagnosis and criteria for inclusion:

Healthy male subjects, between 18 and 45 years of age.

Test product:

Roflumilast

Dose:

1 tablet of 250 µg and 500 µg respectively, once daily for 15 days.

Mode of administration:

Oral

Batch No.:

BY217-155

Duration of treatment:

15 days per period; wash-out phase of at least 10 days between treatment periods.

Reference product:

Placebo

Dose:

1 tablet of placebo once daily for 15 days.

Mode of administration:

Oral

Batch No.:

BY217-155

Criteria for evaluation:

Hormones:

Testosterone, FSH, LH, inhibin-B and progesterone levels; changes of ACTH and aldosterone levels, as well as cortisol levels before and after ACTH stimulation.

Safety:

Adverse events, clinical laboratory, vital signs, ECG.

Pharmacokinetic (drug/compliance monitoring):

Plasma concentrations of roflumilast and roflumilast N-oxide.

Statistical methods:

Hormones and safety parameters were analyzed descriptively.

SUMMARY - CONCLUSIONS

Summary:

Hormones:

The following tables display median hormone levels before (pre-dose) and after (2h post-dose) the administration of 500 µg and 250 µg roflumilast, as well as placebo at study day 1 and study day 14 (steady state).

500 µg roflumilast: Median hormone levels in healthy male subjects before (pre-dose) and after (2h post-dose) the administration of study medication at study day 1, and study day 14 (steady state)

Hormone	Day 1/ Pre-dose	Day 1/ 2h Post-dose	Day 14/ Pre-dose	Day 14/ 2h Post-dose
Testosterone (ng/ml)	5.32	6.05	5.70	5.92
FSH (U/l)	1.64	1.94	1.66	1.59
LH (U/l)	4.95	4.88	4.16	3.58
Inhibin B (ng/l)	136.0	150.0	148.5	148.0
Progesterone (ng/ml)	1.05	1.02	0.98	0.91

250 µg roflumilast: Median hormone levels in healthy male subjects before (pre-dose) and after (2h post-dose) the administration of study medication at study day 1, and study day 14 (steady state)

Hormone	Day 1/ Pre-dose	Day 1/ 2h Post-dose	Day 14/ Pre-dose	Day 14/ 2h Post-dose
Testosterone (ng/ml)	5.47	5.45	5.66	5.85
FSH (U/l)	1.63	1.87	1.55	1.73
LH (U/l)	3.82	3.81	4.25	3.07
Inhibin B (ng/l)	129.5	136.5	135.0	142.0
Progesterone (ng/ml)	1.13	0.95	0.97	0.96

Placebo: Median hormone levels in healthy male subjects before (pre-dose) and after (2h post-dose) the administration of study medication at study day 1, and study day 14 (steady state)

Hormone	Day 1/ Pre-dose	Day 1/ 2h Post-dose	Day 14/ Pre-dose	Day 14/ 2h Post-dose
Testosterone (ng/ml)	5.76	5.32	5.78	5.72
FSH (U/l)	2.04	2.06	1.68	1.72

Hormone	Day 1/ Pre-dose	Day 1/ 2h Post-dose	Day 14/ Pre-dose	Day 14/ 2h Post-dose
LH (U/l)	4.80	4.32	4.18	3.92
Inhibin B (ng/l)	146.0	143.0	138.5	139.5
Progesterone (ng/ml)	1.08	1.05	1.08	0.90

Median values of testosterone, FSH, LH, inhibin B, progesterone, as well as aldosterone, ACTH, sodium and potassium did not show any changes evaluated as clinically relevant during the study. Cortisol showed normal increments after stimulation with ACTH.

Safety:

A total of 25 subjects were included in the study, 24 completed the study according to protocol. After treatment with 500 µg roflumilast, 41 adverse events occurred in 11 subjects. After treatment with 250 µg roflumilast, 27 adverse events occurred in 13 subjects. After treatment with placebo, 21 adverse events occurred in 12 subjects. Adverse events reported most frequently were headache, diarrhea, arthralgia, neck pain and eye disorder. The intensity of adverse events was predominantly mild or moderate. Subject No. 5 alone reported 19 adverse events after treatment with 500 µg roflumilast. Subject No. 20 dropped out after treatment with placebo due to an adverse event which was unrelated to the treatment. No serious adverse events occurred. For hematological and clinical chemical parameters, no changes of clinical relevance in mean or median values were observed. For blood pressure, pulse rate, ECG times and intervals, no changes of clinical relevance in mean or median values were observed. A systematic influence on QTc values was not detected.

Pharmacokinetic (drug/compliance monitoring):

The pharmacokinetic results revealed that all subjects received the respective dose. Trough values at study days 14 and 15 showed comparable values. The trough values of roflumilast and roflumilast-N-oxide at study days 14 and 15 were approximately as double as high after 500 µg roflumilast compared to trough values after 250 µg roflumilast.

Conclusions:

There was no indication that roflumilast had a clinically relevant influence on hormone levels in this study. Roflumilast was safe and well tolerated at doses of 250 µg and 500 µg once daily during 15 days. Dose-linearity between 250 µg and 500 µg roflumilast in steady state could be assumed.