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Ibuprofen and pseudoephedrine hydrochloride as granules for oral solution. A comparative pharmacokinetic study

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ABSTRACT

Introduction: *Conventional oral formulations can be difficult to swallow for patients with dysphagia, children, and the elderly. A new pharmaceutical form containing a combination of ibuprofen/ pseudoephedrine designed to provide easier administration and more flexible dose adjustment while maintaining similar pharmacokinetic profile to other conventional formulations already on the market was developed.*

The objective of this study was to evaluate the bioequivalence of a fixed oral combination of 400 mg ibuprofen and 60 mg pseudoephedrine granules for oral solution, compared with a reference market standard formulated in soft capsules after single dose administration.

Methods: *An open, randomized, single dose, two-period, crossover trial was conducted. Subjects were randomly assigned to receive either 1 sachet of granules for oral solution (400 mg/60 mg – Test product), or 2 soft capsules with liquid content of SpaltGrippal® (200 mg/30 mg - Reference product) under fasting conditions. For the evaluation of bioequivalence, the 90% CI of log-transformed values were calculated for the ratios Test vs Reference for AUC(0-t) and C_{max} of ibuprofen (racemic) and (1S,2S)-pseudoephedrine and then compared to the corresponding acceptance ranges. Safety and tolerability were assessed during the clinical period and one week after the last dose.*

Results: *Bioequivalence was demonstrated for both C_{max} and AUC(0-t) of pseudoephedrine, as well as for the total exposure of ibuprofen, while the C_{max} of ibuprofen slightly exceeded the upper acceptance limit by approximately 6%. For both actives, T_{max} was lower with the granule's formulation. The overall safety and tolerability of the study medications were identical*

Conclusions: *Although the bioequivalence criteria between Test and Reference product were not completely met, the new formulation of ibuprofen/pseudoephedrine granules for oral solution is able to pro-*

vide a therapeutic equivalence to conventional solid forms, ensuring a more convenient administration, faster onset of analgesia for the patient without altering its total exposure.

KEYWORDS: Ibuprofen; pseudoephedrine; granules for oral solution; bioavailability, pain relief.

INTRODUCTION

Cold and influenza (flu) are the most common infectious syndromes in humans. These diseases are diagnosed based on symptomatology, and treatments are mainly symptomatic (1).

The association between an analgesic/antipyretic drug and a nasal decongestant drug is known and long used in clinical practice for the symptomatic treatment of acute upper respiratory tract infections (URTI) or common cold, often associated with pain, fever and nasal obstruction (2-4).

Ibuprofen is widely used for the relief of mild to moderate pain. It also may be used for self-medication for the temporary relief of minor aches and pains associated with the common cold, flu, or sore throat; headache (including migraine); toothache; muscular aches; backache; and minor pain of arthritis (5).

Pseudoephedrine hydrochloride is a peripherally acting adrenergic receptors stimulant used as a nasal decongestant for self-medication for the temporary relief of nasal congestion associated with upper respiratory allergy and to provide temporary relief of sinus congestion and pressure (6).

The fixed ibuprofen/pseudoephedrine combinations, administered principally as tablets and capsules, are approved and used for decades throughout Europe to relieve the symptoms of the common cold and flu when associated with stuffy nose (nasal congestion) and sinuses (sinusitis), with a well-established and accepted risk/benefit ratio.

However, some categories of people, such as children, the elderly, and dysphagics have difficulty swallowing solid oral formulations.

Dysphagia is increasingly common in the elderly and is particularly prevalent in long-term care facilities (7,8). Administration of crushed medication mixed with a soft food or liquid vehicle, or through a feeding tube, is a common strategy to circumvent swallowing difficulties in patients with dysphagia. However, inappropriate drug use and improper crushing technique can reduce the dose of drug received by the patient, alter drug pharmacokinetics and pharmacodynamics, and compromise treatment efficacy and patient safety (8).

For these patients, as well as children and the elderly, therefore, the availability of alternative formulations, such as liquid, orodispersible, or effervescent forms that are easier to administer, is particularly beneficial.

The main objective of this study was to assess the bioequivalence of a new oral fixed combination of 400 mg ibuprofen and 60 mg pseudoephedrine formulated as granules for oral solution (Test product) as compared to a market standard in the form of soft capsule (2 x SpaltGrippal® 200 mg/30 mg - Reference product) after single dose administration under fasting conditions in two different periods, at least 3 days apart.

The secondary objective was to investigate the safety and tolerability of the two preparations based on safety clinical and laboratory examinations and

registration of adverse events and/or adverse drug reactions.

METHODS

Subjects

Thirty-three male and female healthy volunteers aged 18 to 55 years, with a body mass index (BMI) between 18.5 and 30 kg/m^2, and in good health based on medical history, physical examination, and laboratory screening were eligible to participate.

Main exclusion criteria included history of drug abuse or use of illegal drugs; alcohol abuse; regular consumption of beverages or food containing methylxanthines; pregnancy; known hypersensitivity or intolerance to NSAIDs; presence or a history of clinically significant cardiovascular, renal, hepatic, pulmonary, metabolic, endocrine, haematological, gastrointestinal neurological, psychiatric or other diseases; any chronic disease which might interfere with resorption, distribution, metabolism or excretion of the drug; history of difficulty in swallowing; positive serologic findings for HIV antibodies, HBsAg, and/or HCV antibodies.

All volunteers provided written informed consent.

Ethics

The trial was performed in accordance with the Declaration of Helsinki and its last amended (9), ICH Topic E8. Note for Guidance on General Considerations for Clinical Trials (10), ICH Topic E6. Guideline For Good Clinical Practice E6(R2) Step 5 (11), CHMP Guideline on the Investigation of Bioequivalence (12), Ibuprofen oral use immediate release formulations 200-800 mg product-specific bioequivalence guidance (13).

Before the start of the study, the protocol and other appropriate documents (CRF, information for subject and informed consent) were submitted to the competent Ethics Committee For Clinical Trials (ECCT) in accordance with local and European legal requirements.

Study design

This was a monocentric, open, randomized, single-dose, two-period, crossover trial conducted in healthy volunteers.

Each subject received in a random way an oral single dose of either 1 sachet of granules for oral solution (Test product = 400 mg of ibuprofen and 60 mg of pseudoephedrine) dissolved in 240 mL of table water or 2 capsules of SpaltGrippal® 200 mg/30 mg (Reference product = 400 mg ibuprofen and 60 mg of pseudoephedrine) with 240 mL of table water on two single occasions under fasting conditions. The order in which the treatments was given was defined in a randomization schedule.

The wash-out phase between the two treatment periods was initially scheduled for at least 3 days, however, the actual wash-out phase was between 4 and 9 days in all subjects.

The volunteers were fasted from food and beverages other than water, from 9 p.m. on the evening before dosing until lunchtime on the following day, approximately 4 hours post-dose. Water was provided *ad libitum* until 1 hour before and from 1 h after the drug administration on day 1 in each study period. The use of concomitant medication (except from paracetamol) was strictly forbidden for the whole trial period.

Criteria for evaluation

The primary endpoints of the trial were the comparison of pharmacokinetic parameters and the bioequivalence assessment of the two formulations (Test and Reference product) considering AUC(0-t) and C_{max} of ibuprofen (racemic) and (1S,2S)-pseudoephedrine, while the evaluation of t_{max} was the secondary endpoint. AUC(0-∞), AUCres, MRT, and t½ of analytes were also calculated as additional endpoints.

Determination of plasma concentrations

Blood samples for analysis of ibuprofen (racemic) and (1S,2S)-pseudoephedrine in plasma (total number of 40 blood samples for two study periods, 8 mL each) were drawn at the following times: 0:00 (pre-dose), 0:15, 0:30, 0:45, 1:00, 1:15, 1:30, 1:45, 2:00, 2:20, 2:40, 3:00, 3:30, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00, 24:00 in each period.

All blood samples were collected into tubes using EDTA K2 as anticoagulation agent. After the end of clinical part of the trial the plasma samples were transported frozen to the bioanalytical center for the bioanalytical procedures.

Plasma concentrations were analyzed using liquid chromatography by tandem mass spectrometry (LC-MS/MS). For ibuprofen (racemic), the calibration range was 150.14 - 60054.00 ng/mL with an inter-assay precision of 2.52, 1.73, 1.43, 1.49 % CV; for (1S,2S)-pseudoephedrine, the calibration range was 1.00 - 1000.00 ng/mL with an inter-assay precision of 2.93, 1.86, 1.40, 1.75 % CV. In order to eliminate the influence of the inter-assay imprecision on the assessment, all plasma samples of the same subject were measured in a single analytical batch.

Statistical and Pharmacokinetic analysis

The sample size of 28 was calculated in respect of the primary endpoints AUC(0-t) and C_{max} of ibuprofen and pseudoephedrine. The following parameters were taken into consideration: α (consumer's risk) = 0.05, β (producer's risk) = 0.2 (power=80%), θ_0 (mean 'true' ratio) = 94% and 95% for ibuprofen and pseudoephedrine respectively, a bioequivalence limit acceptance range of 80% –125%.

The *Safety Population* set, defined as all subjects who were administered at least 1 dose of the investigational drugs, was used for summaries of safety and other variables such as, demographics, disposition, AEs, physical examination including vital signs, ECG measurement and clinical laboratory test results.

The *Per Protocol* set, defined as all subjects with no major protocol deviation(s), was used for the bioequivalence assessment.

Pharmacokinetic parameters were derived from plasma concentration–time data using a noncompartmental approach and summarized by descriptive statistics, namely arithmetic and geometric means, standard deviation (SD), coefficient of variation (CV), median and ranges (lower and upper). These parameters included AUC(0-t), AUC(0-∞), C_{max}, t_{max}, AUCres, MRT and t½.

For each subject and each treatment, the primary endpoints were calculated by means of parametric method (ANOVA-log). The descriptive statistic was used for the evaluation of secondary and additional endpoints.

The 90% confidence intervals (CI) of the log-transformed values were calculated for the ratios

Test vs. Reference for AUC(0-t) and C_{max} of ibuprofen (racemic) and (1S,2S)-pseudoephedrine and subsequently compared with the pre-set BE acceptance ranges.

Bioequivalence between the Test and Reference formulations was demonstrated if the 90%Cis for ln C_{max} and AUC0-t were within the acceptable range of 80%–125%.

The biostatistical evaluation was carried out by means of the validated statistical software package SAS for Windows, last available version 9.4

Safety

Adverse events were monitored during the clinical period and one week after the last dose of study treatment, and throughout clinical and laboratory examinations at entry and final visit. Descriptive statistics were used to summarize all safety data.

RESULTS

Subject Disposition and Characteristics

A total of 28 subjects were randomized and treated at least once with one of the study medications. One subject withdrew from the trial prematurely; thus, twenty-seven subjects completed the trial according to the protocol. All samples of 28 subjects (27 study completers 17 male and 10 female, and one drop-out) were analysed. The statistical evaluation was based on the data of the 27 completers. The baseline demographic characteristics of the study population are summarized in Table 1.

Table 1: Baseline demographic data of subjects

BMI: Body Mass Index

(n=27)	**Mean ± SD**	**Min – Max**
Age (years)	39.9 ± 9.0	19.0 - 53.0
Height (cm)	172 ± 12.5	150.0 - 195.0
Weight (kg)	77.7 ± 13.7	53.7 - 107.5
BMI (kg/m^2)	26.3 ± 3.2	19.8 - 29.8
White	100%	
male : female	17 : 10	

The mean ± SD age was 39.9 ± 9.0 years, body weight was 77.7±13.7 kg, and body mass index was 26.3±3.2 kg/m^2.

PK parameters

The plasma concentration time profiles and all pharmacokinetic parameters of ibuprofen (racemic) and (1S,2S)-pseudoephedrine for the Test formulation in granules for oral solution and the Reference formulation as soft capsules are summarized in Figure 1 and in Table 2 and. Both formulations showed similar concentration time profiles, with a rapid increase until the maximum concentration of the two analytes was reached within 1 to 1.5 hours; however, a slight difference in C_{max} was observed, with a higher peak observed with the granule formulation (Ibuprofen: mean C_{max} 44.2 ± 8.6 µg/mL for the Test product and 37.1 ± 8.8 µg/mL for the Reference product; Pseudoephedrine hydrochloride: mean C_{max} 0.27 ± 0.06 µg /mL for the Test product and 0.24 ± 0.5 µg /mL for the Reference product).

Table 2: Pharmacokinetic parameters of ibuprofen (racemic) and (1S,2S)-pseudoephedrine after an oral single dose of 400 mg of ibuprofen and 60 mg of pseudoephedrine of test and reference formulations

	Test formulation granules for oral solution					Reference formulation soft capsules				
PK Parameter	N	Arithmetic mean	SD	CV	median	N	Arithmetic mean	SD	CV	median
Ibuprofen (racemic)										
AUC (0-t) (µg*h/mL)	27	107.5	27.7	25.8	105.5	27	108.9	24.3	22.1	108.3

AUC (0-∞) (µg*h/mL)	27	109.1	28.1	25.8	107.9	27	111.8	24.6	22.0	109.8
Cmax (µg/mL)	27	44.2	8.6	19.4	46.0	27	37.1	8.8	23.8	37.2
tmax (h)	27	0.36	0.19	52.0	0.25	27	0.97	0.78	80.3	0.75
AUCres (%)	27	1.46	0.66	44.9	1.59	27	1.75	0.82	46.9	1.78
MRT (h)	27	2.87	0.5	17.4	2.84	27	3.28	0.55	16.9	3.05
t ½ (h)	27	2.02	0.37	18.3	1.99	27	1.99	0.31	15.7	1.98
(1S, 2S)-Pseudoephedrine										
AUC (0-t) (µg*h/mL)	27	2.11	0.52	24.6	1.94	27	2.11	0.44	20.7	2.07
AUC (0-∞) (µg*h/mL)	27	2.23	0.59	26.6	2.02	27	2.27	0.62	27.3	2.14
Cmax (µg/mL)	27	0.27	0.06	20.9	0.27	27	0.24	0.05	19.4	0.24
tmax (h)	27	1.08	0.81	74.8	0.75	27	1.65	0.79	48.3	1.5
AUCres (%)	27	5.05	3.45	68.3	4.13	27	5.57	5.16	92.6	4.56
MRT (h)	27	8.11	1.65	20.3	7.73	27	8.68	2.39	27.5	8.42
t ½ (h)	27	5.54	1.21	21.9	5.26	27	5.56	1.66	29.9	5.19

AUC(0-t): area under the plasma concentration-time curve from zero to last observed concentration at time t; AUC(0-∞): area under the plasma concentration-time curve from zero extrapolate to infinity; AUCres: residual area in percent; Cmax: observed maximum plasma concentration; CV: coefficient of variation; MRT: mean residence time; SD: standard deviation; tmax: observed time point of maximal concentration; t1/2, half-life.

Assessment of Bioequivalence

The statistical analysis with the assessment of bioequivalence limit for C_{max} and AUC(0-t), of ibuprofen (racemic) and (1S,2S)-pseudoephedrine and the geometric mean ratios (test/reference) and 90%CIs of the two analytes between the 2 formulations are summarized in Table 3.

Table 3: Statistical analysis of bioequivalence

Variable	Method	Point estimator	Confidence intervals	CV%
Ibuprofen (racemic)				
AUC (0-t) (ratio test/reference)	ANOVA-log	97.20%	94.40% - 100.07%	6.28%
Cmax (ratio test/reference)	ANOVA-log	120.60%	111.00% - 131.04%	17.98%
(1S, 2S)-Pseudoephedrine				
AUC (0-t) (ratio test/reference)	ANOVA-log	98.77%	93.25% - 104.61%	12.39%
Cmax (ratio test/reference)	ANOVA-log	108.36%	102.17% - 114.93%	12.70%

AUC(0-t): area under the plasma concentration-time curve from zero to last observed concentration at time t; C_{max}: observed maximum plasma concentration

As shown, the results revealed that the fixed combination of ibuprofen/pseudoephedrine formulated as granules for oral solution had an equivalent AUC(0-t) to the soft capsules formulation: geometric mean ratio [90%CI], 97.20% (94.40%-100.07%) and 98.77% (93.25%-104.61%), for ibuprofen and

pseudoephedrine respectively.

Differently, for C_{max}, the geometric mean ratio [90%CI] resulted within the pre-set acceptance range for pseudoephedrine (108.36% (102.17%-114.93%)) while, for ibuprofen, the upper limit of the acceptance range was exceeding (120.60% (111.0%-131.04%)).

Safety

Twenty-seven healthy volunteers were exposed to an oral single dose of 400 mg of ibuprofen and 60 mg of pseudoephedrine corresponding to 1 sachet of granules for oral solution of the Test product and 2 capsules of SpaltGrippal® 200 mg/30 mg of the Reference product on two single occasions. Therefore, the total exposure for the 27 subjects who all regularly completed the trial was 400 mg of ibuprofen and 60 mg of pseudoephedrine per period, per subject.

During the trial, a total of 3 non-serious adverse events (AEs) were registered in 3 subjects and only 2 of them where treatment-emergent AEs (Table 4): one AE (presyncope) was observed in 1 subject before dosing, one AE (headache) observed in 1 subject after administration of the Test, one AE (somnolence) was observed in 1 subject after administration of the Reference.

Table 4: Number of treatment emergent adverse events by System Organ Class, Preferred Term and treatment

System Organ Class/PT	Test formulation Granules for solution	Reference formulation Soft capsules
Total number of TEAEs	1	1
Nervous system disorders	1	1
Headache	1	0
Somnolence	0	1

PT: preferred term TEAEs: treatment emergent adverse events

Discussion

The present study was designed to assess the bioequivalence between a new fixed formulation of Ibuprofen/Pseudoephedrine formulated as granules for oral solution (1 sachet = 400mg /60mg) compared to a marked standard formulated as soft capsules (2 x SpaltGrippal® 200mg /30mg = 400mg /60mg) in healthy volunteers.

As previously reported, while the extent of total exposure (AUC) was confirmed to be bioequivalent between the two formulations for both active ingredients, the rate of absorption (C_{max}) met the pre-set BE acceptance criteria (80.00 - 125.00%) only for pseudoephedrine hydrochloride. The upper limit of the bioequivalence acceptance range for the C_{max} of ibuprofen was exceeded by approximately 6%,

However, considering the significantly deviating biopharmaceutical properties of both medicinal products, this result cannot surprise. In fact, while the granules are administered as solution and thus, the active ingredients can rapidly be absorbed, capsules must necessarily be dissolved before absorption can begin, consequently, it is quite predictable that peak concentrations can be reached earlier and

with a tendency to higher values in the case of products administered in solution.

Furthermore, consistent with literature evidence, the presence in the Test formulation of ibuprofen as sodium dihydrate could have further promoted a faster absorption (14-16).

The slightly higher C_{max} of ibuprofen together with the lower t_{max} found in this study is therefore almost definitely attributable to the different pharmaceutical form along with the presence of ibuprofen as sodium dihydrate.

Regarding safety, Ibuprofen is known to have a wide therapeutic index, between 10 to 50 mg/L, and a toxic concentration of >100 mg/L. (17). The use of low-dose ibuprofen (≤ 1200 mg/day for ≤ 10 days), without a prescription, was based on marketing approval in 1983 (UK) and 1984 (USA) and is now available in over 80 countries. Its relative safety at low doses has been supported by large-scale controlled studies (18)

It was also reported that Ibuprofen, alone or in combination with pseudoephedrine, has an excellent safety/tolerability profile even after multiple doses (19, 20).

The lack of accumulation (20) along with the short plasma half-life of elimination (t½ about 2h) would provide further assurance of low toxicity even at slightly higher concentrations, provided the drug is administered as product information.

Given the pharmacokinetic characteristics, the tolerability data together with the wide therapeutic window of ibuprofen and its low toxic plasma concentration, there is therefore no reason to think that the slightly higher C_{max} value found for the new granular formulation compared to the control product could in any way alter the safety profile of the product, especially considering the equivalence of both medicinal products in terms of total exposure.

In addition, safety results of this study confirmed that both investigational products were equally well tolerated. Only two not serious treatment related adverse events were observed and no clinically important laboratory changes or trends was evidenced.

CONCLUSION

Due the major differences in the biopharmaceutical properties of granules for oral solution compared with soft gelatin capsules, the bioequivalence between the formulations has not been fully met. However, the newly developed formulation of ibuprofen/pseudoephedrine granules for oral solution can provide therapeutic equivalence to conventional solid forms, ensuring a more convenient administration and faster onset of analgesia for the patient without altering the total exposure and overall safety profile.

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