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An oral fixed combination of ibuprofen and N-acetylcysteine as granules for oral solution. A drug-drug interaction study

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ABSTRACT

Introduction: *The common cold and other upper respiratory tract infections, although self-limiting, are highly prevalent and can be debilitating. Over-the-counter medications such as analgesics, antipyretics and mucolytics are widely used in all population groups for symptomatic treatment of acute upper respiratory tract infections, especially when associated with pain, fever, and cough. A new pharmaceutical form containing a combination between an analgesic and a mucolytic has been developed. The objective of this study was to assess if a drug-drug interaction (DDI) exists in terms of relative bioavailability of an oral fixed combination of 400 mg ibuprofen and 200 mg N-acetylcysteine (NAC) compared to two market standards, containing the two components separately.*

Methods: *An open, randomized, single dose, three-period, crossover trial in 24 healthy volunteers was conducted. Subjects were randomly assigned to receive either 1 sachet of granules for oral solution (400 mg ibuprofen + 200 mg NAC – Test product) or 1 sachet of granules for oral solution (400 mg ibuprofen – Reference 1) or 1 effervescent tablet (200 mg NAC – Reference 2) on three single occasions under fasting conditions. To investigate the DDI in terms of relative bioavailability of the products, the 90% confidence intervals were calculated for the ratios Test vs. Reference 1 and Test vs. Reference 2 of the pharmacokinetic endpoints AUC(0-t) and C_{max} of ibuprofen and NAC and then compared to the corresponding acceptance ranges. Safety and tolerability were assessed during the entire duration of the study.*

Results: *No relevant pharmacokinetic interaction between ibuprofen and NAC formulated as fixed combination was detected. All the three medications (Test, References 1 and 2) were similarly well tolerated and did not show any relevant differences regarding safety.*

Conclusions: *A new oral fixed combination of ibuprofen and NAC as granules for oral solution was*

developed. No drug- drug interaction in term of relative bioavailability between the two drug substances was detected.

KEYWORDS: Ibuprofen; N-acetylcysteine; granules for oral solution; interaction study

INTRODUCTION

Upper respiratory tract infections, such as cold and influenza (flu) are the most common infectious syndromes in humans. These diseases are practically always diagnosed based on symptomatology, and treatments are mainly symptomatic (1).

The association between an analgesic/antipyretic drug and a mucolytic is known and long used in clinical practice for the symptomatic treatment of acute upper respiratory tract infections (URTI) or common colds, often associated with pain, fever and hyperproduction of mucus. “Empirical” antibiotic treatment is often overused in these conditions (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). Dosages go from 200 to 1200 mg/day and over (5).

N-Acetylcysteine (NAC) is a precursor to the amino acid cysteine, which is a key component in the synthesis of glutathione, one of the body’s most important antioxidants. Glutathione helps neutralize free radicals and reactive oxygen species (ROS), protecting cells from oxidative stress. NAC has also mucolytic (mucus-thinning) properties. It breaks the disulfide bonds in mucoproteins, reducing the viscosity of mucus and making it easier to clear from the respiratory tract. This makes it useful in conditions where thick mucus is a problem. NAC itself also has direct antioxidant effects, scavenging free radicals and reducing oxidative damage in tissues. This is particularly useful in conditions where oxidative stress plays a role (6). Dosages in adults go from 600 mg/day (in respiratory conditions) to several grams in the treatment of paracetamol poisoning (6)

A formulation associating ibuprofen and NAC would be beneficial in terms of convenience of use and adherence to treatment in all those respiratory conditions, mainly of viral origin, characterized by pains, fever and hyperproduction of mucus.

Ideally, such a formulation should also be in a soluble form, in order to facilitate treatment to all patients suffering from transient or chronic dysphagia and problems to swallow (7, 8).

The main objective of this study was to establish whether a drug-drug interaction (DDI) exists in terms of relative bioavailability of an oral fixed combination of 400 mg ibuprofen and 200 mg NAC granules for oral solution (Test product) as compared to two market standards (MOMENTACT ANALGESICO 400®, ibuprofen 400 mg granules for oral solution – Reference 1) and NAXIL ®200 mg, NAC 200 mg, effervescent tablet – Reference 2) after single dose administration under fasting conditions in three different periods, at least 3 days apart.

The secondary objective was to investigate the safety and tolerability of the preparations based on

safety clinical and laboratory examinations and registration of adverse events and/or adverse drug reactions.

METHODS

Subjects

Thirty 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 absorption, distribution, metabolism or excretion of the drug; history of difficulty in swallowing; positive serologic findings for HIV antibodies, HBsAg, and/or HCV antibodies.

Ethics

All volunteers provided written informed consent.

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, three-period, crossover trial conducted in healthy volunteers.

Each subject received, in a random way, an oral single dose of either one sachet of granules for oral solution (Test product = 400 mg of ibuprofen and 200 mg of NAC) dissolved in 240 mL of table water or one sachet of granules for oral solution (Reference 1 = 400 mg ibuprofen) dissolved in 240 mL of table water or 1 effervescent tablet (Reference 2 = 200 mg NAC) dissolved in 240 mL of table water on three single occasions under fasting conditions. The order in which the treatments was given was defined in a randomization schedule. The wash-out phase was 3 days to 6 days between the treatment day 1 in the respective trial period.

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 one hour before and from one hour after the drug administration on day 1 in each study period. The total intake of water on day 1 of dosing later than 1 hour after study drug administration was at least 1.5 liters. The use of concomitant medications (except 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 DDI assessment (Test and Reference product) considering AUC(0-t) and C_{max} of ibuprofen (racemic) and N-acetylcysteine, 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 NAC in plasma were drawn at the following times: pre-dose and 0:05, 0:10, 0:20, 0:30, 0:40, 0:50, 1:00, 1:15, 1:30, 1:45, 2:00, 2:15, 2:30, 3:00, 4:00, 6:00, 8:00, 10:00 and 12:00 in each period.

The blood samples (n=20) were taken by means of a short intravenous catheter. The blood samples for Test (8 mL), and for Reference 1 and Reference 2 (4 mL) were collected into tubes using an anticoagulating 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 149.86 - 59944.00 ng/mL with an inter-assay precision of 1.07-2.87 % CV; for N-acetylcysteine, the calibration range was 10.00 - 2499.40 ng/mL with an inter-assay precision of 2.02-12.16 % CV. To minimize the effect of variability among analytical batches, all plasma samples from each subject were analyzed in the same batch (except reanalysis).

Statistical and Pharmacokinetic analysis

The sample size of 24 was calculated in respect of the primary endpoints AUC(0-t) and C_{max} of ibuprofen and NAC. The following parameters were taken into consideration: α (consumer's risk) = 0.05, β (producer's risk) = 0.20 (power=80%), θ_0 (mean 'true' ratio) = 94% and 95% for ibuprofen and NAC respectively, a bioequivalence limit acceptance range of 80%–125%.

The *Safety Population* set, defined as all subjects who received study treatment at least once during the trial, 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 (PP), defined as all subjects with no major protocol deviation(s) who completed all trial periods for the respective comparison: PP 1 set for comparison Test *vs.* Reference 1 and PP 2 set for the comparison Test *vs.* Reference 2, was used for assessment of drug-drug-interaction.

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}, AUC_{res}, MRT and t½.

For each subject and each treatment, the primary endpoints were calculated by means of a 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 1 and Test vs Reference 2 for AUC(0-t) and C_{max} of ibuprofen and N-acetylcysteine and then compared to the corresponding acceptance ranges. According to protocol, no pharmacokinetic interaction between both components could be declared if the point estimates of the 90% confidence intervals for the ratios of both primary endpoints between the test and the reference products were within an interval of 80.00-125.00%.

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

Safety

Adverse events (AEs) were evaluated as secondary objective of the trial with regards of safety of all preparations. AEs were recorded by questioning the subjects during the total duration of the trial. Descriptive statistics were used to summarize all safety data. Treatment Emergent Adverse Events (TEAEs) are summarized in Table 4.

RESULTS

Subject Disposition and Characteristics

A total of 24 subjects (14 male and 10 female) completed the trial according to the protocol.

The plasma samples of the 24 completers were analyzed.

The baseline demographic characteristics of the study population are summarized in Table 1.

Table 1: Baseline demographic data of subjects

(n=24)	Mean ± SD	Min – Max
Age (years)	36.2 ± 9.9	19.0 - 53.0
Height (cm)	170.1 ± 9.8	155.0 - 190.0
Weight (kg)	72.8 ± 14.4	47.0 - 94.0
BMI (kg/m^2)	25.0 ± 3.2	19.1 - 29.7
White	100%	
male : female	14 : 10	

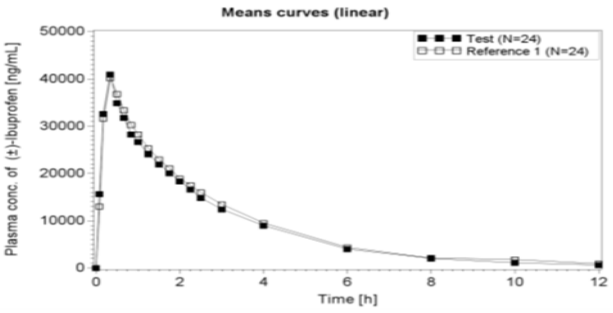
BMI: Body Mass Index

The mean ± SD age was 36.2 ± 9.9 years, body weight was 72.8±14.4 kg, and body mass index was 25.0±3.2 kg/m^2.

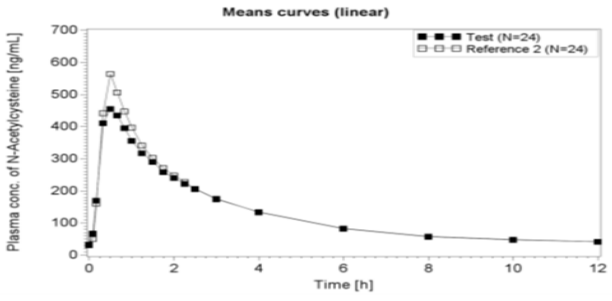
PK parameters

The plasma concentration time profiles and all pharmacokinetic parameters of ibuprofen (racemic) and NAC for the Test formulation and the two Reference products are summarized in Figure 1 and in Table 2.

Figure 1: Mean (arithmetic) ibuprofen (racemic) and N-acetylcysteine plasma concentration-time profile



Ibuprofen



N -acetylcysteine

Table 2: Pharmacokinetic parameters of ibuprofen (racemic) and N-acetylcysteine after an oral single dose of 400 mg of ibuprofen and 200 mg of N-acetylcysteine of test and reference formulations

	Test Ibuprofen 400mg/NAC 200mg granules for oral solution					Reference 1 MOMENTACT ANALGESICO 400 granules for oral solution				
PK Parameter	N	Arithmetic mean	SD	CV	median	N	Arithmetic mean	SD	CV	median
Ibuprofen (racemic)										
AUC (0-t) (µg*h/mL)	24	102.2	21.2	20.7	96.8	24	108.8	22.0	20.3	105.9
AUC (0-∞) (µg*h/mL)	24	104.0	22.7	21.9	98.3	24	112.9	26.6	23.5	107.5
AUCres (%)	24	1.62	1.18	73.0	1.30	24	2.87	5.6	194.8	1.51
Cmax (µg/mL)	24	44.0	6.5	14.8	44.8	24	43.9	8.17	18.6	44.6
tmax (h)	24	0.34	0.21	61.9	0.33	24	0.40	0.32	81.4	0.33
MRT (h)	24	2.75	0.57	20.8	2.59	24	3.09	1.31	42.5	2.79
t ½ (h)	24	1.95	0.32	16.3	1.89	24	2.10	0.71	34.0	1.96
	Test Ibuprofen 400mg/NAC 200mg granules for oral solution					Reference 2 NAXIL 200 effervescent tablet				
PK Parameter	N	Arithmetic mean	SD	CV	median	N	Arithmetic mean	SD	CV	median
N-acetylcysteine										
AUC (0-t) (µg*h/mL)	24	1.55	0.47	30.3	1.45	24	1.60	0.42	26.1	1.49
AUC (0-∞) (µg*h/mL)	24	1.79	0.48	27.1	1.65	24	1.83	0.43	23.4	1.70
AUCres (%)	24	13.9	4.50	32.2	13.9	24	12.7	3.67	28.8	12.4
Cmax (µg/mL)	24	0.52	0.22	42.9	0.46	24	0.61	0.22	36.6	0.58
tmax (h)	24	0.60	0.42	68.9	0.50	24	0.58	0.38	66.0	0.50
MRT (h)	24	5.69	1.16	20.4	5.71	24	5.33	0.94	17.7	5.23
t ½ (h)	24	4.03	1.07	26.5	3.80	24	3.77	0.76	20.3	3.68

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.

Both formulations showed similar concentration time profiles, with a rapid increase until the maximum concentration of the two analytes was reached within 0.34 to 0.60 hours (mean);

The observed mean C_{max} for ibuprofen was practically identical, (44.0±6.5 SD µg/mL for Test vs. 43.9±8.7 µg/mL for Reference). A slightly lower Cmax for NAC was found for the Test formulation (0.52±0.22 µg/mL vs. 0.61±0.22 µg/mL.

Very similar results were found also for exposure, with ibuprofen AUC (0-∞) of 104.0 ± 22.7 µg*h/mL for Test and of 112.9 ± 26.6 µg*h/mL for Reference.

Same finding for NAC, with AUC (0-∞) of 1.79 ± 0.48 µg*h/mL for Test and of 1.83 ± 0.43 µg*h/mL

for Reference.

Assessment of drug-drug interaction

The evaluation of drug-drug interaction in terms of relative bioavailability was based on a parametric method (ANOVA-log) for both endpoints AUC(0-t) and C_{max} of ibuprofen and N-acetylcysteine. The results from the comparative statistical evaluation of the Test preparation compared to the Reference 1 and Reference 2 drugs are summarized in Table 3.

Table 3: Statistical analysis of drug-drug interaction

Variable	Method	Point estimator	Confidence intervals	CV%
Ibuprofen (racemic)				
AUC (0-t) (ratio test/reference 1)	ANOVA-log	93.82%	89.64% - 98.20%	9.20%
Cmax (ratio test/reference 1)	ANOVA-log	101.08%	91.96% - 111.11%	19.21%
N-acetylcysteine				
AUC (0-t) (ratio test/reference 2)	ANOVA-log	95.34%	88.20% - 103.06%	15.78%
Cmax (ratio test/reference 2)	ANOVA-log	84.56%	76.05 - 94.03%	21.60%

AUC(0-t): area under the plasma concentration-time curve from zero to last observed concentration at time t; Cmax: observed maximum plasma concentration.

Comparison TEST vs. REFERENCE 1 (ibuprofen)

The 90% CI calculated by means of ANOVA-log for the primary endpoint, i.e. the ratio (T/R1) of AUC (0-t) of (±)-ibuprofen was between 89.64% and 98.20% and thus within the bioequivalence acceptance range. The 90% CI calculated by means of ANOVA-log for the primary endpoint ratio (T/R1) of C_{max} of (±)-ibuprofen was between 91.96% and 111.11% and thus again within the bioequivalence acceptance range.

Table 4: Number of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and treatment

System Organ Class/PT	Test	Reference 1	Reference 2
Total number of TEAEs	0	0	2
Cardiac disorders	-	-	1
Atrioventricular block first degree			1
Investigations	-		1
White blood cell counts increased			1

PT: preferred term TEAEs: treatment emergent adverse events

The point estimator of the Test formulation compared with the Reference 1 based on the primary end-points AUC(0-t) and C_{max} of ibuprofen was 93.82% for AUC(0-t) and 101.08% for C_{max}, respectively. The median (range) t_{max} of (±)-ibuprofen was 0.333 h (0.167- 1.250 h) for the Test formulation and 0.333 h (0.167 - 1.750 h) for the Reference 1. The medians and ranges for t_{max} of both products were comparable.

In conclusion, a pharmacokinetic interaction regarding ibuprofen in the fixed combination with N-acetylcysteine was not detected, since the point estimate of the 90% CIs for the ratios of the primary endpoints AUC(0-t) and C_{max} for the comparison Test vs. Reference 1 was within the interval of 80.00- 125.00%. Furthermore, the extent and rate of absorption based on AUC(0-t) and C_{max} of (±)-ibuprofen were within the bioequivalence acceptance range.

Comparison TEST vs. REFERENCE 2 (NAC)

The 90% CI calculated by means of ANOVA-log for the primary endpoint, i.e the ratio (T/R2) of AUC(0-t) of N-acetylcysteine, was between 88.20% and 103.06% and thus within the bioequivalence acceptance range. The 90% CI calculated by means of ANOVA-log for the primary endpoint ratio (T/R2) of C_{max} of NAC was between 76.05% and 94.03% and thus slightly outside the bioequivalence acceptance range.

The point estimator of the Test formulation compared with the Reference 2 formulation based on the primary endpoints AUC(0-t) and C_{max} of NAC was 95.34% for AUC(0-t) and 84.56% for Cmax.

The median (range) t_{max} of NAC was 0.500 h (0.167 - 2.250 h) for the Test formulation and 0.500 h (0.333 - 2.250 h) for the Reference 2. The medians and the ranges for t_{max} of both products are comparable.

In conclusion, a pharmacokinetic interaction regarding NAC in the fixed combination with ibuprofen was not detected since the point estimate of the 90% CIs for the ratios of the primary endpoints AUC(0-t) and C_{max} for the comparison Test vs. Reference 2 was within the interval of 80.00- 125.00%. The extent of absorption based on AUC(0-t) of N-acetylcysteine was within the bioequivalence acceptance range. The rate of absorption based on C_{max} of NAC was slightly outside the bioequivalence acceptance range.

Safety

Twenty-four healthy volunteers were exposed to an oral single dose of 400 mg ibuprofen and 200 mg NAC of the Test, 400 mg ibuprofen of Reference 1 and 200 mg NAC of the Reference 2 on 3 single occasions in a fasting state. Therefore, the total exposure for the 24 subjects all of whom regularly completed the trial was 800 mg of ibuprofen per subject and 400 mg of NAC.

During the trial, a total of 2 non-serious adverse events (AEs) were reported in 2 subjects during the trial: one "*atrioventricular block first degree*" and one "*white blood cell counts increased*" were observed in 2 subjects after administration of the Reference 2.

The investigator judged the causal relationship of the AE to the investigational product administration in both cases as "not related".

At final visit, a total of 31 out of range laboratory values were documented in 13 subjects. These laboratory results were evaluated as out of range and non-clinically relevant.

Only one out of range clinically relevant laboratory value (White blood cell increase, judged as "not related") was detected in one subject at final visit and this finding was documented as AE. The subject did not return for control laboratory examination, thus the AE remained with a 'not recovered/ not resolved' outcome.

Discussion

The present study was designed to assess the bioequivalence between a new fixed formulation of Ibuprofen/NAC formulated as granules for oral solution (1 sachet = 400mg /200mg) compared to a market standard of ibuprofen formulated as granules for oral solution (MOMENTACT ANALGESICO 400®) and another marketed standard of NAC, formulated in effervescent tablets (NAXIL® 200 mg) in healthy volunteers.

The analysis of the results shows very similar or practically identical values of T_{max}, C_{max} and AUC with the Test and the Reference formulations, with only a slight reduction in the C_{max} of Test vs. Reference 2 for NAC (0.52 vs. 0.61 µg/mL).

As far as the statistical analysis is concerned, the point estimates for the Test/Reference ratio are very close to 100%, while the CIs range between 88.20 and 111.11%, with the only exception of the C_{max} of NAC, where slightly lower values were observed (point estimate 84.56% and IC 76.05-94.03%.

Given the pharmacodynamics of NAC, however, it can be assumed that this difference is not of clinical significance.

As previously mentioned, in fact, given the mechanism of action and the pharmacodynamic "target" (14) of the compound when acting as a mucolytic (i.e. the breaking the disulfide bonds in mucus glycoproteins) a slight difference in PK parameters, and especially of C_{max}, is not going to affect the efficacy and safety of the treatment.

The relative lack of importance of C_{max} has been confirmed also by some published evidence: in a large trial run in Germany, in fact, NAC proved effective and well tolerated also when administered once a day at the dosage of 600 mg (15), while a PK trial in adults (16) showed a higher C_{max}, but no significant difference in AUC after the administration of a single dose of 600 mg vs. three doses of 200 mg.

Regarding safety and tolerability, given the results observed and the very wide therapeutic range of both ibuprofen and NAC, no issues or relevant differences can be expected during the use of the association vs. the two substances used separately.

CONCLUSION

The findings of this study confirm that the new fixed formulation of Ibuprofen/NAC (400 mg/200 mg per sachet) in granules for oral solution can be considered as bioequivalent to the separate administration of marketed ibuprofen granules (MOMENTACT ANALGESICO 400®) and NAC effervescent tablets (NAXIL® 200 mg). The pharmacokinetic parameters, including T_{max}, C_{max}, and AUC, demonstrated very similar values between the combined product and the separate formulations, with only a slight and clinically insignificant reduction in C_{max} for NAC in the test formulation.

Importantly, the slight difference observed in NAC's C_{max} is not expected to impact its clinical efficacy, as supported by the pharmacodynamic role of NAC and existing literature. The overall pharmacokinetic profile supports that the combined formulation does not lead to any significant interaction between ibuprofen and NAC, thus confirming that the association product can effectively substitute the concurrent administration of NAC and ibuprofen.

Moreover, the safety and tolerability profile ob-

served in the study, along with the broad therapeutic range of both ibuprofen and NAC, suggests that the fixed-dose combination is as safe and well-tolerated as the individual components used separately. Therefore, this fixed formulation offers a convenient and effective alternative to the co-administration of ibuprofen and NAC in clinical practice.

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