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Bioequivalence of 2 Naproxen Sodium Tablet Formulations in Healthy Male and Female Volunteers

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ABSTRACT

Background: Naproxen is an established, effective treatment for pain management in acute musculoskeletal disorders and traumatic sports injuries. Reckitt Benckiser Health Limited have developed a naproxen sodium tablet with the same pharmacokinetic and pharmacodynamic properties as existing marketed naproxen products with the intention of increasing the number of naproxen products available for prescribers and pharmacies.

Objective: This study aimed to assess comparative bioavailability between a test medicinal product developed by Reckitt Benckiser Health Limited (RB, 103-105 Bath Rd, Slough, SL1 3UH, United Kingdom; RB naproxen sodium 220 mg tablets), and a reference medicinal product, Aleve naproxen sodium 220 mg (Bayer B.V., Energieweg 1, 3641 RT Mijdrecht, Netherlands), in the fasted state.

Methods: This was a randomized, single-dose, 2-way crossover, open-label, comparative bioavailability, pharmacokinetic study in 18 healthy male and female volunteers with a 5- to 8-day washout permitted between doses (based on the anticipated minimum washout period for naproxen determined from the known terminal elimination half-life of up to 17 hours). Blood samples were taken periodically over a 72-hour period following dosing and analyzed for plasma naproxen concentration using a validated LC-MS method. Noncompartmental pharmacokinetic analysis was used to derive pharmacokinetic parameters for naproxen; safety and tolerability were evaluated throughout the study.

Results: Following a single-dose administration of naproxen sodium tablets (2×220 mg), the C_{max} and AUC_{0-t} (geometric least squares mean) for the test product was 65.88 μg/mL and 893.37 h*μg/mL, respectively; and for the reference product was 64.59 μg/mL and 890.60 h*μg/mL. The geometric least squares mean test/reference ratio 90% CI for both C_{max} (93.98–110.70) and AUC_{0-t} (98.04–102.63) was contained entirely within the predefined 80.00% to 125.00% lower and upper limits; additionally, there was no statistically significant difference in T_{max} ($P = 0.9878$) following fasted administration of the test and reference product. There was 1 treatment-emergent adverse event reported during the study; there were no serious adverse events, no suspected unexpected serious adverse events, and no clinically significant changes in laboratory safety, vital signs, or 12-lead ECG measurements reported.

Conclusions: This single-dose study found that the test product (RB naproxen sodium tablets) and reference product (Aleve naproxen sodium tablets) met the regulatory criteria for bioequivalence in these fasted male and female volunteers; both test and reference products were found to be safe and well tolerated.

Introduction

Acute musculoskeletal disorders and traumatic sports injuries, although self-limiting, often benefit from pain management therapy and it has been shown that pain, or fear of pain, is the biggest single factor in delaying full rehabilitation.[1] Naproxen, a propionic acid derivative nonsteroidal anti-inflammatory drug that

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exerts a potent analgesic, anti-inflammatory, and antipyretic activity through modulation of prostaglandin synthesis and other inflammatory pathways, is among the most effective treatments for such conditions.[1,2]

The efficacy and tolerability of prescription doses of naproxen in approved rheumatologic indications, including osteoarthritis, has been established since its approval in 1976; Naproxen was first sold as a prescription drug under the trade name Naprosyn (Laboratorios Syntex SA, Mexico City, Mexico; subsequently acquired by Roche Group in 1994).[3] The sodium salt has been available in the United States for prescription use since 1980 and was approved by the US Food and Drug Administration for down-scheduling to over-the-counter status under the trade name Aleve (Bayer Healthcare, Morristown, New Jersey) in 1994. The first approval outside of the United States was in 1981.[4,5]

Naproxen can be administered as an acid or as a salt such as naproxen sodium. In salt form the formulation has a more rapid onset of action due to faster dissolution in the gastric fluid; however, on absorption the active molecule dissociates from the salt so is pharmacologically and therapeutically identical to the standard naproxen formulation. The 2 formulations therefore have similar overall bioavailability and duration of activity.[6]

The naproxen sodium tablet manufactured by Reckitt Benckiser Health Limited (RB, 103-105 Bath Rd, Slough, SL1 3UH, United Kingdom) contains 220 mg naproxen sodium per tablet as the only active ingredient (RB naproxen sodium tablet). Naproxen and naproxen sodium are pharmacologically and therapeutically equivalent at comparable dosages (200 mg naproxen = 220 mg naproxen sodium), although naproxen sodium has a more rapid absorption rate. This more rapid absorption is ideally suitable for indications where a rapid onset of action is desirable, such as headache or dysmenorrhea, whereas standard naproxen acid is often recommended for more chronic pain states such as arthritis.[1,7]

The primary objective of this study was to assess comparative bioavailability between the RB naproxen sodium tablet and a reference formulation of Aleve naproxen sodium 220 mg in the fasted state to support a marketing authorisation application for a generic version of naproxen in the European Union. This product was chosen as a reference product because it meets the European Medicines Agency reference product criteria of being granted marketing authorization in the European Union on the basis of a complete dossier in accordance with Articles 8(3), 10a, 10b, or 10c of Directive 2001/83/EC. The tolerability of both formulations was also examined.

Subjects and Methods

Study population

Healthy male and female (nonpregnant, nonlactating) volunteers aged 18 to 50 years and with a body mass index within the range of 20 to 30 were eligible to participate in the study. Volunteers' health and eligibility against the study inclusion and exclusion criteria was assessed at the screening visit by review of past medical history, physical examination, vital signs, ECG, and laboratory tests. Participants agreed to use an effective method of contraception (unless a woman of nonchildbearing potential, where abstinent from sexual intercourse, or where anatomically sterile), from the first dose until 3 months after the final dose of study medication.

Key exclusion criteria included a history of allergy or intolerance related to treatment with naproxen or other nonsteroidal anti-inflammatory drugs, or the excipients of the formulations; a history and/or presence of significant disease of any body system, including psychiatric disorders as specified in Chapter 5 of the International Statistical Classification of Diseases and Related Health Problems 10 Classification of Mental and Behavioural Disorder; any condition that could have interfered with the absorption, distribution, metabolism, or excretion of drugs; a history of or active peptic or duodenal ulcers or gastrointestinal bleed or upper gastrointestinal bleed, or other significant gastrointestinal disorders; ingestion of a prescribed drug at any time during the 14 days before the first dose of study medication or ingestion of an over-the-counter preparation within 7 days before the first dose of study medication; and any deviation from normal parameters in ECG, vital signs, hematology, biochemistry, or urinalysis.

Study design

This was a randomized, single-dose, 2-way crossover, open-label, comparative bioavailability, pharmacokinetic study in healthy male and female volunteers, with all sample collection, processing, bioanalysis, and subsequent pharmacokinetic and statistical analysis conducted at the Clinical Pharmacology Unit, Simbec Research Ltd, Merthyr Tydfil, United Kingdom. The study consisted of a prestudy screening visit (day –21 to day –1), 2 treatment periods (day –1 to day 4), and a poststudy follow-up (2–7 days after the final blood sample was taken) and was conducted in accordance with the Declaration of Helsinki 2013,[8] International Council on Harmonisation Good Clinical Practice guidelines,[9] and applicable regulatory requirements. The study received clinical trial authorization from the United Kingdom Medicines and Healthcare Products Regulatory Agency and a favorable ethical opinion from Wales Research Ethics Committee 1 (reference No. 16/WA/0247).

A sample size of 18 volunteers was estimated based on %CV for naproxen C_{max} of 15% taken from previous similar studies reporting bioequivalence assessments under fasted conditions.[10] This sample size also satisfied 2010 European Medicines Agency bioequivalence guideline requirements that specify that the minimum required sample size is 12.[11] To secure 16 volunteers providing key pharmacokinetic parameters, the sample size was increased to 18 volunteers. Sample size calculations were performed using nQuery Advisor 7.0 (Statistical Solutions Ltd, Boston, Massachusetts).

Investigational medicinal products

The test product used was RB naproxen sodium tablets 220 mg (batch No. WO4891082; expiration date January 2018). The reference product was Aleve naproxen sodium tablets 220 mg (batch No. BTT1AGU; expiration date October 2018). Volunteers each received a single oral dose of 2 × 220 mg RB naproxen sodium tablets or 2 220 mg Aleve naproxen sodium tablets as determined by the randomization schedule at treatment period 1 (day 1) and the alternative treatment at treatment period 2 (day 1) following an overnight fast of 10 hours. Both test and reference investigational medicinal product (IMPs) were swallowed whole with 200 mL water with the fasting period continued until 4 hours postdose. A 5- to 8-day washout period was permitted between each IMP administration was chosen based on being >5 times the mean half-life of the reference product of approximately 13 to 17 hours.

Study assessments and blood sampling

Blood samples (2.7 mL) were drawn into lithium heparin tubes at predose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 9, 15, 24, 36, 48, and 72 hours postdose for determination of naproxen plasma concentrations. The sampling schedule was based on the known pharmacokinetic parameters of the reference product and exceeded 3 times the mean half-life of approximately 13 to 17 hours. Samples were separated by centrifugation at 1500 × g and 4°C for 10 minutes. The resulting plasma was stored at approximately –20°C before analysis by Seirian Laboratories, Simbec

Research Ltd, using a validated method. Analysis was performed by LC-MS detection using the instrument in turbo ionspray negative ion MRM mode. The system consisted of an MDS Sciex API 365 triple quadrupole, atmospheric pressure ionization mass spectrometer (Applied Biosystems, Foster City, California). Automated injection of samples took place using a PerkinElmer Series 200 Series pump and autosampler (PerkinElmer, Waltham, Massachusetts). Analysis was performed on a Luna C18 column (Phenomenex; Torrance, California) using an isocratic method. The following multiple reaction monitoring transitions were monitored in negative ion mode: naproxen: m/z 229 → m/z 170, typical retention time 4.2 minutes. 1-Naphthaleneacetic acid (internal standard): m/z 185 → m/z 141, typical retention time 3.2 minutes. Instrument control, data acquisition, and integration were achieved using proprietary Applied Biosystems MDS Sciex Analyst software version 1.4.1. Each test, standard, and quality control plasma sample was extracted with internal standard using a dichloromethane solvent extraction before LC-MS-MS analysis. The lower limit of quantitation for naproxen was 1.00 μg/mL, with a validated calibration range of 1.00 to 99.47 μg/mL. Throughout study sample analysis, assay performance was acceptable with demonstrated interassay accuracy ranging from 95.7% to 100.5% and interassay precision ranging from 3.1% to 6.6%.

Safety assessments were conducted at predetermined times throughout the study through recording of adverse events, vital signs, ECG, and safety laboratory test measurements.

Pharmacokinetic methods and statistical analysis

Noncompartmental pharmacokinetic analysis was performed using validated Phoenix WinNonlin version 6.3 software (Certara USA Inc, Princeton, New Jersey) to derive pharmacokinetic parameters from plasma naproxen versus time data; primary end points were C_{max}, and AUC_{0-t}. The following secondary end points were derived; $AUC_{0-\infty}$, $AUC_{\%extrap}$ (residual area), k_e, and $t_{½}$. Actual sampling times were used for all pharmacokinetic analyses, and the predose timepoint set to 0 hours. For all concentrations below the lower limit of quantification, plasma concentration was set to 0 μg/mL, and in the instance of missing samples the trapezoidal rule was employed between the samples immediately before and after the missing sample for AUC calculations.

Following logarithmic transformation, an ANOVA model was fitted to naturally log transformed AUC_{0-t} and C_{max} with fixed effects for treatment, period, and treatment with subject nested within sequence. The exponentiated least square (LS) means from each ANOVA model were presented as the LS geometric means for each treatment. The exponentiated differences and 90% CIs for the differences between LS means were presented as the LS geometric mean ratios and corresponding 90% CIs. Bioequivalence was demonstrated between the test and reference IMPs if each 90% CI for the ratio between LS geometric means (test/reference) lay within 80.00% and 125.00% for both AUC_{0-t} and C_{max}. Statistical analysis was performed using SAS version 9.3 (SAS Institute Inc, Cary, North Carolina).

Results

Study population

Thirty-two healthy volunteers were consented. Of these, 6 failed the screen, 2 were surplus to requirements, 6 were reserve participants, and 18 (11 men and 7 women) were randomized according to a randomization schedule generated using SAS version 9.2. On randomization, volunteers were allocated a unique subject number in numerical sequence. Issue of the IMP in this sequence ensured randomization. There were no withdrawals and all 18 subjects completed the study, with all subjects having a 7-day washout between periods. Subject disposition is summarized in Figure 1. The mean age of subjects was 33.6 years (range=20–50 years) and mean body mass index was 25.025 (range=21.30–29.87), a summary of subject demographic characteristics is presented in Table 1. There were no clinically significant concurrent/ongoing conditions reported for any subject and with the exception of contraception, no subject who reported a concurrent/ongoing condition was receiving concomitant medication. There were no positive pregnancy test results during the study and no subject took concomitant medication during the study.

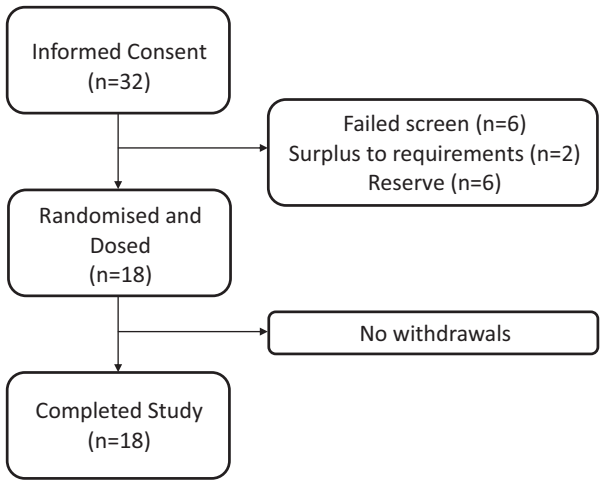

Figure 1. Consort diagram for subject disposition.

Table 1
Summary of patient demographic parameters.

Parameter	Statistic	Overall
Age, y	n	18
	Mean	33.6
	SD	9.55
Weight, kg	n	18
	Mean	74.69
	SD	14.676
Height, m	n	18
	Mean	172.0
	SD	11.77
Body mass index	n	18
	Mean	25.025
	SD	2.7857
Race		
White	n (%)	18 (100)
Other	n (%)	0 (0)
Gender		
Male	n (%)	11 (61.1)
Female	n (%)	7 (38.9)

Plasma pharmacokinetic parameters

Plasma naproxen concentrations were sufficient to allow derivation of primary and secondary pharmacokinetic parameters. The mean plasma concentration versus time profiles for naproxen after single administration of the test (RB naproxen sodium tablets) and reference (Aleve naproxen sodium tablets) IMPs are presented in Figure 2A and 2B. Review of the primary pharmacokinetic end points (C_{max} and AUC_{0-t}) demonstrate that the test IMP (RB naproxen sodium tablets) was considered bioequivalent to the reference IMP (Aleve naproxen sodium tablets) with the geometric LS mean test/reference ratio 90% CI for C_{max} of 93.98 to 110.70 and AUC_{0-t} of 98.04 to 102.63 contained entirely within the predefined 80.00% to 125.00% lower and upper limits when

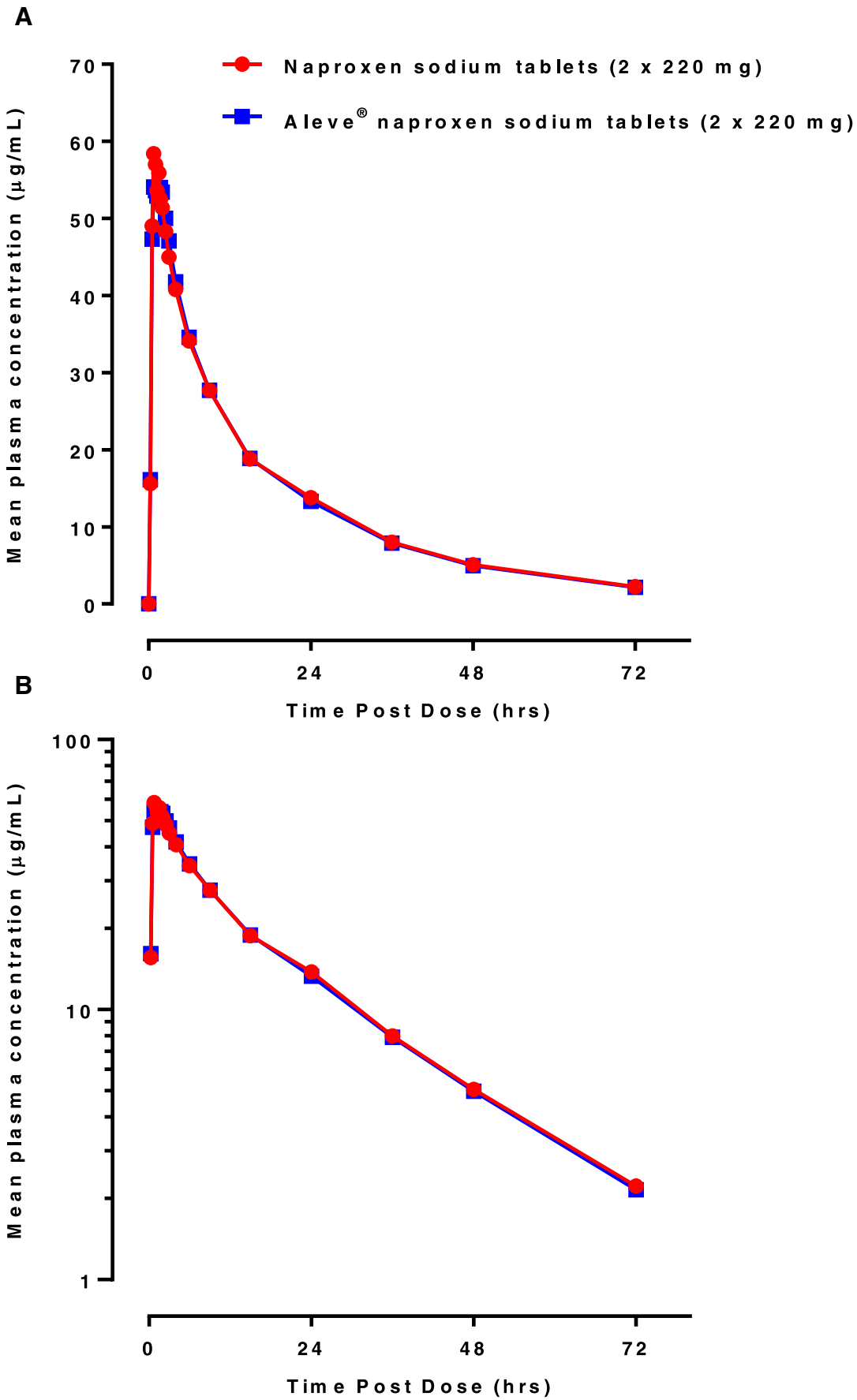

Figure 2. Mean plasma concentration versus time curves for naproxen following single oral administration of Test (2 × 220 mg Naproxen Sodium Tablets; red) or Reference (2 × 220 mg Aleve® Naproxen Sodium Tablets; blue) products in healthy male and female volunteers on a linear (Figure 2a) and semi-log (Figure 2b) scale.

Table 2
Summary of statistical analysis of derived plasma pharmacokinetic parameters.

Parameter	Test* geometric least squares mean (n = 18)	Reference† geometric least squares mean (n = 18)	Geometric least squares mean test/ref ratio (90% CI) (n = 18)	Geometric %CV based on ANOVA model (n = 18)
C_{max} (μg/mL)	65.88	64.59	102.00 (93.98 to 110.70)	14.1
AUC_{0-t} (h * μg/mL)	893.37	890.60	100.31 (98.04 to 102.63)	3.9
$AUC_{0-\infty}$ (h * μg/mL)	947.33	943.40	100.42 (97.94 to 102.96)	4.3
	Test* median (n = 18)	Reference† median (n = 18)	Median difference (95% CI)‡	*P* value§
T_{max} (h)	0.75	1.00	0.13 (−0.25 to 0.50)	0.9878

Results obtained using a fixed-effects ANOVA with fixed effects of treatment, study period, treatment sequence, and subject nested within sequence.
* Reckitt Benckiser Health Limited (RB, 103-105 Bath Rd, Slough, SL1 3UH, United Kingdom) naproxen sodium tablets (2 × 220 mg).
† Aleve naproxen sodium tablets (Bayer Healthcare, Morristown, New Jersey) (2 × 220 mg).
‡ Obtained using Hodges-Lehman method.
§ Obtained using the Wilcoxon signed-rank test.

administered fasted. The observed maximum $AUC_{\%extrap}$ was 8.69%, indicating that AUC_{0-t} covers more than 80% of $AUC_{0-\infty}$ for each subject in the sample. There was no statistically significant difference in T_{max} following fasted administration of the test and reference IMP ($P = 0.9878$) and the k_e (mean values) was 0.0413 1/h and 0.0414 1/h following administration of the test and reference IMPs, respectively, indicating little difference in the rate of elimination between the 2 formulations, with $t_{1/2}$ (mean values) of 17.3 hours and 17.1 hours, respectively. The pharmacokinetic parameters for naproxen are summarized in Table 2.

Safety assessments

There were 2 adverse events reported by 2 subjects during the study. One adverse event was reported by 1 subject before dosing (mild herpes labialis). No concomitant medication (or other intervention) was administered and the event resolved within approximately 15 days. One adverse event of dyspepsia was reported by 1 subject postdose (ie, treatment-emergent adverse event). The dyspepsia was mild in severity and, because it occurred approximately 9 days after receiving the test IMP, was considered unlikely related to IMP. No concomitant medication (or other intervention) was administered and the event resolved within approximately 2 hours without sequelae. There were no serious adverse events or suspected unexpected serious adverse reactions reported during the study.

Discussion

In recent times, the pace of pharmaceutical research and development has slowed with much of the sector refocussing on niche markets such as personalized medicine in preference to more established traditional branches of development such as that of pharmaceutical equivalents.[12,13] However, in a landscape where rising drug prices are increasingly influencing health care budgets, the development and authorization of generic alternatives to innovator products continues to offer huge cost saving potential.[14]

It is estimated that unintentional injuries, such as sports injuries, account for approximately 6 million Accident & Emergency attendances annually in the United Kingdom[13,15,16] and in the case of sports injuries alone, treatment with nonsteroidal anti-inflammatory drugs such as naproxen have long been shown to provide a beneficial recovery response.[1,17,18] At the recommended over-the-counter doses, naproxen sodium demonstrates either a similar or even a better therapeutic and safety profile compared with other agents currently available for the treatment of musculoskeletal injuries and disorders.[1,3] Consequently, the availability of pharmaceutically equivalent naproxen products has the real potential to widen the market resulting in cost savings for these treatments.[14]

Reckitt Benckiser Health Limited developed a naproxen sodium tablet containing 220 mg naproxen sodium per tablet with proposed therapeutic indications, including muscular pain, back pain, more chronic pain states such as arthritis, dysmenorrhoea, acute pain and fever associated with cold and flu, and fever following vaccination. These are similar to that for Aleve Classic for Pain and Fever 220, a product that is already authorized for marketing in the European Union (2010) and United States (2014). The data obtained from this study will support a marketing authorization application for a generic version of naproxen in the European Union, thereby increasing the number of naproxen products available for prescribers and pharmacies.

This study sought to examine the comparative bioavailability of RB naproxen sodium tablets with the commercially available Aleve Classic product. The findings from this study demonstrated that there were no statistically significant differences between the test and reference naproxen sodium tablet formulations with respect to pharmacokinetic parameters representing peak and extent of exposure. Analysis of the primary pharmacokinetic end points (C_{max} and AUC_{0-t}) demonstrated that the differences in the geometric LS mean test/reference ratio was <15% for both parameters.

A $t_{1/2}$ (mean value) of 17.3 hours seen for the test naproxen product is in line with the usual human plasma half-life (12–17 hours) seen in other studies with naproxen.[19] The pharmacokinetic parameters therefore support its long half-life and the twice-daily posology.[6] This prolonged half-life is believed to lend it a prolonged analgesic effect and allow for twice-daily administration. Previous evaluation of the pharmacokinetic–pharmacodynamic relationship between plasma and synovial fluid naproxen concentrations and prostanoid concentrations in these fluids suggests a half maximal effective concentration (EC50) value of 7.7 ± 4.4 μg/mL,[20] which further supports the posology based on the plasma concentrations observed in this pharmacokinetic study (Figure 2A and 2B).

The study was designed and powered sufficiently to allow recognition of differences in primary pharmacokinetic parameters and complied with the regulatory requirements of the European Medicines Agency.[11] Additionally, the overall pharmacokinetic profile for both products was comparable to that reported in a previous similar study presenting the RB naproxen sodium tablet as a potential alternative to currently marketed naproxen sodium products.[10]

Conclusions

This single-dose study found that the test and reference products met the regulatory criteria for bioequivalence in these fasted healthy male and female volunteers with test/reference LS geometric mean ratios 90% CI calculated for C_{max} and AUC_{0-t} entirely contained within the prespecified 80.00% to 125.00% range. Additionally, both formulations were well tolerated; the incidence of treatment emergent adverse effects was low during the study and there was little difference in the treatment emergent adverse

effects profile observed between the test and reference IMPs. These results support the use of RB naproxen sodium tablets as an alternative naproxen tablet formulation.

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Kathryn Harries and Stuart Jones (Simbec Research, Ltd) and Caroline Tabor (Reckitt Benckiser Health Limited) contributed to study conduct and reporting.

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Conflicts of Interest

Sponsorship for this study and article preparation was funded by Reckitt Benckiser Health Limited and conducted at Simbec Research Ltd, a commercial Phase I unit in the United Kingdom. D. Sugár and T. da Silva were employees of Reckitt Benckiser Health Limited at the time of this publication. At the time of publication S. Hutchings, D. Francombe, and R. Adams were employees of Simbec Research Ltd. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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