CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Nurofen Zavance Tex 200 mg and 400 mg tablet, coated tablets Nurofen Zavance Tex 200 mg tablet ovaal, coated tablets Reckitt Benckiser Healthcare B.V., the Netherlands

ibuprofen (as sodium dihydrate)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.
It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 100658, 100657, 1020659

11 January 2013

Pharmacotherapeutic group:	antiinflammatory and antirheumatic products, non-steroids, propionic acid derivatives
ATC code:	M01AE01
Route of administration:	oral
Therapeutic indication:	symptomatic relief of mild to moderate pain including headache, backache, pain during menstrual bleeding, dental pain, rheumatic pain and muscular pain, migraine, fever and pain due to common cold or influenza
Prescription status:	non prescription
Date of authorisation in NL:	29 July 2010
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Nurofen Zavance Tex 200 mg and 400 mg tablet and Nurofen Zavance Tex 200 mg tablet ovaal, coated tablets from Reckitt Benckiser Healthcare B.V. The date of authorisation was on 29 July 2010 in the Netherlands.

The product is indicated for symptomatic relief of mild to moderate pain including headache, backache, pain during menstrual bleeding, dental pain, rheumatic pain and muscular pain, fever and pain due to common cold or influenza. In addition, the 400 mg product is indicated for migraine.

A comprehensive description of the indications and posology is given in the SPC.

Ibuprofen is a propionic acid derivative NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.
Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 h before or within 30 min after immediate release aspirin dosing (81mg), a decreased effect of ASA on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional use.

This national procedure concerns a line extension to the approved products Nurofen 200 mg tablet oval (NL License RVG 25190), Nurofen 200 mg tablet (RVG 10674) and Nurofen 400 mg tablet (RVG 22100), all from the same marketing authorisation holder, Reckitt Benckiser Healthcare B.V. The line extension concerns the introduction of a new ibuprofen salt, ibuprofen sodium, as a line extension to Nurofen (ibuprofen acid). Several other ibuprofen sodium formulations are already registered on the Dutch market.

The marketing authorisation is granted based on article 8(3) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired.
The MAH submitted a bioavailability study with Nurofen Zavance Tex 200 mg tablet to be marketed and registered Nurofen 200 mg tablets. The MAH also submitted four previously conducted human pharmacokinetic studies, with different ibuprofen formulations, as supportive data.
One 4-arm efficacy study NL0406 has been conducted with the formulation to be marketed, Ibuprofen sodium 256 mg tablets (Nurofen Zavantace Tex 200), an additional ibuprofen test formulation containing 60 mg Poloxamer 407, an approved paracetamol formulation (Tylenol Extra Strength) and placebo in patients with postoperative dental pain. The MAH also conducted a safety study NL9609 to compare the effects of sodium ibuprofen with standard ibuprofen acid and placebo on the mucosal integrity of the upper gastrointestinal tract in healthy volunteers.

No new pre-clinical were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a line extension.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance ibuprofen sodium is not described in the European Pharmacopoeia (Ph.Eur.*). It is a new salt of the well known Ph.Eur. described substance ibuprofen. Ibuprofen sodium is freely soluble in methanol and ethanol, very slightly soluble in acetone and practically insoluble in toluene and ether. It is practically insoluble in water at pH 1, but is freely soluble at higher pH values. It contains one chiral centre. The substance used is the racemate. Polymorphism is not known. The substance has a soft and soap-like appearance.

The Active Substance Master File (ASMF) procedure is used for all three suppliers of the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
For two suppliers the synthesis is limited to the conversion of ibuprofen to ibuprofen sodium and the quality of the starting material ibuprofen is certified by a Certificate of Suitability. For the third supplier, the synthesis comprises five steps. Used catalyst and solvents are controlled acceptably. Ibuprofen sodium has been characterized acceptably. Acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance
The drug substance specification is based on the Ph.Eur. monograph on ibuprofen with additional requirements for sodium, catalyst, water content, residual solvents and particle size. The specification is appropriate in view of the route of synthesis and the various European Guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production batches from each supplier.

Stability of drug substance
Stability data on the active substance have been provided for three batches from each supplier stored at 25°C/60%RH and 40°C/75%RH packed in the commercial packaging for all three suppliers. The stability results show that ibuprofen sodium is stable at both tested conditions. A re-test up to 3 years has been approved, without specific storage condition.

* *Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Nurofen Zavance Tex 200 mg is a white to off-white, round biconvex, sugar coated tablet printed with an identifying logo in black on one face.

Nurofen Zavance Tex 400 mg is a white to off-white, round biconvex, sugar coated tablet printed with an identifying logo in red on one face.
Nurofen Zavance Tex 200 mg tablet ovaal is a white to off-white, sugar coated caplet printed with an identifying logo in black on one face.

The sugarcoated tablets contain ibuprofen sodium corresponding with respectively 200 and 400 mg ibuprofen. The two 200 mg tablets, round and oval caplets, are fully similar except for the shape of the tablets and the imprint.

The coated tablets are packed in white opaque PVC/Al blisters, white opaque PVC-PVdC/Al blisters or white opaque PVC-PE-PVdC/Al blisters. The 200 mg round tablet is also available in HDPE tablet containers.

The excipients are: croscarmellose sodium, xylitol, microcrystalline cellulose, magnesium stearate and colloidal anhydrous silica, in the tablet core, and carmellose sodium, talc, acacia, sucrose, titaniumdioxide, macrogol 6000 in the sugarcoating.

The 200 mg and 400 mg tablets are dose-proportional.

Pharmaceutical development
Extensive information has been provided on the development of the products. As ibuprofen sodium has a soft, soap-like appearance, a melt-extrusion process has been developed for granulation and tabletting. The choice of the packaging and manufacturing process is justified. Adequate information on the batches used in the clinical studies has been provided. The composition of the round 200 mg tablets used in the bioequivalence and clinical study is as proposed for marketing, except for the absence of the print on the tablets used in the clinical study. This is considered to have no impact on the results of the clinical studies. Dissolution profiles of all three tablets are similar.

Manufacturing process
A blend of the active substance ibuprofen sodium, croscarmellose sodium and xylitol is melt-extruded. The extrude is discharged and cooled, sets solid and milled to produce a suitable granulate. Microcrystalline cellulose, colloidal anhydrous silica and magnesium stearate are added to the granulate and a pre-compression blend is formed. The tablets are compressed and sugar coated. Adequate validation has been done on minimum production-size batches. Validation of the first production batches will be performed on all three tablets.

Control of excipients
Adequate specifications have been set for the excipients.

Quality control of drug product
The product specification includes tests appearance, average mass, identification of ibuprofen, sodium and titanium dioxide, ibuprofen content, disintegration, dissolution, related substances, and microbial quality. Some parameters, *e.g.* uniformity of mass, are tested as in-process control on the tablet cores. The analytical methods have been adequately described and validated. Results of batch analysis have been provided of seven semi-production scale (50%) batches demonstrating compliance with the release specification. Results of full-scale batches will be provided.

Stability of drug product
Stability data have been provided after storage at 25°C/60%RH, 30°C/65%RH and 40°C/75%RH, 24 months for the 400 mg and 200 mg tablet. Observed trends are increases in disintegration time and average mass, decrease of dissolution, and change in appearance with out-of-specification results at 40°C/75%RH for 400 mg product and in the PVC/Al blister packaging. Degradation is not observed. In view of this, a storage condition ‘Do not store above 30°C’ is required for both strengths in PVC/Al blister and for the 400 mg tablet in PVC-PVDC/Al en PVC-PE-PVDC/Al blister. For the other presentations no

specific storage condition on temperature is required. Proposed shelf lives of 24 months are deemed acceptable. The tablets packed in the primary packaging are not sensitive to light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a line extension to Nurofen tablets, which is available on the European market. The ibuprofen sodium tablets have been shown to be therapeutically equivalent to Nurofen tablets (ibuprofen acid). Therefore, no further nonclinical data are provided since the nonclinical data for the original formulation are still valid. The Board agreed that no further non-clinical studies are required.

Environmental risk assessment
The product is intended as an addition to products existing on the market. It is expected that the use of the additional formulations will replace other available ibuprofen products, and thus the amount of active substance emitted to the environment is not expected to increase.

II.3 Clinical aspects

Ibuprofen is a well-known active substance with established efficacy and tolerability.

In the Netherlands Nurofen is marketed with the active ingredient ibuprofen, ibuprofen sodium dihydrate and ibuprofen lysine. Furthermore, ibuprofen is also available as arginine salt marketed by other companies.

To support the application, the MAH submitted data of:

- A bioequivalence study, where the pharmacokinetics of ibuprofen sodium (test tablet) was compared to ibuprofen acid (reference product), in an equipotent dose of 400 mg.
- A parallel, placebo, active comparator (paracetamol 1000 mg and ibuprofen acid) controlled clinical study in patients after tooth extraction. For the test tablet, a single dose equivalent to 400 mg ibuprofen acid was used.
- A gastric safety study, where oesophageal-gastric changes were studied in healthy volunteers after one week of high daily dose of ibuprofen test and reference (4 x 400 mg/day) by means of endoscopy.

The study results are discussed below.

II.3.1 Clinical pharmacokinetics

Bioavailability study
Design
This was an open-label, bioavailability, 3-way crossover, randomised, single centre study in 23 healty volunteers (15 males/7 females) aged 18-45 years to compare the bioavailability of the reference product Nurofen® (2 x standard tablets containing 200 mg ibuprofen) to that of sodium ibuprofen tablets (2 x 256 mg, equivalent to 2 x 200 mg ibuprofen) and ibuprofen acid tablets incorporating poloxamer 407 (2 x 200 mg tablets, each incorporating 60 mg of poloxamer 407). The latter tablets are not part of the evaluation.
Three single doses of 400 mg IBU (ibuprofen), or equivalent, were administered, with a 2-7 day wash-out period between doses. On each trial day, subjects were dosed orally after an overnight fast. Blood was collected before dosing and at 5, 10, 15, 20, 25, 30, 35, 40, 50 min and 1, 1.25, 1.5, 1.75, 2, 3, 6, 9 and 12 hours post-dose.

Analytical procedures/statistical methods
Plasma determination procedures were fully validated. Statistical methods were sufficiently justified.

Results

Figure 1 **Mean Plasma Ibuprofen Concentrations (µg/ml) after Administration of the Reference and Test Formulations to 22 Healthy Volunteers in Trial NL0405**

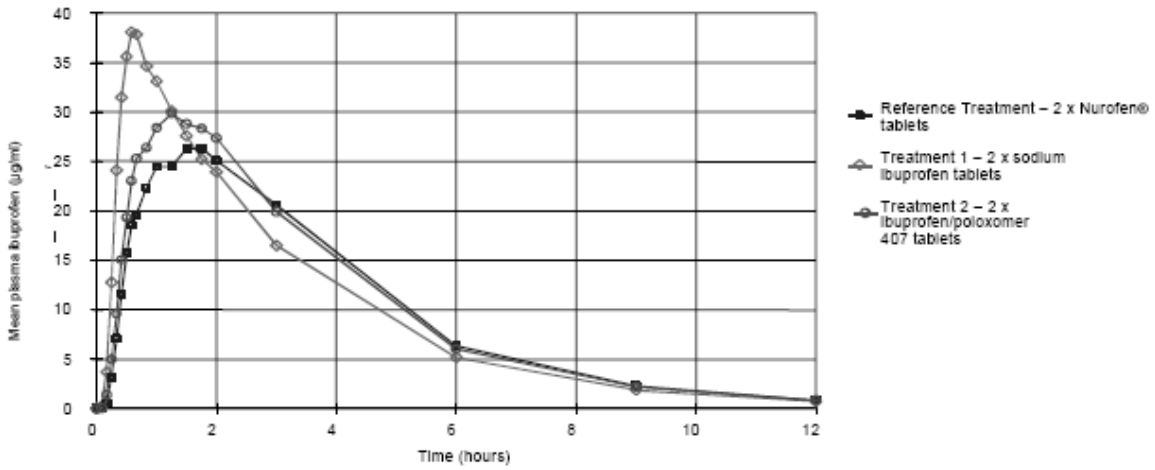


Table 1. Pharmacokinetic parameters for Sodium IBU and the reference product (non-transformed values; arithmetic mean ± SD, t_{max} median, range).

Treatment	**AUC_{0-t}** µg/ml/h	**$AUC_{0-\infty}$** µg/ml/h	**C_{max}** µg/ml	**t_{max}** h
Reference (Nurofen)	115.28 ± 26.548	117.71 ± 28.672	31.88 ± 7.65	1.5 (0.58-3.00)
Test 1 (Sodium Ibuprofen)	117.79 ± 23.323	119.73 ± 25.331	41.47 ± 10.72	0.58 (0.25-2.00)
***Ratio (90% CI) Test1/Reference**	102.17 (98.08-106.44)	101.71 (97.62-105.98)	130.06 (118.86 - 142.32)	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
T_{max} time for maximum concentration

**ln-transformed values*

The time to reach the peak plasma concentration (t_{max}) for IBU was statistically significantly faster for the Sodium IBU tablets (35 min) compared with the Nurofen® reference tablets (90 min). This was accompanied by an increase in the peak plasma concentration. The confidence interval of the ratio of the Sodium Ibuprofen/Nurofen® reference tablets for C_{max} was outside the 80-125% limit.
The overall extent of absorption of the formulation to be marketed was similar to that of the Nurofen® reference formulation, with test/reference ratios of both AUC_{0-inf} and AUC_t within 80-125% limits.

It is concluded that Sodium IBU 256 mg Tablets are equivalent to the standard Nurofen® 200 mg Tablets in terms of total extent of absorption, but its rate of absorption is significantly higher. The IBU-Poloxamer formulation, not relevant or this application, however, was bioequivalent to the standard Nurofen®.

Biowaiver for the 400 mg strength and 200 mg caplet-shaped tablet
A bioavailability study was carried out on the 200 mg strength only. A biowaiver for the 400 mg strength was granted based on the following:

- Nurofen Zavance Tex 200 mg and 400 mg tablets are manufactured on identical equipment, by the same production process and by the same manufacturer
- The drug input is know to be linear over the therapeutic dose range
- The qualitative composition of the two strengths is linear
- Nurofen Zavance Tex 200 mg and 400 mg Tablets are dose-proportional
- The dissolution profiles of Nurofen Zavance Tex 200 mg and 400 mg tablets determined at pH 2.0, 4.0, 6.8 are mathematically similar. Dissolution is fast (> 10% within 45 min at pH 2, > 43% within 45 min at pH 4, > 73% within 30 min at pH 6.8).The dissolution specification complies with that of the United States Pharmacopoeia in which not less than 80% (Q) is dissolved after 60 min.

The biowaiver for Nurofen Zavance Tex 200 mg ovaal was granted based on the following:

- Nurofen Zavance Tex 200 mg tablets and Nurofen Zavance Tex 200 mg caplets are manufactured on identical equipment, by the same production process and by the same manufacturer
- The drug input is know to be linear over the therapeutic dose range
- The qualitative and quantitative composition of the two strengths is the same
- The dissolution showed a similar dissolution profile.

II.3.2 Clinical experience

Efficacy study NL0406
Design
This was a double-blind, four parallel-group, placebo-controlled, randomised, single-dose, two-centre study comparing the efficacy and onset of action of two ibuprofen (400 mg) formulations, paracetamol (1000 mg) and placebo in postoperative adult dental pain (NL0406). The study was conducted with 321 patients (123 males, 198 females), aged 16-40 years.
Patients included had a moderate or severe pain intensity score of at least 50 mm but no more than 85 mm on the 100 mm Visual Analogue Scale (VAS) following extraction of either 1 mandibular third molar with a score of no less than 4 on the impaction grading scale, or 2 ipsilateral third molars with a total score of 4, 5 or 6 (minimum score of 2 for each molar) under local anaesthesia using standard surgical techniques.

The study was conducted in two research centres and subjects at each site were stratified according to sex and baseline pain intensity.
Subject underwent standard oral surgery procedures under local anaesthesia using lidocaine with epinephrine. Subjects were not to receive intravenous or oral sedation. However, nitrous oxide insufflations were permitted, if required. Opioids and other anaesthetics were not permitted.
Following the surgery, eligible subject (i.e., those who had an impaction score of 4, 5 or 6, had rated their pain intensity as moderate or severe, and had a VAS score equal to or greater than 50 mm but less than or equal to 85 mm) received a single dose containing 4 tablets (2 sodium IBU or 2 IBU acid and/or matching placebos) and 2 caplets (acetaminophen and/or matching placebos) with approximately 300 ml of water in a blinded fashion according to randomisation schedule. Dummy form was applied for every active compound.
If rescue medication was needed within the first 4 hours following administration of the study medication, Toradol (ketorolac tromethamine) 60 mg IM was administered. If rescue medication was needed after the first 4 hours after study drug administration, then Lortab (acetaminophen 500 mg/hydrocodon 5 mg) or Toradol was provided. Only one dose of Toradol was permitted during subject's time in the clinic.

The intent-to-treat (ITT) population consisted of all subjects who were randomised to the study, who completed the baseline efficacy assessments, and who had at least 1 post- baseline efficacy assessment. This was the primary efficacy analysis population and all efficacy variables were analysed using this set.

The per-protocol (PP) population consisted of all subjects who satisfied the inclusion and exclusion criteria, took the dose of study medication, did not violate the protocol, and completed pain assessment readings at a majority of time points during the 6-hour study window. Subjects who took rescue medication within 90 minutes of the dose were excluded from this set. All subjects excluded from the PP analysis were determined prior to code break. The PP population was restricted to the primary measure of efficacy only.

Subjects received either:
Treatment A: 2 x 256 mg sodium IBU tablets (each tablet equivalent to 200 mg IBU acid), plus 2 matched placebo for IBU acid tablets plus 2 matched placebo for Tylenol Extra Strength caplets.
Treatment B: 2 x 200 mg IBU acid tablets, each tablet incorporating 60 mg of the surfactant poloxamer 407, plus 2 matched placebo for sodium IBU tablets, plus 2 matched placebo for Tylenol Extra Strength caplets.
Treatment C: 2 x 500 mg Tylenol Extra Strength (500 mg paracetamol) caplet, plus 2 matched placebo for sodium IBU tablets, plus 2 matched placebo for IBU acid tablets.
Treatment D: 2 matched placebo for sodium IBU tablets, plus 2 matched placebo for IBU acid tablets, plus 2 matched placebo for Tylenol Extra Strength caplets.

The primary endpoint was the onset of analgesia defined as time to first confirmed perceptible pain relief using the 2-stopwatch method. Key secondary efficacy endpoints were the area under the pain relief (PR) and pain intensity differences (PID) curve (SPRRID) from 0 to 6 hours and the time to meaningful pain relief (MPR) using 2-stopwatch method.

Criteria for evaluation
All pain assessments were recorded by the subject in a diary in response to questioning by a trained observer. The trained observer questioned the subject for all observations and provided instructions as needed. The sequence of the pain intensity and relief assessments remained consistent for each subject at each assessment interval throughout the study. That is, the pain intensity categorical assessment was completed first, the pain intensity VAS second, the pain relief categorical third. Subjects were not allowed to compare their responses with their previous responses.

Primary Endpoint
Onset of action measured as the ***time to first confirmed perceptible pain relief*** (the time to first unconfirmed perceptible pain relief taken from the stopwatch for subjects who went on to subsequently experience meaningful pain relief). It was determined using the 2-stopwatch method. Patients were given two stopwatches that were started when study medication was taken. Each patient was instructed, ‘’Stop the first watch when you first feel any pain relief whatsoever. This does not mean you feel completely better, although you might, but when you first feel any relief I the pain you have now. Stop the second watch when the pain relief is meaningful to you.

Key secondary endpoints
1. Pain intensity difference (PID) curve (SPRID) from 0 to 6 hours
2. The time to meaningful pain relief

Pain intensity (categorical and VAS) and pain relief (categorical) were recorded at 5, 10, 15, 20, 25, 30, 35, 40, 45, 60, 90, 120, 180, 240, 300 and 360 min after receiving the study medication. Pain intensity was rated on a four point categorical scale: 0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain in response to the question ‘’What is your pain level at this time?’’. The pain intensity VAS was a horizontal 100 mm line labelled: left anchor=no pain (0 mm), right anchor=worst pain (100 mm).
Pain relief was rated on a five point categorical scale: 0=none, 1=a little, 2=some, 3=a lot, 4=complete in response to the question ‘’How much relief have you had from your starting pain?”

The chosen study-end points, apart of pain intensity difference curve (SPRID) which is difficult to interpret and not very informative, are in accordance to the guidelines.

Statistical methods

Primary Endpoint
Pairwise differences between the 2 IBU formulations and placebo were assessed using the Wilcoxon rank sum test. For this analysis, subjects who did not report confirmed perceptible pain relief were assigned a relief time of 4 hours. A sensitivity analysis was also performed. Differences between IBU formulations and placebo were assessed using a Cox regression analysis, with treatment group, study site, gender, and baseline pain intensity (categorical) included in the model. The hazard ratio' and associated 97.5% CIs were calculated for the pairwise comparisons.

Results Clinical Efficacy
Rescue medication
Twenty-three subjects took rescue medication within 90 minutes of dosing and were excluded from the PP population.
The distribution of the patients who took any rescue medication was 32.5%, 22.5%, 43.8% and 82.7% in the Sodium IBU 256 mg Tablets, IBU acid, paracetamol and placebo groups, respectively. There was no statistically significant difference in proportion of patients taking rescue medication between Sodium IBU group and paracetamol group and between the two IBU formulations. Because of the relatively small proportion of subjects reporting the use of rescue medication in the active treatment groups the Kaplan-Meier median times could not be calculated.

Primary Endpoint- Onset of Action as a 'Time to First Confirmed Perceptible Pain Relief'

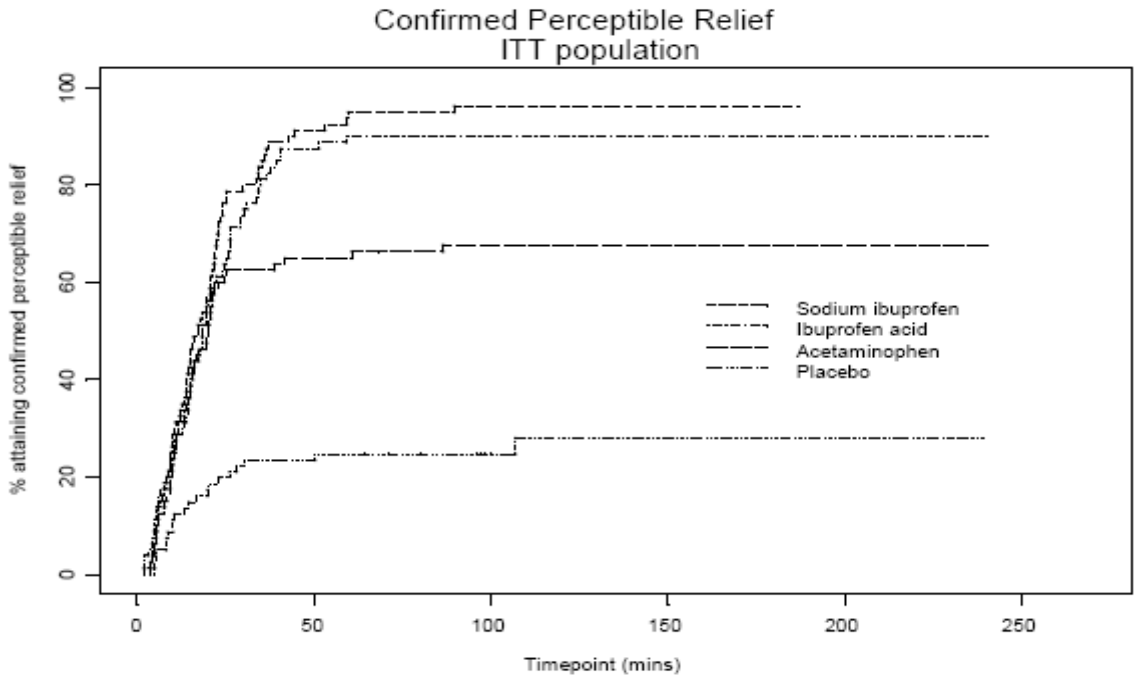
Table 2. Time to First Confirmed Perceptible Pain Relief. ITT and PP Populations.

	Treatment Group				
	Sodium Ibuprofen	Ibuprofen Acid	Acetaminophen	Placebo	p-value [a]
N (ITT population)	80	80	80	81	< 0.001
Number of events (%)	77 (96.3)	72 (90.0)	54 (67.5)	21 (25.9)	
Kaplan-Meier median (min)	17.0	18.5	20.1	> 240.0	
95% Confidence interval	14.0, 20.8	15.3, 22.5	15.1, 24.6	-	
Pairwise comparison		Hazard ratio	97.5% CI for ratio	p-value	
Sodium Ibuprofen versus Placebo		7.76	4.42, 13.62	< 0.001	
Ibuprofen Acid versus Placebo		6.88	3.91, 12.11	< 0.001	
N (PP population)	79	77	77	61	< 0.001
Number of events (%)	76 (96.2)	70 (90.9)	54 (70.1)	20 (32.8)	
Kaplan-Meier median (min)	17.0	18.4	19.6	> 240.0	
95% Confidence interval	14.0, 20.8	15.1, 21.6	14.9, 21.8	-	
Pairwise comparison		Hazard ratio	97.5% CI for ratio	p-value	
Sodium Ibuprofen versus Placebo		6.12	3.44, 10.88	< 0.001	
Ibuprofen Acid versus Placebo		5.63	3.14, 10.07	< 0.001	

Treatment definitions: Sodium Ibuprofen = 2 x 256 mg sodium ibuprofen tablets (each tablet equivalent to 200 mg ibuprofen acid); Ibuprofen Acid = 2 x 200 mg ibuprofen acid tablets; Acetaminophen = 2 x 500 mg acetaminophen caplets.
Abbreviations: CI = confidence interval.
[a] p-value for treatment from a Cox regression analysis model with factors for treatment, study site, gender, and baseline pain intensity (categorical).
Source: Section 14.2, Tables 14.2.1.1 and 14.2.1.2.

Statistically significantly greater proportions of subjects reported confirmed perceptible pain relief in the 2 IBU formulation groups than the paracetamol group ($p < 0.0001$ [sodium IBU] and $p = 0.0005$ [IBU acid]): 96.3%, 90.0%, 67.9% and 25.9% for the Sodium IBU 256 mg Tablets, IBU acid, paracetamol and placebo, respectively.

Figure 2 **Kaplan-Meier Curves for Time to First Confirmed Perceptible Pain Relief**



The Kaplan-Meier median times to reporting for the three active treatment groups were 17.0 min (Sodium IBU 256 mg Tablets), 18.5 min (IBU acid) and 20.1 min (paracetamol), respectively. The statistical analysis showed significant difference between 2 IBU formulations and placebo.

There was no significant difference in onset of action between the two IBU formulations and between IBU formulations and paracetamol. The 95% CI largely overlap.

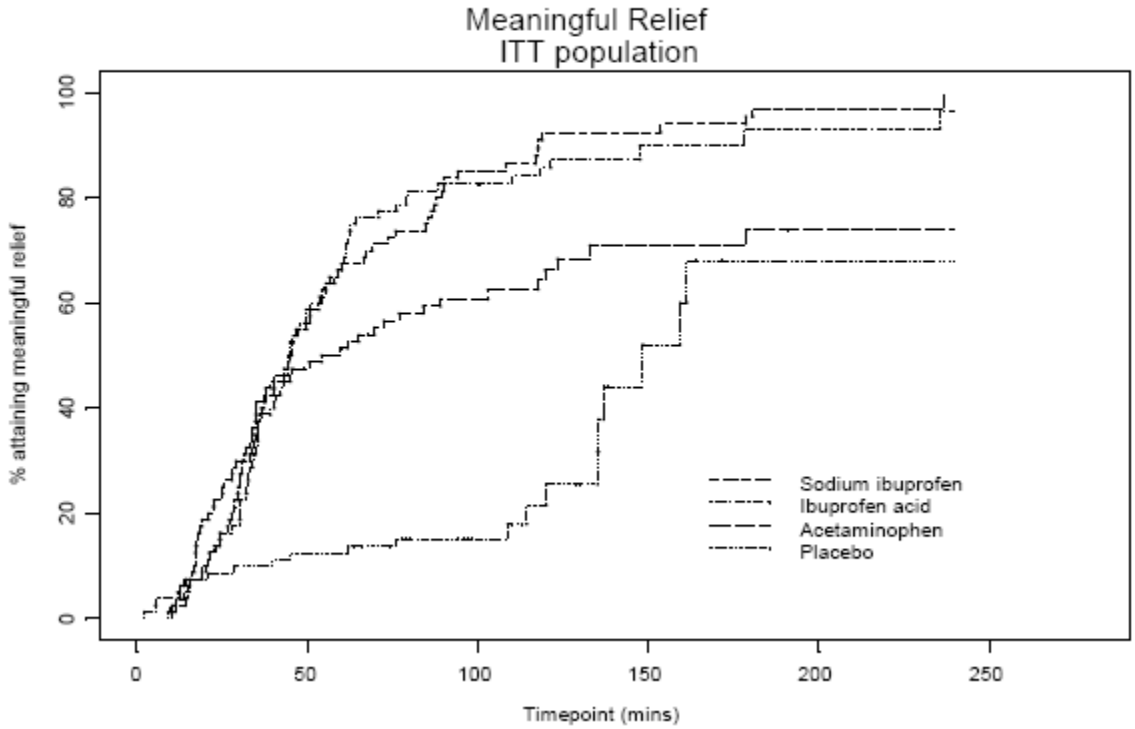
Key secondary endpoints

The area under the pain relief and pain intensity differences curve (SPRID) from 0 to 6 hours (0-6 h). The mean AUC values for ITT population were 3.46, 3.49, 2.25, and 0.73 for Sodium IBU 256 mg Tablets, IBU acid, paracetamol and placebo groups, respectively. The two IBU formulations were highly statistically significantly superior to paracetamol ($p<0.001$). There were no statistically significant differences between the IBU formulations.

The Time to Meaningful Relief as Recorded by the Stopwatch

For ITT population, the percentage of patients reporting meaningful pain relief was 96.3%, 90.0%, 67.5% and 25.9% for Sodium IBU 256 mg Tablets, IBU acid, paracetamol and placebo groups, respectively. Statistically significantly greater proportions of subjects reported meaningful pain relief in the 2 IBU formulation groups than the acetaminophen group ($p < 0.0001$ [sodium IBU] and $p = 0.0005$ [IBU acid]). However, there was no significant difference in terms of time to relief between the two IBU formulations and IBU formulations and paracetamol.

Figure 3 Kaplan-Meier Curves for Time to Meaningful Pain Relief



The Kaplan-Meier survival curves are very similar up to 45 minutes post-dose but the curve for acetaminophen becomes considerably less steep from this time onward. The Kaplan- Meier median times to meaningful relief for the 3 active treatment groups were 45.1 minutes (sodium IBU), 44.7 minutes (IBU acid), and 54.1 minutes (acetaminophen), indicating that the IBU formulations were favoured. However, this difference was apparent only after 45 min.

The SPRID is difficult to interpret. There was no statistically significant difference in terms of time to meaningful pain relief between the two IBU formulations.

Conclusion

In conclusion, the two ibuprofen test formulations, in an equipotent single dose of 400 mg, were superior to placebo and active comparator paracetamol 1000 mg, in the treatment of acute pain after tooth extraction under local anaesthesia. There were no statistically significant differences between the two ibuprofen test formulations in the time to onset to achieve pain relief and the percentage of subjects reaching clinical relevant pain relief, nor in the need of rescue medication within 4 hours post-operative (32.5 and 22.5%, for IBU sodium and regular IBU formulation, respectively).

II.3.3 Safety

Endoscopy study NL9609

This study was a single-blinded, placebo-controlled, multiple-dose parallel group comparison of the gastrointestinal effects of Sodium Ibuprofen (400 mg Ibuprofen Unit Dose), Ibuprofen Lysine (400 mg Ibuprofen Unit Dose), Ibuprofen Standard (400 mg Ibuprofen Unit Dose), and placebo assessed by endoscopy (NL9609). Sixty subjects were included (32 males/28 females), aged 18-53 years. Subjects were healthy volunteers with normal gastroendoscopy, not taking alcohol or concomitant medication liable to cause damage to the gastric mucosa during the course of the study.

Test products were Sodium Ibuprofen (2 x 256 mg q.i.d.) and Ibuprofen Lysine (2 x 342 mg q.i.d.), both equivalent to ibuprofen 1600 mg daily. Reference products were Ibuprofen Standard (2 x 200 mg q.i.d.) and placebo (two tablets q.i.d.).

The duration of the treatment was 7 days and one or two doses on the eighth day.

Sixty subjects were randomised to one of the four study treatments and all completed the study. Sixteen subjects were assigned to placebo, 15 each to ibuprofen lysine and to ibuprofen, and 14 to sodium ibuprofen. One subject in placebo group (subject 31) was excluded from the endoscopy analysis (because of an initial endoscopy score of 1), but not from the analysis of safety.
Before Day 0, subjects fasted overnight. At Day 0, subjects underwent upper GI endoscopy. Mucosal scores were derived from the endoscopist's notes of lesion, ulcers, haemorrhages and petechiae using modified Lanza scoring scale. Randomisation of the subjects took place on Day 7. Subjects then were taking study treatment for seven days. At the fourth study visit on Day 14, subjects underwent a second upper GI endoscopy, after fasting overnight. Mucosal damage scores were derived as at Day 0.The assigned treatments were taken with water four times daily at 07:00, 12:00, 17:00 and 22:00 for seven days with up to two doses at 07:00 and 12:00 on the eighth day (Day 14). The medication was taken at least one hour before food. Subjects could be tranquillised during endoscopy with 5-10 mg diazepam (Diazemuls® Pharmacia) i.v., an injectable diazepam.

Medications were presented as unmarked tablets in identical blister packs. Because of some differences in tablet appearance among some of the treatments, the study cannot be considered fully double blinded. Investigators conducting the endoscopies were unaware of the subjects' treatments.

Aims of the study
The primary aim of the study was to compare the effects on gastrointestinal mucosal integrity of sodium ibuprofen and ibuprofen lysine with standard ibuprofen and placebo.

The effects of each treatment on the GI mucosa were assessed by endoscopic evaluation 7 days before the start of the treatment and after 7 days of treatment. Mucosal damage was rated on a five point modified Lanza scale where 0 - no visible lesions, 1 – 1 haemorrhage or erosion, 2 – 2 -10 haemorrhages or erosions, 3 – 11-25 haemorrhages or erosions and 4 = >25 haemorrhages or erosions, or an ulcer of any size.
For each subject, both the pre- and post-medication endoscopies were performed by the same endoscopist. All mucosal changes were score during endoscopy and videotaped to confirm the mucosal score in case of discrepancies.

An additional aim of the study was to compare the incidence and severity of all adverse events (AE) between treatments. The severity of AE was rated as mild (does not limit usual activities; the subject might experience slight discomfort), moderate (some limitation of usual activities; the subject might experience significant discomfort) or severe (inability to carry out usual activities; the subject might experience intolerable discomfort).

Statistical methods
Applicant's original statistical plan was to calculate the 95% confidence intervals for the differences in the means of the Lanza scores between sodium ibuprofen and ibuprofen, and between ibuprofen lysine and ibuprofen, in order to draw inferences about the relative safety of sodium ibuprofen and ibuprofen lysine. However, because of the nature of the abnormal distribution of the Lanza scores at all anatomical locations in each group, a rank number of the Lanza score was introduced. A median of the rank number of the Lanza score and its 25th - 75th (Q1-Q3) percentile was calculated and plotted. General linear regression and Dunnett's two-tailed *t* test were used to calculate any statistical differences between groups when applicable.
All statistical analyses were performed with SAS computer software. Considering the small sample size in each subgroup, the choice for a non-parametric statistical method is supported.

Endoscopy results

Table 3. Change in Mucosal Scores Before and After Treatment Expressed as Mean ± SD.

Table 4. Change in Mucosal Scores Before and After Treatment Expressed as mean ± SD.

Treatment group	No. subjects	Mucosal scores (mean ± SD)					
		Oesophagus		Gastric body		Duodenum	
		Before	After	Before	After	Before	After
Standard ibuprofen	15	0±0	0±0	0±0	1.87±0.83#	0±0	0.33±0.72
Sodium ibuprofen	14	0±0	0.14±0.36	0±0	2.86±0.77*	0±0	0.36±0.74
Ibuprofen lysine	15	0±0	0.67±1.18*	0±0	2.67±1.05*	0±0	0.73±0.88#
Placebo	15	0±0	0±0	0±0	1.20±0.94	0±0	0.07±0.26

*p<0.05 vs placebo and standard ibuprofen, #p<0.05 vs placebo by Dunnett's two-tailed t test.

No significant differences between sodium ibuprofen and ibuprofen lysine.

Both sodium IBU and IBU lysine caused mild damage in the oesophagus, whereas no mucosal damage was seen with IBU acid and placebo. In the stomach, the two salts of IBU induced significantly more mucosal damage than did either IBU acid or placebo, whilst IBU acid caused significantly more damage than placebo. In comparison with the other groups, IBU lysine was more irritant to the duodenal mucosa.

The dose of IBU used in this study was higher than the non-prescription dose currently recommended (1200 mg/day as a maximum), which may have contributed to the mucosal damage scores in sodium IBU group than in standard IBU acid. The mean Lanza score was near 3 in the IBU sodium group, compared to near 2 in the IBU acid group. The mean mucosal damage scores are higher for Sodium IBU than for IBU acid. As long-term safety data are lacking, the clinical relevance of this findings is difficult to assess.
The MAH presented a review from the literature and available data, on the potential for mucosal damage of ibuprofen salts, including sodium ibuprofen, compared to ibuprofen acid. The resulting data indicate that the safety profile of sodium ibuprofen is not significantly different compared to regular ibuprofen formulations. Besides, other sodium ibuprofen formulations are already available in the Netherlands. In the SPC (section 4.2) it is mentioned that the patient should consult a doctor in case the symptoms persist or worsen during short-term use.

Gastric safety results
A total of 24 subjects reported 36 adverse events (AE) during the treatment period and after the treatment. Seventeen (47.2%) were judged to be possibly related to study medication, two (5.6%) in the standard IBU group, two (5.6%) sodium IBU, seven (41.2%) IBU lysine and six (16.6%) placebo. All of the AE were mild and did not prompt any change in dose or withdrawal from the study, or necessitate concomitant medication. Numerically more AE were reported by subjects receiving placebo than by subjects given sodium IBU and IBU. IBU lysine caused more AE than IBU and sodium IBU , although, apart from moderately severe headache in one subject, these were mild. There were no statistically significant differences between the groups. Nineteen (52.8%) AE were not considered to be drug-related.

Table 5. Adverse Events Possibly Related to the Study Medications During Days 8–14 and Days 15–21 (n=60).

Adverse event	Mild (Sub. ID)	Moderate (Sub. ID)	Total
Headache	4(6.7%) N16(P) N74(P) N17(IL) N43(IL)	1(1.7%) N49(P)	5(8.3%)
Gastric/abdominal pain	4(6.7%) N44(SI) N41(NaI) N46(P) N49(P)	—	4(6.7%)
Skin rashes	1(1.7%) N74(P)	—	1(1.7%)
Heartburn	—	1(1.7%) N10(IL)	1(1.7%)
Nausea	1(1.7%) N4(IL)	—	1(1.7%)
Fever/chills	1(1.7%) N4(IL)	—	1(1.7%)
Tight chest	1(1.7%) N41(NaI)	—	1(1.7%)
Elevated ALT	3(5%) N38(SI)* N45(IL)* N80(IL)*	—	3(5%)

No statistical differences among the four groups by Fisher's exact test

P=placebo, SI=Ibuprofen standard, NaI=sodium ibuprofen, IL=ibuprofen lysine. *post treatment period. No severe adverse events recorded.

Bioavailability study; Safety data

There were four AE reported by three of 22 subjects. None was considered to be related to the study treatment. One event (mild bruising at the cannula site) was reported following administration of the formulation to be marketed. There were three AE following administration of Nurofen 200 mg Tablets (mild bruising at the cannula site, mild upper respiratory tract infection and moderate injury to the right thumb).There were no serious AE or withdrawals due to an AE.

Efficacy study NL0406; Safety data

A total of 28.6% of patients experienced AEs during the study: 30.0% in the sodium IBU 256 mg Tablets group, 23.8% in the IBU/poloxamer group, 30.9% in the paracetamol group and 28.6% in the placebo group. A total of 11.8% of patients had AE that were considered to be possibly related to the study medication.

Overall, 7.8% of patients experienced a severe AE: 6.3% in the sodium IBU 256 mg Tablets group (headache, vomiting, nausea, constipation, dry socket, post-operative infection and swelling), 2.5% in the IBU acid group, 12.3% in the paracetamol group and 9.9% in the placebo group.

Severe AEs in order of decreasing frequency were: vomiting (14 reports), nausea (9 reports), dizziness (4 reports), abdominal pain (2 reports) and headache (2 reports).

Table 4. Summary of adverse events. Safety population.

	Treatment Group							
	Sodium Ibuprofen (N = 80)		Ibuprofen Acid (N = 80)		Acetaminophen (N = 81)		Placebo (N = 81)	
	Number of events	Number of subjects n (%)[a]	Number of events	Number of subjects n (%)[a]	Number of events	Number of subjects n (%)[a]	Number of events	Number of subjects n (%)[a]
Mild	15	12 (15.0)	15	12 (15.0)	16	12 (14.8)	9	8 (9.9)
Moderate	21	12 (15.0)	9	7 (8.8)	13	12 (14.8)	16	14 (17.3)
Severe	7	5 (6.3)	3	2 (2.5)	12	10 (12.3)	14	8 (9.9)
Vomiting	1	1 (1.3)	1	1 (1.3)	6	6 (7.4)	6	6 (7.4)
Nausea	1	1 (1.3)	1	1 (1.3)	2	2 (2.5)	5	5 (6.2)
Dizziness	0	0 (0.0)	0	0 (0.0)	2	2 (2.5)	2	2 (2.5)
Abdominal pain	0	0 (0.0)	0	0 (0.0)	2	2 (2.5)	0	0 (0.0)
Headache	1	1 (1.3)	0	0 (0.0)	0	0 (0.0)	1	1 (1.2)
Constipation	1	1 (1.3)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Dry socket	1	1 (1.3)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Postoperative infection	1	1 (1.3)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Swelling	1	1 (1.3)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Swelling face	0	0 (0.0)	1	1 (1.3)	0	0 (0.0)	0	0 (0.0)

Treatment definitions: Sodium Ibuprofen = 2 x 256 mg sodium ibuprofen tablets (each tablet equivalent to 200 mg ibuprofen acid); Ibuprofen Acid = 2 x 200 mg ibuprofen acid tablets; Acetaminophen = 2 x 500 mg acetaminophen caplets.

[a] Percentages based on total number of subjects per treatment group.

Source: Section 14.3, Table 14.3.2.

In conclusion, the overall safety profile was similar for both ibuprofen test formulations. However, it should be noted that the subgroups were small, and only single doses were given in the clinical efficacy study and the bioequivalence study.

II.3.4 Benefit-risk assessment

The bioequivalence of Nurofen Zavance Tex 200 mg tablets to the standard Nurofen® 200 mg Tablets has been demonstrated in terms of total extent of absorption, but its rate of absorption, as measured by C_{max} was significantly higher (about 30%).
In the clinical study, the time to achieve any notable relief in pain was 1.5 minutes shorter for the sodium ibuprofen formulation compared to the test formulation containing Poloxamer 704 (17 versus 18.5). However, this difference did not reach statistical significance. Neither is a shortening of 1.5 minutes in experiencing pain relief considered clinically relevant. The percentage of patient achieving satisfactory pain relief was similar in both subgroups. Other secondary efficacy outcomes, such a change in pain intensity scores and the number of patients using rescue medication, were also similar in both ibuprofen groups. Pain relief in both ibuprofen groups was however significantly better than in the placebo or paracetamol group, indicating assay sensitivity.

A major safety concern was raised as mucosal damage (measured by Lanza-scores) was significantly more severe after the new ibuprofen-sodium formulation compared to some regular Nurofen formulations when applied in healthy subjects for one week. A review from the literature and available data was presented, concerning the potential for mucosal damage of ibuprofen salts, including sodium ibuprofen, compared to ibuprofen acid. The MAH provided sufficient indications that the safety profile of sodium ibuprofen is not significantly different compared to regular ibuprofen formulations.

In conclusion, the benefit-risk balance of Nurofen Zavance Tex is considered positive.

Risk management plan

Ibuprofen was first approved in 1969, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of ibuprofen can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the national procedure is acceptable and has been adapted in accordance with the MEB's comments. The indication 'migraine' was only accepted for the 400 mg. This indication was approved earlier for the product Nurofen 400 Migraine (NL License RVG 29737). For the 200 mg tablet, effectivity in this indication is not considered proven.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 5 participants, followed by two rounds with 10 participants each. Fifteen questions were asked. These questions covered the following areas sufficiently: traceability, comprehensibility and applicability. In the first test round, 94.6% of the questions was answered correctly, in the second round this was 98%. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Nurofen Zavance Tex 200 mg and 400 mg tablet and Nurofen Zavance Tex 200 mg tablet ovaal, coated tablets have a proven chemical-pharmaceutical quality and are approvable line extensions to Nurofen tablets. Nurofen tablets is a well-known medicinal product with an established favourable efficacy and safety profile.

The line extension concerns the introduction of a new ibuprofen salt, ibuprofen sodium, as a line extension to Nurofen (ibuprofen acid). Efficacy and safety of Nurofen Zavance Tex have been demonstrated to be comparable to the existing Nurofen tablets.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other ibuprofen containing products with the non-prescription legal status.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that efficacy and safety have been demonstrated, and has therefore granted a marketing authorisation. Nurofen Zavance Tex 200 mg and 400 mg tablet and Nurofen Zavance Tex 200 mg tablet ovaal, coated tablets were authorised in the Netherlands on 29 July 2010. The status of supply is non-prescription in line with similar ibuprofen containing products.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
IBU	Ibuprofen
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
Q.I.D.	Four times a day
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States
VAS	Visual Analogue Scale

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Update of the formulation, a minor change to the description of the manufacturing process, an amendment of the finished product specification supported by stability data.	--	II/G	30-11-2010	15-7-2011	Approval	N
Changes to an existing pharmacovigilance system as described in the DDPS.	--	IA/G	14-9-2011	13-11-2011	Approval	N
Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking.	--	IA/G	21-2-2012	23-3-2012	Approval	N
Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system.	--	IA	24-4-2012	24-5-2012	Approval	N