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PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Vimovo 500 mg/20 mg, modified-release tablets AstraZeneca B.V., the Netherlands

naproxen/esomeprazole (as magnesium trihydrate)

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 and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states 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.

EU-procedure number: NL/H/1848/001/DC
Registration number in the Netherlands: RVG 106235

17 January 2011

Pharmacotherapeutic group:	antiinflammatory and antirheumatic products, non steroids - priopionic acid derivatives
ATC code:	M01AE52
Route of administration:	oral
Therapeutic indication:	symptomatic treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, in patients who are at risk for developing non-steroidal anti-inflammatory drug (NSAID)-associated gastric and/or duodenal ulcers and where treatment with lower doses of naproxen or of other NSAIDs is not considered sufficient.
Prescription status:	prescription only
Date of authorisation in NL:	18 November 2010
Concerned Member States:	Decentralised procedure with AT, BE, BG, CZ, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, LV, NO, PL, PT, RO, SE, SI, SK, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10b

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 member states have granted a marketing authorisation for Vimovo 500 mg/20 mg, modified-release tablets from AstraZeneca B.V. The date of authorisation was on 18 November 2010 in the Netherlands.

The product is indicated for symptomatic treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, in patients who are at risk for developing non-steroidal anti-inflammatory drug (NSAID)-associated gastric and/or duodenal ulcers and where treatment with lower doses of naproxen or of other NSAIDs is not considered sufficient.

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

Vimovo has been developed as a sequential-delivery tablet formulation combining an immediate release esomeprazole magnesium layer and an enteric coated delayed-release naproxen core. As a result, esomeprazole is released in the stomach prior to the dissolution of naproxen in the small intestine. The enteric coating prevents naproxen release at pH levels below 5 providing protection against possible local gastric toxicity of naproxen.
Due to the delayed-release of naproxen, Vimovo is not intended for, and has not been studied in, acute pain.
Naproxen is a NSAID with analgesic and antipyretic properties. The mechanism of action of the naproxen anion, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.
Esomeprazole is the *S*-enantiomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H+K+-ATPase – the acid pump and inhibits both basal and stimulated acid secretion.

This decentralised procedure concerns a so-called fixed dose application. Fixed dose combinations contain active substances from medicinal products already authorised in the EU but not hitherto used in combination for therapeutic purposes. For this kind of application the results of new pre-clinical tests or new clinical trials relating to that combination are provided. However, it is not necessary to provide pre-clinical and clinical data relating to each individual active substance.

The marketing authorisation is granted based on article 10b of Directive 2001/83/EC.
Both actives substances have been authorised for over 10 years in Europe. Naproxen is a well-known NSAID and esomeprazole is a well-established PPI (proton pump inhibitor). The EMA guideline on fixed combinations is relevant for this application.
The rationale for product development was to combine drugs that counteract an adverse reaction of one compound (naproxen) by another (esomeprazole), and to simplify of therapy. These are both acceptable benefits according to the EMA guideline on fixed combination products. As far as known to the RMS, one other combination product of an NSAID (ketoprofen) + PPI is registered in Europe.

Naproxen was chosen as active ingredient because of its relatively low risk of cardiovascular events compared to some other NSAIDs. The 500 mg bid dose was chosen for product development as it is the most commonly prescribed dose in the chronic treatment of the sought indications, i.e. rheumatoid arthritis and osteoarthritis. Approximately 75% of total naproxen use is at the 500-mg bid dose in FR, IT, ES, UK, and DE (source IMS Health). The MAH stated that another reason for developing a combination product with the highest available naproxen dose of 500 mg is that the need for gastro-protection by PPIs might be most relevant for chronic treatment at the highest NSAID dose level.

In support of the application, the MAH submitted pharmacokinetic and pharmacodynamic studies as a *proof of concept* and to demonstrate that immediate-release esomeprazole does not alter the absorption of enteric-coated naproxen. Efficacy and safety were further assessed in six studies. These are discussed in section II.3 ‘Clinical aspects’.

Scientific advice has been sought before this application in NL, DE, SE, UK and FR. Some of the advices were given on earlier development plans for different tablet strengths and formulations, and are therefore not applicable for the final 500 mg/20 mg formulation. The MAH followed CHMP guidance on fixed combinations.

A waiver for paediatric studies was granted by the Paediatric Committee, on grounds that the specific medicinal product does not represent a significant benefit over existing treatments for paediatric patients. The main rationale for this decision was that the naproxen 500 mg dose is not suitable for children. A sufficient number of elderly people were included in the studies.

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 naproxen
The active substance naproxen is an established drug substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is practically insoluble in water, soluble in ethanol and in methanol. The active substance is the S-enantiomer.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. and the CEP, with an additional test for particle size. The specification is acceptable 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 eight full-scale batches.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** 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.*

Active substance esomeprazole magnesium trihydrate
The active substance esomeprazole magnesium trihydrate is an established drug substance described in the European Pharmacopoeia. The active substance is a white to slightly coloured crystalline powder, which is slightly soluble in water and soluble in methanol. The active substance is the S-enantiomer. One polymorphic form of trihydrate compound is used.

Manufacturing process

The active substance is synthesised in five reaction steps followed by purification. The product is crystallized. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur., with additional requirements for absorbance of solution, residual solvents and several components. The specification is acceptable 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 full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for 3 pilot-scale batches stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). Furthermore, stability data have been provided for 3 commercial-size batches from the intended production site, stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The data do not show any out of specification results or trends. Based on the data, the proposed re-test period and storage condition were accepted.

Medicinal Product

Composition
Vimovo 500 mg/20 mg contains as active substance 500 mg naproxen and 20 mg esomeprazole (as magnesium trihydrate). The product is an oval, biconvex, yellow tablet marked '500/20' in black ink.
Vimovo tablets consist of a core with naproxen 500 mg enteric coated, covered by a layer of immediate-release esomeprazole 20 mg.

The modified-release tablets are packed in Aluminium/aluminium blister packs or HDPE bottles containing silica-gel desiccant with either a child resistant or non-child resistant (dispensing pack) polypropylene closure with an induction seal.

The excipients are:
Tablet core - croscarmellose sodium, magnesium stearate, povidone K90, colloidal anhydrous silica.
Coating - Carnauba wax, glycerol monostearate 40-55, hypromellose, iron oxide yellow (E172), macrogol 8000, methacrylic acid-ethyl acrylate copolymer (1:1), methyl parahydroxybenzoate E218, polydextrose, polysorbate 80, propyl parahydroxybenzoate (E216), sodium laurilsulfate, titanium dioxide (E171), triethyl citrate.
Printing ink - hypromellose, iron oxide black (E172), propylene glycol.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The packages are usual for this type of dosage form. Formal compatibility studies between naproxen and esomeprazole magnesium trihydrate were not required, as a film-coat barrier is present. The tablets are formulated to release esomeprazole immediately followed by the delayed release of naproxen. Therefore, the tablets are developed as a combination of two distinct formulations, an inner enteric-coated component of naproxen and an outer immediate release component of esmoprazole. The stability of the tablet formulations used in the phase 1 and phase 3 studies is essentially similar. The pharmaceutical development of the product has been adequately explained.

Dissolution profiles
Esomeprazole degrades rapidly in acidic solutions; more than 80% of esomeprazole drug substance is degraded within 10 minutes. Therefore, it is not relevant to quantitatively determine the amount and rate of esomeprazole dissolution under acidic conditions. The dissolution of naproxen was evaluated in three different pH media, pH 4.5, 6.8 and 7.4. The naproxen component of the product is enteric coated, therefore no naproxen is released in pH 4.5 or below. The selection of the most suitable dissolution parameters was discussed in sufficient detail. Separate acid-stage and buffer-stage testing was performed, which is appropriate in view of the nature of the tablet.

To demonstrate the safety and efficacy of the naproxen component, a bioequivalence study was conducted comparing the proposed product to the EU reference product, EC Proxen® S 500 mg. The bioequivalence study also included the Canadian reference product, EC NAPROSYN® E 500 mg. A representative Phase 3 batch was used in this study (PN400-108).The dissolution profiles of the batch used in this study were provided.
As supportive evidence of the validity of the bioequivalence strategy for the EC naproxen comparator, dissolution profiles are provided of naproxen from the US reference product used in the bioequivalence study PN400-102 and the EU reference product used in the bioequivalence study PN400-108. The dissolution profiles for the two reference products are similar.

Manufacturing process
The manufacturing process starts with producing a core tablet with naproxen. This core tablet is manufactured by a conventional wet granulation process. The core tablet is coated with six layers of film-coating. An enteric coat and barrier coat are applied prior to the active coat. The fourth coat is the esomeprazole magnesium trihydrate coat.
The manufacturing process has been adequately validated according to relevant European guidelines. Process evaluation data on the product has been presented for three lower scale production batches. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification and assay of naproxen and esomeprazole, impurities, dissolution, uniformity of dosage units and microbial quality. The release and shelf-life limits differ for the assay of esomeprazole and for the impurities. All tests and limits are acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on 12 lower-scale production batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for 6 lower-scale production batches stored at 25°C/60%RH (24 months), 30°C/65%RH (12 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the HDPE bottles with screw cap and in the Al/Al-blisters.
In the blister out of specification results were observed at accelerated conditions for total and individual impurities related to esomeprazole. At intermediate conditions a rise in these parameters was also observed. At long term conditions no out of specification results were observed. However an upward trend for the total impurities and individual known impurities was observed. A photostability study demonstrated that the drug product is photostable. The granted shelf-life is 24 months stored below 30°C in an Al/Al-blister and bottle.
The storage conditions are: ‘store in the original package and keep the bottle tightly closed in order to protect from moisture’ (bottle), ‘store in the original package in order to protect from moisture’ (blister), and ‘do not store above 30°C’ (both).

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

The single-dose toxicity, the repeat-dose toxicity, the genotoxicity, carcinogenicity and reproductive and developmental toxicity of both single compounds, naproxen and esomeprazole, were sufficiently reviewed and discussed based on literature. No studies with the combination are available.

Two non-GLP studies were provided on Quantitative Structure Activity Relationships (QSAR) analysis regarding genotoxic and carcinogenic potential of (potential) impurities in esomeprazole formulations (Nexium) for oral administration and for intravenous administration. For none of the tested impurities evidence of potential genotoxicity or carcinogenicity was found, using a combination of outcomes for the compounds from MCASE (Multiple Computer Automated Structure Evaluation) and DEREK (Deductive Estimation of Risk from Existing Knowledge).

Since the current formulation of esomeprazole on the market is an enteric coated formulation that is released after passage through the stomach, and because it is known that esomeprazole is degraded in an acidic environment, the MAH performed additional studies to show that the non-clinical studies originally provided for the authorisation of Nexium and omeprazole, are also applicable to Vimovo. Based on these studies it is plausible that all degradation products of esomeprazole formed in the human stomach have been tested in the toxicity studies in rats and dogs provided for the authorisation of Nexium. The identified degradation products described in the gastric fluid degradation studies were also examined as (potential) impurities of the drug product in both above mentioned QSAR reports and no evidence of genotoxic potential of these degradation products was found.
Based on these (non-GLP) additional studies it can be concluded that the degradation products formed at the pH in the human stomach have been sufficiently covered in the non-clinical package of data, provided for the authorisation of Nexium and the QSAR studies done for the qualification of impurities/potential degradants in Nexium drug product for IV and/oral oral use.

Environmental risk assessment
The MAH provided ERAs for both naproxen and esomeprazole. The assessment of these data resulted in the following conclusions:

- Naproxen:
  - Is not PBT (Persistent, Bioaccumulive and Toxic) nor vPvB (very Persistent, very Bioaccumulative).
  - The risk quotients for surface water, groundwater, STP and sediment are below 1, hence, no risk of naproxen due to use of Vimovo is anticipated.
- Esomeprazole:
  - Is not PBT, nor vPvB.
  - Based on the Phase IIA risk quotients for surface water, groundwater, STP (Sewage Treatment Plant) and sediment, no risk of esomeprazole due to use of Vimovo is anticipated.

In conclusion, no adverse effects on the environment due to the use of Vimovo are anticipated.

II.3 Clinical aspects

Quality of clinical studies, compliance with GCP
The MEB has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

Pharmacokinetics
Bioequivalence for naproxen between enteric-coated (EC) naproxen in Vimovo and the German reference product, Proxen S has been demonstrated both in fasting state and after a high-fat meal. Additionally, bioequivalence has been shown between Vimovo and EC naproxen component of Vimovo (Vimovo without esomeprazole in the film coat) indicating that IR esomeprazole in the film coating does not alter the absorption of EC naproxen in Vimovo. AUC and C_{max} were within accepted bioequivalence limits of 80-125%. The results of the studies are summarized in the table below.

Study No	Treatment (Number of subjects)	C_{max} (µg/ml) Mean	T_{max} (hr) Median (range)	AUC_t (µg/ml) Mean	AUC_{inf} (µg/ml) Mean
PN400-102	PN400	57.6	6.00 (3.00 – 24.0)	1178	1290

	Naproxen component of PN400	62.6	6.00 (2.00 – 36.00)	1264	1389
	GLSM ratio (90% CI)	0.91 (0.827 – 0.993)		0.941 (0.899 – 0.985)	0.942 (0.901 – 0.985)
PN400-108 A : fasted	PN400	69.8	4.00 (2.50 – 16.00)	1219	1300
	Proxen-S	70.6	4.00 (2.00 – 10.20)	1242	1327
	GLSM ratio (90% CI)	0.98 (0.92 – 1.05)			0.98 (0.96 – 1.00)
PN400-108 A : fed	PN400 (N=42)	66.5	12.00 (4.00 – 24.00)	1199	1321
	Proxen-S (N=40)	64.9	11.00 (2.00 – 24.00)	1199	1328
	GLSM ratio (90% CI)	1.03 (0.96 – 1.10)			0.99 (0.97 – 1.02)

GLSM Geometric least squares mean

The esomeprazole Innovator is currently marketed as an EC formulation (Nexium) and therefore the PK profile of this new IR formulation needed to be defined.

After repeated bid dosing of the combination product, there was 2 to 4-fold increase in C_{max} of esomeprazole and 4 to 6-fold increase in AUC as compared to the first day of dosing. The half-life slightly increased from 1 to approximately 1.1 -1.5 hours after bid dosing. This is probably due to the increased gastric pH, decreased degradation of esomeprazole after repeated dosing. This rate of accumulation is comparable to the innovator product.

There was an influence of circadian rhythm on PK of esomeprazole. There was a tendency for significantly higher C_{max} and AUC after morning dosing compared to the evening dosing. This greater absorption of the morning dose as compared to the evening dose, is probably caused by the difference in the fasting state (10 hrs overnight fast vs 2 hrs fasting before the evening dose). However, since the target intragastric pH level above 4 was maintained throughout the day and evening, the circadian rhythm does not have any clinical consequences.

In contrast to IR esomeprazole in Vimovo, the absorption of Nexium was delayed with the t_{max} of 1.5 hrs. This absorption difference is consistent with the known PK behavior of EC esomeprazole and the IR characteristics of Vimovo. Even though the AUC range at steady state was comparable for Nexium 20 mg and Vimovo: 292.0 – 2279.0 ng/ml and 189.0 – 2931.0 ng/ml, respectively, the mean exposure was 60% higher (CI: 1.28 – 1.93) for Vimovo. This could be expected due to the different total dose of esomeprazole given as Vimovo or Nexium (20 mg IR bid versus 20 mg EC qd). C_{max} was 60% higher (CI: 1.27 – 2.02), for Vimovo, which was expected for an IR formulation.

The mean half-life estimates of Nexium on Day 1 and the last day are comparable to those following Vimovo. Steady state is reached by day 9. The range of C_{max} was higher for Vimovo (112.0 – 1300.0 ng/ml) compared to Nexium (98.0 – 939.0 ng/ml), which could be expected for IR formulation. The mean half-life estimates of Nexium on Day 1 and the last day are comparable to those following Vimovo.

Single and repeated doses of Vimovo produced larger intra-subject variability in the PK parameters of esomeprazole than reported in the literature for Innovator EC omeprazole (50 versus 20%).This could be expected based on differences in the formulation. The larger intra-day variability did however not lead to less efficacy or specific safety problems (see clinical part below).

Interactions

It is agreed that this higher exposure as compared to Nexium 20 mg, does not result in higher potential for drug-drug interactions. This is also true for interaction with methotrexate. The only exception is

concomitant use with atazanavir which should be contraindicated for Vimovo. This is because in case of concomitant use with atazanavir, it is recommended not to exceed 20 mg of omeprazole. Due to similar pharmacodynamic and pharmacokinetic properties of omeprazole and esomeprazole and due to the lack of flexibility in dose adjustment of Vimovo, the concomitant use of atanazavir and Vimovo is contraindicated. Moreover, in line with CHMP decision form March 2010, a new warning on interaction between clopidogrel and PPIs is added and sections 4.4 and 4.5 of SPC have been updated accordingly. Additional warning on precautious use with aspirin in doses higher than used in the clinical studies, *i.e.* > 325 mg/day is well justified, and thus agreed to be added in section 4.5.

Food-interaction and posology

The proposed posology for Vimovo is to be taken at least 30 min prior to the meal.
Administration either with food or 30 min prior to the food intake yielded a small decrease in the C_{max} of naproxen, by 12-17%. T_{max} was delayed only by 2 hours compared to fed conditions.
There was a significant food effect for IR esomeprazole in Vimovo (52 and 75% reduction in the AUC and C_{max} and delay in absorption of about 1 hour compared to the fasting conditions). For IR esomeprazole, bioavailability was comparable when Vimovo was taken under either fasting conditions or 30 prior to the food intake.
Based on the above presented data, the Vimovo is proposed to be taken at least 30 min prior to the food intake. For naproxen, it may be preferred to take it with food, for gastro-protective reasons. However, as esomeprazole is released before the naproxen component, it provides gastric protection. Moreover, a delay of naproxen release is prevented when taken in fasted state, which may also be beneficial from clinical point of view.

Pharmacodynamics

The *proof of concept* of the combination product was confirmed in Study 101, a Phase I study in healthy volunteers. In this study, the incidence and severity of gastric damage (using Lanza scores) of the combination product Vimovo with different doses of esomeprazole (10/20/30mg) was compared to naproxen monotherapy. The majority of the subjects of the unprotected naproxen group developed more than 10 gastric and duodenal hemorrhages and erosions, and 32% even developed gastric ulcers. None of the subjects in the esomeprazole groups developed ulcers, though erosions and hemorrhages were not uncommon. These data confirm that adding esomeprazole prevents NSAID-related gastric damage and ulcers. There was a tendency that higher esomeprazole doses lead to lower Lanza scores.

Dose finding of the esomeprazole dose was primarily based on Study 104, a PD study in healthy volunteers where effect of different doses of esomeprazole on maintenance of high gastric pH level (>4) was studied (Study 104). A gastric pH >4 is generally accepted as a substitute endpoint for clinical efficacy. Different fixed-combination Vimovo formulations with 500 mg naproxen EC and 10/20/ 30 mg esomeprazole were compared to each other and conventional treatment, i.e. Nexium 20 mg EC once daily + Naproxen 500 mg IR bid as separate tablets. Based on the literature, it is not expected that Naproxen IR would provide another effect on the primary outcome of this study, i.e. gastric pH, than Naproxen EC. The results of this PD study are thus relevant for Vimovo, containing naproxen EC, as well.

Based on the outcome of this PD study, the MAH chose for the 20 mg esomeprazole Vimovo formulation as final product, instead of 10 or 30 mg esomeprazole Vimovo formulations, as both the 20/30 mg esomeprazole Vimovo formulations were clearly superior compared to 10 mg dose regarding the maintenance of high gastric pH level. There was not much additional benefit of increasing the dose from 20 to 30 mg according to an Emax model (ceiling effect). Because the Vimovo + 20 esomeprazole is most similar compared to the current standard treatment in terms of pharmacodynamic effects, the choice of the MAH is considered well justified.

At day one, period of gastric pH levels >4 were similar for conventional treatment with separate elements and the final combination tablet with 20 mg esomeprazole IR.
In steady state, maintenance of a high gastric pH level (>4) was slightly more prolonged with Vimovo compared to conventional treatment with Nexium 20 mg once daily (Mean period pH>4 of 70% versus 55% per 24 hrs, meaning a surplus of 2-5 hrs day of high gastric pH pro day, see table below). This PD effect is probably due to more frequent dosing of Vimovo.

Percent Time of pH Greater than 4.0 – Day 9 – Per-Protocol Population

	A PN 400/E30 N=25	B PN 400/E20 N=25	C PN 400/E10 N=25	D EC E20 + naproxen N=25
% Time of pH > 4.0				
Mean (SD)	76.50 (12.26)	71.35 (13.01)	40.85 (22.51)	56.85 (10.06)
Median	78.79	70.42	35.76	55.14
% Coefficient of variation	16	18	55	18
Range	49.79 – 95.32	51.76 – 97.61	10.30 – 85.26	40.63 – 75.51
LS Mean (SD)	76.75 (3.02)	71.46 (3.02)	41.09 (3.02)	57.23 (3.02)
LS Mean Difference (SE)	A vs. D 19.52 (3.25)	B vs. D 14.23 (3.25)	C vs. D -16.14 (3.25)	--
95% Confidence Interval	13.04 – 26.01	7.75 – 20.71	-22.26 – -9.66	--

Clinical efficacy
The following Phase III studies were performed:

Table Clinical efficacy 1: Overview of performed clinical studies

Study ID	Study Objective	Design	Duration (m)	Study Posology	Subjs by arm entred/ compl.	Gender, Median Age	Diagnosis Incl. criteria	Primary Endpoint
301	Efficacy of combination in prevention of NDAID-related GI ulcers	DB, parallel, active controlled randomised	6	PN400 bid Naproxen EC 500 mg bid	218/180 216/153	69% F, 60	Patients in need of chronic NSAID, at risk to develop GU/DU, due to age or earlier GU	Incidence of GU
302	Identical to 301				210/151 210/153	67% F 60	Identical to 301	
304	Long-term safety	OL, observational, no comparator	12	PN400 bid	239/135	70% F, 60	Same as 301	AEs
307	Efficacy in treatment of OA symptoms (Non-inferiority)	DB, parallel, active controlled placebo controlled randomised	3	PN400 bid Celecoxib 200 mg QD Placebo	246/208 242/208 124/105	64% F, 62	Diagnosis of OA < 6 m	WOMAC (pain, function)
309	Identical to 307				241/203 244/188 122/98	64% F, 62	Identical to 307	
303*	Efficacy/ safety	DB, parallel, active controlled randomised	6	PN400 bid Arthrotec	9 11	-	High risk on DU/GU#	Incidence of GU/DU

AEs: adverse events, bid=twice daily, DB=double-blind, m=months, OA = osteo-arthritis, OL=open label, PN400: study code for Vimovo formulation with 20 mg esomeprazole + 500 mg naproxen, QD=quod daily, *study ended preliminary due to recruitment problems, # patients with a history of complicated DU/GU like bleedings

Study 301 and 302, with prevention of gastric ulcers as primary outcome, were considered as pivotal by the MAH. Studies 307 & 309, with pain and functioning in OA as primary outcome were considered as supportive by the MAH.

Study 303, a comparative study with Arthrotec® (diclofenac + misoprostole) in patients at high risk (with prior history of gastro-intestinal ulcer complications) was cancelled because of slow recruitment. As sufficient data are available in the intended target population of patients at risk to develop UGI (Upper Gastro-Intestinal) ulcers from other studies (about 1200 were exposed to the new combination product), this is accepted.

Primary gastric safety studies (301 + 302)

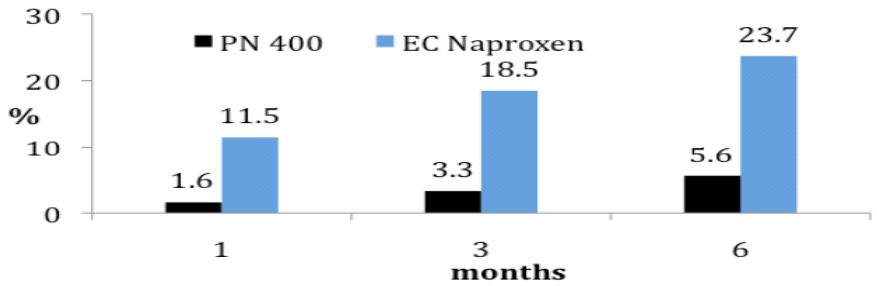
To establish efficacy of combination of esomeprazole + naproxen, the proportion of patients with gastric ulcers, measured by endoscopy and of at least 3 mm, after six months of treatment with either the combination or Naproxen EC monotherapy, were compared in two identical randomised Phase III trials (*301 & 302*). Patients at risk to develop gastric complications, based on age (>50 y) and prior history of gastric ulcer, were eligible for inclusion. Patients were stratified based on concomitant low-dose-aspirin use.

Outcomes; Gastric and duodenal ulcers

Pooled data are presented by the RMS, as the study design and the included population were similar for both studies, and outcomes of each separate study were in the same range (Note: separate study reports were available). After 6 months, the incidence of gastric ulcers, detected by endoscopy, was significantly higher in the Naproxen EC group (102/431, 23.7%) compared to the combination treatment (PN 400) group (24/430, 5.6%) (95% CI of the difference: 16.1-19.8, p<0.001). The incidence of duodenal ulcers was overall much lower compared to gastric ulcers. The incidence was however again higher in the Naproxen group compared to the PN400 group (18 (5.1%) vs 3 (0.5%) cases).

Although the results strongly indicate clinical relevant effect the interpretation is hampered because the endoscopic observed damage is not strongly correlated to a clinical benefit of prevention of complications[1]. However, this endpoint was accepted before in the registration of other PPI for the preventive indication.

Figure Clinical efficacy 1: Incidence of gastric ulcers in pivotal studies (pooled data, ITT population)



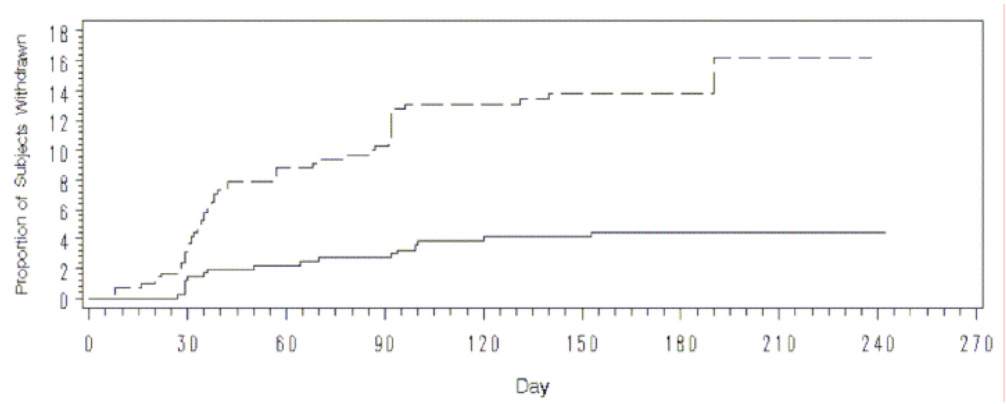
Secondary outcomes: Rescue drugs

There was no significant difference between treatment groups in percentage of subjects who used acetaminophen as rescue drug for the overall population (Study 301 + 302 pooled). This indicates that esomeprazole had no significant influence on the effect of naproxen regarding pain reduction. As could be expected, the use of antacid rescue drug was higher in the naproxen only arm.

[1] A Moore, I Bjarnason, B Cryer, et al. Evidence for Endoscopic Ulcers as Meaningful Surrogate Endpoint for Clinically Significant Upper Gastrointestinal Harm. Clinical Gastroenterology and Hepatology November 2009 (Vol. 7, Issue 11, Pages 1147-1150)

Study withdrawal
In line with increased incidence of UGI ulcers, the percentage of subjects who left the study because of upper-gastro-intestinal AEs and duodenal ulcers (DU) was significantly higher in the Naproxen EC only group versus combination treatment (16 versus 4%).

Figure Clinical efficacy 2 Kaplan-Meier plot of time to discontinuation due to pre-specified NSAID-associated UGI AE or DU (PN400-301 and PN400-302 combined, ITT populations)



Legend: PN 400 ————, EC Naproxen ----------

Based on the results of the pivotal studies study, it can be concluded that PN 400 significantly reduces the incidence of both gastric and duodenal ulcers compared to Naproxen EC alone. This difference is not only statistically, but also clinically relevant. Gastric ulcers may lead to possible life threatening complications like bleeding and perforation. More subjects left the study because of AEs in the Naproxen EC group than in the Vimovo group. The UGI related events not only occurred more frequently in the Naproxen EC group, but the AEs were also more serious in nature.

Supportive studies
Study 307 & 309 were identically-designed short-term, placebo-controlled, non-inferiority trials in osteo-arthritis patients, with WOMAC scale outcomes on pain, function and patient-global-assessment (PGA) scores as co-primary outcomes. Eligible subjects were males or females ≥ 50 years of age with a 6-month history of OA of the knee. Patients were either randomised to Vimovo bid, Celecoxib 200 mg QD or placebo in a 2:2:1 ratio. A non-inferiority margin of 10 mm on the Pain and Function Domains and the PGA Visual Analogue Scale (VAS) was chosen. This was considered adequate. Approximately 625 subjects were included in each study. There was no disproportional discontinuation over the three study arms.

Non-inferiority between celecoxib and Vimovo was shown regarding pain, function and patients' global assessment scores (see Table below). Vimovo deterred significantly from placebo, indicating assay sensitivity of the study. Withdrawal rate and tolerability was similar between Vimovo and celecoxib.

Table Clinical Safety 2. LS mean changes in WOMAC pain, function, and PGA-VAS from baseline to 12 weeks (Study-307 and -309 combined, ITT populations)

	PN 400	Celecoxib	PN 400 minus celecoxib (95% CI)
WOMAC pain	-43.1	-42.3	-0.8 (-4.0, 2.5)[a]
WOMAC function	-37.6	-36.6	-1.0 (-4.3, 2.2)[a]
PGA-VAS	25.0	23.6	1.4 (-1.9, 4.8)[b]

[a] A negative difference favours PN 400.
[b] A positive difference favours PN 400.

As supportive evidence for efficacy the combination product this study is less important as it confirms the known efficacy of naproxen. This was already expected, as the naproxen component of the combination product is bioequivalent to European reference product, and no PK interaction was observed between naproxen and esomeprazole.

Comparison to historical data
No direct head-to-head comparisons were provided between Vimovo and the combination of separate elements. Similar efficacy to conventional treatment is expected based on the PD studies, showing that gastric pH levels of the combination tablets was more enhanced compared to separate elements.
The results from trials PN400-301 and PN400-302 were consistent in demonstrating efficacy versus placebo with 70% to 90% Relative Risk Reduction (RRR) in the occurrence of GU and/or DUs for patients on Vimovo through 6 months as compared to EC naproxen 500 mg bid. These data can be compared with data from 2 similar trials conducted by AstraZeneca with the same primary endpoint over the same treatment duration for NSAIDs and EC esomeprazole (NEXIUM) versus NSAIDs and placebo. These 2 trials (PLUTO and VENUS, Scheiman et al 2006) demonstrated a 70% to 75% RRR for NEXIUM 20 mg and NEXIUM 40 mg qd versus placebo. The studies were of similar design and had similar inclusion criteria. A comparison is thus considered meaningful.

Clinical safety
In total 1157 patients were treated with Vimovo in the Phase III trials. The following dataset are used in the assessment of safety:

		Source data (Studies)	Exposure period (months)	N (exposed to Vimovo)
PSP	Pivotal Safety Population	301 +302	6	428
LSP	Long-term Safety Population	304	12	239
SSP	Supportive Safety Population	307 + 309	3	490
ESP	Extended Safety Population	301+302+304+307+309	3-12	1157

The populations included in the different trials were highly similar regarding age and gender (i.e. majority of women, median age around 60). The SSP consisted 100% of OA patients, but OA was also the most common diagnosis in the PSP/LSP dataset (about 80%).

Table Safety 1: Safety of PN400 by system organ class (>5% scores), from different sets of Phase III studies

System organ class	PN 400 ESP (%) N=1157	PN 400 PSP (%) N=428	PN 400 SSP (%) N=490	PN 400 LSP (%) N=239
Subjects with any TEAEs	66.6%	78.3%	53.3%	73.2%
Gastrointestinal Disorders	41.7%	63.6%	25.7%	35.6%
Infections and Infestations	16.1%	18.0%	10.0%	25.1%
Musculoskeletal and Connective Tissue Disorders	11.8%	8.9%	8.8%	23.0%
Nervous System Disorders	8.9%	8.6%	8.0%	11.3%
Investigations	5.7%	3.0%	6.1%	9.6%
Respiratory, Thoracic and Mediastinal Disorders	5.7%	6.1%	5.3%	5.9%
General Disorders and Administration Site Conditions	5.1%	3.3%	5.1%	8.4%

GI disorders were extremely frequent in the PSP database (63.6 %), and exceeded even the occurrence in the Long-term safety database (LSP) nearly 30% (See Table Safety 1 above). This may have been influenced by the fact that, in the PSP studies, all subjects underwent regular endoscopy and specific questionnaires were applied to register GI symptoms.

Conclusions of the safety of esomeprazole component of the combination tablet can be drawn indirectly from the comparison between the combination product of Naproxen + Esomeprazole and Naproxen alone (Table 2).

Safety Table 2: Safety of Vimovo by system organ class: comparison to active comparator Naproxen, reports from Study 301 + 302

System organ class	PN 400 N=428	EC Naproxen N=426
Subjects with any Adverse Event	78.3%	87.6%
Gastrointestinal Disorders	63.6%	80.3%
Infections and Infestations	18.0%	16.9%
Musculoskeletal and Connective Tissue Disorders	8.9%	7.7%
Nervous System Disorders	8.6%	5.9%
Respiratory, Thoracic and Mediastinal Disorders	6.1%	5.4%

The esomeprazole component in the combination tablet provided a significant protective effect against gastric complaints (e.g. dyspepsia 26.8 vs 18%) and UGI ulcers.

Gastro-intestinal (GI) AEs that were more frequently reported in the PN 400 (Vimovo) arm compared to Naproxen alone, were diarrhoea (6.1 vs 5.2%), and abdominal pain (2.3 vs 1.6%). This numerical difference is considered not clinical relevant and is probably attributed to change. The safety outcomes are in line with the SPC of Nexium, where these items were classified as common AEs (defined as incidence of 1-10%). These frequencies are also in line with large omeprazole databases (OMERACT study). Other AEs that are classified as common in the SPC of Nexium are constipation, flatulence,

nausea/vomiting and headache. These AEs were indeed commonly reported when Vimovo was used (2-5%), but in the same range as reported for naproxen alone.

The incidence of (non-serious) infections was similar in the combination treatment compared to Naproxen alone (upper respiratory tract infection (4.9 vs 3.8%), bronchitis (2.3 vs 1.8%), lower urinary tract infections (2.3 vs 1.4%). No cases of enterocolitis and pneumonia, which might be also associated with PPI use, were reported.
The incidence of SAE of the combination product (including serious infections) was low similar as reported for Naproxen alone (see Table 3 below). There were no fatal cases.

Safety Table 3 Summary of serious adverse events by system organ class for all Phase III studies (Celecoxib was only administered for 3 months, whereas Naproxen EC was given for 6 months, and Vimovo for 3-12 months).

System organ class	PN 400 n (%) (N=1166)	EC Naproxen n (%) (N=426)	Celecoxib n (%) (N=488)
All SAEs	34	14	9
Subject with any SAE	31 (2.7%)	13 (3.1%)	8 (1.6%)
Cardiac disorders	6 (0.5%)	2 (0.5%)	1 (0.2%)
Infections and infestations	4 (0.3%)	4 (0.9%)	1 (0.2%)
General disorders and administration site conditions	3 (0.3%)	1 (0.2%)	3 (0.6%)
Injury, poisoning, and procedural complications	3 (0.3%)	3 (0.7%)	1 (0.2%)
Musculoskeletal and connective tissue disorders	5 (0.4%)	0	1 (0.2%)
GI disorders	4 (0.3%)	1 (0.2%)	0
Nervous system disorders	4 (0.3%)	0	0
Immune system disorders	0	0	2 (0.4%)

Safety conclusions
In general, esomeprazole is known to be a well-tolerated drug, and this was confirmed in the clinical studies on Vimovo. The nature and frequencies of the AEs were in line as earlier reported for Nexium and omeprazole. Most reported safety problems could be rather contributed to naproxen.

The fixed combination with esomeprazole provided a significant reduction of NSAID related GI AE, such as gastric and duodenal ulcers, in patients at risk. The addition of esomeprazole to naproxen could not fully prevent dyspepsia, which was still commonly reported for the combination product, but both incidence and severity was considerably less.

Overall conclusion on efficacy and safety
Benefits
- The use of PPI's like esomeprazole in the prevention of NSAID-related gastric events is well established. It is generally accepted in treatment guidelines of RA and OA that preventive measures should be taken in patients who are anticipated to be treated with high doses of NSAID for a prolonged period. Treatment with COX-2 inhibitors might be an alternative option, but this is not recommended in patients with increased cardiovascular risks. Other acid inhibiting treatments than PPIs, e.g. histamine-2-receptor antagonists or misoprostol, are either considered less effective or are less tolerated (Lanza, *Am J Gastroenterol* 2009; 104:728-38, and Lazzaroni & Bianchi-Porro, Drugs 2009; 69(1):51-69).

- Naproxen is a well-known NSAID that is well-established in the treatment of the sought indications of OA, AS and RA. Vimovo is bioequivalent to market leader product of naproxen EC in Europe, which is widely accepted in Europe for treatment of the sought indications. The choice for naproxen as NSAID component is supported, as in a review by the EMEA from 2006, it was concluded that naproxen may provide lower cardiovascular risk at long-term use compared to other NSAIDs like ibuprofen and diclofenac (EMA/CHMP/442130/2006).

- Efficacy of Vimovo in prevention of GI ulcers was clearly demonstrated in patients at risk to develop NSAID-related events, i.e. elderly, patients with prior history of complicated gastric or duodenal ulcer, and patients using low-dose aspirin. Prevention of upper-GI ulcers is relevant because of possible complications like bleeding, perforation and strictures, which are potential lethal. It has been estimated that 2-4% of all NSAID users develop these complications (Lanza, *Am J Gastroenterol* 2009; 104:728-38).

- Esomeprazole is dosed automatically with naproxen in the combination tablet. This is considered as a benefit as adherence to naproxen might be disproportional larger than for esomeprazole, if given as separate tablets, because patients do not directly benefit from a PPI in contrast to the NSAID with pain-killing effect. Regular esomeprazole use is however recommended, as an optimal effect is only achieved in steady state. Moreover, in contrast to conventional treatment with PPI's, esomeprazole is released before naproxen, as esomeprazole is incorporated in the outer shell of the Vimovo tablet as an immediate release form. This may also have attributed to the improved tolerance

Risks

- ***Naproxen 500 mg bid dose***

  A limitation of the combination product is that only one, high strength of naproxen has been developed, allowing no flexibility in dosing.

  The general principle of treatment with NSAIDs is that these should be used at the lowest dose and shortest term possible. This is clearly emphasized in section 4.2 of the SPC.

  As no lower doses are possible with this product, the indication is restricted to patients where therapy with lower doses of NSAIDs is not considered sufficient (see section 4.1 of the SPC).

  It was discussed whether the naproxen 500 mg bid dose is appropriate for the treatment of OA symptoms, as symptoms may be less severe than for RA and lower doses may be sufficient. From the literature it became clear that there is indeed a relevant subgroup of OA patients that do not respond sufficiently to lower doses. Moreover, the main reason for restricting the use of NSAIDs in OA is the risk of gastric events, but this is considerably limited by the combination of esomeprazole for this product. Therefore, the OA indication is considered acceptable, given the dosing limitations as defined in section 4.1 and 4.2.

  Because of the high naproxen dose, Vimovo is not suitable for every patient in need of NSAIDs.
  In the opinion of the RMS, this is made sufficiently clear in the SPC, by the limited, second-line, indication together with the strict dosing criteria.

- ***Esomeprazole bid dosing: Safety risks***

  Preclinical studies did not identify any risks if additional and/or higher levels of degradation products are formed. All potential degradation products have been adequately qualified in previous toxicity studies on esomeprazole.

  In the literature, it is a matter of debate whether PPI's might be associated with infections (upper respiratory tract infections, community acquired pneumonia, tuberculosis, *Cl difficile* and other serious forms of entero-colitis), and malabsorption of iron, calcium, magnesium and vitamin B12. There was no signal from the Vimovo studies regarding these risks compared to naproxen alone arm. Common side effects were similar in the Vimovo arm compared to naproxen alone, with the exception of gastric events, which were more common in the unprotected naproxen study arm.

However, the Vimovo studies may not have been powered enough to detect rare adverse events. As concerns were raised whether the prolonged period of low gastric pH of twice daily dosing with Vimovo versus regular once daily dosing of esomeprazole EC (gastric pH was elevated >4 for 71% of the day versus 56%, respectively), the MAH was asked to discuss in detail the risk of higher dose level of esomeprazole at long-term use regarding malabsorption and infections.
The MAH submitted a review of epidemiological data and safety analyses of randomised studies where 40 mg esomeprazole was dosed once or twice daily in about 1600 subjects, for a period of 6 months. In the latter studies, the incidence of respiratory tract infections was similar between Nexium 40 mg and placebo. In a long-term study, Nexium 20 mg qd (or bid if needed) for up to 7 years was compared to laparoscopic anti-reflux surgery (the LOTUS study). In the LOTUS study, there were no differences in s-iron, vitamin B12 or calcium levels between the treatment arms. In extensive Post-Marketing Surveillance databases of (es-)omeprazole, no new safety signals other than already known were observed. The RMS agrees with the MAH that the data provided support a comparable safety profile of Vimovo and NEXIUM 20 mg qd.

As the concerns relate to rare issues, these can not be solved by clinical trials including the non-inferiority study proposed by some member states because of the large number of patients required and the long treatment duration. Therefore, in the RMP monitoring of these possible events related to high gastric pH has been included.
Mixed signals are available regarding the risk of vitamin B12 deficiency due to PPI's from different safety surveillance and case-control studies. As this issue is not fully clarified, a warning on the possible risk of vitamin 12 deficiency, especially in patients with reduced body stores or risk factors for reduced absorption, has been included in section 4.4. The possible risk of hypomagnesaemia and gastrointestinal infections is adequately described in the SPC.

Regarding the risk of osteoporosis, it is agreed with the MAH that data are awaited from the pharmacoepidemiological study, and that the issue will be re-evaluated at that moment, or earlier if indicated, by data from post-marketed use of Vimovo. It is agreed that it is not feasible to include Vimovo users based on the timelines for the planned observational study.

Conclusion
Given the second line indication (only for patients where lower doses of NSAIDs are not considered sufficient), and the strict criteria to reduce the use the of NSAIDs, the naproxen 500 mg bid dose is acceptable for the sought indications (symptoms of rheumatoid arthritis, ankylosing spondylitis and osteoarthritis). The MAH sufficiently explored and discussed the possible risks of long-term use of esomeprazole 20 mg twice daily.

Pharmacovigilance system
The member states consider that the Pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan
The RMP submitted during the procedure included the issues previously discussed, but two issues were not implemented in the last submitted version of the RMP. The MAH committed to submit an updated version of the RMP within one month after finalisation of the procedure as a follow-up measure. Changes in this version will be limited to the information provided during the procedure.
The issues concern:
1) the possibility of off-label use, due to the change in indication to second line. The MAH proposes a Drug Utilization Study regarding outcomes regarding prior NSAID usage in patients prescribed Vimovo. The MAH indicated that the Study Design Concept will be submitted as soon as available and committed to submit the study protocol (as an update of the RMP) for assessment by means of an appropriate variation procedure and the protocol needs to be agreed upon before the study will be initiated.

2) an extended text on the precise nature of close surveillance activities.

Summary of ongoing safety concerns for both components in Vimovo

Important identified risks	Aseptic meningitis, Agranulocytosis, Aplastic and haemolytic anaemia, Hypersensitivity reactions, Depression, Hypertension, Heart failure and pulmonary oedema, MI, Asthma, Bronchospasm, Serious GI AEs including bleeding, ulceration, obstruction and perforation of the stomach or intestines, Hepatitis, Hepatic failure, Hepatic encephalopathy, EM, SJS/TEN, Renal failure, Renal papillary necrosis and other renal injury, Nephritis interstitial
Important potential risks	Thrombotic stroke, Renal failure, Blindness/Blindness transient, Rhabdomyolysis, Osteoporosis/Osteoporotic fractures, Haemolytic anaemia, Microscopic colitis, Iron deficiency, Vitamin B12 deficiency, Lower respiratory tract infection, Clostridium difficile infection, Potential interaction with clopidogrel
Newly identified safety concerns	Risks identified for both the naproxen and esomeprazole components of VIMOVO (Agranulocytosis, Depression, Hepatitis, Hypersensitivity reactions, Severe skin reactions) GI bleeding, ulceration, obstruction and perforation of the stomach or intestines, Myocardial infarction Interaction with digoxin, Haemolytic anaemia, Microscopic colitis, Iron deficiency, Vitamin B12 deficiency, Lower respiratory tract infection, Clostridium difficile infection
Important missing information	Pregnant and lactating women, Patients with renal impairment
Identified and potential interactions	Warfarin or other coumarine derivates, NSAID preparations and ASA, Other platelet aggregation inhibitors, SSRIs, Antihypertensives, Diuretics, Methotrexate, Lithium, Cyclosporin/Tacrolimus, Corticosteroids, Phenytoin, Atazanavir, Nelfinavir, Digoxin, Clopidogrel

Summary of the Risk Management Plan

Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimisation activities (routine and additional)**
Osteoporotic fractures including hip fractures	In addition to routine pharmacovigilance activities, a pharmacoepidemiological study is ongoing.	Routine risk minimisation activities, as described in Section 3, are considered to be sufficient.
Potential interaction with clopidogrel	In addition to routine pharmacovigilance activities, a pharmacoepidemiological study of the potential interaction between clopidogrel and PPIs is ongoing. In addition, a PK/PD study is planned.	Routine risk minimisation activities, as described in Section 3, are considered to be sufficient.
Other important identified and potential risks and important missing information, as described	Routine pharmacovigilance process.	Routine risk minimisation activities, as described in Section 3, are considered to be

in Section 1.2.4.2		sufficient.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with the current knowledge on naproxen and esomeprazole. Regarding the issue of thrombotic stroke and NSAIDs, the standardised text as agreed by the Pharmacovigilance Working Party (December 2006) has been included in the SPC. A warning on interaction between clopidogrel and PPIs was added and sections 4.4 and 4.5 of SPC have been updated accordingly. Additional warning on precautious use with aspirin in doses higher than used in the clinical studies, i.e. > 325 mg/day is well justified, and thus agreed to be included in section 4.5. Overall the SPC has been adequately adapted in accordance with the member states' comments.

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 2 participants, followed by two rounds with 10 participants each. Fifteen questions specifically addressing key safety messages of the leaflet were asked. At the end of the interview were asked for their general comments on the leaflet.
The results of the user testing are acceptable according to the guideline on readability, because it was demonstrated that 90% of literate adults were able to find the information requested within the package leaflet, of whom 90% could show that they understand it.
The main objective of the readability testing has been examined, *i.e.* well-finding and well understanding. The key messages for the safe use of Vimovo were identified and they were included in the questionnaire.
In summary, the package leaflet is in line with the current readability requirements. The results show that the leaflet is easy to read and understandable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The member states, on the basis of the data submitted, considered that Vimovo 500 mg/20 mg, modified-release tablets demonstrated adequate evidence of efficacy for the approved indications as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation. The other member states mutually recognised the Dutch evaluation for the marketing authorisation.

Vimovo 500 mg/20 mg, modified-release tablets have a proven chemical-pharmaceutical quality.

Non-clinical aspects of both single compounds, naproxen and esomeprazole, were sufficiently reviewed and discussed based on literature.

Bioequivalence was demonstrated between Vimovo and EC naproxen component of Vimovo (Vimovo without esomeprazole in the film coat), indicating that IR esomeprazole in the film coating does not alter the absorption of EC naproxen in Vimovo.
The *proof of concept* of the combination product was confirmed in one pharmacodynamic study and an additional dose finding study. Efficacy was studied in five studies, which sufficiently demonstrated a positive benefit/risk balance.
Given the second line indication (only for patients where lower doses of NSAIDs are not considered sufficient), and the strict criteria to reduce the use of NSAIDs, the product was approved for the sought indications.

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

The SPC contains sufficient information on the separate components, as well as the combination. The SPC, package leaflet and labelling are in the agreed templates and have been adapted in accordance with requirements laid down during the procedure.

In the Board meetings of 23 December 2009 and 14 January 2010, the efficacy and safety of Vimovo were discussed. Ultimately the Board followed the advice of the assessors and considered the product approvable.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that a favourable benefit/risk profile has been established, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 7 October 2010 Vimovo 500 mg/20 mg, modified-release tablets was authorised in the Netherlands on 18 November 2010.

The PSUR submission cycle is 1-yearly. The international birthdate for Vimovo is 30 April 2010. The first PSUR will be submitted with a data lock point of 30 April 2011.

The date for the first renewal will be: 7 October 2015.

The following post-approval commitments have been made during the procedure:

<u>Quality - medicinal product</u>
- The MAH committed to complete validation for tablet cores and film coating operations prior to launch of the product.
- The MAH committed to continue the long-term stability studies on primary batches will be continued during the intended shelf-life.
- The MAH committed to place three commercial batches packed in either bottles or blisters on the long term storage condition of 25°C/60% RH. At each set time point, tablet description and testing for both components (naproxen and esomeprazole) regarding assay, organic impurities and dissolution will be performed.

Pharmacovigilance system

- The MAH committed to submit an updated version of the RMP within one month after finalisation of the procedure as a follow-up measure. Changes to this version will be limited to implementing information provided during the procedure.
- The MAH committed to submit the study protocol of the Drug Utilization Study (as an update of the RMP) for assessment by means of an appropriate variation procedure. The protocol will be agreed upon before the study will be initiated.

List of abbreviations

AE	Adverse Event
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
bid	Twice daily
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
DEREK	Deductive Estimation of Risk from Existing Knowledge
DU	Duodenal Ulcer
EC	Enteric-coated
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
GU	Gastric Ulcer
ICH	International Conference of Harmonisation
IR	Immediate-release
ITT	Intent-to-treat
MAH	Marketing Authorisation Holder
MCASE	Multiple Computer Automated Structure Evaluation)
MEB	Medicines Evaluation Board in the Netherlands
NI	Non-interiority
NSAID	Non-Steroidal Anti-Inflammatory Drug
OA	Osteo-arthritis
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
PBT	Persistent, Bioaccumulive and Toxic
PD	Pharmacodynamic
PGA	Patient Global Assessment
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PK	Pharmacokinetic
PN400	Study code for Vimovo
PPI	Proton Pump Inhibitor
PSUR	Periodic Safety Update Report
QSAR	Quantitative Structure Activity Relationships
RA	Rheumatoid Arthritis
RRR	Relative Risk Reduction
SAE	Serious Adverse Event
SD	Standard Deviation
SPC	Summary of Product Characteristics
SS	Steady State
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

UGI	Upper Gastro-Intestinal
VAS	Visual Analogue Scale
vPvB	very Persistent, very Bioaccumulative
WOMAC	Western Ontario and McMaster Universities Index of Osteoarthritis

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