Ipswich and East Suffolk
Clinical Commissioning Group

Suffolk PCT Drug & Therapeutics Committee
New Medicine Report (Adopted by the CCG until review and further notice)

This drug has been reviewed because it is a product that may be prescribed in primary care.

Medicine	Naproxen/esomeprazole (Vimovo, AstraZeneca)
Document status	Reviewed at May 2011 Suffolk D&TC meeting . Ratified at June CPG.
Date of last revision	14th June 2011.
Traffic light decision	**Double Red-** Prescribing not supported in either general practice or secondary/tertiary care
Prescriber's rating	**Not acceptable -** Product without evident benefit over others but with potential or real disadvantages.
Mechanism of action	Delayed release non-steroidal anti-inflammatory drug (NSAID) and proton-pump inhibitor (PPI) combination. Vimovo has been designed as a sequential-delivery tablet formulation. (1,2) The outer, immediate release layer contains esomeprazole and the inner part is an enteric-coated, delayed-release naproxen core. This design results in release of esomeprazole in the stomach and naproxen in the small intestine. (1)
Medicine class	New formulation NSAID and PPI combination. (BNF class 10.1.1 NSAIDs)
Indication	Symptomatic treatment of osteoarthritis (OA), rheumatoid arthritis (RA) and ankylosing spondylitis (AS), in patients who are at risk for developing NSAID associated gastric and/or duodenal ulcers and where treatment with lower doses of naproxen or of other NSAIDs is not considered sufficient. Vimovo is not intended for the treatment of acute pain due to the delayed-release of naproxen. (2)
Dosage	One tablet of modified release Vimovo containing 500mg naproxen and 20mg esomeprazole taken twice daily. (2) Vimovo must be swallowed whole with water, and not split, chewed or crushed. It is recommended that Vimovo is taken at least 30 minutes prior to food: the absorption of naproxen can be delayed by ~8 hours and the extent of esomeprazole absorption is reduced by >50% if Vimovo is taken with food. (1) NB: Generic naproxen preparations (both coated and uncoated) should be taken with or after food. The dose is 500mg – 1g

	daily in one or two doses. These preparations are licensed for treating RA, OA, AS and juvenile RA (1) Why is the esomeprazole dose in Vimovo 20mg BD? (1) The usual dose for esomeprazole for prophylaxis in patients at risk of gastro-duodenal complications but who require continuous NSAID therapy is 20mg daily. In a phase I dose finding study, a more rapid rise of gastric pH was seen with the immediate release (IR) formulation of esomeprazole vs. enteric coated (EC) esomeprazole. This rapid rise in pH occurred prior to the dissolution of naproxen, consistent with the sequential release design of the tablets. The IR esomeprazole 20mg BD dose was found to provide a comparable level of gastric acid suppression to EC esomeprazole 20mg daily. (1,3)
Treatment alternatives	NICE guidance for the treatment of OA and RA recommend that an oral NSAID should be co-prescribed with a PPI, choosing the one with the lowest acquisition cost. The Better Care, Better Value indicators also recommend low-cost PPI prescribing (1)
Place in therapy	Not clear
Future alternatives	None known at present
Evidence for use	In the clinical studies, Vimovo was taken by 491 patients for 6 months and 135 patients for 12 months. (2) In two randomised, double-blind, active-controlled studies, (published together) the incidence of gastric and duodenal ulcers was significantly lower after Vimovo treatment compared to enteric-coated naproxen 500mg twice daily (without esomeprazole or other PPI) during a 6 month treatment period. (4) See appendix 1 for summary. The gastric ulcer incidences for Vimovo were 5.6%, and for enteric-coated naproxen 23.7% (pooled data). Vimovo also significantly reduced the occurrence of duodenal ulcers relative to enteric-coated naproxen (0.7 versus 5.4%) (pooled data). (2) Vimovo also significantly reduced the occurrence of pre-specified NSAID associated upper gastrointestinal (GI) adverse events compared to enteric-coated naproxen during these trials; 53.3% vs 70.4% (pooled data). (2) Only patients at risk of developing NSAID related gastro-duodenal ulcers such as >50 years of age or prior uncomplicated ulcer were included; concomitant users of low-dose aspirin (LDA) were permitted. Subgroup analyses confirmed the same trend as observed for overall population regarding efficacy of GI ulcer prevention by Vimovo. In users of LDA, the incidence of gastro-duodenal ulcers was 4.0% (95%

	CI 1.1-10.0%) in the Vimovo group (n=99) vs. 32.4% (95% CI 23.4-42.3%) in the EC naproxen-only group (n=102). In elderly ≥ 60 years of age, the incidence of gastro-duodenal ulcers was 3.3% (95% CI 1.3-6.7%) versus 30.1% (95% CI 24.0-36.9%) in the Vimovo group (n=212) and in the EC naproxen-only group (n=209), respectively. (2) In two clinical trials, Vimovo had less upper abdominal discomfort over a 6-month period compared with EC naproxen as measured by dyspepsia symptoms. A significantly lower proportion of patients taking Vimovo discontinued the studies due to adverse events compared to patients taking EC naproxen alone (7.9% vs. 12.5% respectively). 4.0% and 12.0% was due to upper gastric-related adverse events, respectively. Patients on Vimovo had a mean duration of therapy of 152 days compared to 124 days in patients receiving EC naproxen alone. (2) In two 12-week studies in patients with OA of the knee, (poster abstract only) Vimovo (500 mg/20 mg given twice daily) had similar improvement in pain and function, time to onset of pain relief, and discontinuation due to adverse events compared to celecoxib 200mg once daily. (5) **What is adherence to concomitant PPI therapy like? (1)** • The target population for Vimovo use are those who are at high risk of NSAID-associated GI events. Retrospective studies, have shown that in patients newly prescribed NSAIDs who are also prescribed concomitant gastroprotective agents (GPAs), adherence to treatment with the GPA can be suboptimal. (4,6,7) In these studies, non-adherence to concomitant GPA therapy was associated with a 2.5-4 fold increase in the risk of upper GI complications. Higher risks were associated with lower adherence rates. (1) • The studies also showed that as the duration of the NSAID increased, adherence to PPI treatment decreased. Adherence was also adversely affected as the number of concomitant medications increased, and that even having recognised risk factors for upper GI complications did not improve compliance. **Critical evaluation** • There are limitations to these retrospective studies. No actual pill counts were performed and there was no direct monitoring of drug use. This could have affected the actual calculated drug exposure, although this would be the case for both the case and control groups. The databases used in the studies may not be an accurate reflection of the general population and could affect data extrapolation. (1)

	• A potential limitation of the published studies (4) and acknowledged by the authors may be the low combined incidence of patients with a previous history of ulcer within 5 years (8.1%). A majority of patients were assessed to be at risk for NSAID-associated ulcers based on age ≥50years (97.3%). However these studies differ from many studies that have been evaluated to assess GI safety from COX-2 inhibitors and that included all patients regardless of risk factors.
NNT	Not calculated
Cautions / side effects (2)	**Contraindications (2)** • Known hypersensitivity to naproxen, esomeprazole, substituted benzimidazoles, or to any of the excipients • History of asthma, urticaria or allergic-type reactions induced by administration of aspirin or other NSAIDs • Third trimester of pregnancy • Severe hepatic or renal impairment • Severe heart failure • Active peptic ulceration • Gastrointestinal bleeding, cerebrovascular bleeding or other bleeding disorders • Vimovo must not be used concomitantly with atazanavir and nelfinavir. **Cautions/precautions (2)** Mild to moderate renal impairment. Use cautiously and renal function should be monitored closely. A reduction in the total daily naproxen dose should be considered. When total daily dose of 1000mg of naproxen is considered not appropriate, alternative therapeutic regimens should be utilized. Mild to moderate hepatic impairment. Use cautiously and hepatic function should be monitored closely. A reduction in the total daily naproxen dose should be considered. When total daily dose of 1000 mg of naproxen is considered not appropriate, alternative therapeutic regimens should be utilized. The elderly are at an increased risk of the serious consequences of adverse reactions. When total daily dose of 1000 mg of naproxen is considered not appropriate (e.g. in elderly with impaired renal function or low body weight), alternative therapeutic regimens should be utilized. **Side effects (2)** Undesirable effects of naproxen may be minimised by using the lowest effective dose for the shortest duration possible. In patients not treated with a NSAID previously, a lower daily dose of naproxen or of another NSAID should be considered. When total daily dose of 1000mg of naproxen is not considered appropriate, alternative therapeutic regimens should be utilised. Treatment should be continued to achieve individual treatment

	goals, reviewed at regular intervals and discontinued if no benefit seen. **Summary of safety profile (2)** No new safety findings were identified during Vimovo treatment in the overall study population (n=1157) compared to the well-established safety profiles of the individual active substances naproxen and esomeprazole. **Description of selected adverse reactions, naproxen (2)** Clinical trial and epidemiological data suggest that use of coxibs and some NSAIDs (particularly at high doses and in long-term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Although data suggest that the use of naproxen (1000mg daily) may be associated with a lower risk, some risk cannot be excluded. Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. The most commonly observed adverse events are GI in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease have been reported following administration. Less frequently, gastritis has been observed. Vimovo has been developed with esomeprazole to decrease the incidence of gastrointestinal side effects from naproxen and has been shown to significantly decrease the occurrence of gastric and/or duodenal ulcers and NSAID associated upper gastrointestinal adverse events compared to naproxen alone. For further detailed information and experiences reported in patients taking Vimovo during the clinical trials refer to the SPC. In addition for a summary of adverse experiences reported in patients taking naproxen during clinical trials and through post-marketing reports and adverse events identified or suspected in the clinical trials programme for enteric-coated esomeprazole and/or from post-marketing use. Please refer to the Vimovo SPC. www.medcines.org.uk			
Cost within PbR tariff?	Yes			
Cost (prices from April 2011 MIMS)	60 tablets cost £14.95 Vimovo (naproxen 500mg + esomeprazole 20mg) dose; ONE tablet twice daily therefore cost is £14.95 per month.			
Cost of comparators	**Product**	**Dose**	**Cost per 28 days**	**Cost NSAID + PPI per 28**

				days
	Naproxen (generic)	500mg-1g daily, in 1-2 divided doses	£1.69	Naproxen £1.69
	Naproxen gastro-resistant tablets	500mg -1g daily in 1-2 doses	£5.17	Gastro-resistant naproxen £5.17
	Lansoprazole (generic)	15-30mg daily	£1.37 - £2.08	£3.06 - £3.77
	Omeprazole (generic)	20mg daily	£1.68	£3.37
	Pantoprazole (generic)	20mg daily	£1.50	£3.19
	Esomeprazole	20mg daily	£18.50	£20.19

Potential number of patients & usage in Suffolk PCT

- NICE estimate that in England, approximately 1,130,700 people will be taking a NSAID and a PPI for treating osteoarthritis. (8)
- Based on a population of ~51,000,000 in England, this suggests that approximately 2000/100,000 will be taking combined therapy. [1,130,700 is ~2.2% of 51,000,000].
- If 2000 patients were prescribed generic naproxen 500mg BD plus generic omeprazole 20mg daily, the cost per year would be:
  - £43,940 + 43,680 = £87,620 / 100,000 population.
- If 15% (n=300) were switched to Vimovo, the cost per 100,000 would be:
  - [£37,349 + £37,128 = £74,477] + £53,820 = £128,297.
  - This is an increase of £40,677 (46%).

Given the population of NHS Suffolk to be ~ 585,000. Approximately 12,870 patients within NHS Suffolk will be taking combined therapy.

If these patients were prescribed generic naproxen plus generic omeprazole 20mg daily the cost per year would be: £495,053.

If 15% (= 1931) were switched to Vimovo, the cost for NHS Suffolk would be £750,537

This is an increase of £255,484 (34%).

Note that this is for patients treated for osteoarthritis: the cost differential will be higher when patients with RA and AS are included. The prevalence of RA and AS is lower.

The incidence of RA is low, with approximately 50/100,000 population developing it each year. The exact incidence and prevalence of OA is harder to determine, with estimates that up to 8.5 million people in the UK affected by joint pain that may be

	attributed to OA. About 20% of adults aged 45-64 years and about 35% of women aged >75 years of age have OA pain in the knee. Approximately 31% of people > 45 years report hand pain and about 12% of adults >65 years report hip pain. (1)
Points for consideration	• Esomeprazole-naproxen (Vimovo) combined tablet, taken twice a day, does not represent a significant therapeutic advance from existing alternatives. • Where a NSAID is recommended in combination with a PPI in national guidance, a PPI with the lowest acquisition cost should be chosen. • The place in therapy and advantages of Vimovo over existing products is unclear and the potentially high acquisition cost is not compatible with current financial constraints and QIPP programmes.
Is the drug on the WSH or IHT formularies?	West Suffolk Hospital – no Ipswich Hospital – no
Decisions from other bodies	**Cambridgeshire JPG** – not considered **Norfolk TAG** – not considered **SMC –** not considered **NICE** – not considered
Comments sought from	Rheumatologist consultants and specialists IHT and WSH Gastroenterologist consultants and specialists IHT and WSH
Decision review date	To be decided

This review is based on the **DRAFT** UKMI London New Drugs Group, Primary Care Briefing; Vimovo (naproxen + esomeprazole) April 2011

References

1. Vimovo (naproxen + esomeprazole). UKMI London New Drugs Group Primary Care Briefing. April 2011 available via www.nelm.nhs.uk **DRAFT**
2. Summary of product characteristics: Vimovo 500mg/20mg modified-release tablets. Date of revision of the text: 5/11/10. AstraZeneca UK Limited www.emc.medicines.org.uk
3. Miner P, Plachetka J, Orelmans E et al. Clinical trial: evaluation of gastric acid suppression with three doses of immediate-release esomeprazole in the fixed-dose combination of PN 400 (naproxen; esomeprazole magnesium) compared with naproxen 500 mg and enteric-coated esomeprazole 20 mg: a randomized, open-label, Phase I study in healthy volunteers. Aliment Pharmacol Ther 2010; 32:414-424.
4. Goldstein JL, Howard KB, Walton SM et al. Impact of adherence to concomitant gastroprotective therapy on nonsteroidal-related gastroduodenal ulcer complications. Clin Gastroenterol Hepatol 2006; 4:1337-1345

5. Hochberg MC, Cryer BL, Fort JG et al. A fixed-dose combination of naproxen and esomeprazole magnesium (Vimovo) has comparable efficacy and tolerability to celecoxib in patients with osteoarthritis (OA) of the knee: results from two randomised, controlled trials, Poster abstract presented at the 74th Annual Scientific Meeting of the American College of Rheumatology, Atlanta, GA, USA, November 7-11, 2010.
6. Sturkenboom MCJM, Burke TA, Tangelder MJD et al. Adherence to proton pump inhibitors or H2 receptor antagonists during the use of non-steroidal anti-inflammatory drugs . Aliment Pharmacol Ther 2003; 18:1137-1147
7. van Soest EM, Sturkenboom MCJM, Dieleman JP et al. Adherence to gastroprotection and the risk of NSAID-related upper gastrointestinal ulcers and haemorrhage. Aliment Pharmacol Ther 2007; 26:265-275
8. Osteoarthritis. Costing report: Implementing NICE guidance . February 2008. NICE http://guidance.nice.org.uk/nicemedia/live/11926/39712/39712.pdf

NHS
Ipswich and East Suffolk
Clinical Commissioning Group

Appendix 1
Summary of phase III RCTs (published together Goldstein et al)

Trial	Trial design	Trial population	Treatment	Primary endpoint
PN 400-301	Randomised, double-blind, multicentre studies. Patients [stratified by low-dose (≤25mg) use aspirin use] aged ≥years or 18-49 years with a history of ulcer.	N=218	Vimovo one tablet twice daily or EC naproxen 500mg twice daily	The cumulative incidence of endoscopic gastric ulcers was significantly lower with Vimovo vs. EC naproxen in low dose aspirin users (N=201) (3.0% vs. 28.4%, P<0.001) and non-users (N=653) (6.4% vs. 22.2%, P<0.001). The incidence or, and discontinuations due to, upper gastrointestinal adverse events was significantly lower with Vimovo relative to EC naproxen. (p<0.01 both studies).
PN 400-302		N=210		

Ipswich and East Suffolk
Clinical Commissioning Group

Grids used to assist the NHS Suffolk PCT Drug & Therapeutics Committee in reaching a decision about new medications

For many years scientists have recognised two types of research:

- Primary: original studies, based on observation or experimentation on subjects.
- Secondary: reviews of published research, drawing together the findings of two or more primary studies.

In biomedical science there is general agreement over a hierarchy: the higher up a methodology is ranked, the more robust and closer to objective truth it is assumed to be. The orthodox hierarchy looks something like this-

Rank:	Methodology	Description
1	Systematic reviews and meta-analyses	Systematic review: review of a body of data that uses explicit methods to locate primary studies, and explicit criteria to assess their quality. Meta-analysis: A statistical analysis that combines or integrates the results of several independent clinical trials considered by the analyst to be "combinable" usually to the level of re-analysing the original data, also sometimes called: pooling, quantitative synthesis. Both are sometimes called "overviews."
2	Randomised controlled trials (finer distinctions may be drawn within this group based on statistical parameters like the confidence intervals)	Individuals are randomly allocated to a control group and a group who receive a specific intervention. Otherwise the two groups are identical for any significant variables. They are followed up for specific end points.
3	Cohort studies	Groups of people are selected on the basis of their exposure to a particular agent and followed up for specific outcomes.
4	Case-control studies	"Cases" with the condition are matched with "controls" without, and a retrospective analysis used to look for differences between the two groups.
5	Cross sectional surveys	Survey or interview of a sample of the population of interest at one point in time
6	Case reports.	A report based on a single patient or subject; sometimes collected together into a short series

7	Expert opinion	A consensus of experience from the good and the great.
8	Anecdotal	Something a bloke told you after a meeting or in the bar.

Adapted from Systematic reviews, What are they and why are they useful? ScHARR 2008

To Decide if a Medication Is To Be Used In Suffolk

Criterion to be measured	**Tends to poor**	2	**Medium**	4	**Tends to good**
Quality of evidence in the papers reviewed	7 - 8	5 - 6	3 – 4	2	1
Magnitude of effect inferred from trials reviewed	Low		Medium		High
Are trial end-points surrogate markers or clinical outcomes?	Surrogate markers				
Clinical usefulness of trial end-points		x			
Known Side Effect Profile	High	x	Medium		Low
Known Interactions	High		Medium		Low
Concern re Possible Side Effects Not Yet Uncovered	High	x	Medium		Low
Balance of Benefit To Harm (side effects toxicity interactions etc)	Poor		Medium		Good
NNT - none	High				Low
Comparison Of Effectiveness With Other Medicines In Use For The Same Condition	Poor		Medium		Good
Severity of Condition to be Treated	Trivial		Medium		Severe
Novel drug or member of existing class	existing				
Uptake (estimated proportion of people with this condition likely to be prescribed the medication under consideration – maximum and minimum uptake)	10 to 15 %				
Is the drug to be used in Suffolk? (QIPP recommendation)	Double Red				

Ipswich and East Suffolk
Clinical Commissioning Group

Prescriber's Rating Definitions

Bravo! -The drug is a major therapeutic advance in an area where previously no treatment was available.
A real advance - The product is an important therapeutic innovation but has certain limitations.
Offers an advantage - The product has some value but does not fundamentally change present therapeutic practice.
Possibly Helpful - The product has minimal additional value, and should not change prescribing habits except in rare circumstances.
Judgement reserved - The Committee postpones its judgement until better data and a more thorough evaluation of the drug are available.
Nothing New - The product may be a new substance but is superfluous because it does not add to the clinical possibilities offered by previous products available. In most cases these are "me-too" products.
Not acceptable - Product without evident benefit over others but with potential or real disadvantages.

(With acknowledgement to Prescrire)

To Decide Where A Medication Is To Be Used In Suffolk

Criterion		Red	Amber	Green	Blue
Skills of the prescriber	Experience Of The Condition	Specific	Specific	Specific	General
	Diagnosis	Specific	Specific	Specific	General
	Monitoring Progress Of Treatment	Difficult	Specific	General	General
Therapy	Patient Selection	Difficult	Specific	Specific	Easy
	Initiation Of Treatment	Difficult	Difficult	Easy	Easy
	Dose Titration	Difficult	Specific	Easy	Easy
	Monitoring Of Side Effects	Complex	Easy	Easy	Easy
	Method Of Administration	Complex	Normal	Normal	Normal
	Discontinuation Of Treatment	Complex	Complex	Easy	Easy

References

Jonsen A. Bentham in a box: Technology assessment and health care allocation. Law Med. Health Care. 1986;14:172-174
[1] Suffolk Drug & Therapeutics Committee Responsibility for prescribing, Hospital Trust or GP Attached as Appendix 1 & Appendix 2