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MIDLANDS

TRENT MEDICINES INFORMATION SERVICE

QIPP DetailAid Support Document

Providing support for quality in prescribing

NSAIDs- ibuprofen or naproxen preferred

KEY MESSAGES

- **Recent cohort data have confirmed previous safety warnings that diclofenac has a higher risk of thrombotic events (including MI and stroke) than naproxen or low-dose ibuprofen. Even a few days of treatment may increase risk, both in healthy individuals and those with cardiovascular disease. High doses of ibuprofen may also have an increased risk.**
- **Two meta-analyses have both estimated that, compared with placebo, diclofenac causes around three additional major vascular events per 1000 patients per year, with one such event causing death.**
- **Diclofenac continues to be widely prescribed; in some areas of the East Midlands nearly a third of NSAID prescribing is for diclofenac.**
- **Ibuprofen (1200mg per day or less) or naproxen (1000mg per day or less) are recommended first-line agents,combined with gastro-protection if at high risk for gastrointestinal adverse events. NSAIDs should be prescribed for the shortest timeand lowest dose necessary to control symptoms.**

WHAT IS THE PROBLEM?

- *Over the last 8 years there have been several warnings from the MHRA regarding the cardiovascular risks with some non-steroidal anti-inflammatory agents (NSAIDs), specifically diclofenac.*
- *Despite this, there continues to be significant prescribing of diclofenac; it accounts for 21% of all NSAID items in the East Midlands. In some areas nearly a third of prescriptions for NSAIDs are for diclofenac.*

The table below charts the change in prescribing patterns of the three main NSAIDs in the East Midlands over the last three financial years. Broadly there has been a shift from diclofenac towards naproxen with little major change in overall NSAID prescribing.

East Midlands	Total Items					% of total NSAIDs items	
	Financial year 2010/2011	Financial year 2011/2012	Financial year 2012/2013	% change 10/11 to 12/13		Financial year 2010/2011	Financial year 2011/2012	Financial year 2012/2013
Diclofenac Sodium	506,914	400,446	295,640	-42%		34%	28%	21%
Ibuprofen	417,045	407,230	396,175	-5%		28%	28%	28%
Naproxen	277,709	400,289	503,554	81%		19%	28%	36%
All NSAIDs	1,471,696	1,454,176	1,411,766	-4%				

Whilst there has been considerable reduction in diclofenac use over the past three years, significant prescribing rates still occur. The following table shows the highest and lowest PCT prescribing rates for each agent as a percentage of total NSAID prescribing in the most recent financial year.

East Midlands	% of total NSAIDsitems (Financial year 2012-13)		
	Lowest PCT prescribing rate	Highest PCT prescribing rate	East Midlands mean prescribing rate
Diclofenac Sodium	14%	30%	21%
Ibuprofen	18%	43%	28%
Naproxen	31%	43%	36%

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- *Ibuprofen and naproxen make up 64% of all NSAID prescriptions in the East Midlands. However, in some areas only half of all NSAID prescriptions are for these preferred agents.*

The percentage of all NSAIDs which are prescribed as ibuprofen or naproxen is anational QIPP prescribing comparator. The following table shows the change in this indicator in the East Midlands over the last three financial years. For the most recent financial year we have also shown the highest and lowest PCT values.

East Midlands	Financial year 2010/2011	Financial year 2011/2012	Financial year 2012/2013		Financial year 2012/2013	
					Lowest PCT prescribing rate	Highest PCT prescribing rate
% of all NSAIDs as ibuprofen or naproxen	47.2%	55.5%	63.7%		50%	76%

WHAT IS THE EVIDENCE?

- *In 2005 the European Committee for Medicinal Products for Human Use (CHMP) identified an increased risk of thrombotic events, such as myocardial infarction (MI) or stroke with COX-2 inhibitors. In 2006, they advised that a similar link may exist with non-specific NSAIDs, in particular diclofenac, particularly if used at high doses for long-term treatment.*

Advice from the Medicines and Healthcare Regulatory Agency (MHRA) in 2006 included the following[1]:

- Non-selective NSAIDs may be associated with a small increased risk of thrombotic events (such as heart attack or stroke) when used at high doses and for long-term treatment.
- Evidence for diclofenac (particularly at the 150mg dose) suggests that this drug may have a small thrombotic risk, similar to that of licensed doses of etoricoxib, and possibly other coxibs.
- For ibuprofen, at high doses (e.g. 2400mg a day) there may be a small thrombotic risk, but overall, at low doses (e.g. 1200mg or below), epidemiological data do not suggest an increased risk of MI.
- Naproxen is associated with a lower thrombotic risk than coxibs and, overall, epidemiological data do not suggest an increased risk of MI; however, some increase in risk cannot be excluded on the basis of available evidence.

- *In October 2012, the MHRA confirmed the previous findings, based on a more recent review of the evidence. The currently available data consistently indicate that the risk of MI, stroke or other thrombotic events is higher for diclofenac than other widely used non-selective NSAIDs and similar to selective COX-2 inhibitors.*

In 2012, the CHMP assessed evidence on the cardiovascular safety of NSAIDs from newly available published data sources, including a meta-analysis of clinical trials and observational studies and an EU-funded independent research project[2,3]. They concluded that the available data confirm findings from previous reviews, conducted in 2005 and 2006.

There were important limitations in all the recently available data due to the methodologies used and the populations studied[4]. Nevertheless, for diclofenac, the CHMP concluded that the latest study results were in line with previous evidence of a consistent but small increased risk of MI, stroke or other thrombotic events compared with other NSAIDs, similar to the risks of COX-2 inhibitors[3].

In relation to naproxen and ibuprofen, the CHMP was of the opinion that the current treatment advice 'adequately reflects the knowledge regarding the safety and efficacy of these medicines'[3].

As a follow-on to this review, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) will now assess all available data on diclofenac (both published and unpublished) to consider the need for updated treatment advice. This advice is expected in mid-2013.

- *Two meta-analyses have both estimated that, compared with placebo, a COX-2 inhibitor or diclofenac causes around three additional major vascular events per 1000 patients per year, with one such event causing death. The risk was increased regardless of the patient's background vascular risk. High-dose ibuprofen (2400mg daily) also significantly increased the risk of major coronary events, but its safety requires further study as there were many fewer relevant vascular events. Naproxen did not seem to increase the risk of major vascular events.*

One meta-analysis, published in the BMJ in 2006, attempted to quantify the increased risk. It included randomised trials of at least four weeks' durationthat compared a selective COX-2 inhibitor with placebo or a traditional NSAID and reported information on serious vascular events (defined as MI, stroke, or vascular death)[5]. In placebo comparisons, allocation to a COX-2 inhibitor was associated with a 42% relative increase in the incidence of serious vascular events (1.2%/year *v* 0.9%/year; rate ratio 1.42, 95% confidence interval (CI) 1.13 to 1.78; P = 0.003). This was chiefly attributable to an increased risk of MI, with little apparent difference in other vascular outcomes. The summary rate ratio for vascular events for other NSAIDs, compared with placebo, was 0.92 (95%CI 0.67 to 1.26) for naproxen, 1.51 (0.96 to 2.37) for high dose ibuprofen (800mg three times daily), and 1.63 (1.12 to 2.37) for diclofenac.

A further meta-analysis has recently been published in the Lancet[6]. Funded by the UK Medical Research Council and British Heart Foundation it included 280 trials of NSAIDs versus placebo and 474 trials of one NSAID versus

another NSAID. The main outcomes were major vascular events (non-fatal MI, non-fatal stroke, or vascular death); major coronary events (non-fatal MI or coronary death); stroke; mortality; heart failure; and upper gastrointestinal complications (perforation, obstruction, or bleed). Major vascular events were increased by about a third by diclofenac (rate ratio [RR] 1·41, 1·12—1·78; p=0·0036), chiefly due to an increase in major coronary events (RR 1·70, 1·19—2·41; p=0·0032). Ibuprofen (99% of trials used 2400mg daily) also significantly increased major coronary events (2·22, 1·10—4·48; p=0·0253), but not major vascular events (1·44, 0·89—2·33). Compared with placebo, of 1000 patients allocated to diclofenac for a year, three more had major vascular events, one of which was fatal. Naproxen did not significantly increase major vascular events (0·93, 0·69—1·27). Vascular death was increased significantly by diclofenac (1·65, 0·95—2·85, p=0·0187), non-significantly by ibuprofen (1·90, 0·56—6·41; p=0·17), but not by naproxen (1·08, 0·48—2·47, p=0·80). The proportional effects on major vascular events were independent of baseline characteristics, including vascular risk.

A Danish population cohort study estimated the risk of death and MI associated with the use of NSAIDs in1,028,437 healthy individuals[7]. Compared to no NSAID use, hazard ratios (95% CI) for death/MI were 1.01 (0.96-1.07) for ibuprofen, 1.63 (1.52-1.76) for diclofenac and 0.97 (0.83-1.12) for naproxen. A dose-dependent increase in cardiovascular risk was seen for selective COX-2 inhibitors and diclofenac.

- *Ibuprofen (1200mg per day or less) and naproxen (1000mg per day or less) are considered to have the most favourable cardiovascular safety profiles of all non-selective NSAIDs. All NSAIDs increased the risk of heart failure and of gastro-intestinal (GI) events; naproxen having a higher risk of GI events than ibuprofen or diclofenac.*

In October 2006, the MHRA concluded that for naproxen 1000mg daily, epidemiological data do not suggest an increased risk of MI[8]. For ibuprofen at high doses (eg, 2400mg daily), as previously discussed, there may be a thrombotic risk which, on current data is of borderline statistical significance, but at lower doses (eg, 1200mg daily or less) epidemiological data do not suggest an increased risk of MI. This was reiterated in the CHMP review of the evidence in 2012[3].

In the recent meta-analysis in the Lancet, heart failure risk was roughly doubled by all NSAIDs[6]. All NSAID regimens increased upper gastrointestinal complications (diclofenac 1·89, 1·16—3·09, p=0·0106; ibuprofen 2400mg daily 3·97, 2·22—7·10, p<0·0001; and naproxen 4·22, 2·71—6·56, p<0·0001)[6].

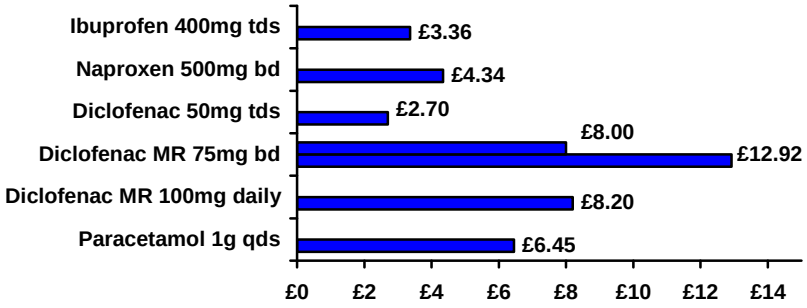
- *Results from a Danish cohort study of patients who had suffered a MI suggested that even short-term use of NSAIDs (in some cases for as little as one week) was associated with an increased risk of death or recurrent MI. Consistent with other studies, diclofenac was found to have the highest risk, and naproxen the lowest.*

A Danish cohort study identified an increased risk of death or recurrent MI with NSAIDs in patients with prior MI[9]. The risk was independent of the duration of treatment, and became apparent within the first weeks of treatment. Overall, the highest risk was associated with diclofenac, and the lowest risk was associated with naproxen.

The study found that NSAID treatment was associated with a significantly increased risk of death/recurrent MI (hazard ratio [HR] 1.45, 95% CI 1.29 to 1.62) at the beginning of treatment (up to 7 days) and the risk persisted throughout the treatment course (>90 days, HR 1.55, 95%CI 1.46 to 1.64). Analysis of individual NSAIDs showed that diclofenac was associated with the highest risk of death/recurrent MI for most durations of treatment (up to 7 days: HR 3.26, 95%CI 2.75 to 3.86; >90 days 1.92, 95%CI 1.66 to 2.22). The authors found that ibuprofen was associated with a lower risk of death/ recurrent MI than diclofenac (>90 days treatment HR 1.53, 95% CI 1.40-1.69), and that naproxen was associated with the lowest cardiovascular risk.

Although this study benefited from having data from a large nationwide cohort, it has a number of major limitations which need to be considered[10]. As results are not stratified according to dose, we do not know whether the increased risk seen with ibuprofen would have been apparent at doses less than 1200mg. As this was an observational study, many confounding factors may have influenced the results. For instance, there was no information with which to adjust for important cardiovascular risk factors (e.g. blood pressure, smoking habit, lipid levels, body mass index), nor was it possible to adjust for the specific indication requiring the NSAID. Furthermore, the duration of treatment was estimated from prescription data, which provided only an indirect assessment of the dose and period over which the medicines were taken.

WHAT ARE THE COSTS?



Costs for 28 days supply. Taken from Drug Tariff June 2013
Doses are a guide and do not imply therapeutic equivalence.

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