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Assessment report for diclofenac containing medicinal products (systemic formulations)

Procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure number: EMEA/H/A-31/1344

Assessment Report as adopted by the PRAC with all information of a confidential nature deleted.



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1. Background information on the procedure

The cardiovascular (CV) safety of non-steroidal anti-inflammatory drugs (NSAIDs) has been continuously reviewed over the last years. Previous reviews, including the one conducted in 2006, have concluded that NSAIDs as a class were associated with an increased risk of arterial thrombotic events, although the risk was considered to be higher for selective cyclooxygenase-2 (Cox-2) inhibitors (also known as coxibs)¹. The data available at the time, in particular from the MEDAL programme, did suggest that the risk of arterial thrombotic events with diclofenac was similar to that of Cox-2 inhibitors, but firm conclusions could not be drawn. Further epidemiological studies were needed to obtain additional data on pertinent safety aspects of NSAIDs and therefore the Agency recommended that the European Commission fund an independent study to further explore the gastrointestinal and cardiovascular safety of NSAIDs. The results of the 'safety of non-steroidal anti-inflammatory drugs' (SOS) research project funded by the European Commission (EC) under the Seventh Framework Programme, were considered in a review of cardiovascular risks of NSAIDs conducted by the Committee for Medicinal Products for Human Use (CHMP) in 2012, together with a number of new studies which had since become available. The CHMP considered that the available evidence regarding diclofenac seemed to consistently point towards a less favourable cardiovascular risk profile compared to other NSAIDs such as naproxen and ibuprofen, and similar risks as those of Cox-2 inhibitors. The reported increases in the risks for diclofenac rarely exceeded a two-fold increase compared to no-use, but it could not be excluded that relatively small increases in the risk are likely to have a public health impact. The CHMP concluded that it could be appropriate to consider this matter and the need for any regulatory action under a formal referral procedure².

In light of the above, the United Kingdom initiated, on 17 October 2012, a procedure under Article 31 of Directive 2001/83/EC for diclofenac containing products (systemic formulations) and referred the matter to the Pharmacovigilance Risk Assessment Committee (PRAC) to assess the above safety concern and give its recommendation on the whether risk of thrombotic events impacts on the balance of benefits and risks and also whether the marketing authorisations for medicinal products containing diclofenac should be maintained, varied, suspended or withdrawn. As the request results from the evaluation of data resulting from pharmacovigilance activities, the PRAC should issue a recommendation to the Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMDh).

After reviewing all the available data to address the concerns discussed, the PRAC adopted its recommendation on 13 June 2013.

2. Scientific discussion

2.1. Introduction

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID). NSAIDs, such as diclofenac, are indicated in the relief of all grades of pain and inflammation associated with a wide range of conditions, including arthritic conditions, acute musculo-skeletal disorders and other painful conditions resulting from trauma. NSAIDs mechanism of action is considered to include inhibition of prostaglandin biosynthesis, through inhibition of cyclooxygenase (Cox) enzymes. The adverse event profile of NSAIDs, including Cox-2 inhibitors, is known. Gastrointestinal adverse events, including serious events of PUB (perforation, ulcer, bleeding) are one main reason for discontinuation of treatment with NSAIDs. Other events such as hypersensitivity or skin reactions, cardiorenal effects and hepatotoxicity are also class effects. Diclofenac containing medicinal products are available in different formulations, such as tablets, capsules for oral administration (including immediate-release (IR), gastro-resistant, soluble effervescent, extended-release (ER), combined IR and ER formulations), suppositories for rectal administration and solutions for intravenous or intramuscular injection.

Epidemiological and clinical trial data were previously reviewed by the CHMP. In the 2006 review the Committee concluded that a small increase in the absolute risk of thrombotic events could not be

¹ Information on the review conducted in 2006 can be found at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/01/WC500054344.pdf

² Information on the review conducted in 2012 can be found at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/11/WC500134717.pdf

excluded for NSAIDs as a class, especially when used at high-doses and long-term therapy. Further epidemiological studies were needed to obtain additional data on pertinent safety aspects of NSAIDs, and in particular diclofenac. In 2012, the CHMP reviewed available published evidence from meta-analysis of clinical trials and observational studies, and also epidemiological studies. Results of the SOS research project funded by the EC under the Seventh Framework Programme, were also included in the review. The CHMP concluded that available evidence regarding diclofenac seemed to consistently point towards a less favourable cardiovascular risk profile compared to other NSAIDs such as naproxen and ibuprofen, and similar risks as those of Cox-2 inhibitors.

The present review focused on the cardiovascular safety of diclofenac. Several data sources informed the recommendation of the Committee, including available data from previous reviews, clinical studies, published literature, data submitted by marketing authorisation holders (MAHs) of medicinal products containing diclofenac and data from an independent research group that became available during the review.

An overview of the relevant information for the discussion is presented hereinafter. Of note, as most data were reviewed previously by the CHMP, and the PRAC acknowledged previous conclusions, the current report mostly focuses on any new evidence available on thrombotic risks from newly available studies on diclofenac. A complete list of references is provided at the end of the report.

2.2. Summary of evidence from previous reviews³

Previous reviews have concluded that the data available from clinical trials, observational studies and respective meta-analysis were suggestive that diclofenac was associated with similar thrombotic risks as those of Cox-2 inhibitors. The cardiovascular risks of coxibs are considered well established and are a useful baseline to characterise the risks of traditional NSAIDs. It is important to remember when interpreting the results that most of the studies were not designed to compare the cardiovascular safety profiles of the drugs involved, and used the NSAIDs as a comparator to demonstrate efficacy or non-inferior gastrointestinal safety. Other aspects considered include the inter-trial differences in the doses, patient populations, choice of endpoints and duration of treatment. Study limitations and details of the evaluation of these studies were considered in the previous reviews and are therefore not herein repeated. Only a relevant summary is provided.

The Successive Celecoxib Efficacy and Safety Study-I (SUCCESS-I) conducted in patients with osteoarthritis, did not show any differences between celecoxib and diclofenac for thrombotic cardiovascular event endpoints. However the study was limited due to its very short duration (12 weeks).

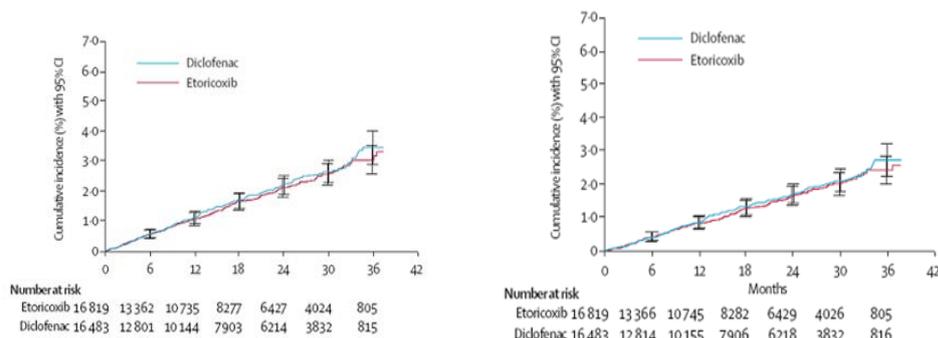
The Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme⁴ was a pooled analysis of three trials (EDGE, EDGE II and MEDAL) in patients with osteoarthritis and rheumatoid arthritis treated with etoricoxib (60 or 90mg) or diclofenac (150 mg). The primary objective of the programme was to compare the cardiovascular safety of the two drugs. Median duration of therapy was 16 months (range from 1 to 42). No differences were observed between etoricoxib and diclofenac for any of the cardiovascular outcomes as illustrated by the Kaplan-Meier plots below in the per protocol analysis of the programme. Similar results were observed with the Intention-To-Treat (ITT) analysis.

Figure 1
Kaplan Meier plots for per-protocol analysis of all arterial thrombotic events (left panel) and Antiplatelet Trialists' Collaboration Composite outcome (APTC) events (myocardial infarction, stroke or vascular death) (right panel) in the MEDAL programme, adapted from Cannon et al, 2006

³ Information on the review conducted in 2006 can be found at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/01/WC500054344.pdf

Information on the review conducted in 2012 can be found at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/11/WC500134717.pdf

⁴ For more details on the MEDAL programme, including its components, please refer to the previous CHMP assessment report detailed in footnote 3 for the review conducted in 2006.



The possibility that the MEDAL study was not capable of detecting differences between the two treatment arms could not be excluded. Interpretation of the results was further limited by the lack of a placebo-treated group to confirm whether or not the results were due to an increased risk from baseline with the two drugs. However, further evidence in support of the notion that diclofenac is associated with similar thrombotic risks to coxibs was provided by meta-analyses of clinical trials and observational studies.

The study by *Chen and Ashcroft* (2007) showed that diclofenac was associated with similar levels of risk to the combined coxib group despite excluding the results of the MEDAL programme. The network meta-analysis by *Trelle et al* (2011), largely confirmed the conclusions of the MEDAL study that the cardiovascular risks associated with etoricoxib and diclofenac were very similar for each individual endpoint investigated, as shown below.

Table 1
Estimated rate ratios of cardiovascular outcomes for NSAIDs compared with placebo, as reported by *Trelle et al*

	RR (95% CI)				
	MI	Stroke	CV death	All-cause mortality	APT ^c *
Naproxen	0.82 (0.37-1.67)	1.76 (0.91-3.33)	0.98 (0.41-2.37)	1.23 (0.71-2.12)	1.22 (0.78-1.93)
Ibuprofen	1.61 (0.50-5.77)	3.36 (1.00-11.60)	2.39 (0.69-8.64)	1.77 (0.73-4.30)	2.26 (1.11-4.89)
Diclofenac	0.82 (0.29-2.20)	2.86 (1.09-8.36)	3.98 (1.48-12.70)	2.31 (1.00-4.95)	1.60 (0.85-2.99)
Celecoxib	1.35 (0.71-2.72)	1.12 (0.60-2.06)	2.07 (0.98-4.55)	1.50 (0.96-2.54)	1.43 (0.94-2.16)
Etoricoxib	0.75 (0.23-2.39)	2.67 (0.82-8.72)	4.07 (1.23-15.70)	2.29 (0.94-5.71)	1.53 (0.74-3.17)
Rofecoxib	2.12 (1.26-3.56)	1.07 (0.60-1.82)	1.58 (0.88-2.84)	1.56 (1.04-2.23)	1.44 (1.00-1.99)
Lumiracoxib	2.00 (0.71-6.21)	2.81 (1.05-7.48)	1.89 (0.64-7.09)	1.75 (0.78-4.17)	2.04 (1.13-4.24)

*APT^c: Antiplatelet Trialists' Collaboration composite outcome; MI: myocardial infarction

In terms of observational studies, the risk of stroke with diclofenac in the meta-analysis by *Varas-Lorenzo* (2011) was the second highest after rofecoxib and exceeded that reported for celecoxib.

Table 2
Relative risk (RR) of stroke associated with various NSAIDs and coxibs, compared to no NSAID use in the various studies included in the meta-analysis by *Varas-Lorenzo et al*

Reference Cases (N)	RR (95% CI)				
	Naproxen	Ibuprofen	Diclofenac	Celecoxib	Rofecoxib
Abraham et al	2.00 (1.49-2.70)	1.70 (1.24-2.32)	NA	1.70 (1.14-2.54)	3.00 (2.04-4.42)
Andersohn et al 684	1.16 (0.80-1.70)	1.12 (0.91-1.37)	1.32 (1.10-1.57)	1.07 (0.79-1.44)	1.71 (1.33-2.18)
Bak et al	0.70	1.30	1.10	NA	NA

158	(0.44-1.13)	(1.03-1.64)	(0.70-1.70)		
Haag et al 52	2.63 (1.47-4.72)	1.47 (0.73-3.00)	1.60 (1.00-2.57)	NA	3.38 (1.48-7.74)
Roumie et al 574	0.94 (0.80-1.11)	0.88 (0.73-1.06)	0.94 (0.59-1.49)	1.04 (0.87-1.23)	1.28 (1.06-1.53)
Solomon et al 1904	0.83 (0.67-1.04)	0.95 (0.78-1.16)	0.98 (0.75-1.29)	1.00 (0.92-1.09)	1.15 (1.04-1.26)

NA: not applicable

Further evidence of an increased risk for diclofenac compared to the other NSAIDs was provided by the meta-analysis by *McGettigan et al* (2006). In this meta-analysis the risks associated with diclofenac were indistinguishable from those associated with rofecoxib and higher than those reported for celecoxib or some other NSAIDs. The number of studies included in this analysis for etoricoxib was limited to only 3. Nevertheless diclofenac, unlike other NSAIDs, was not associated with a statistical significant difference in the overall risks compared to etoricoxib.

Table 3

Pair wise comparison of individual drugs for myocardial infarction, ratios of relative risks (RRR) and their corresponding 99% confidence interval in the study by McGettigan and Henry

Drug Tested	Reference Drug in the Comparison				
	Rofecoxib	Diclofenac	Ibuprofen	Naproxen	Celecoxib
Etoricoxib	1.29 (0.86, 1.93), n=3 studies	1.36 (0.89, 2.09), n=3 studies	1.68 (1.14, 2.49), n=3 studies	1.75 (1.16, 2.64), n=3 studies	
Etodolac		0.95 (0.78, 1.16), n=5 studies	1.04 (0.88, 1.24), n=7 studies	1.10 (0.96, 1.26), n=7 studies	
Diclofenac	1.0 (0.89, 1.12), n=18 studies		1.13 (1.03, 1.24), n=27 studies	1.22 (1.11, 1.35), n=25 studies	1.15 (1.02, 1.30), n=19 studies
Naproxen			0.92 (0.87, 0.99), n=32 studies	—	0.96 (0.81, 1.13), n=23 studies
Meloxicam				1.11 (1.0, 1.23), n=6 studies	
Indomethacin				1.23 (1.10, 1.39), n=15 studies	

Emboldened results indicate significance at $p < 0.0033$

In the individual observational studies diclofenac and rofecoxib were the two drugs most consistently linked with the highest levels of cardiovascular risk.

The SOS project was designed to assess and compare the risk of cardiovascular and gastrointestinal events in users of NSAIDs and coxibs. A meta-analysis on the risk of stroke in association with NSAIDs was described by *Varas Lorenzo et al*, 2011 and additional studies, including a meta-analysis on the risk of myocardial infarction and case-control studies on the risks of stroke, myocardial infarction, heart failure and upper gastrointestinal complications were also conducted. A summary of the results from the meta-analysis and preliminary results from the case-control studies are presented in this section of the report.

The pooled estimate of the relative risk of acute myocardial infarction for most commonly prescribed NSAIDs and coxibs and the effect of NSAID dose (based on reported low-high definition in each study) on this risk are presented in the table below. Random and fixed effect models were used in the meta-analysis which, in most cases, yielded very similar results.

Table 4

Overall pooled estimates on the relative risk of acute myocardial infarction for most commonly prescribed NSAIDs compared with no NSAID use in the SOS meta-analysis

	Naproxen	Ibuprofen	Diclofenac	Celecoxib	Rofecoxib
Acute Myocardial Infarction					
No of studies	17	13	11	18	18
Random effects	1.06 (0.94-1.20)	1.14 (0.98-1.31)	1.38 (1.26-1.52)	1.12 (1.00-1.24)	1.34 (1.22-1.48)
Fixed effects	1.07 (1.01-1.13)	1.08 (1.04-1.13)	1.40 (1.33-1.47)	1.07 (1.01-1.14)	1.33 (1.25-1.40)
Heterogeneity (p-value)	<0.00001	<0.00001	0.005	<0.0001	0.0005

Dose effect: Low dose					
No of studies	5	6	6	7	9
Random effects	0.93 (0.75-1.16)	0.97 (0.76-1.22)	1.26 (1.03-1.53)	1.14 (0.99-1.31)	1.23 (1.12-1.34)
Fixed effects	0.91 (0.76-1.09)	0.83 (0.77-0.90)	1.25 (1.12-1.40)	1.11 (1.00-1.23)	1.22 (1.12-1.34)
Heterogeneity (p-value)	0.30	0.0001	0.02	0.13	0.42
Dose effect: High dose					
No of studies	6	7	6	8	9
Random effects	0.97 (0.80-1.16)	1.20 (0.99-1.46)	1.32 (1.07-1.63)	1.24 (0.99-1.57)	1.69 (1.39-2.05)
Fixed effects	0.98 (0.87-1.10)	1.11 (0.98-1.25)	1.40 (1.27-1.53)	1.17 (1.00-1.36)	1.69 (1.39-2.05)
Heterogeneity (p-value)	0.21	0.08	0.0007	0.09	0.87

An increased risk with diclofenac was also observed in the SOS nested-cases control studies across all databases and for both myocardial infarction and ischaemic stroke.

Table 5
Odds ratios and 95% CI for acute myocardial infarction and ischaemic stroke for the most commonly studied NSAIDs in the SOS studies compared to remote NSAID use

Database	Naproxen	Ibuprofen	Diclofenac	Celecoxib	Rofecoxib
Acute Myocardial Infarction					
GePaRD	1.87 (1.20-2.89)	1.36 (1.23-1.50)	1.22 (1.13-1.33)	0.79 (0.46-1.37)	-
IPCI	1.27 (0.74-2.17)	1.23 (0.74-2.06)	1.07 (0.79-1.47)	-	-
OSSIF	1.07 (0.83-1.38)	1.02 (0.83-1.25)	1.36 (1.24-1.50)	1.11 (0.98-1.26)	1.27 (1.12-1.44)
PHARMO	1.34 (1.13-1.59)	1.43 (1.24-1.65)	1.44 (1.30-1.59)	1.73 (1.32-2.27)	1.46 (1.17-1.77)
SISR	1.01 (0.81-1.24)	1.23 (1.09-1.39)	1.39 (1.29-1.50)	1.08 (0.97-1.20)	1.16 (1.00-1.35)
THIN	1.12 (0.96-1.32)	1.14 (1.04-1.26)	1.23 (1.14-1.34)	1.10 (0.95-1.28)	1.28 (1.09-1.50)
Pooled	1.19 (1.04-1.37)	1.24 (1.13-1.32)	1.31 (1.26-1.36)	1.09 (1.00-1.32)	1.26 (1.17-1.36)
p-value	0.09	0.018	0.02	0.017	0.41
Ischaemic stroke					
GePaRD	1.68 (1.05-2.69)	1.41 (1.27-1.55)	1.37 (1.26-1.49)	-	-
IPCI	-	-	-	-	-
OSSIF	1.09 (0.76-1.55)	1.11 (0.85-1.46)	1.26 (1.10-1.45)	1.04 (0.88-1.24)	1.13 (0.94-1.36)
PHARMO	-	-	-	-	-
SISR	0.96 (0.70-1.31)	1.07 (0.89-1.28)	1.38 (1.24-1.54)	1.03 (0.89-1.18)	1.22 (1.00-1.48)
THIN	0.88 (0.66-1.19)	1.04 (0.88-1.23)	1.12 (0.96-1.30)	1.08 (0.83-1.41)	1.09 (0.82-1.46)
Pooled	1.06 (0.84-1.35)	1.16 (0.97-1.39)	1.30 (1.19-1.42)	1.02 (0.93-1.13)	1.18 (1.05-1.34)
p-value	0.14	0.0035	0.084	0.42	0.793

Results using the fixed effect model yielded very similar results, except for ibuprofen and ischaemic stroke.

In common with other epidemiological studies, the level of risk reported for diclofenac was the highest together with rofecoxib. Furthermore, the only study that provided risks in relation to duration of exposure (*Schjerning Olsen et al 2011*) (and in which exposure misclassification should also be expected to be minimal) found that the risks associated with diclofenac were very similar to that of rofecoxib and considerably higher than that reported for other NSAIDs at all time points.

Schjerning-Olsen et al, 2011 was a cohort study investigating the cardiovascular effect of NSAIDs in patients hospitalised with first time myocardial-infarction. Data were collected from individual-level linkage of nationwide registries with drug dispensing from pharmacies in Denmark. The endpoints for this study were all cause mortality and a composite of recurrent myocardial infarction and mortality. Hazard ratios were estimated according to duration of NSAID treatment by multivariable time-stratified Cox proportional-hazard models.

The study identified 83,677 patients who had been hospitalised and subsequently discharged in Denmark for a first episode of myocardial infarction between 1997 and 2006. Of these patients, 42.3% received at least 1 prescription for a NSAIDs during follow-up, and there were 35 257 death and myocardial infarctions (42.1%) and 29 234 deaths (35.0%) registered during the observation period. The authors acknowledged the lack of information on various potential confounding factors (blood pressure, body mass index, smoking). The results of this study suggested that the diclofenac is associated with a high level of risk, which in contrast to the other drugs, from the beginning of the treatment. Of particular concern was the fact the reported risk for diclofenac was consistently higher than that associated with rofecoxib regardless of duration of treatment.

The reported risks for the composite endpoint and for death were very similar.

Table 6
Time dependent hazard analysis of risk of death for various NSAIDs as reported by Schjerning Olsen et al, 2011

	HR (95% CI)				
	0-7 days	7-14 days	14-30 days	30-90 days	>90 days
Naproxen	1.63 (0.88-3.03)	1.60 (0.83-3.08)	1.22 (0.71-2.10)	1.31 (0.90-1.91)	1.55 (1.10-2.17)
Ibuprofen	0.92 (0.71-1.20)	1.57 (1.27-1.94)	1.43 (1.22-1.67)	1.91 (1.73-2.11)	1.52 (1.38-1.69)
Diclofenac	3.52 (2.93-4.20)	2.57 (2.03-3.24)	2.08 (1.71-2.53)	2.61 (2.25-3.02)	2.02 (1.73-2.36)
Celecoxib	1.10 (0.71-1.68)	1.39 (0.90-2.13)	2.33 (1.79-3.02)	1.74 (1.42-2.13)	1.71 (1.47-1.99)
Rofecoxib	1.04 (0.68-1.58)	2.57 (1.91-3.46)	2.11 (1.62-2.75)	1.97 (1.62-2.41)	1.57 (1.30-1.88)

Available information from the SOS study on the dose effect of diclofenac is also limited but appears to point towards a dose dependency for the thrombotic risks associated with diclofenac use. However, it was considered difficult to establish a clear cut-off dose above which the risks become significantly increased as the various studies use different definitions of low and high doses of diclofenac.

Of note, one of the most detailed studies with respect to the dose effect (*Garcia-Rodriguez et al, 2008*) showed that doses above 75mg/day are associated with progressively higher thrombotic risks. The analysis conducted by *Garcia-Rodriguez et al, 2008* looked at the effect of the administered NSAID dose and degree of Cox-2 inhibition and the reported cardiovascular risk. This analysis showed a dose-response effect for diclofenac (p for trend <0.0001) with a statistical significant risk for myocardial infarction in patients receiving 100mg diclofenac/day (OR: 95% CI: 1.65, 1.26-2.18) or 150mg/day (OR: 95% CI: 1.80, 1.49-2.18). For patients receiving lower doses the risk did not reach statistical significance (50mg, OR 95% CI: 1.12, 0.57-2.19 and 75mg/day OR, 95%CI: 1.31, 0.8-2.16). The authors also reported a statistically significant correlation ($r^2=0.7458$, $p=0.0027$) between the degree of inhibition of whole blood Cox-2 in vitro produced by average circulating therapeutic concentrations and the relative risk of myocardial infarction associated with individual NSAIDs. Grouping individual NSAIDs with a degree of Cox-2 inhibition <90% at therapeutic dose (ibuprofen, meloxicam, celecoxib, and etoricoxib), users of these NSAIDs presented an RR of 1.18 (95% CI: 1.02 to 1.38), whereas users of rofecoxib, indomethacin, diclofenac, and piroxicam (Cox-2 inhibition $\geq 90\%$) had an RR of 1.60 (95% CI: 1.41 to 1.81, p for interaction=0.01). For diclofenac, no safe dose could be identified as both low and high dose were associated with an increased risk of cardiovascular events. However, low dose diclofenac was a mixture of ≤ 100 mg in six studies, <100mg in two studies and <150mg in two studies, and the data therefore cannot be used to draw conclusions on safety of doses lower than 100mg. A two-fold increased risk associated with 50mg or 75mg of diclofenac cannot be ruled out given the upper limits of the 95% confidence intervals.

Six cohort studies also investigated the relationship between NSAID dose and cardiovascular risk. *Gislason et al, 2006* reported a dose dependent statistical significant increased mortality with ibuprofen and diclofenac. However, only diclofenac was associated with an increased risk of recurrent myocardial infarction. In the study by *Van Staa et al, 2008* diclofenac was associated with an increased risk for any use, but also with a slightly increased risk for patients receiving 150mg diclofenac/day. The second study by *Gislason et al, 2009* largely confirmed the previous findings from 2006 with regards to ibuprofen and diclofenac with a statistically significant increased mortality associated with higher doses (>500 mg/day) of naproxen. Similar findings for ibuprofen and diclofenac were reported in another Danish cohort study (*Fosbøl et al, 2009*). *Ray et al, 2009* reported an inverse dose correlation between

diclofenac and the risks of serious coronary heart disease and serious cardiovascular disease or death. Finally, Fosbøl et al, 2010 reported a dose effect in the association between diclofenac, but not ibuprofen or naproxen, and cardiovascular death, coronary death or non-fatal myocardial infarction and stroke which was increased in patients receiving $100 \geq \text{mg/day}$.

The PRAC noted that the studies by *Gislason et al* (2006, 2009) and *Ray et al* (2009) were conducted in patients with co-morbid cardiovascular conditions (previous myocardial infarction, heart failure, coronary heart disease) and may not be applicable to the general population. However, the results (increased cardiovascular risk) among these high risk patients appear to be consistent between studies.

In the studies conducted in healthy populations (*Van Staa et al*, 2008, Fosbøl et al, 2009, Fosbøl et al, 2010), diclofenac $< 100 \text{ mg}$ appeared to be safer than $\geq 100 \text{ mg}$, but up to two-fold increased risks could not be ruled out with the low doses given the upper 95% confidence limits.

Overall, the PRAC acknowledged that the data from previous reviews was consistent for diclofenac and pointed towards an increased risk which was sometimes higher than the one seen for some other NSAIDs and in some instances higher than those reported for some of the coxibs, particularly celecoxib.

2.3. Presentation and discussion on new data

Further to the conclusions of the previous reviews, and data assessed therein, the MAHs of diclofenac containing medicinal products were invited to provide any new evidence of how diclofenac is used, the risk of arterial thrombotic events and possible mechanism for the increased cardiovascular risk. The impact of the previous conclusions on the benefit risk balance of medicinal products containing diclofenac (systemic formulations) and the need to additional risk minimisation measures was also discussed. Hereinafter we present a summary of the relevant data considered within the current review.

2.3.1. Use in clinical practice

To identify trends in diclofenac use in clinical practice, prescription insights were analysed by the MAHs. The results provided indicate that systemic diclofenac is available in different formulations and strengths and is prescribed most frequently for musculoskeletal and connective tissue disorders (including both acute and chronic diseases) and that prescriptions for these disorders were most frequently made for doses of $> 100 \text{ mg}$ to 150 mg for 10 days to 4 weeks duration. Data also showed that diclofenac is one of the most commonly prescribed NSAID and, together with ibuprofen, it accounts for the majority of NSAID prescriptions in patients 60 years of age or older. It was noted with concern that older patients are more likely to have underlying cardiovascular disease or risk factors for cardio and cerebrovascular thrombotic events.

Although the usage of diclofenac appears to have decreased since 2006, it remains one of the most widely prescribed NSAIDs. A recently published paper by *McGettigan and Henry*, 2013 sought to establish whether the Essential Medicines Lists (EMLs) and sales data across several countries reflect the known differences in cardiovascular risk between individual NSAIDs. The findings indicated that NSAIDs with higher risk of cardiovascular complications are widely used. Diclofenac and etoricoxib together accounted for approximately one-third of all NSAIDs in the 15 countries included in the analysis. The authors suggest that the continued high use of diclofenac indicates that the previous risk minimisation measures have not been effective and further measures are warranted to minimise risk through further communication of the current understanding of the arterial thrombotic risk of diclofenac and reduce prescribing in those at most risk. It was noted that England was the only country of the European Economic Community included in the analysis of usage data.

The PRAC considered that the prescription data available is presently limited, and it may not accurately represent actual patient exposure. A drug utilisation study could be useful in examining trends in diclofenac use since 2006, and collect information on the extent of use, the populations in which diclofenac is being used (age, newly contraindicated populations), dose and duration of use.

2.3.2. Evidence for the risk of thrombotic events

The PRAC noted and agreed with the previous assessment of the data on diclofenac considered by CHMP (see also section 2.2. Summary of evidence from previous reviews), including the assessment of

the strengths and limitations of the data. Meta-analyses and pooled analyses of clinical trial data (including the MEDAL program), meta-analyses of observational studies (including the SOS programme) and numerous individual observational studies including case-control and cohort studies (including four from the SOS Programme) were previously considered. In addition, the MAHs provided answers and its assessment, including any newly published data, is presented hereinafter.

Clinical trial data

No new relevant MAH sponsored clinical trial data has become available since 2006. However, one new analysis of clinical trial data on the cardiovascular effects of individual NSAIDs was submitted for review.

The study by *Krum et al* 2012, evaluated the relationship between baseline blood pressure and change in blood pressure on cardiovascular events in patients receiving NSAIDs or Cox-2 inhibitors in the MEDAL (Multinational Etoricoxib and Diclofenac Arthritis Long-term) programme. The results of the post hoc analysis of the MEDAL programme by *Krum et al* showed no significant differential effect between etoricoxib and diclofenac in relation to cardiovascular events, except for confirmed congestive heart failure, for which the risk was significantly higher with etoricoxib ($p=0.019$). In addition, the results also showed that baseline systolic blood pressure was associated with a significantly higher risk of all cardiovascular outcomes ($p<0.001$) and baseline diastolic blood pressure was inversely and significantly associated with risk of all events ($p<1.001$ to $p=0.016$) except cardiovascular/congestive heart failure mortality ($p=0.054$). Only the congestive heart failure risk was significantly associated with a change in blood pressure from months 0-4.

The PRAC noted that the results of this analysis could potentially add to knowledge about important risk factors for NSAID-induced cardiovascular events. The authors concluded that baseline blood pressure, but not change in blood pressure, was significantly associated with risk of thrombotic cardiovascular events. However a relationship between the blood pressure-elevating effects of NSAIDs and their cardiovascular risk cannot be definitively excluded due to the relatively short duration (18 months) of the trials.

It PRAC considered that the results should be interpreted with caution. This was a post hoc analysis and the exploratory nature of the study means that the results should be interpreted accordingly. Although the authors consider that the large sample size and general consistency of the results with those from similar trials (in addition to what is known clinically about the relationship between blood pressure and cardiovascular events) support the validity of the findings, it is not clear from the publication how exactly the statistical analyses were performed. It could be that different methods were employed to produce the effect of baseline blood pressure results in comparison to those employed in producing the effect of change in blood pressure results. It was also noted that the MEDAL study was not intended to be a blood pressure outcomes trial and thus blood pressure measurements may not be accurate and the exclusion criteria mean that the results may not be generalisable to all patients (particularly those with severe or uncontrolled cardiovascular disease).

Published clinical trial data

A new meta-analysis of clinical trial data became available and was considered in this review. The results from the Coxib and traditional NSAID (tNSAID) Trialists' Collaboration 'Vascular and Upper Gastro-intestinal effects of NSAIDs: meta-analysis of individual participant data from randomised clinical trials', were independently submitted for review by the PRAC. The study was published online in May 2013⁵.

The study was a meta-analysis of individual participant (or summary) data from randomised trials of NSAID versus placebo or an NSAID regimen versus another NSAID regimen. Eligible trials were randomised, over four weeks duration, with results available before January 2011, and included NSAID vs. placebo or other NSAID comparison and no other systematic differences in drug treatment between treatment arms. Estimation of the effects of tNSAIDs was achieved mainly through indirect comparisons. Effects on major vascular events (nonfatal myocardial infarction, nonfatal stroke or vascular death), mortality (subdivided by cause), heart failure and upper gastrointestinal complications (perforation, obstruction or bleed) were estimated.

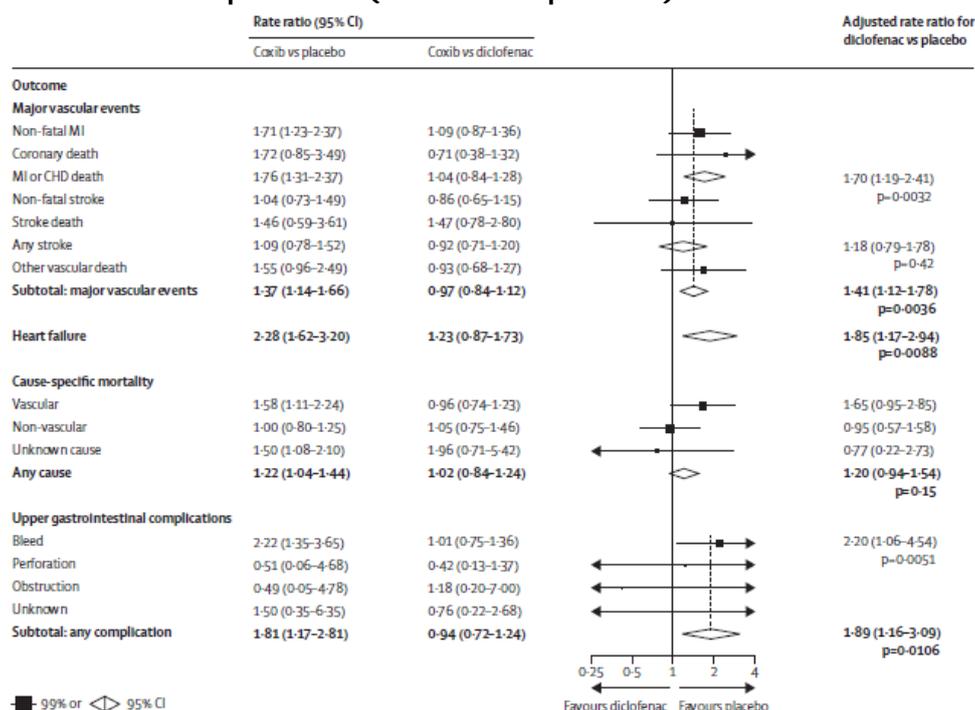
Almost all (~99%) of primary outcomes occurred in trials involving a coxib, diclofenac 150mg daily, ibuprofen 2400mg daily, or naproxen 1000mg daily. The patients characteristics (from trials providing

⁵ The early online publication can be found at [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(13\)60900-9/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)60900-9/fulltext).

individual participant data) included a mean age at randomisation of 61 years, two-thirds of the patients were female and 79% were Caucasian. Some patients had a medical history of atherosclerosis (9%), diabetes (9%) or upper gastrointestinal peptic ulcer (7%). The mean body mass index (BMI) was 29 kg/m²; blood pressure (BP) was 132/79mmHg; approximately one-fifth of patients were aspirin users at randomisation; 17% were receiving a proton-pump inhibitor; 13% were current smokers. The indications considered were rheumatoid arthritis or osteoarthritis in four-fifths of the participants but in coxib vs. placebo trials the indication was prevention of colorectal adenomata or of Alzheimer's disease in around one-fourth of the participants.

Information was available from more than 600 randomised clinical trials. Most outcomes occurred in trials involving a coxib regimen or high-dose tNSAID regimens (mainly diclofenac 150mg daily, ibuprofen 2400mg daily, or naproxen 1000mg daily): individual participant data were provided for most trials. Compared with placebo, the risk of major vascular events were increased by about one third by a coxib (rate ratio [RR] 1.37, 95% confidence interval [CI] 1.14-1.66; p=0.0009) or diclofenac (1.41, 1.12-1.78; p=0.0036), mainly due to an increase in major coronary events (coxibs: 1.76, 1.31-2.37; p=0.0001; diclofenac: 1.70, 1.19-2.41; p=0.0032). In these trials, among 1000 patients allocated to a coxib or diclofenac for a year, three would experience a major vascular event, with one fatal. The proportional effects on major vascular events appeared similar irrespective of vascular risk. Vascular death was increased by any coxib (1.58, 99% CI 1.00-2.49; P=0.0103) or diclofenac (1.65, 99% CI 0.95-2.85; p=0.0187), but not by other NSAIDs. Heart failure was approximately doubled by all NSAIDs (coxibs 2.28, 1.62-3.20; p<0.0001 diclofenac (1.85, 1.17-2.94); p=0.0088; ibuprofen (2.49, 1.19-5.20); p=0.0155; naproxen 1.87, 1.10-3.16; p=0.0197). All NSAID regimens increased upper gastrointestinal complications (coxibs 1.81, 1.17-2.81, p=0.0070; diclofenac 1.89, 1.16-3.09, p=0.0106; ibuprofen 3.97, 2.22-7.10, p<0.0001 and naproxen 4.22, 2.71-6.56; p<0.0001). Results are also shown in the figure below.

Figure 2
Effects of diclofenac on major vascular events, heart failure, cause-specific mortality, and upper gastrointestinal complications (indirect comparisons)



Rate ratios (RRs) are for comparisons of a tNSAID versus placebo, calculated indirectly from ratio of RRs for a coxib versus placebo and RRs for a coxib versus tNSAID, each of which is shown in the vertical columns. MI=myocardial infarction. CHD=coronary heart disease.

There was limited evidence that the risk of major vascular events might be increased during the first six months for coxibs and diclofenac and no evidence that any proportional excess increased with greater exposure to treatment. For symptomatic upper gastrointestinal ulcers a more definite pattern of clear excesses within the first six months was observed for coxibs, diclofenac, ibuprofen and naproxen.

The authors noted that the vascular risks of high-dose diclofenac, and possibly ibuprofen, are comparable to coxibs, whereas high-dose naproxen is associated with less vascular risk than other NSAIDs. Although NSAIDs increase vascular and gastrointestinal risks, the authors argued that the size of these risks can be predicted, which could help guide clinical decision-making.

The PRAC considered the new evidence available and noted its results and limitations, such as the exclusion of trials because of unavailability of events, differences in the patient population with and without cancer pain/treatment studied, and the statistical methods followed.

It was noted that the results for the coxibs were driven by the MEDAL study, and so the results and the magnitude of the point estimates were in line with what is already known. The PRAC considered that the results reported for diclofenac were also in line with other available evidence showing that the cardiovascular risk of these medicines is similar to that observed with Cox-2 inhibitors. The PRAC considered the new evidence, which overall aids in the quantification of the risks associated with various forms of pain relief including traditional NSAIDs and coxibs. The risks are well known, and the balance between gastrointestinal and cardiovascular risk, as well as attaining effective pain relief should be taken into account for all patients.

Epidemiological data

No new MAH sponsored pharmacoepidemiological studies or meta-analysis of pharmacoepidemiological studies were submitted.

Case-control studies

Three new case-control studies were published since the review of the literature performed for the 2012 review (*Grimaldi-Bensouda et al 2011, Shau et al 2012, Fosbøl et al 2012*). The results of these studies for the primary endpoints are summarised in the table below, however it should be noted that a number of these studies included additional analyses (e.g. subpopulation or dose effect analysis). Two of the studies reported on the risk of myocardial infarction (*Grimaldi-Bensouda 2011, Shau 2012*); the third (*Fosbøl 2012*) reported on the risk of ischaemic and haemorrhagic stroke.

Grimaldi-Bensouda et al (2011)

This matched case-control study investigated the association of NSAID with ST-segment elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI). STEMI is usually associated with total coronary occlusion by thrombus, whereas NSTEMI is more likely to be associated with incomplete thrombotic occlusion and more extensive atheromatous disease. NSAIDs with some Cox-2 selectivity are believed to facilitate the development of small platelet thrombi in the vascular surface. Although this may be sufficient to provoke an occlusion in already atheromatous coronaries, it is thought insufficient to produce a complete occlusion of a large epicardial coronary artery, the classic mechanism of STEMI.

Between 2007 and 2009, 1125 incident cases of myocardial infarction (67.3% STEMI; 32.7% NSTEMI) were identified from a French nationwide registry of 55 cardiology centres; 2790 controls matched to myocardial infarction by age and sex were identified from general practice. The study reported a significant increased risk for non-ST elevation MI associated with diclofenac (OR 2.8, 95% CI 1.2-6.4) but not for ibuprofen or naproxen grouped with other arylpropionic acid NSAID. The results were consistent with previous studies, but the finding of a significantly differential risk for NSTEMI vs. STEMI (for all main groups of NSAIDs) was considered interesting in terms of possible underlying mechanisms.

The study adjusted for past use of cardiology drugs of interest (including aspirin), risk factors for myocardial infarction (smoking, BMI, history of stroke, hyperlipidaemia, hypertension, diabetes) and other potential confounders including rheumatoid arthritis indication. Current use of aspirin and antiplatelet use within two years were excluded. The authors note that residual confounding may still be possible. Furthermore, whilst most risk factors, potential confounders and exposures were identified through medical records, documentation of behavioural (e.g. level of exercise) and familial risk factors was based on interview of subjects, as was reporting of over-the-counter use of medicines.

Shau et al (2012)

Shau et al examined the risk of new acute MI hospitalisation with the current use of 14 different NSAIDs. The case-cross over study used Taiwan's National Health Insurance claim database. Eight thousand three hundred and fifty four (8354) new acute myocardial infarction admissions were identified. The 1-30 days and 91-120 days prior to hospital admission were defined as the case and matched control period for each patient respectively. The use of co-medications was adjusted for and comorbidities and co-mediators were more frequent in the case compared to control periods.

Hypertention was the most frequent condition (42% case period; 37% control period) followed by diabetes mellitus (23% in case period; 22% in control period).

The study reported significant greater risk for acute myocardial infarction hospitalisation with parenteral than oral NSAIDs. Ketorolac was associated with the highest AMI risk among both oral and parenteral NSAIDs studied. The use of oral diclofenac, among others, was also significantly associated with increased acute myocardial infarction risk. The authors also performed an analysis of the risk of new acute myocardial infarction hospitalisation stratified by hypertension and use of low dose aspirin. Oral celecoxib (OR: 1.81; 95%CI: 1.07-3.05), diclofenac (OR: 1.33; 95% CI: 1.11-1.60) and ketorolac (OR: 7.64; 95% CI: 1.74-33.47) but not naproxen (OR: 1.30; 95% CI: 0.81 – 2.10), were associated with significant increased risk in patients with a hypertension diagnosis. In patients without a hypertension diagnosis, only oral diclofenac was associated with a significant increase in risk for new acute myocardial infarction hospitalisation (OR: 1.26; 95% CI: 1.04-1.52).

A significant interaction effect between the use of NSAIDs and low-dose aspirin on acute myocardial infarction risk was not found in this study. However, the limited number of patients on low-dose aspirin and possible over-the-counter use of low-dose aspirin limit the results in this respect.

Overall the study suggested that the risk of new acute myocardial infarction hospitalisation was increased for oral diclofenac compared to naproxen and similar to celecoxib. Furthermore the effect of hypertension diagnosis was more strongly related to cases than controls.

The case-cross over design reduces the potential confounding but it may be sensitive to the time window selected for the analysis. Sensitivity analyses were conducted based on case and control periods – strength of association and associated statistical significance was altered for oral diclofenac by removing the proximate seven days prior to index date, or by using 61-90 days prior to index date as the control period.

Fosbøl et al (2012)

In their case cross-over analysis *Fosbøl et al (2012)* reported on the risk of haemorrhagic and ischaemic stroke in 1,028,437 healthy individuals through individual-level linkage of nationwide administrative databases in Denmark. The median age was 39-years and at least one NSAID was prescribed to 47% of the study population. The study reported that high dose ibuprofen and diclofenac were associated with an increased risk for ischaemic stroke [Hazard ratio (HR): 2.15 (95% confidence interval (CI) 1.66-2.79) and 2.37 (1.99-2.81) respectively]. Diclofenac was also associated with increased risk of haemorrhagic stroke. However, in this study, naproxen which has consistently been shown to have the most favourable cardiovascular risk profile of the NSAIDs, was associated with a significantly increased risk of haemorrhagic stroke [HR: 2.15 (1.35-3.42)], which may reflect its greater selectivity for COX-1. Although a dose response was observed, the confidence intervals were wide limiting the conclusions that can be drawn (see figures 3 and 4 below).

Figure 3
Ischaemic stroke. Odds and hazard ratios derived from case crossover and Cox models, respectively.
Strokes: strokes during treatment. NNH: unadjusted number needed to harm per year of treatment

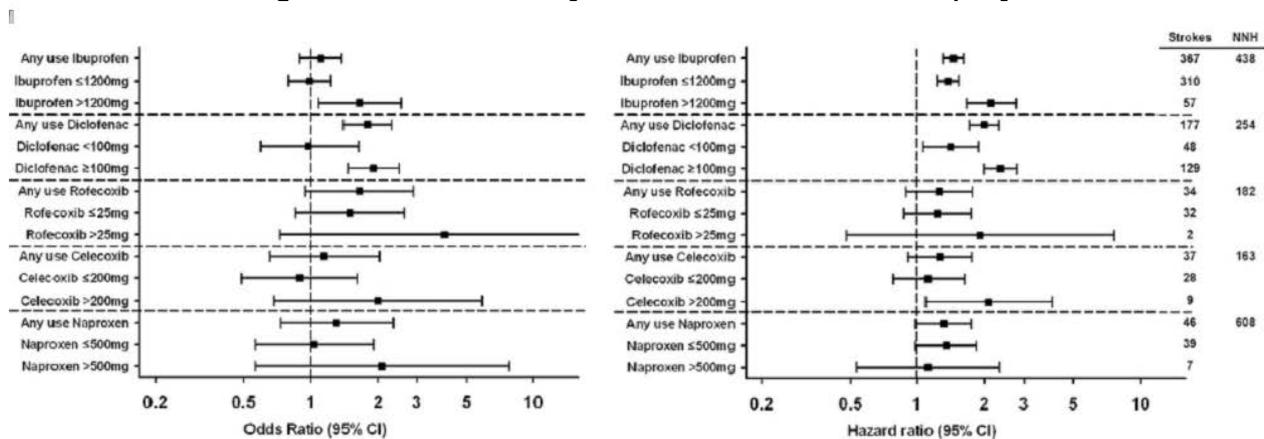
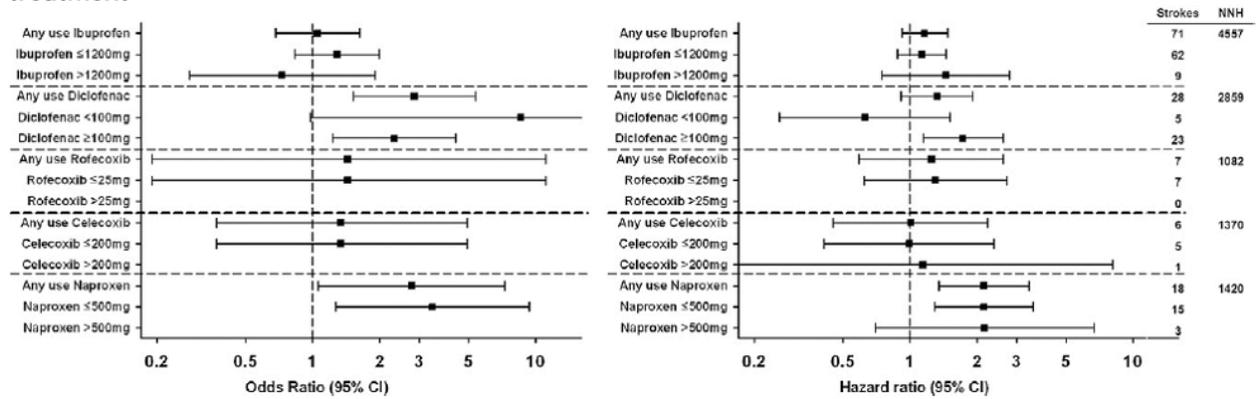


Figure 4
Haemorrhagic stroke. Odds and hazard ratios derived from case crossover and Cox models, respectively. Strokes: strokes during treatment. NNH: unadjusted number needed to harm per year of treatment



The table below provides a summary of the new case-control studies which had not previously been considered.

Table 7 Summary of new case-control studies reporting on cardiovascular risk of diclofenac, not previously considered

Study	Endpoints	Cases/controls (n)	Non-adjusted factors	OR (95% CI)
Grimaldi-Bensouda (2011)	Incident non-fatal MI	1125 patients (aged 18-79 years) presenting with incident MI identified from French PGRx-MI Registry (55 cardiology centres) between 2007 and 2009. 2790 age (+/- 5years) and sex matched controls, randomly selected from national list of GPs in France	OTC use (if not recalled by subject)	<u>MI</u> Diclofenac: 1.47 (0.87-2.48) Ibuprofen: 0.91 (0.65-1.27) Naproxen & other AA* NSAID: 0.72 (0.45-1.16) All NSAIDs: 0.96 (0.75-1.23) <u>STEMI</u> Diclofenac: 0.90 (0.43-1.87) Ibuprofen: 0.98 (0.65-1.48) Naproxen & other AA* NSAID: 0.97 (0.55-1.68) All NSAIDs: 0.95 (0.70-1.28) <u>NSTEMI</u> Diclofenac: 2.82 (1.23-6.48) Ibuprofen: 0.75 (0.41-1.38) Naproxen & other AA* NSAID: 0.37 (0.15-0.91) All NSAIDs: 0.96 (0.63-1.46)
Shau (2012)	New AMI hospitalisation	Case cross-over study using Taiwan's National Health Insurance claims database N=8354 patients hospitalised for new AMI in 2006. Index date: date of AMI hospitalisation Case period: 1-30 days prior to index Control period: 91-120 days prior to index		<u>Oral</u> Celecoxib: 1.36 (0.95-1.96) Ketorolac: 2.02 (1.00-4.09) Flurbiprofen: 1.71 (1.06-2.74) Ibuprofen: 1.45 (1.19-1.76) Sulindac: 1.44 (1.02-2.03) Diclofenac: 1.29 (1.13-1.47) Naproxen: 1.26 (0.88-1.81) Ketoprofen: 1.17 (0.64-2.11) <u>Parenteral</u> Diclofenac: 1.88 (0.95-3.75) Ketorolac: 4.27 (2.90-6.29) Ketoprofen: 2.34 (1.31-4.19)
Fobøl (2012)	Fatal or non-fatal ischaemic or haemorrhagic stroke	Case crossover study using record-linkage between Danish national registries 1,028 437 healthy individuals aged ≥10 years on Jan1, 1997 with ≥1 NSAID prescription. Index date: date of outcome of interest Case period: 0-30 days before index Control period: 60-90 and 90-120 days before index		<u>Ischaemic stroke</u> High dose ibuprofen: 2.15 (1.66-2.79) High dose diclofenac: 2.37 (1.99-2.81) <u>Haemorrhagic stroke</u> High dose diclofenac: Increased (numbers not provided) Naproxen: 2.15 (1.35-3.42)

* AA: arylpropionic acid; STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST elevation myocardial infarction.
MI: myocardial infarction; AMI: acute myocardial infarction

Cohort studies (retrospective)

Three retrospective cohort studies (*Lamberts et al 2012*; *Schjerning-Olsen et al 2012*; and *Gudbjornsson et al 2010*) relating to the cardiovascular safety of NSAIDs including diclofenac were submitted for review.

Lamberts et al (2012)

Lamberts et al used the same Danish healthcare databases as used by *Fosbøl et al (2012)*. The purpose of the study was to examine the effect of ongoing NSAID treatment at the time of admission for myocardial infarction on prognosis.

All patients aged above 30 years admitted with first time myocardial infarction in 1997-2006 were included. By claimed prescription of NSAIDs, availability of tablets was estimated within 14 days prior to inclusion and defined ongoing use. To control for possible confounding adjustments were made for age, gender, calendar year, concomitant drug use, and co-morbidities. A total of 97,458 patients were included (mean age 69.9 years). Sixty two per cent (62%) of the study population was male. The day 30 and one year mortality rates were 18.1% and 27.7% respectively. Ongoing NSAID treatment was identified in 12,156 (12.5%) patients and 30-day mortality was significantly increased in patients receiving rofecoxib and celecoxib compared to no use of NSAIDs.

Correspondingly, the one-year rate of death or recurrent MI was significantly increased in patients receiving rofecoxib, celecoxib, diclofenac or any NSAID compared to no use. No association was found for naproxen or ibuprofen. The authors conclude that ongoing treatment with rofecoxib, celecoxib and diclofenac is associated with worsened prognosis in patients admitted with first-time myocardial infarction.

Gudbjornsson et al (2010)

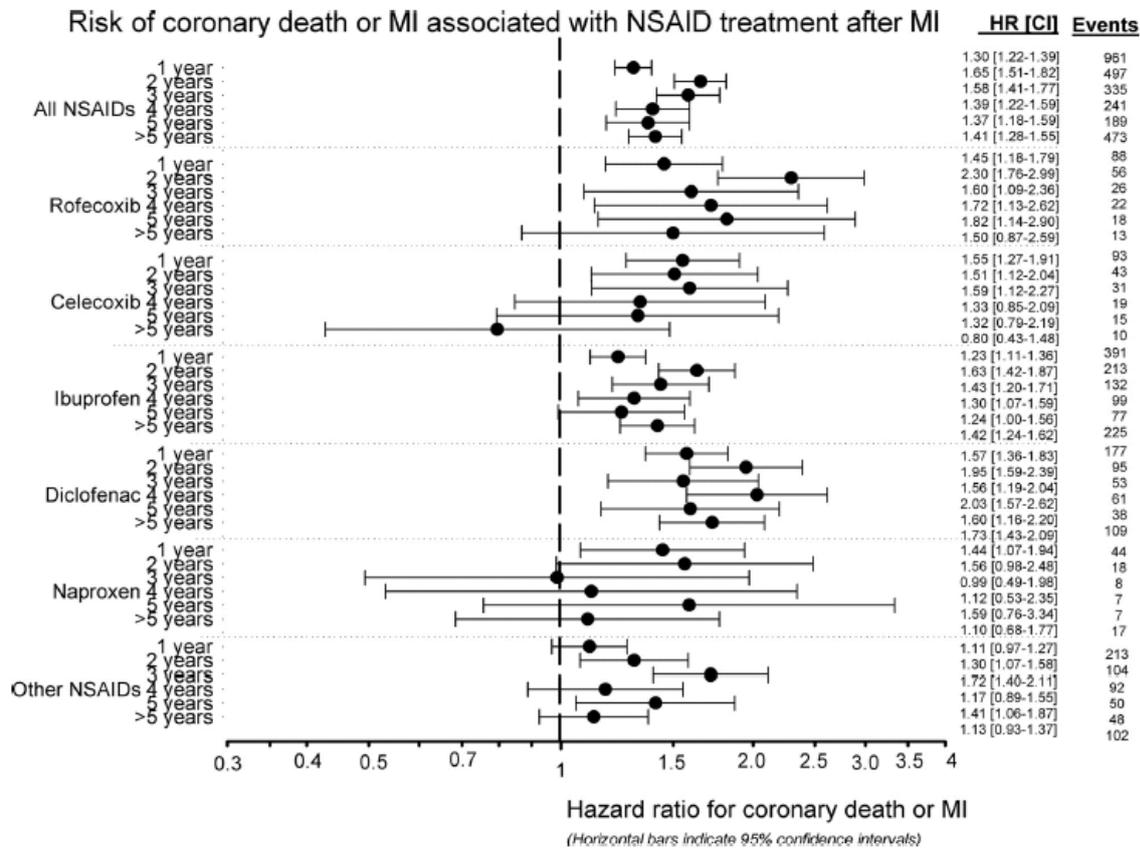
The objective of this Icelandic national registry-based study was to examine the risk of thromboembolic cardiovascular events in users of coxibs and NSAIDs. During the 3-year study period, 78,539 individuals were included in the study - concurrent use of more than one NSAID was excluded. Incidence ratios compared to diclofenac (most prescribed NSAID in Iceland; prescription only) use were calculated since individuals in nursing homes and hospitals are included in the hospital medical records but not prescription records and thus relative risks calculated in comparison to the general population are not reliable. Exposure period was defined as time between first and last prescription and was calculated to be 163,406 person-years. However, exposure may be over-estimated depending on the level of adherence to medication.

In comparison to diclofenac, the incidence ratios, adjusted for age and gender, were significantly higher for cerebral infarction, myocardial infarction and for unstable angina pectoris for users of rofecoxib. In contrast to most other studies, the incidence ratio was also increased for myocardial infarction for naproxen compared to diclofenac. However, the results were likely to be subject to significant confounding, with adjustments made only for age and gender. No information was provided on indication, medical history, concurrent medical conditions, other medications, or life-style factors such as smoking or alcohol consumption.

Schjerning Olsen et al 2012

Schjerning Olsen (2012) examined the cardiovascular risk (coronary death or myocardial infarction) in patients receiving NSAIDs in relation to the time elapsed after first-time myocardial infarction in a nationwide study in Denmark. The study reported that the use of NSAIDs was associated with a persistently increased cardiovascular risk in the years following myocardial infarction (see Figure below). The authors stated that the incidence rates show persistent increased absolute risks during the 5 years among the patients taking any NSAID, whereas the risk among the patients not taking NSAIDs declines. In accordance with previous studies, the risk for naproxen was lowest. The risk of coronary death or myocardial infarction associated with NSAID treatment after myocardial infarction was significantly increased for diclofenac at all time points and overall increased compared to other NSAIDs and similar to coxibs.

Figure 5
Time-dependent Cox proportional hazards analysis of the risk of coronary death or non-fatal MI according to the time of NSAID treatment among patients with previous MI



The authors acknowledge that due to the observational nature of the study unmeasured confounding cannot be excluded but calculations show that this is highly unlikely. Furthermore, since rheumatoid arthritis is associated with an increased cardiovascular risk, the authors performed an analysis excluding patients with rheumatoid arthritis, which did not change the results.

Other data

Data on suspected adverse drug reactions were submitted but the PRAC considered it did not allow a conclusion regarding the risk of arterial thrombotic events associated with diclofenac. Given the indications for diclofenac, most cases were confounded by the patients' age and/or underlying illnesses, and the presence of concomitant or co-suspect medication.

Discussion

The PRAC considered that the new evidence provided to not alter the conclusions of the most recent reviews by the CHMP. Diclofenac is associated with a risk of arterial thrombotic events, similar to that seen with Cox-2 inhibitors. The limitations of the data, such as low number of patients and short study duration were acknowledged. It was also noted that they would apply to all medicines included in the study, not just diclofenac. Considering that the risk with diclofenac appears similar to that of selective Cox-2 inhibitors, it therefore follows that any risk minimisation in place for Cox-2 inhibitors with respect to cardiovascular risk should also apply to diclofenac. The product information for diclofenac only includes a contraindication in patients with severe heart failure. However, based on the available evidence the PRAC considered that the product information should be updated to reflect a contraindication in patients with established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease. In addition, patients with certain cardiovascular risk factors (such as hypertension, hyperlipidaemia, diabetes mellitus, and smoking) should only use diclofenac after careful consideration and therefore the warnings should be updated to reflect this. Moreover, the general rule that NSAIDs should be used at the lowest dose for the shortest duration possible should be consistently implemented in the posology section of the product information.

Following that contraindicating the use of diclofenac in patients most at risk from its adverse cardiovascular effects is recommended, it would be of interest to monitor prescribing patterns to assess whether the risk minimisation measures are followed in clinical practice in a drug utilisation study to monitor and measure the effectiveness of the implemented risk minimisation measures. The trends in diclofenac use from 2006 onwards and focus on the extent of use, the populations in which diclofenac is being used (age, newly contraindicated populations), the doses and the duration of treatment could be examined by marketing authorisation holders.

2.3.3. Potential mechanisms

A number of potential mechanisms for the arterial thrombotic effects of NSAIDs have been previously discussed. Available data on possible mechanisms is not yet sufficient to determine with certainty exactly how the cardiovascular risks of individual NSAIDs are mediated, or why/how the risks differ between products. Examples of potential mechanisms are the imbalance between vasodilatory and prothrombotic prostanoids, selectivity for Cox-1 and Cox-2, inhibition of platelet TXA2, cardio renal effects of NSAIDs, among others. The PRAC noted that no single mechanism appears to explain all the observed results from clinical trials and epidemiological studies, and thus it appears likely that the thrombotic risks associated with NSAIDs in general, and with diclofenac in particular, are due to the combination of more than one of these mechanisms. Based on the current knowledge the pathophysiology underlying NSAID-induced, and in particular diclofenac-induced arterial thrombotic risks, remains speculative.

2.4. Product information

The PRAC considered all available evidence and recommended the below changes to the product information for all diclofenac containing medicinal products affected by this review. The lowest dose of diclofenac should be used for the shortest duration of treatment possible, and this information should be included in the posology. The cardiovascular risks of diclofenac were acknowledged and therefore a contraindication and corresponding review of the content of the clinical part of the product information was undertaken to ensure that the cardiovascular risk is captured and that the most up to date safety information is reflected for healthcare professionals and patients.

Summary of Product Characteristics

Section 4.2 Posology and method of administration:

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4 Special warnings and precautions for use).

Section 4.3 Contraindications:

Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

Section 4.4 Special warnings and precautions for use:

Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration. As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.

Section 4.8 Undesirable effects:

Clinical trial and epidemiological data consistently point towards an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, particularly at high dose (150mg daily) and in long term treatment. (see section 4.3 and 4.4 for Contraindications and Special warnings and special precautions for use).

Package Leaflet

Section 2 'What you need to know before you take <diclofenac containing medicinal product>

Do not use diclofenac

- if you have established heart disease and /or cerebrovascular disease e.g. if you have had a heart attack, stroke, mini-stroke (TIA) or blockages to blood vessels to the heart or brain or an operation to clear or bypass blockages
- if you have or have had problems with your blood circulation (peripheral arterial disease)

Make sure your doctor knows, before you are given diclofenac

- If you smoke
- If you have diabetes
- If you have angina, blood clots, high blood pressure, raised cholesterol or raised triglycerides.

Side effects may be minimised by using the lowest effective dose for the shortest duration necessary.

3. Overall discussion and benefit/risk assessment

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID). NSAIDs, such as diclofenac, are indicated in the relief of all grades of pain and inflammation associated with a wide range of conditions, including arthritic conditions, acute musculo-skeletal disorders and other painful conditions resulting from trauma. Diclofenac containing medicinal products (systemic formulations) are available as tablets, capsules for oral administration, suppositories for rectal administration and solutions for intravenous or intramuscular injection.

Epidemiological and clinical trial data on the cardiovascular risks of NSAIDs, including diclofenac, were previously reviewed by the Committee for Medicinal Products for Human Use (CHMP).

In 2006 it was concluded that a small increase in the absolute risk of thrombotic events could not be excluded for NSAIDs as a class, especially when used at high-doses and long-term therapy, although the risk was considered to be higher for the selective cyclooxygenase-2 (Cox-2) inhibitors (also known as coxibs) compared to NSAIDs. Risk minimisation measures (in the form of contraindications and warnings in the product information) were implemented at the time for Cox-2 inhibitors. The data available (in particular data from the MEDAL⁶ programme) suggested that the risk of arterial thrombotic events with diclofenac was similar to that for coxibs, but firm conclusions could not be drawn and further epidemiological studies were needed to obtain additional data.

Another evaluation conducted by the CHMP in 2012⁷ considered all available published evidence to date from meta-analysis of clinical trials and observational studies, and also epidemiological studies. Results of the 'safety of non-steroidal anti-inflammatory drugs' (SOS) research project funded by the European Commission under the Seventh Framework Programme were considered in the review that concluded that available evidence regarding diclofenac seemed to consistently point towards a less favourable cardiovascular risk profile compared to other NSAIDs, and similar risks as those of Cox-2 inhibitors.

A new review was considered necessary and was initiated to address the cardiovascular safety concerns for diclofenac and their impact on the benefit-risk balance of diclofenac containing medicinal products (systemic formulations). This review was conducted by the Pharmacovigilance Risk Assessment Committee (PRAC).

The PRAC acknowledged the conclusions of previous reviews with regards to the cardiovascular safety of diclofenac. Data provided by the MAHs in writing and at an oral explanation and relevant data made available by independent researchers were also considered.

The PRAC concluded that diclofenac is effective in reducing inflammation and pain. Recognised risks associated with NSAID treatment in general, and with diclofenac treatment in particular, include serious gastrointestinal effects including PUB (perforation, ulcer, bleeding), cardio-renal effects, hepatic effects and skin reactions (including Stevens Johnson syndrome and toxic epidermal necrolysis). These are appropriately reflected in the product information.

With regards to cardiovascular risks, the PRAC noted that the initial signal from the MEDAL programme was confirmed by the meta-analyses of randomised clinical trials conducted by *Trelle et al* (2011) and *Chen and Ashcroft* (2007). Meta-analyses of observational data and individual observational studies also consistently indicated that diclofenac is associated with a similar level of risk as Cox-2 inhibitors.

⁶ For more details on the MEDAL programme, including its components, please refer to the assessment report for the review conducted in 2006 at

http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/01/WC500054344.pdf.

⁷ For more information on the review conducted in 2012, please refer to the assessment report for the procedure at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/11/WC500134717.pdf

An increased risk with diclofenac was also observed in the SOS nested-cases control studies across all databases and for both myocardial infarction and ischaemic stroke. *Schjerning Olsen et al* (2011) provided data on risks in relation to duration of exposure and found that the risks associated with diclofenac were very similar to those of coxibs at all time points.

The new evidence provided by marketing authorisation holders including evidence from new case-control studies and retrospective studies add to the evidence of an increased risk with diclofenac compared to other NSAIDs and that the risk with diclofenac is similar to that of coxibs. The study by *Krum et al* 2012, a post hoc analysis of the MEDAL trial, showed that there was no significant differential effect between etoricoxib and diclofenac in relation to cardiovascular events, except for confirmed congestive heart failure.

Evidence available from a new meta-analysis of randomised clinical trials conducted by an independent research group was included in the review. The study, which looked at more than 600 randomised clinical trials, concluded that the vascular risks of high dose diclofenac are comparable to Cox-2 inhibitors. Major vascular events were increased by about one third by a coxib (rate ratio [RR] 1.37, 95% confidence interval [CI] 1.14-1.66; p=0.0009) or diclofenac (1.41, 1.12-1.78; p=0.0036), mainly due to an increase in major coronary events (coxibs: 1.76, 1.31-2.37; p=0.0001; diclofenac: 1.70, 1.19-2.41; p=0.0032).

The data available today do not allow conclusion on the specific mechanisms underlying the cardiovascular thrombotic risks of diclofenac, although several studies have explored different options and it can be noted that is unlikely that one single mechanism would explain the risk.

Considering that an increased cardiovascular risk with diclofenac is observed, and this appears similar to that of selective Cox-2 inhibitors, it therefore follows that any risk minimisation in place for Cox-2 inhibitors with respect to cardiovascular risk should also apply to diclofenac. The PRAC therefore recommended an amendment to the product information for diclofenac to include an updated contraindication in patients with established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease. In addition, patients with certain cardiovascular risk factors (such as hypertension, hyperlipidaemia, diabetes mellitus or smoking) should only use diclofenac after careful consideration and therefore the warnings should also be updated to reflect this. Moreover, the general rule that NSAIDs should be used at the lowest dose for the shortest duration possible should be consistently implemented in the posology section of the product information. Furthermore, a proactive communication of these new measures through a direct healthcare professional communication (DHPC) was recommended.

The PRAC considered that the recommendation for update of the product information should be applicable to all medicinal products containing diclofenac (systemic formulations), regardless of dose. The available information on the dose effect of diclofenac is limited. Although the data point towards a dose dependent effect on thrombotic risk associated with the use of diclofenac, particularly at high dose, it is difficult to establish a clear cut-off dose above which the risks become significantly increased. Some studies also report an association with lower doses. Based on the available data to date, the PRAC therefore concluded that the cardiovascular thrombotic risk cannot be excluded across all doses of diclofenac, especially in patients with pre-existing co-morbidities.

Benefit/risk balance

Having noted all of the above, the PRAC concluded that the benefit-risk balance for diclofenac containing medicinal products (systemic formulations) remains favourable subject to the agreed restrictions, warnings, other changes to the product information and additional risk minimisation measures, in the form of a DHPC letter.

Divergent positions are appended to the Recommendation.

4. Action plan and direct healthcare professional communication

The PRAC considered that a Direct Healthcare Professional Communication (DHPC) was needed to provide an update to the prescribing advice for diclofenac on the risk of cardiovascular side effects, including new contraindications and warnings.

Relevant European healthcare professional organisations were consulted for input on the draft DHPC. The key elements to be reflected in the DHPC were agreed by the PRAC together with the communication plan (see attachments to this report).

The MAHs should agree the translations and local specificities of the DHPC with national competent authorities. The DHPC should be sent after CMDh Position or Agreement to physicians who treat patients with diclofenac (e.g. general practitioners, internal medicine physicians, rheumatologists) and pharmacists.

5. Conclusion and grounds for the recommendation

Whereas,

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, for diclofenac containing medicinal products (systemic formulations).
- The PRAC considered the totality of the data available in relation to the cardiovascular safety of diclofenac containing medicinal products, acknowledging the conclusions from previous reviews by the CHMP, the submissions by marketing authorisation holders in writing and at an oral explanation, and emerging data from independent researchers.
- The PRAC considered that with regards to the arterial thrombotic risks of diclofenac, the data available to date from randomised clinical trials, observational studies and individual epidemiological studies, including meta-analysis thereof, allow the conclusion that diclofenac is associated with increased cardiovascular risks. It was observed that these are similar to those of selective Cox-2 inhibitors.
- The PRAC considered that diclofenac containing medicinal products are effective in their approved indications.
- The PRAC concluded that in view of the currently available safety data in order to maintain a favourable benefit/risk, diclofenac containing medicinal products should be contraindicated in patients with established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease. In addition, patients with certain cardiovascular risk factors (hypertension, hyperlipidaemia, diabetes mellitus, and smoking) should only use diclofenac after careful consideration and therefore the warnings should be updated to reflect this. Moreover, the general rule that NSAIDs should be used at the lowest dose for the shortest duration possible should be consistently implemented in the posology section of the product information.
- The PRAC also concluded that there was need for further risk minimisation measures such as information to healthcare professionals. Key elements for a direct healthcare professional communication were agreed, together with the timelines for distribution.

The PRAC concluded that the benefit-risk balance for diclofenac containing medicinal products (systemic formulations) remains favourable subject to the agreed restrictions, warnings, other changes to the product information and additional risk minimisation measures, in the form of a communication letter.

Therefore in accordance with Articles 31 and 32 of Directive 2001/83/EC, the PRAC recommends the variation of the marketing authorisations for all medicinal products referred to in Annex I and for which the amendments to the product information are set out in annex III of the recommendation.

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Appendix 1

Divergent position to PRAC recommendation

Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-31/1344

Diclofenac-containing medicinal products (systemic use)

Divergent statement

Restriction of dose and duration in those with established cardiovascular disease is a more appropriate current option than to totally contraindicate at all doses and durations in those patients.

The evidence of hazard is best shown by the CPT systematic review [Lancet, 2013] with indirect comparisons. It shows that high-dose diclofenac is as hazardous as Cox-2 inhibitors and ibuprofen in terms of cardiac problems. This translates to a low absolute risk, on average of 3 extra major vascular events (one fatal) per thousand patients treated for a year. While the evidence that the risk is markedly less at lower doses it seems likely to be so, and the absolute risk is clearly duration-related.

The best evidence from the CPT review suggests that ibuprofen at high dose is as cardio-toxic and more gastro-toxic than diclofenac. In addition, ibuprofen, but not diclofenac, has been known for some years to reduce the efficacy of low-dose aspirin in preventing cardiac disease. In this context, a much stronger restriction for diclofenac is currently unjustified.

PRAC member expressing a divergent position:

Stephen Evans	13 June 2013	Signature:
Marieke De Bruin	13 June 2013	Signature:
Herve Le Louet	13 June 2013	Signature:
Jolanta Gulbinovic (LT)	13 June 2013	Signature: