PUBLIC SUMMARY DOCUMENT
Product: Diclofenac sodium with misoprostol, tablet, 50 mg–200 micrograms, Arthrotec® 50
Sponsor: Pfizer Australia Pty Ltd
Date of PBAC Consideration: November 2009

1. Purpose of Application

The submission sought an Authority Required (STREAMLINED) listing for osteoarthritis or rheumatoid arthritis in patients who require prophylaxis against non-steroidal anti-inflammatory drug (NSAID)-induced peptic ulcers.

2. Background

The PBAC has considered four previous applications for listing of the combination product diclofenac sodium with misoprostol.

3. Registration Status

Diclofenac sodium with misoprostol was TGA registered on 29 October 1997 for the treatment of patients who require a non-steroidal anti-inflammatory drug (NSAID) together with misoprostol. The diclofenac component is indicated for the treatment of osteoarthritis and rheumatoid arthritis. The misoprostol component is indicated for the prophylaxis of NSAID induced gastric and duodenal ulceration. Known risk factors for NSAID induced gastropathy include age in excess of 60 years, a history of peptic ulcer disease, smoking, previous NSAID gastrointestinal intolerance and the presence of a concomitant disease.

4. Listing Requested and PBAC's View

Authority Required (STREAMLINED)
Osteoarthritis or rheumatoid arthritis in patients who require prophylaxis against NSAID-induced peptic ulcers.

NOTE:
Known risk factors include age in excess of 60 years, a history of peptic ulcer disease, smoking, previous NSAID gastrointestinal intolerance, and serious co-morbid disease.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Gastric and duodenal ulcers and serious gastrointestinal (GI) complications have been commonly reported in patients receiving NSAIDs. These events can occur at any time during treatment, and in the majority of cases, serious GI complications are asymptomatic and result in hospitalisations and increased mortality.

The fixed dose combination of diclofenac sodium with misoprostol may simplify the management of osteoarthritis and rheumatoid arthritis in those patients where the use of diclofenac and misoprostol concomitantly is appropriate.

6. Comparator

The submission nominated the individual components of the fixed combination, diclofenac and misoprostol, as the main comparators. This is in accordance with the PBAC Guidelines for Fixed Combination Products. A supplementary analysis was undertaken with a

combination on an NSAID and proton pump inhibitor (PPI) as the comparator, because this is the treatment regimen most prescribed in clinical practice.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The submission presented seven trials comparing Arthrotec with diclofenac monotherapy for the treatment of the symptoms of arthritis. Ulcer prevention was assessed using an indirect comparison of one Arthrotec trial and two concomitant diclofenac and misoprostol trials with diclofenac monotherapy as the common reference. Supplementary evidence was based on three trials comparing NSAID + PPI versus NSAID + misoprostol. Five pharmacokinetic trials were provided as supportive evidence. Details of the trial publications are presented in the table below.

Trial ID / First author	Protocol title / Publication title	Publication citation
Arthrotec vs. diclofenac monotherapy – arthritis outcomes		
Trial 289 Stead H et al (1992)	Gastroduodenal safety of Arthrotec in rheumatoid arthritis patients: subgroup analyses of the effects of age and gender.	*Br J Rheumatol* 1992a; 31(Suppl 2): 178
Verdickt W et al (1992)	A double-blind comparison of the gastroduodenal safety and efficacy of diclofenac and a fixed dose combination of diclofenac and misoprostol in the treatment of rheumatoid arthritis.	*Scand J Rheumatol* 1992; 21: 85-91
Trial 292 De Queiroz MV et al (1994)	Double-blind comparison of the efficacy of diclofenac/misoprostol and diclofenac in the treatment of rheumatoid arthritis.	*Eur J Rheumatol Inflamm* 1994; 14: 5-13
Hannequin JR (1992)	Efficacy of Arthrotec in the treatment of rheumatoid arthritis.	*Scand J Rheumatol Suppl* 1992; 96: 7-14
Woods EM et al (1992)	Antiarthritis efficacy of Arthrotec in rheumatoid arthritis patients: subgroup analyses of the effects of disease duration and functional capacity.	*Br J Rheumatol* 1992; 31(Suppl 2): 179
Trial 296 Bolten W et al (1992)	The gastroduodenal safety and efficacy of the fixed combination of diclofenac and misoprostol in the treatment of osteoarthritis.	*Br J Rheumatol* 1992; 31: 753-758
Stead H et al (1992)	Gastroduodenal safety of Arthrotec in osteoarthritis patients: subgroup analyses of the effects of age and gender.	*Br J Rheumatol* 1992b; 31(Suppl 2): 178
Trial 298 Doherty M (1992)	The efficacy of Arthrotec in the treatment of osteoarthritis.	*Scand J Rheumatol Suppl* 1992; 96: 15-21
Trial 349 Bocanegra TS et al (1998)	Diclofenac/misoprostol compared with diclofenac in the treatment of osteoarthritis of the knee or hip: a randomized, placebo-controlled trial. Arthrotec Osteoarthritis Study Group.	*J Rheumatol* 1998; 25:1602-11

Trial 352 Bocanegra JA et al (1997)	Safety and tolerability of diclofenac/misoprostol (Arthrotec) versus diclofenac alone in the treatment of elderly osteoarthritis (OA) patients.	*Gastroenterology* 1997; 112 (Suppl): A74
Trial 003 Kiff PS et al (1994)	Arthrotec, diclofenac and ibuprofen in general practice.	*Eur J Rheumatol Inflammation* 1994; 14: 31-7
Arthrotec vs. diclofenac and misoprostol – prevention of NSAID-induced ulcers		
Trials 289, 296, 349	As above.	
Trial 269 Agrawal NM et al (1995)	Misoprostol coadministered with diclofenac for prevention of gastroduodenal ulcers. A one-year study.	*Dig Dis Sci* 1995; 401125-31
Geis GS et al (1991)	Prevalence of mucosal lesions in the stomach and duodenum due to chronic use of NSAID in patients with rheumatoid arthritis or osteoarthritis, and interim report on prevention by misoprostol of diclofenac associated lesions.	*J Rheumatol* 1991; 18 (Suppl 28): 11-4
Geis GS et al (1992)	Prevention of diclofenac-induced gastroduodenal mucosal ulcers by misoprostol: a one year study.	*Br J Rheumatol* 1992; 31 (Suppl 2): 180
Misoprostol and NSAID vs. PPI and NSAID		
Bianchi Porro et al (1994)	Misoprostol vs two different dosages of omeprazole in the prevention of NSAIDs-induced ulcers.	*Gastroenterology* 1994; 106 (Suppl 4): A51
Hawkey C et al (1998)	Omeprazole compared with misoprostol for ulcers associated with nonsteroidal anti-inflammatory drugs.	*NEJM* 1998; 338: 727-34
Stupnicki T et al (2003)	Efficacy and tolerability of pantoprazole compared with misoprostol for the prevention of NSAID-related gastrointestinal lesions and symptoms in rheumatic patients.	*Digestion* 2003; 68: 198-208

8. Results of Trials

A meta-analysis using a random effects model was undertaken to demonstrate non-inferiority of Arthrotec to diclofenac for the treatment of the symptoms of arthritis.

The pooled results for all comparisons showed no statistically significant difference between Arthrotec and diclofenac monotherapy for arthritis outcomes. The re-submission used 0.8, a pre-defined minimal clinically important difference (MCID) from the original clinical trials, as the criteria for non-inferiority. This was considered reasonable by the PBAC. As the lower confidence interval around the relative risk for each comparison was greater than the MCID, the re-submission claimed Arthrotec met the criterion for non-inferiority to diclofenac. The PBAC noted that the meta-analysis has low power for detecting heterogeneity if the included number of trials is small.

The comparison of Arthrotec and concomitant misoprostol and diclofenac for the prevention of NSAID-induced ulcers was based on an indirect comparison using diclofenac as the common reference. The indirect comparison only used trials in which patients had a history of

gastro-intestinal (GI) damage at trial enrolment. The table below provides the results of this comparison.

Summary of results of the indirect comparison – ulcer prevention

Trial ID	Trial of proposed drug			Trials of main comparator			Indirect estimate of effect RR (95% CI)
	Arthrotec n/N (%)	Diclo n/N (%)	Tmt effect RR (95% CI)	Miso + Diclo n/N (%)	Diclo n/N (%)	Tmt effect RR (95% CI)	
Gastric ulcer							
349	4/849	15/840	0.26 (0.09, 0.79)	—	—	—	—
Pooled results of 269 and 320				22/4,404	70/4,464	0.33 (0.20, 0.53)	0.79 (0.24, 2.55)
Duodenal ulcer							
349	8/849	9/840	0.88 (0.34, 2.27)	—	—	—	—
Pooled results of 269 and 320				26/4,392	45/4,476	0.60 (0.37, 0.97)	1.47 (0.51, 4.26)
Gastroduodenal ulcer							
349	12/849	23/840	0.52 (0.26, 1.03)	—	—	—	—
Pooled results of 269 and 320				46/4,404	108/4,464	0.44 (0.31, 0.62)	1.18 (0.54, 2.57)

Tmt = treatment; CI=confidence interval; n = number with event; N = number in group; RR = relative risk; Miso=misoprostol; Diclo=diclofenac

The re-submission claimed the results of the indirect comparison indicated that Arthrotec is non-inferior to concomitant diclofenac and misoprostol.

The re-submission undertook a direct comparison of the incidence of ulcers with Arthrotec and diclofenac monotherapy in patients who do not have a history of GI damage. The re-submission claimed that this analysis demonstrated Arthrotec is superior to diclofenac monotherapy for GI outcomes. However, the evaluation noted the claimed advantage for Arthrotec was not consistent across trials and so should be interpreted with caution.

The re-submission included a comparison of misoprostol and NSAID versus PPI and NSAID as supplementary evidence to demonstrate that misoprostol and PPIs are similar in terms of prevention of NSAID-induced ulcers. The results of the misoprostol and PPI comparison are shown in the table below.

Comparison of occurrence of GI ulcers with misoprostol + NSAID vs. PPI + NSAID

Trial ID	Misoprostol + NSAID n/N (%)	Omeprazole + NSAID n/N (%)	Misoprostol + NSAID versus omeprazole + NSAID		
			RR (95% CI)	RD (95% CI)	NNT (95% CI)
Gastric ulcer					
4 weeks					
Bianchi Porro 1994	2/30 (6.7)	1/30 (3.3)	2.00 (0.19, 20.90)	0.03 (-0.08, 0.14)	33
Hawkey 1998	NR	NR	—	—	—
24 weeks					
Bianchi Porro 1994	NR	NR	—	—	—

Trial ID	Misoprostol + NSAID n/N (%)	Omeprazole + NSAID n/N (%)	Misoprostol + NSAID versus omeprazole + NSAID		
			RR (95% CI)	RD (95% CI)	NNT (95% CI)
Hawkey 1998	31/296 (10.5)	35/274 (12.8)	0.82 (0.52, 1.29)	-0.02 (-0.08, 0.03)	-50
Duodenal ulcer					
4 weeks					
Bianchi Porro 1994	0/30 (0)	0/30 (0)	NA	NA	N/A
Hawkey 1998	NR	NR	—	—	—
24 weeks					
Bianchi Porro 1994	NR	NR	—	—	—
Hawkey 1998	30/296 (10.1)	7/274 (2.6)	3.97 (1.77, 8.88)	0.08 (0.04, 0.11)	13 (9, 25)
Gastroduodenal ulcer					
12 weeks					
Stupnicki 2003	1/258 (0.4)	1/257 (0.4)	1.00 (0.06, 15.84)	0.00 (-0.01, 0.01)	N/A
24 weeks					
Stupnicki 2003	1/258 (0.4)	0/257 (0)	2.99 (0.12, 73.02)	0.00 (-0.01, 0.01)	N/A

Abbreviations: GI = gastrointestinal; NR = not reported; RR=relative risk; RD=risk difference; CI=confidence interval; NNT=number needed to treat; NSAID=non-steroidal anti-inflammatory drug; N/A=not applicable

The re-submission concluded that misoprostol and NSAID treatment is similar to PPI and NSAID treatment. However, the PBAC considered there was not a strong basis for the conclusion of similarity, given the wide confidence intervals, which indicated some uncertainty, the small number of trials included, and the greater efficacy of the PPI omeprazole at 24 weeks in the Hawkey (1998) trial. The re-submission did not present a meta-analysis of these trials. The PBAC noted that the conclusions of the published trials differed from those made in the re-submission.

The PBAC noted that all meta-analyses undertaken in the re-submission combined in the least two and at most three trials. As a result, there was substantial uncertainty about the effect of heterogeneity in the clinical trials combined in the meta-analysis.

The re-submission compared percentages of adverse effects and concluded rates were similar. The re-submission did not conduct any statistical analysis on the safety data, or attempt to prove that the rates of adverse effects with Arthrotec were similar to those with concomitant diclofenac and misoprostol. The PBAC considered the methods used by the re-submission to assess safety data were inappropriate given a non-inferiority claim should be demonstrated with both efficacy and safety analyses.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The re-submission claimed that Arthrotec is non-inferior to diclofenac monotherapy for arthritis outcomes. With regard to the reduction in NSAID-induced GI complications

endpoints, the re-submission claimed that Arthrotec is non-inferior to both concomitant diclofenac and misoprostol and combination NSAID and PPI.

The PBAC considered the evidence provided demonstrated that Arthrotec is non-inferior to diclofenac monotherapy for treating the symptoms of arthritis. However, the PBAC considered the evidence did not conclusively prove Arthrotec is non-inferior to concomitant diclofenac and misoprostol and combination NSAID and PPI for the reduction of NSAID-induced ulcers.

The PBAC considered that the submission's claim was not reasonable because it failed to account for the higher cardiovascular risk associated with diclofenac in comparison with other NSAIDs.

10. Economic Analysis

The submission presented a cost-minimisation analysis.

Arthrotec taken twice daily was assumed to be equivalent to concomitant treatment with diclofenac 100 mg and misoprostol 400-800 micrograms per day. Arthrotec taken three times daily was assumed to be equivalent to concomitant treatment with diclofenac 150 mg and misoprostol 400-800 micrograms per day.

For the sensitivity analysis, Arthrotec taken twice daily was assumed to be equivalent to concomitant treatment with diclofenac 100 mg and PPI 20 mg per day. Arthrotec taken three times daily was assumed to be equivalent to concomitant treatment with diclofenac 150 mg and PPI 20 mg per day.

11. Estimated PBS Usage and Financial Implications

The submission asserted that the majority of patients prescribed Arthrotec would receive a dose of one tablet twice daily for an average duration of four months.

The submission estimated the likely number of patients per year to be between 50,000 and 100,000 in Year 5 with an estimated financial cost per year to the PBS of less than $10 million in Year 5.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC agreed that the main comparators, the individual components of the fixed combination diclofenac and misoprostol, were appropriate and was in accordance with the PBAC Guidelines for Fixed Combination Products. The PBAC noted that a supplementary analysis was undertaken with a combination of a non-steroidal anti-inflammatory drug (NSAID) and proton pump inhibitor (PPI) as the comparator, because this is the treatment regimen most prescribed in clinical practice which was also appropriate.

The PBAC noted that even though diclofenac is termed a "traditional" NSAID, there is significant scientific evidence to indicate that it is a relatively COX-2 selective drug with a similar degree of COX-2 selectivity to celecoxib in some studies. Diclofenac has also been shown to be associated with a significant elevated risk of thrombotic cardiovascular events,

which appears to be similar to what was observed with rofecoxib, and the increased vascular event risk for diclofenac is apparent at commonly used doses (up to 150 mg/day).

The PBAC was concerned that the patient group targeted by the proposed Arthrotec restriction was inappropriate given the cardiovascular toxicity associated with diclofenac, and did not consider that this issue had been adequately addressed in the submission. In particular, there is the possibility that patients might be switched from other NSAIDs to Arthrotec, which do not carry the same cardiovascular risk as diclofenac. Should switching occur, it would also increase the market compared to current clinical practice.

The PBAC considered that the evidence from the trials does not conclusively prove Arthrotec is non-inferior to concomitant diclofenac and misoprostol and combination NSAID and PPI for the reduction of NSAID-induced ulcers and that there is both clinical and statistical uncertainty given the small patient numbers and variability. The PBAC noted that the confidence intervals are wide and there were a number of important differences in the underlying trial populations of the trials included in the indirect comparison.

The PBAC noted that both the individual components were currently available on the PBS, which allows for dose titration of each drug. However, the Arthrotec twice daily regimen results in misoprostol dosing of 400mcg, which has been shown to be less effective than higher doses (600-800mcg) of misoprostol (Raskin et al 1995) and the three time daily regimen would mean an up-titration of diclofenac to 150 mg which may lead to increased adverse events. The PBAC also noted that proton pump inhibitors listed on the PBS are a viable alternative to misoprostol. However, the patient would have to pay two co-payments if prescribed with diclofenac.

The PBAC considered that there was not good evidence provided that Arthrotec would be prescribed and used only as a four month course as both osteoarthritis and rheumatoid arthritis are chronic conditions and that the likely number of patients and the financial costs to the PBS may have been underestimated.

The PBAC therefore, rejected the submission based on lack of clinical need and the potential for unwanted clinical outcomes.

The PBAC noted that the submission meets the criteria for an independent review.

Recommendation:
Reject

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Pfizer Australia notes the PBAC recommendation but considers that there is an unmet need for the prevention of NSAID-induced gastroduodenal ulceration.