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**Department of Health**

Therapeutic Goods Administration

# Safety review of diclofenac

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**TGA** Health Safety  
Regulation

## About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<http://www.tga.gov.au>>.

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## Version history

<b>Version</b>	<b>Description of change</b>	<b>Author</b>	<b>Effective date</b>
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V2.0	Revision following comments from sponsors	Office of Product Review	29/08/2014
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## Executive summary

In 2012, the TGA conducted a review into the cardiovascular safety of non-steroidal anti-inflammatory drugs (NSAIDs). It emerged from this review that diclofenac demonstrated a worse cardiovascular risk profile than the other traditional NSAIDs.

As a result of the cardiovascular safety review and concerns regarding hepatotoxicity, in 2013, the Office of Product Review (OPR) decided to conduct a full safety review of diclofenac.

Diclofenac is widely used in the treatment of pain where there is an inflammatory component. It is available in oral, rectal and topical forms. There are 78 products listed in the Australian Register of Therapeutic Goods (ARTG) for diclofenac and there is limited funding support from the Pharmaceutical Benefits Scheme and the Repatriation Pharmaceutical Benefits Scheme.

A search of the literature was conducted and pertinent information was reviewed and synthesised. A limited search of adverse event databases was conducted with specific reference to topical preparations as there was a paucity of published information regarding the safety of these.

The safety concern most prominently published upon was cardiovascular. The recent literature on gastrointestinal (GI) risk was reviewed and hepatic safety was specifically examined. The following conclusions and recommendations were made.

## Conclusions and recommendations

### Prescription oral and rectal diclofenac (S4)

There is no emerging safety information regarding GI or hepatic effects. The risk/benefit remains favourable and the Product Information (PI) conveys appropriate warnings/precautions.

There is consistent evidence that there is an increased risk of serious cardiovascular events with the use of diclofenac. The overall risk/benefit remains favourable, however the PI needs to be updated to more appropriately convey the risks. The following additions are recommended:

- adding patients with severe heart failure to the contraindications list
- adding stronger warnings about the cardiovascular risk to the precautions section together with the need to consider carefully the risks and benefits of treatment in individuals at higher risk of cardiovascular disease in line with those recommended for other traditional NSAIDs.

### OTC oral diclofenac (S3, S2 and unscheduled)

The use of diclofenac as an over-the-counter (OTC) product for short-term use at a low dose remains appropriate. The current Required Advisory Statements for Medicine Labels (RASML) for S2 products contain sufficient warnings regarding the potential for GI side effects however they do not contain any warnings about the potential risk of cardiovascular side effects or serious hepatic side effects.

The RASML are undergoing review. The proposed RASML states 'do not use if you have heart failure' (see Appendix 10). This does not adequately cover the risk to those with heart disease who have not developed heart failure and those at high risk of heart disease. The following additions to the RASML are recommended:

- adding a statement to convey the risk to those people with heart disease in line with those recommended for the other traditional NSAIDs
- adding the following statement to convey the risk of hepatic injury: 'Warning: In rare cases, diclofenac has been associated with serious liver injury.'

## Topical diclofenac

Based on the available information the risk/benefit for topical diclofenac remains favourable. There is a paucity of evidence of serious systemic side effects with topical diclofenac. Despite this relative lack of evidence, it is recommended:

- the Consumer Medicine Information (CMI) for topical diclofenac include warnings that systemic absorption is likely and that adverse cardiovascular events have been associated with oral diclofenac.

## Risk communication

These changes should be communicated via a TGA web statement, a *Medicines Safety Update* article and liaison with NPS MedicineWise.

# 1. Issue under investigation

Non-steroidal anti-inflammatory drugs (NSAIDs) have been used for the management of inflammatory pain for decades. There are two major classes of NSAIDs, the traditional NSAIDs and the selective inhibitors of cyclooxygenase-2 (COX-2 inhibitors). It is well known that the traditional NSAIDs are associated with serious gastrointestinal (GI) side effects. The COX-2 inhibitors were developed to reduce the GI side effect profile while maintaining the efficacy of the traditional NSAIDs. The first COX-2 inhibitor, celecoxib, was registered in Australia in 1999.

In the early 2000s it emerged that COX-2 inhibitors (especially rofecoxib) were associated with high rates of cardiovascular adverse events. In 2012, the TGA conducted a review into the cardiovascular safety of NSAIDs. It emerged from this review that diclofenac demonstrated a worse cardiovascular risk profile than the other traditional NSAIDs. As a result of the cardiovascular safety review and concerns regarding hepatotoxicity, in 2013 the TGA's Office of Product Review (OPR) decided to conduct a full safety review of diclofenac.

# 2. Objectives/scope of review

The requirements of the review are as follows:

*To review the recent medical literature relating to the safety of diclofenac when used orally or topically as a prescription or non-prescription medicine and provide a report that summarises and assesses the information and, based upon the findings, recommend whether any changes need to be made to the use, labelling, Product Information (PI) and Consumer Medicine Information (CMI) for the medicines concerned.*

There are 78 products on the Australian Register of Therapeutic Goods (ARTG) that contain diclofenac. They are tabulated in Appendix 1 with information on pack size, indication and scheduling. Diclofenac is available as a prescription medicine as well as over-the-counter (OTC).

The indications for prescription (S4) diclofenac are as follows:

**Tablets (25 mg and 50 mg):**

Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis and osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.

**Suppositories (12.5 mg, 25 mg, 50 mg or 100 mg):**

Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis and osteoarthritis. Short term (up to three days) treatment of post-operative pain in children.

**Diclofenac rapid release (50 mg):**

As short-term treatment (up to one week) for the relief of acute pain states in which there is an inflammatory component. Treatment of acute migraine attacks (with or without aura). Symptomatic treatment of primary dysmenorrhoea.

**3% diclofenac gel**

Management of actinic keratoses.

There are several OTC products (S3, S2 and unscheduled), the indications are as follows:

**Diclofenac rapid release (25 mg) tablet (S3)**

As short-term treatment (up to one week) for the relief of acute pain states in which there is an inflammatory component. Treatment of acute migraine attacks (with or without aura). Symptomatic treatment of primary dysmenorrhoea.

**Diclofenac rapid release (12.5 mg) tablet (S2)**

Relief of headache, dental pain, period pain, rheumatic and muscular pain, backache. Relief of symptoms of colds and flu, including aches and pains, sore throat pain. Reduction of fever.

**Dermal products containing  $\leq 1\%$  diclofenac (unscheduled)**

For the short term (up to 2 weeks) local symptomatic treatment of the following musculoskeletal inflammatory conditions. Acute soft tissue injuries, including sprains, strains, tendinitis and sports injuries. Localised forms of soft tissue rheumatism, e.g. tendinitis (tennis elbow) and bursitis. For the short term (up to 3 weeks) relief of pain in non-serious arthritis (i.e. mild and localised forms of osteoarthritis) of the knee or fingers. Relief of osteoarthritic pain.

## 3. Background

### 3.1 Pharmacology

The exact mechanism of action for diclofenac, like that of other NSAIDs, is unknown. They appear to have anti-inflammatory, anti-pyretic, and analgesic properties. These are thought to be mediated via inhibition of prostaglandins. This inhibition of prostaglandins is itself mediated via the inhibition of the cyclooxygenase (COX) enzyme. There are two forms of the COX enzyme. COX-1 is involved in 'housekeeping' activities, such as mediating normal platelet function, regulating renal blood flow and providing cytoprotection of the gastric mucosa. COX-2 is

involved in the response to tissue damage and mediates inflammation and pain. The COX-2 inhibitors are more selective in their inhibition of COX-2 relative to COX-1.

The COX-2 inhibitors have been associated with higher rates of cardiovascular adverse events and it is hypothesised that this effect is a result of relative COX-2/COX-1 inhibition. While diclofenac is a traditional NSAID, it does display a preferential inhibition of COX-2 compared to COX-1(1).

## 3.2 Regulatory history in Australia

Diclofenac was grandfathered in the ARTG in 1991 and had been used in Australia prior to this. The regulatory history is extensive and does not materially contribute to informing the decision-making process of this review and is therefore not discussed further.

## 3.3 Utilisation

Diclofenac is available as a prescription medicine (S4) as well as OTC (S3, S2 and unscheduled). The current Pharmaceutical Benefits Scheme listings for diclofenac are in Table 1.

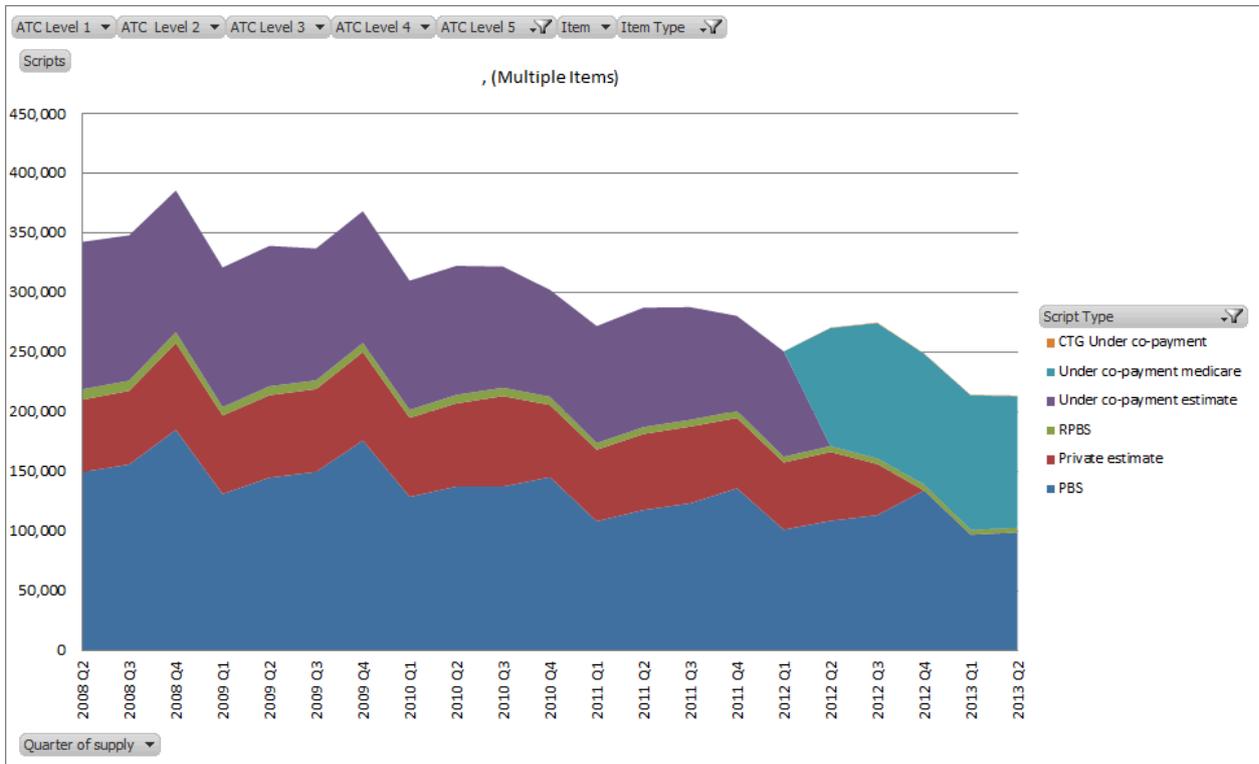
**Table 1: Pharmaceutical Benefits Scheme listing of diclofenac**

Drug, dose, form	Restricted benefit	Authority required
Diclofenac 25 mg, 50 tablets	Chronic arthropathies (including osteoarthritis) with an inflammatory component  Bone pain due to malignant disease	Initial supply, for up to four months, for a palliative care patient where severe pain is a problem
Diclofenac 50 mg, 50 tablets	Chronic arthropathies (including osteoarthritis) with an inflammatory component  Bone pain due to malignant disease	Initial supply, for up to four months, for a palliative care patient where severe pain is a problem
Diclofenac 100 mg, 20 suppositories	No restriction	Not required
Diclofenac 3% gel	Authority required	For the management of actinic keratoses in patients where other standard treatments are inappropriate, and topical drug therapy is required as field treatment for clinically visible and subclinical lesions

The figures below demonstrate the usage of prescription diclofenac. The usage is widespread. There are hundreds of thousands of prescriptions per quarter and the majority of these are for the 50 mg enteric coated tablet. The reviewer notes the apparent trend for decrease in use;

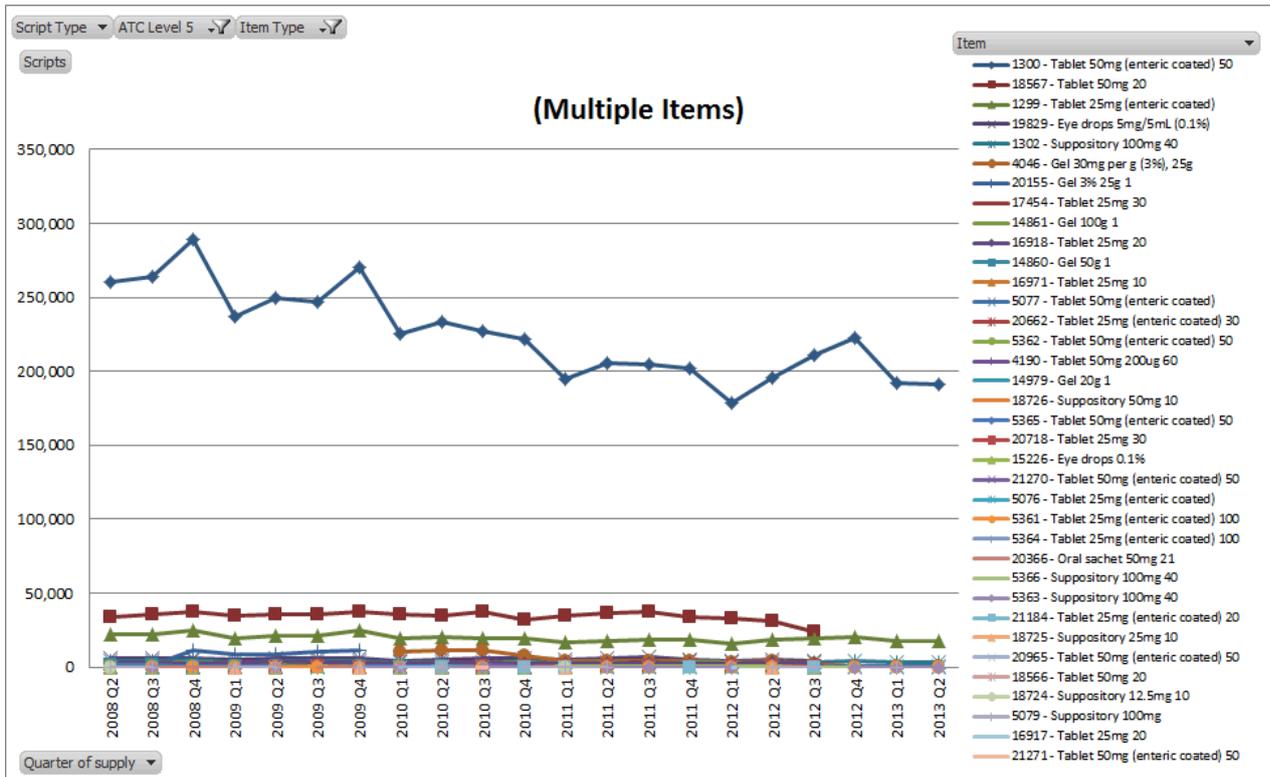
however, the reasons for this decrease are uncertain. There are no data available on OTC products.

**Figure 1: Diclofenac prescriptions 2008-2013 script type**



\*CTG: Closing The Gap; PBS: Pharmaceutical Benefits Scheme; RPBS: Repatriation Pharmaceutical Benefits Scheme

**Figure 2: Diclofenac prescriptions by item**



## 3.4 Regulatory status in other countries

Diclofenac is widely used around the world. The indications for use in the UK and USA are given in Appendix 2 and are similar to those in Australia.

The international product information warnings/precautions for these products, with particular reference to cardiovascular, GI and hepatic effects, are provided in Appendices 3 and 4.

The safety of diclofenac-containing products has recently been examined by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee. On 25 September 2013, the EMA released its safety advice for diclofenac. The Summary of Product Characteristics (SPC) and Package Leaflet changes that it recommended are provided below. A search of the websites of the major international regulators did not reveal any other planned changes to diclofenac.

### A. Summary of product characteristics

The EMA recommended that the following text be inserted into the following sections.

#### **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, and 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).

### B. 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.

## 4. Overview of data considered in this review

The data used in this review is mainly sourced from the literature. Database searches were conducted using several different strategies (details of the search strategies can be found in Appendix 5). The abstracts of articles identified were examined and those deemed not relevant were excluded. Additional articles were found by hand searching the reference lists of pertinent review articles. The total number of full text articles examined was 250. These comprised a mixture of randomised trials, observational studies, systematic reviews and non-systematic narrative reviews. These articles were all reviewed and the results presented are considered representative of the material identified. Data from adverse event report databases was only used in the consideration of hepatic effects and in the use of topical diclofenac preparations. This was due to the paucity of data from randomised controlled trials or observational research.

## 5. Oral diclofenac products

### 5.1 Efficacy

Diclofenac was first released in Japan in 1974(1). It is mainly used for pain relief and therefore treats a wide variety of conditions. For the treatment of acute pain the Australian Therapeutic Guidelines suggests using traditional NSAIDs and particularly diclofenac as a second line agent after paracetamol for moderate pain(2). The comparative analgesic effects of NSAIDs for acute pain was evaluated by the Oxford Pain Group and formulated into a league table based on systematic reviews of randomised, double-blind, single dose post-operative studies (see Appendix 6). They report the number needed to treat to achieve at least 50% reduction in pain compared to placebo for diclofenac 100 mg was 1.9 (95% CI 1.6-2.2)(3). The comparative efficacy of diclofenac was among the best of the NSAIDs. There is little evidence from longer term efficacy studies versus placebo. Trelle et al. in their systematic review conducted extensive searching to find randomised controlled trials of any NSAID versus placebo that had 100 patient years of follow up and found none for diclofenac(4). Despite the relative paucity of evidence for diclofenac versus placebo, diclofenac is generally regarded as efficacious. In more recent trials, where COX-2 inhibitors were compared to standard treatment, diclofenac has often been used as the standard treatment. The Australian PI for diclofenac does not cite any efficacy studies.

A systematic review was conducted by Pavelka into the efficacy of diclofenac in osteoarthritis(5). The review reported that diclofenac has been studied in comparisons with

many different NSAIDs and other treatments for pain and provides similar efficacy to these other treatments. Often these other treatments (that is COX-2 inhibitors) have been trialled against placebo and this provides good indirect evidence for the efficacy of diclofenac.

## 5.2 Safety

Examining the recent literature regarding the safety of diclofenac, cardiovascular safety is the most published topic. The cardiovascular safety of NSAIDs was examined in a TGA review in 2012, however an additional review of the evidence for harm incorporating new evidence is presented below. The GI adverse effects of diclofenac are well known and the recent literature on this is summarised. Hepatic adverse effects are specifically examined. There were no other significant safety issues identified in the review of the recent literature.

### 5.2.1 Cardiovascular safety

#### Systematic reviews of randomised controlled trials

For the clinical question, does exposure to drug A cause adverse event B, a systematic review of randomised controlled trials provides the most robust unbiased evidence. Despite the relatively rare incidence of serious cardiovascular events in trials of NSAIDs, the following systematic reviews are well conducted and are able to provide evidence to answer the question: *Does use of diclofenac increase the risk of serious cardiovascular adverse events?*

The most recent systematic review was published in August 2013(6). The authors conducted a meta-analysis using individual participant data from randomised controlled trials and were able to calculate indirect estimates of the rate ratio of major cardiovascular events for diclofenac versus placebo (major cardiovascular events being non-fatal myocardial infarction, non-fatal stroke, or death from a vascular cause). They report a rate ratio of 1.41 (95% CI 1.12-1.78). They also calculated an annual absolute effect size based on two different baseline risks. For 1000 patients taking diclofenac for one year who have a baseline risk of 2% per year, there would be seven extra major cardiovascular events. For 1000 patients with a baseline risk of 0.5% per year there would be two extra major cardiovascular events.

Trelle et al. in their 2011 systematic review performed an indirect estimate of the cardiovascular effects of diclofenac compared to placebo(4). They did not group the cardiovascular events together and report separately for myocardial infarction 0.82 (95% CI 0.29-2.20), stroke 2.86 (95% CI 1.09-8.36) and cardiovascular death 3.98 (95% CI 1.48-12.7).

Kearney et al. in their 2006 systematic review performed an indirect estimate of the effect of diclofenac in comparison to placebo for serious vascular events (defined as non-fatal myocardial infarction, non-fatal stroke, or vascular death)(7). They found a rate ratio of 1.63 (95%CI 1.12-2.37).

#### Systematic reviews of observational studies

After considering systematic review of randomised controlled studies, the next best evidence to consider is systematic reviews of observational studies. Golder et al. in 2011 conducted research into the methodological merit of systematic reviews and meta-analysis of observational studies that looked at adverse effect data(8). They concluded that the average risk estimates of adverse effects of an intervention derived from meta-analyses of RCTs and meta-analyses of observational studies were very similar.

The following table displays the results from the systematic reviews identified. The reviews do not all ask the same question or examine the same data. They often review clinically and

methodologically heterogeneous studies and have very high measures of statistical heterogeneity between the studies included in the meta-analyses. This is considered appropriate for the purposes of this review as we are concerned with overall effects.

**Table 2: Systematic reviews of observational studies**

Author (year)(reference)	Title	Outcome	Relative risk
McGettigan (2006)(9)	Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2	Serious cardiovascular events diclofenac versus non-use	1.40 (95% CI 1.16-1.70)
McGettigan (2011)(10)	Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies	Major cardiovascular events diclofenac versus non-use	1.40 (95% CI 1.27-1.55)
Singh (2006)(11)	Risk of acute myocardial infarction with nonselective non-steroidal anti-inflammatory drugs: a meta-analysis	Acute myocardial infarction diclofenac versus non-use	1.38 (95% CI 1.22-1.57)
Varas-lorenzo (2011)(12)	Stroke risk and NSAIDs: a systematic review of observational studies	Stroke diclofenac versus non-use	1.20 (95% CI 1.05-1.36)

### Individual studies

Serious cardiovascular outcomes are rare enough that no single randomised controlled trial is able to provide strong evidence. Given the number of systematic review of randomised controlled trials and the strength of evidence that they provide, the results of individual trials will not be presented here.

The strength of evidence that diclofenac increases the risk of serious cardiovascular events supplied from systematic reviews of observational studies is very strong.

The search did not find any observational cohort/case control studies that seriously challenge the direction of effect or the weight of the evidence. There were several studies identified which did not find a statistically significant association between serious cardiovascular events and diclofenac. They are listed in Appendix 7.

Given the wide spectrum of use of diclofenac, it is important to examine whether the risk is greater or smaller depending on the sub-population it is being used in. Individual studies that attempt to answer these questions are discussed in this section.

### **High cardiovascular risk/post-myocardial infarction/heart failure**

Gislason et al. examined the risk of cardiovascular events in patients with established heart failure(13). The study population was taken from a Danish registry database and it covered a period of 10 years. There were 107,092 patients surviving first hospitalisation from heart failure and 36,354 patients using at least one prescription of NSAID after discharge. They report the following hazard ratios for diclofenac compared to no use of any NSAID:

- death: 2.08 (95% confidence interval [CI] 1.95-2.21)
- hospitalisation because of heart failure: 1.35 (95% CI 1.24-1.48)
- hospitalisation due to acute myocardial infarction: 1.36 (95% CI 1.12-1.64).

In a separate paper, using the same database, Gislason et al. studied the risk of death or reinfarction (after surviving a first myocardial infarction) associated with the use of NSAIDs (14). The study period was seven years, with 58,432 patients surviving a first myocardial infarct and 6193 receiving diclofenac. They reported the following hazard ratios for diclofenac versus no NSAID:

- death: 2.40 (95% CI 2.09-2.80)
- reinfarction: 1.54 (95% CI 1.23-1.93).

Schjerning Olsen et al. examined the risk of death and recurrent myocardial infarction in patients with prior myocardial infarction, specifically looking at the time to event(15). They used a Danish database of 83,677 patients, of whom 13.4% took diclofenac post-myocardial infarction. They report that the increased risk of death and myocardial infarction among those taking diclofenac as compared to no NSAID appeared from the beginning of treatment and had the highest hazard ratio of 3.26 (95%CI 2.57-3.86).

Ray et al. studied patients who had been recently hospitalised for coronary heart disease using 48,566 patients from the Saskatchewan and UK General Practice Research Databases(16). The cohort represented more than 111,000 person-years of follow up. They report that current users of diclofenac had an increased risk of serious cardiovascular disease/death of 1.38 (95% CI 1.18-1.61) compared to non-use of any NSAID.

Lamberts et al. studied patients taking NSAIDs post first-time myocardial infarction using a Danish registry database(17). The study period was 10 years and included 97,458 patients, 2.2% of whom used diclofenac. They reported that diclofenac was associated with an increased mortality at one year, hazard ratio 1.13 (95%CI1.04-1.20) compared to no use.

### **Low dose usage and over-the-counter use**

Hasford et al. conducted an observational cohort study which examined the safety of short-term, low-dose diclofenac(18). In the cohort of 446 participants followed for 19 days, none reported a serious cardiovascular adverse event. This gives some support to the safety of low-dose, short-term use. However, even if the relative risk of serious cardiovascular adverse events is high, given the low absolute baseline risk in the group in this study, the result is not absolutely reassuring.

## High dose versus low dose

A dose response relationship provides support to causality. It has been described in several papers that the risk of serious cardiovascular events within the population of diclofenac users is higher among those who take higher doses (this is consistent across several definitions of high and low dose and different lengths of exposure). The following table summarises these results.

**Table 3: Dose response relationship**

Author (year)(reference)	Daily diclofenac use	Relative risk
Garcia Rodriguez (2008)(19)	Low-medium dose	1.51 (95% CI 1.20-1.89)
	High dose	1.80 (95% CI 1.49-2.18)
Van Staa (2008)(20)	<150 mg	1.13 (95% CI 1.04-1.22)
	≥300 mg	2.03 (95% CI 1.09-3.77)
Gislason(2009) (13)	≤100 mg	1.14 (95% CI 0.91-1.43)
	>100 mg	2.43 (95% CI 1.74-3.40)
Gislason(2006)(14)	≤100 mg	1.27 (95% CI 0.92-1.76)
	>100 mg	1.89 (95% CI 1.40-2.55)
Fosbol(2010) (21)	<100 mg	0.96 (95% CI 0.59-1.57)
	≥100 mg	2.01 (95% CI 1.56-2.59)

## Risk among healthy individuals

Fosbol et al. examined the cardiovascular risk associated with NSAIDs in otherwise healthy individuals(22). They used a Danish registry database and selected patients who had not had any contact with the hospital system for five years and had not used serious pharmacological treatments for two years. The study population comprised 1,028,427 individuals of whom 44.7% claimed at least one prescription for any NSAID. In this low-risk population they found an increased odds ratio of coronary death or non-fatal myocardial infarction to be 1.82 (95% CI 1.43-2.33) among users of diclofenac as compared to no NSAID use. In a similar paper, Fosbol et al. examined the cerebrovascular risk of NSAIDs in a healthy population and report that diclofenac was associated with an increased risk of stroke but did not quantify the risk in the article(23).

### 5.2.2 Gastrointestinal safety

GI side effects of NSAIDs, especially upper GI bleeding, are well known. Unlike for cardiovascular risks, the recent literature has remained relatively quiet on the GI side effects of NSAIDs in general and diclofenac specifically. What follows is a summary of the epidemiological evidence found in the literature search for the last 10 years.

Castellsague et al. conducted a systematic review of observational studies that report on the serious upper GI complications of individual NSAIDs (peptic ulcer perforations, obstructions and

bleeding). They report a relative risk of 3.37 (95%CI 2.55-4.46) for diclofenac compared to no use of any NSAID(24).

Bhala et al. in their systematic review and meta-analysis of individual participant data also report on upper GI complications (bleeding, perforation and obstruction)(6). They report a relative risk of 1.89 (95%CI 1.16-3.09) for diclofenac versus placebo.

### 5.2.3 Hepatic safety

The concern regarding the hepatotoxicity of diclofenac was specifically raised at the Advisory Committee on the Safety of Medicines meeting on 11 February 2012 and there was advice given to include hepatotoxicity in any safety review of diclofenac. However, there was no reference to a specific source of concern. The issue was examined in a safety filter (OPR issue 472) in June 2012. The conclusion of this filter was that the issue of hepatotoxicity is adequately covered in the PIs for prescription-only oral formulations but there are no specific warnings with regard to hepatotoxicity in the Required Advisory Statements for Medicine Labels (RASML) for topical products or OTC products. The only recent international regulatory action in this area appears to be from 2009, when the USA Food and Drug Administration added warnings to the prescribing information for Voltaren Gel to include hepatic effects(25). The basis for their decision appears to be post-marketing reports. The exact mechanism for hepatotoxicity with diclofenac is not known, but is thought to be metabolic idiosyncrasy(26).

The following is a summary of the literature regarding the hepatic adverse effects of diclofenac that was identified in the literature search. It excludes individual case reports.

Rostom et al. conducted a systematic review of randomised trials to investigate the hepatic toxicity of NSAIDs and found that, while diclofenac had a higher rate of aminotransferases greater than three times the upper limit of normal, no NSAID had increased rates of liver-related serious adverse events, hospitalisations or deaths(27).

Rubenstein et al. conducted a systematic review of observational studies examining the comparative risk of liver injury resulting in hospitalisation for current NSAID users compared with past NSAID users(28). For diclofenac they report a non-significant rate ratio of 1.5 (95% CI 0.7-3.2).

Laine et al. reported on the rates of liver injury in a large randomised trial of diclofenac for the treatment of arthritis(29). A total of 17,289 patients received diclofenac for a mean of 18 months. The table below reports these rates of liver-related endpoints related to diclofenac. It is important to note that this trial did not include patients at high risk for liver disease (exclusions applied to patients with hepatic disease or who drank 14 or more standard drinks per week) and the rates are not compared to any other treatment (or non-treatment).

**Table 4: Rates of liver-related endpoints with diclofenac**

End Point	Diclofenac
ALT or AST>3xULN	2.1 (95% CI 1.9-2.3) per 100 patient-years
ALT or AST>5xULN	0.9 (95% CI 0.8-1.0) per 100 patient-years
ALT or AST>10xULN	0.3 (95% CI 0.3-0.4) per 100 patient-years
Liver-related discontinuation	1.8 (95% CI 1.7-2.0) per 100 patient-years

End Point	Diclofenac
Hy's Case	8 (95% CI 1-28) per 100,000 patient-years
Liver related hospitalisation	16 (95% CI 4-40) per 100,000 patient-years
Liver failure, transplant or death	0 (95% CI 0-15) per 100,000 patient-years

\*Source: Laine et al (29); ALT: alanine transaminase; AST: aspartate transaminase; ULN: upper limit normal

The total number of reports in the Australian Adverse Drug Reaction System (ADRS) for diclofenac from inception to 20 December 2013 is 2200. There are 186 reports in the hepatobiliary system organ class.

**Table 5: Liver-related disorders in the Adverse Drug Reaction System received in the 10 years January 2002—May 2012**

ADR	Total/Sole-suspected	Deaths	Date range	Reports received
Hepatitis	56/30	6	November 1984 – July 2007	4
Jaundice +/- hepatitis	43/27 (only five list hepatitis also)	1	April 1985 – May 2006	4
Hepatic failure	2 (both list jaundice also)	1	July 1988 – September 2002	1
Hepatic function abnormal/liver function abnormal	74/38	0	November 1982 – October 2012	6
Hepatocellular injury	8/5	1	March 1987 – February 2002	1
Hepatic necrosis	3/1	1	March 1987 – September 2009	1
Total	186/101	10	November 1982 – October 2011	17

## 6. Topical diclofenac

### 6.1 Efficacy

The efficacy of topical 1% diclofenac for the treatment of pain and inflammation has been well studied in short-term studies. Zacher et al. conducted an evidence-based review into the efficacy

of topical diclofenac(30). They do not appear to have performed a statistical meta-analysis, however they conclude, based upon published randomised controlled trials, that diclofenac is an effective treatment for painful inflammatory conditions. The topical 3% diclofenac is used solely for the treatment of actinic keratosis and the efficacy has been established.

## 6.2 Safety

The literature search did not find any research that has specifically examined the safety of topical 3% diclofenac.

Taylor et al. conducted a systematic review looking at the safety profile of topical diclofenac in the treatment of musculoskeletal conditions(31). They included only randomised controlled trials. They do not report any major cardiovascular, GI or hepatic adverse events. The longest study duration in the review was 12 weeks.

There were no observational studies that looked into the safety of topical diclofenac identified in the literature searches. A non-systematic narrative review was found which commented on the fact that the literature regarding adverse events for topical diclofenac is limited and that there are no studies evaluating the long-term safety(1).

The ADRS was searched on 6 January 2014 for adverse events to topical diclofenac. There were 84 events in total. Within the GI, hepatobiliary and cardiac system organ classes, when concurrent use of oral NSAIDs was excluded, there were two reports of liver function test abnormal (one sole suspected) and one report of GI bleeding (sole suspected).

The World Health Organization (WHO) adverse event database was searched by request on 8 January 2014 for adverse events relating to topical diclofenac in the GI, hepatobiliary and cardiac system organ classes(32). There are a total of 3421 reports for diclofenac when administered topically.

**Table 6: World Health Organization adverse event database results for topical diclofenac**

System organ class (total number of reports as at 8 January 2014)	Serious reaction*	Sole suspected	Concomitant oral NSAID use
Cardiovascular (106)	32	22	7
GI (532)	165	79	51
Hepatobiliary (20)	18	8	5

\*Serious cardiovascular reactions include cardiac arrest, myocardial infarction, cardiac failure and angina. Serious GI reactions include GI haemorrhage and ulceration. Serious hepatobiliary reactions include hepatitis, liver function test abnormal, liver injury and hepatic function abnormal.

While mechanistic reasoning as evidence is weak, it is reasonable to examine pharmacokinetic data to help elucidate the risk of topical diclofenac. When comparing 150 g/day of oral diclofenac to high-dose topical diclofenac 1% gel (48 g/day) the oral diclofenac had 40-fold higher peak plasma concentrations and the AUC<sub>0-24</sub> was fivefold higher(33).

The PI for topical 3% diclofenac makes the following statements regarding pharmacokinetics:

*After topical application of 2 g Solaraze three times daily for six days to the calf of the leg in healthy subjects, diclofenac could be detected in plasma. Mean bioavailability parameters were  $AUC_{0-t_{9\pm 19}}$  ng.hr/mL (mean $\pm$ SD) with a  $C_{max}$  of  $4\pm 5$  ng/mL and a  $T_{max}$  of  $4.5\pm 8$  hours. In comparison, a single oral 75 mg dose of diclofenac (Voltaren) produced an AUC of 1600 ng.hr/mL. Therefore, the systemic bioavailability after topical application of Solaraze is lower than after oral dosing.*

## Warnings/precautions/comparison with international regulators

The PI for topical 3% diclofenac makes reference to serious systemic side effects in the following statement:

### Precautions

*The likelihood of systemic side effects occurring following the topical application of Solaraze is small compared to the frequency of side effects with oral diclofenac, owing to low systemic absorption with Solaraze. However, the possibility of systemic adverse events from application of topical diclofenac cannot be excluded if the preparation is used on large areas of skin and over a prolonged period (see product information on systemic forms of diclofenac).*

The current RASML for topical 1% diclofenac mandates the following labelling:

- Do not use [this product/*insert name of product*] if you are allergic to diclofenac or other anti-inflammatory medicines.
- If you get an allergic reaction, stop taking and see your doctor immediately.
- Unless a doctor or pharmacist has told you to, do not use [this product/*insert name of product*] with other medicines that you are taking regularly.

These precautions/warnings are similar to warnings on the UK SPC. In comparison, the USA product information contains much stronger warnings regarding the risk of cardiovascular, GI and hepatic adverse effects. The USA product information for topical diclofenac mirrors that of the oral diclofenac. The full details of the international product information can be found in Appendices 8 and 9.

## 7. Summary of diclofenac safety issues

The recent literature on the safety of diclofenac is focussed on the cardiovascular risks. The GI risks are well known and there is no data that significantly challenges the current risk assessment for serious GI side effects.

Serious hepatic side effects are a known, rare complication associated with the use of oral diclofenac. From the data examined, it is very difficult to quantify the risk in users of topical diclofenac, but it is likely to be low.

There is an increasing and consistent body of evidence that oral diclofenac increases the risk of serious cardiovascular side effects in all users. The relative risk appears to be similar across all groups, with a possibly higher relative risk in those with pre-existing cardiovascular disease. The risk is higher with a higher dose. The cardiovascular risk associated with using topical diclofenac is not clear. There is no trial data or observational research data to suggest an increased risk. Theoretically, if sufficient drug was absorbed then there may be an increased risk but this is difficult to quantify.

## **Current warnings, precautions and contraindications**

For oral/rectal diclofenac for both S4 and S3 preparations the current PI contains precautions regarding the potential cardiovascular, GI and hepatic effects. Despite some S2 preparations having PI documents, these are not required and the only labelling requirements are RASML statements. The relevant PI and RASML can be found in Appendices 10 and 11.

The warnings regarding the GI and hepatic effects of S3 and S2 preparations are in line with international regulators.

The information in the Australian PI regarding cardiovascular risk is not as strong as either the current USA or the proposed European product information. Particularly, the extra contraindications for patients with severe heart failure and in the treatment of pain post-coronary artery bypass graft. The USA and proposed European product information is also stronger in the recommendation to consider carefully the risks and benefits of treatment in individuals at higher risk of cardiovascular disease.

## 8. Conclusions and recommendations

### 8.1 Prescription oral and rectal diclofenac (S4)

There is no emerging safety information regarding GI or hepatic effects. The risk/benefit remains favourable and the PI conveys appropriate warnings/caution.

There is consistent evidence that there is an increased risk of serious cardiovascular events with the use of diclofenac. The overall risk/benefit remains favourable however the PI needs to be updated to more appropriately convey the risks. The following additions are recommended:

- adding patients with severe heart failure to the contraindications list
- adding stronger warnings about the cardiovascular risk to the precautions section, together with the need to consider carefully the risks and benefits of treatment in individuals at higher risk of cardiovascular disease in line with those recommended for other traditional NSAIDs.

It is noted that a safety related request with data has been submitted to the Office of Medicines Authorisation and is currently being reviewed.

### 8.2 Over-the-counter oral diclofenac (S2/S3)

The use of diclofenac as an OTC product for short-term use at a low dose remains appropriate. The current RASML for OTC products contain sufficient warnings regarding the potential for GI side effects, however they do not contain any warnings about the potential risk of cardiovascular side effects or serious hepatic side effects. The RASML are undergoing review. The proposed RASML states 'do not use if you have heart failure' (see Appendix 11). This does not adequately cover the risk to those with heart disease who have not developed heart failure and those at high risk of heart disease. It is recommended that:

- a statement be added to convey the risk to those people with heart disease in line with those recommended for the other traditional NSAIDs
- the following statement be added to convey the risk of hepatic injury: 'Warning: In rare cases, diclofenac has been associated with serious liver injury.'

### 8.3 Topical diclofenac

Based on the available information the risk/benefit for topical diclofenac remains favourable. There is a paucity of evidence of serious systemic side effects with topical diclofenac. Despite this relative lack of evidence it is recommended that:

- the CMI for topical diclofenac include warnings that systemic absorption is likely and that adverse cardiovascular events have been associated with oral diclofenac.

### 8.4 Risk communication

These changes should be communicated via a TGA web statement, an *Medicines Safety Update* article and liaison with NPS MedicineWise.

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## Appendices

### Appendix 1: Diclofenac containing products on the Australian Register of Therapeutic Goods (as at 13 August 2014)

ARTG No.	Product name	Product Strength	Schedule	Dosage Form	Active Ingredient	Approved Indications
90462	AMCAL ANTI-INFLAMMATORY GEL diclofenac sodium 10 mg/g tube	20 g, 50 g, 100 g,	N	gel	Diclofenac sodium	
90636	BLOOMS THE CHEMIST ANTI-INFLAMMATORY PAIN RELIEF GEL diclofenac sodium 10 mg/g tube	30g, 50g, 60g, 100g, 120g	N	gel	Diclofenac sodium	Short term (up to 2 weeks) local symptomatic treatment of the following musculoskeletal inflammatory conditions: a) acute soft tissue injuries, including sprains, tendinitis and sports injury; b) localised forms of soft tissue rheumatism e.g. tendinitis and bursitis.
91595	CHEM MART ANTI-INFLAMMATORY PAIN RELIEF GEL diclofenac sodium 10 mg/g tube	20g, 50g, 100g	N	gel	Diclofenac sodium	Short term (up to 2 weeks) local symptomatic treatment of the following musculoskeletal inflammatory conditions: a) acute soft tissue injuries, including sprains, tendinitis and sports injury; b) localised forms of soft tissue rheumatism e.g. tendinitis and bursitis.

ARTG No.	Product name	Product Strength	Schedule	Dosage Form	Active Ingredient	Approved Indications
90311	CHEMISTS' OWN DICLOFENAC SODIUM 10mg/g ANTI- INFLAMMATORY PAIN RELIEF GEL	50g, 100g	N	gel	Diclofenac sodium	Short term (up to 2 weeks) local symptomatic treatment of the following musculoskeletal inflammatory conditions: a) acute soft tissue injuries, including sprains, tendinitis and sports injury; b) localised forms of soft tissue rheumatism e.g. tendinitis and bursitis.
80232	CHEMPLUS ANTI- INFLAMMATORY PAIN RELIEF GEL diclofenac sodium 10mg/g tube	30g, 60g, 100g, 120g	N	gel	Diclofenac sodium	Short term (up to 2 weeks) local symptomatic treatment of the following musculoskeletal inflammatory conditions: a) acute soft tissue injuries, including sprains, tendinitis and sports injury; b) localised forms of soft tissue rheumatism e.g. tendinitis and bursitis.
82606	DENCORUB ANTI- INFLAMMATORY GEL diclofenac sodium 10mg/g tube	30g, 50g, 60g, 100g, 120g	N	gel	Diclofenac sodium	Short term (up to 2 weeks) local symptomatic treatment of the following musculoskeletal inflammatory conditions: a) acute soft tissue injuries, including sprains, tendinitis and sports injury; b) localised forms of soft tissue rheumatism e.g. tendinitis and bursitis.
97857	GOANNA DICLOFENAC ANTI-INFLAMMATORY PAIN RELIEF GEL diclofenac sodium 1% w/w tube	20g, 30g, 50g, 100g	N	gel	Diclofenac sodium	Short term (up to 2 weeks) local symptomatic treatment of the following musculoskeletal inflammatory conditions: a) acute soft tissue injuries, including sprains, tendinitis and sports injury; b) localised forms of soft tissue rheumatism e.g. tendinitis and bursitis.

ARTG No.	Product name	Product Strength	Schedule	Dosage Form	Active Ingredient	Approved Indications
90461	GUARDIAN ANTI-INFLAMMATORY GEL diclofenac sodium 10mg/g tube	20g, 50g, 100g	N	gel	Diclofenac sodium	Short term (up to 2 weeks) local symptomatic treatment of the following musculoskeletal inflammatory conditions: a) acute soft tissue injuries, including sprains, tendinitis and sports injury; b) localised forms of soft tissue rheumatism e.g. tendinitis and bursitis.
91047	IMFLAC ANTI-INFLAMMATORY PAIN RELIEF GEL diclofenac sodium 1% w/w tube	30g, 50g, 60g, 100g, 120g	N	gel	Diclofenac sodium	Short term (up to 2 weeks) local symptomatic treatment of the following musculoskeletal inflammatory conditions: a) acute soft tissue injuries, including sprains, tendinitis and sports injury; b) localised forms of soft tissue rheumatism e.g. tendinitis and bursitis.
93539	PHARMACY ACTION ANTI-INFLAMMATORY PAIN RELIEF GEL diclofenac sodium 10mg/g tube	20g, 50g and 100g	N	gel	Diclofenac sodium	Short term (up to 2 weeks) local symptomatic treatment of the following musculoskeletal inflammatory conditions: a) acute soft tissue injuries, including sprains, tendinitis and sports injury; b) localised forms of soft tissue rheumatism e.g. tendinitis and bursitis.
134541	PHARMACY CHOICE ANTI-INFLAMMATORY PAIN RELIEF GEL diclofenac sodium 10mg/g tube	20g, 50g, 100g	N	gel	Diclofenac sodium	Short term (up to 2 weeks) local symptomatic treatment of the following musculoskeletal inflammatory conditions: a) acute soft tissue injuries, including sprains, tendinitis and sports injury; b) localised forms of soft tissue rheumatism e.g. tendinitis and bursitis.

ARTG No.	Product name	Product Strength	Schedule	Dosage Form	Active Ingredient	Approved Indications
92107	PHARMACY HEALTH ANTI-INFLAMMATORY PAIN RELIEF gel diclofenac sodium 10mg/g tube	20g, 50g, 100g	N	gel	Diclofenac sodium	Short term (up to 2 weeks) local symptomatic treatment of the following musculoskeletal inflammatory conditions: a) acute soft tissue injuries, including sprains, tendinitis and sports injury; b) localised forms of soft tissue rheumatism e.g. tendinitis and bursitis.
127744	PRICELINE ANTI-INFLAMMATORY PAIN RELIEF GEL diclofenac sodium 10mg/g tube	30g, 60g	N	gel	Diclofenac sodium	Short term (up to 2 weeks) local symptomatic treatment of the following musculoskeletal inflammatory conditions: a) acute soft tissue injuries, including sprains, tendinitis and sports injury; b) localised forms of soft tissue rheumatism e.g. tendinitis and bursitis.
91701	TERRY WHITE CHEMISTS ANTI-INFLAMMATORY PAIN RELIEF GEL diclofenac sodium 10mg/g tube	20g, 50g, 100g	N	gel	Diclofenac sodium	Short term (up to 2 weeks) local symptomatic treatment of the following musculoskeletal inflammatory conditions: a) acute soft tissue injuries, including sprains, tendinitis and sports injury; b) localised forms of soft tissue rheumatism e.g. tendinitis and bursitis.
69604	VICLOFEN GEL diclofenac sodium 10 mg/g tube	20g, 50g, 100g,	N	gel	Diclofenac sodium	Short term (up to 2 weeks) local symptomatic treatment of the following musculoskeletal inflammatory conditions: a) acute soft tissue injuries, including sprains, tendinitis and sports injury; b) localised forms of soft tissue rheumatism e.g. tendinitis and bursitis.

ARTG No.	Product name	Product Strength	Schedule	Dosage Form	Active Ingredient	Approved Indications
223205	GUARDIAN ANTI-INFLAMMATORY GEL diclofenac sodium 10mg/g tube	50g	N	gel	Diclofenac sodium	Short term (up to 2 weeks) local symptomatic treatment of the following musculoskeletal inflammatory conditions: a) acute soft tissue injuries, including sprains, tendinitis and sports injury; b) localised forms of soft tissue rheumatism, e.g. tendinitis and bursitis.
223206	PHARMACY CARE ANTI-INFLAMMATORY GEL diclofenac sodium 10mg/g tube	50g	N	gel	Diclofenac sodium	Short term (up to 2 weeks) local symptomatic treatment of the following musculoskeletal inflammatory conditions: a) acute soft tissue injuries, including sprains, tendinitis and sports injury; b) localised forms of soft tissue rheumatism, e.g. tendinitis and bursitis.
223207	AMCAL ANTI-INFLAMMATORY GEL diclofenac sodium 10mg/g tube	50g	N	gel	Diclofenac sodium	Short term (up to 2 weeks) local symptomatic treatment of the following musculoskeletal inflammatory conditions: a) acute soft tissue injuries, including sprains, tendinitis and sports injury; b) localised forms of soft tissue rheumatism, e.g. tendinitis and bursitis.
225014	PANAFLEX ANTI-INFLAMMATORY PAIN RELIEF GEL diclofenac sodium 10mg/g tube	50g, 100g	N	gel	Diclofenac sodium	Short term (up to 2 weeks) local symptomatic treatment of the following musculoskeletal inflammatory conditions: a) acute soft tissue injuries, including sprains, tendinitis and sports injury; b) localised forms of soft tissue rheumatism, e.g. tendinitis and bursitis.

ARTG No.	Product name	Product Strength	Schedule	Dosage Form	Active Ingredient	Approved Indications
127744	PRICELINE ANTI-INFLAMMATORY PAIN RELIEF GEL diclofenac sodium 10mg/g tube	30g, 50g, 60g	N	gel	Diclofenac sodium	Short term (up to 2 weeks) local symptomatic treatment of the following musculoskeletal inflammatory conditions: a) acute soft tissue injuries, including sprains, tendinitis and sports injury; b) localised forms of soft tissue rheumatism e.g. tendinitis and bursitis.
47676	VOLTAREN EMULGEL diclofenac diethylammonium 11.6mg/g gel tube	10g, 20g, 30g, 50g, 60g, 100g, 120g, 180g, 300g	N	gel	Diclofenac diethylammonium	Short-term (up to 2 weeks) local symptomatic treatment of the following musculoskeletal inflammatory conditions: Acute soft tissue injuries, including sprains, strains, tendinitis and sports injury; Localised forms of soft tissue rheumatism, eg. tendinitis (e.g. tennis elbow) and bursitis. Short term (up to 3 weeks) relief of pain in non-serious arthritis (i.e. mild and localised forms of osteoarthritis) of the knee and fingers.
175889	VOLTAREN OSTEO GEL diclofenac diethylammonium 11.6mg/g tube	10g, 20g, 30g, 50g, 75g, 100g, 120g, 150g, 180g, 300g	N	gel	Diclofenac diethylammonium	Short-term (up to 2 weeks) local symptomatic treatment of the following musculoskeletal inflammatory conditions: Acute soft tissue injuries, including sprains, strains, tendinitis and sports injury; Localised forms of soft tissue rheumatism, eg. tendinitis (e.g. tennis elbow) and bursitis. Short term (up to 3 weeks) relief of pain in non-serious arthritis (i.e. mild and localised forms of osteoarthritis) of the knee and fingers.

ARTG No.	Product name	Product Strength	Schedule	Dosage Form	Active Ingredient	Approved Indications
208848	VOLTAREN EMULGEL 12 HOURLY diclofenac diethylammonium 23.2 mg/g gel tube	10g, 20g, 30g, 50g, 60g, 75g, 100g, 120g, 150g, 180g, 300g	S2	gel	Diclofenac diethylammonium	Short-term (up to 2 weeks) local symptomatic treatment of the following musculoskeletal inflammatory conditions: Acute soft tissue injuries, including sprains, strains, tendinitis and sports injury; Localised forms of soft tissue rheumatism eg tendinitis (eg tennis elbow) and bursitis. Short-term (up to 3 weeks) relief of pain in non-serious arthritis (i.e. mild and localised forms of osteoarthritis) of the knee and fingers.
219514	VOLTAREN OSTEO GEL 12 HOURLY diclofenac diethylammonium 23.2 mg/g gel tube	20g, 30g, 100g, 150g, 300g	S2	gel	Diclofenac diethylammonium	Short-term (up to 2 weeks) local symptomatic treatment of the following musculoskeletal inflammatory conditions: Acute soft tissue injuries, including sprains, strains, tendinitis and sports injury; Localised forms of soft tissue rheumatism eg tendinitis (eg tennis elbow) and bursitis. Short-term (up to 3 weeks) relief of pain in non-serious arthritis (i.e. mild and localised forms of osteoarthritis) of the knee and fingers.
209248	VOLTAREN SPRAY diclofenac sodium 4% w/w bottle	10mL, 15mL, 30mL	S2	Spray solution	Diclofenac sodium	Short-term (up to 2 weeks) local symptomatic treatment of the following musculoskeletal inflammatory conditions: Acute soft tissue injuries, including sprains, strains, tendinitis and sports injury; Localised forms of soft tissue rheumatism eg tendinitis (eg tennis elbow) and bursitis.
116785	SOLARAZE diclofenac sodium 3 % gel tube	25g, 50g tube	S4	gel	Diclofenac sodium	Management of actinic keratosis.

ARTG No.	Product name	Product Strength	Schedule	Dosage Form	Active Ingredient	Approved Indications
51527	VOLTAREN Ophtha diclofenac sodium 0.3mg/0.3mL eye drops, ampoule	5, 20, 30, 40, 100 units	S4	eye drop	Diclofenac sodium	Inhibition of operative miosis during cataract surgery; Post-operative inflammation in cataract surgery and other surgical interventions.
96654	VOLTAREN OPHTHA diclofenac sodium 1mg/mL eye drops bottle	3, 5 mL	S4	eye drop	Diclofenac sodium	Post-operative inflammation in cataract surgery and other surgical interventions.
168061	VOLTAREN RAPID 12.5 diclofenac potassium 12.5 mg film coated tablet blister pack (reformulation)	10, 20 tablets	S2	tablet	Diclofenac potassium	Temporary relief of painful conditions such as headache, dental pain, period pain, rheumatic and muscular pain, backache. Temporary relief of symptoms of colds and flu (including aches and pains, sore throat pain). Reduces fever.
171307	VOLTAREN RAPID 12.5 LIQUID CAPSULE diclofenac potassium 12.5 mg soft capsule blister pack	10, 20, 30 capsules	S2	capsule	Diclofenac potassium	For the temporary relief of painful conditions such as headache, dental pain, period pain, rheumatic and muscular pain, backache. For the temporary relief of pain and discomfort associated with cold and flu. Reduces fever.
90103	IMFLAC Diclofenac Sodium 25 mg tablet blister pack	3, 5, 10, 15, 20, 25, 30 tablets	S3	tablet	Diclofenac sodium	For the temporary relief of pain associated with inflammation (including sprains, strains and minor and joint pain), migraine headaches and period pain.
75245	VICLOFEN TABLETS diclofenac sodium 25mg blister pack	10, 20, 30 tablets	S3	tablet	Diclofenac sodium	For the temporary relief of pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.

ARTG No.	Product name	Product Strength	Schedule	Dosage Form	Active Ingredient	Approved Indications
166496	VOLTAREN 25 diclofenac sodium 25mg tablet blister pack	20 tablets	S3	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis and osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.
201562	VOLTAREN ENTERIC COATED TABS diclofenac sodium 25mg enteric coated tablet blister pack	10, 20, 30 tablets	S3	tablet	Diclofenac sodium	As a short term treatment (for a few days at a time) for the relief of acute pain states (such as dental pain, rheumatic and muscular pain, backache) in which there is an inflammatory component.
42942	VOLTAREN RAPID 25 Diclofenac Potassium 25mg tablet	4, 5, 6, 10, 20 and 30 tablets	S3	tablet	Diclofenac potassium	As short-term treatment (up to one week) for the relief of acute pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea. Treatment of acute migraine attacks (with or without aura).
171306	VOLTAREN RAPID 25 LIQUID CAPSULE diclofenac potassium 25 mg soft capsule blister pack	10, 20, 30 capsules	S3	capsule	Diclofenac potassium	For the temporary relief of painful conditions such as headache, dental pain, period pain, rheumatic and muscular pain, backache. For the temporary relief of pain and discomfort associated with cold and flu. Reduces fever.
160729	APO-DICLOFENAC diclofenac sodium 25mg tablet blister pack	50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea

ARTG No.	Product name	Product Strength	Schedule	Dosage Form	Active Ingredient	Approved Indications
160730	APO-DICLOFENAC diclofenac sodium 50mg tablet blister pack	50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea
171033	ARTHROTEC 50 Diclofenac sodium 50mg and Misoprostol 200 microgram tablet blister pack	10, 20, 60, 90 tablets	S4	tablet	Diclofenac sodium	ARTHROTEC 50 is indicated for patients who require a non-steroidal anti-inflammatory drug (NSAID) together with misoprostol. The diclofenac component of ARTHROTEC 50 is indicated for the treatment of osteoarthritis and rheumatoid arthritis. The misoprostol component of ARTHROTEC 50 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 GI intolerance and the presence of a concomitant disease.
160728	CHEMMART DICLOFENAC diclofenac sodium 25mg tablet blister pack	50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.
78430	CHEMMART DICLOFENAC diclofenac sodium 25mg tablet bottle	50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.

ARTG No.	Product name	Product Strength	Schedule	Dosage Form	Active Ingredient	Approved Indications
160727	CHEMMART DICLOFENAC diclofenac sodium 50mg tablet blister pack	50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.
78431	CHEMMART DICLOFENAC diclofenac sodium 50mg tablet bottle	50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.
145811	CLONAC diclofenac sodium 25mg tablet bottle	50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.
145812	CLONAC diclofenac sodium 50mg tablet bottle	50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.
63664	DICLOFENAC SANDOZ diclofenac sodium 25mg tablet blister pack	50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.

ARTG No.	Product name	Product Strength	Schedule	Dosage Form	Active Ingredient	Approved Indications
61297	DICLOFENAC SANDOZ diclofenac sodium 25mg tablet bottle	20, 50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.
63661	DICLOFENAC SANDOZ diclofenac sodium 50mg tablet blister pack	50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.
61298	DICLOFENAC SANDOZ diclofenac sodium 50mg tablet bottle	50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.
188548	DICLOFENAC-AS diclofenac sodium 25mg enteric-coated tablet blister pack	50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.
188549	DICLOFENAC-AS diclofenac sodium 50mg enteric-coated tablet blister pack	50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.

ARTG No.	Product name	Product Strength	Schedule	Dosage Form	Active Ingredient	Approved Indications
68940	DICLOFENAC-GA diclofenac sodium 25mg tablet blister pack	50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.
68942	DICLOFENAC-GA diclofenac sodium 50mg tablet blister pack	50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.
188546	DICLOFENAC-PS diclofenac sodium 25mg enteric-coated tablet blister pack	50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.
188547	DICLOFENAC-PS diclofenac sodium 50mg enteric-coated tablet blister pack	50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.
81508	FENAC 25 diclofenac sodium 25 mg tablet bottle	100	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis and osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.

ARTG No.	Product name	Product Strength	Schedule	Dosage Form	Active Ingredient	Approved Indications
165707	FENAC diclofenac sodium 25mg tablet blister pack	50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.
145815	FENAC diclofenac sodium 25mg tablet bottle	100 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.
40933	FENAC Diclofenac Sodium 50 mg tablet bottle	10, 20, 50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis and osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.
165706	FENAC diclofenac sodium 50mg tablet blister pack	50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.
145816	FENAC diclofenac sodium 50mg tablet bottle	10, 20, 50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.

ARTG No.	Product name	Product Strength	Schedule	Dosage Form	Active Ingredient	Approved Indications
78432	GENRX DICLOFENAC diclofenac sodium 25mg tablet bottle	50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.
78433	GENRX DICLOFENAC diclofenac sodium 50mg tablet bottle	50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.
160726	TERRY WHITE CHEMISTS DICLOFENAC diclofenac sodium 25mg tablet blister pack	50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.
78436	TERRY WHITE CHEMISTS DICLOFENAC diclofenac sodium 25mg tablet bottle	50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.
160725	TERRY WHITE CHEMISTS DICLOFENAC diclofenac sodium 50mg tablet blister pack	50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.

ARTG No.	Product name	Product Strength	Schedule	Dosage Form	Active Ingredient	Approved Indications
78526	TERRY WHITE CHEMISTS DICLOFENAC diclofenac sodium 50mg tablet bottle	50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis; osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.
60762	ULTRAFEN diclofenac potassium 50mg tablet blister pack	200 tablets	S4	tablet	Diclofenac potassium	Anti-inflammatory, analgesic and anti-pyretic. An anti-rheumatic.
166496	VOLTAREN 25 diclofenac sodium 25mg tablet blister pack	50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis and osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.
66880	VOLTAREN 50 diclofenac sodium 50mg tablet blister pack	10, 50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis and osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea
11073	VOLTAREN 50 diclofenac sodium 50mg tablet bottle	16, 20, 50 tablets	S4	tablet	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis and osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea

ARTG No.	Product name	Product Strength	Schedule	Dosage Form	Active Ingredient	Approved Indications
37582	VOLTAREN diclofenac sodium 100mg suppository blister pack	5, 20 suppositories	S4	suppository	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis and osteoarthritis. Short term (up to three days) treatment of post-operative pain in children.
96797	VOLTAREN diclofenac sodium 12.5mg suppository blister pack	10 suppositories	S4	suppository	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis and osteoarthritis. Short term (up to three days) treatment of post-operative pain in children.
11072	VOLTAREN diclofenac sodium 25 mg tablet	20, 50 tablets	S4	tablet	Diclofenac sodium	Indications as at 19 May 2014: Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis and osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.
96810	VOLTAREN diclofenac sodium 25mg suppository blister pack	10 suppositories	S4	suppository	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis and osteoarthritis. Short term (up to three days) treatment of post-operative pain in children.
96811	VOLTAREN diclofenac sodium 50mg suppository blister pack	10 suppositories	S4	suppository	Diclofenac sodium	Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis and osteoarthritis. Short term (up to three days) treatment of post-operative pain in children.

ARTG No.	Product name	Product Strength	Schedule	Dosage Form	Active Ingredient	Approved Indications
42943	VOLTAREN RAPID 50 diclofenac potassium 50mg tablet blister pack	4, 5, 6, 10, 20 and 30 tablets	S4	tablet	Diclofenac potassium	Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis and osteoarthritis. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea
123192	VOLTFAST diclofenac potassium 50 mg powder for oral solution sachet	3, 9, 21, 30 sachets	S4	powder	Diclofenac potassium	As short-term treatment (up to one week) for the relief of acute pain states in which there is an inflammatory component. Treatment of acute migraine attacks (with or without aura). Symptomatic treatment of primary dysmenorrhoea.

## Appendix 2: Diclofenac indications in the UK and USA

Country	Indications
UK	<p>Rheumatoid arthritis</p> <p>Osteoarthritis</p> <p>Low back pain</p> <p>Migraine attacks</p> <p>Acute musculoskeletal disorders and trauma such as periartthritis (especially frozen shoulder), tendinitis, tenosynovitis, bursitis, sprains, strains and dislocations; relief of pain in fractures</p> <p>Ankylosing spondylitis</p> <p>Acute gout</p> <p>Control of pain and inflammation in orthopaedic, dental and other minor surgery</p> <p>Pyrophosphate arthropathy and associated disorders</p>
USA	<p>For treatment of primary dysmenorrhea</p> <p>For relief of mild to moderate pain</p> <p>For relief of the signs and symptoms of osteoarthritis</p> <p>For relief of the signs and symptoms of rheumatoid arthritis</p>

## Appendix 3: Product information for oral diclofenac USA

### USA product information for oral diclofenac potassium tablet 50 mg [Apotex Corp]<sup>1</sup>

#### Boxed warning

##### *Cardiovascular risk*

NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (See WARNINGS).

Diclofenac potassium immediate-release tablets are contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

##### *Gastrointestinal risk*

NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (See WARNINGS).

#### Contraindications

Diclofenac potassium immediate-release tablets are contraindicated in patients with known hypersensitivity to diclofenac. Diclofenac potassium immediate-release tablets should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactoid-like reactions to NSAIDs have been reported in such patients (see WARNINGS, Anaphylactoid Reactions, and PRECAUTIONS, Pre-existing Asthma).

Diclofenac potassium immediate-release tablets are contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

#### Warnings

##### *Cardiovascular effects*

##### *Cardiovascular thrombotic events*

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur. There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated

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<sup>1</sup> Updated 5/2013 accessed 3/1/14 <<http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=8e6e1aea-d1c9-f6bf-2a8c-0504437be95c>>

with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events (see GI WARNINGS, GI Effects).

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see CONTRAINDICATIONS).

#### *Hypertension*

NSAIDs, including diclofenac potassium immediate-release tablets, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including diclofenac potassium immediate-release tablets, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

#### *Congestive heart failure and oedema*

Fluid retention and oedema have been observed in some patients taking NSAIDs. Diclofenac potassium immediate-release tablets should be used with caution in patients with fluid retention or heart failure.

#### ***Gastrointestinal effects risk of ulceration, bleeding, and perforation***

NSAIDs, including diclofenac potassium immediate-release tablets, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

#### ***Hepatic effects***

Elevations of one or more liver tests may occur during therapy with diclofenac potassium immediate-release tablets. These laboratory abnormalities may progress, may remain

unchanged, or may be transient with continued therapy. Borderline elevations (i.e., less than 3 times the ULN [ULN = the upper limit of the normal range]) or greater elevations of transaminases occurred in about 15% of diclofenac-treated patients. Of the markers of hepatic function, ALT (SGPT) is recommended for the monitoring of liver injury.

In clinical trials, meaningful elevations (i.e., more than 3 times the ULN) of AST (GOT) (ALT was not measured in all studies) occurred in about 2% of approximately 5,700 patients at some time during diclofenac treatment. In a large, open-label, controlled trial of 3,700 patients treated for 2-6 months, patients were monitored first at 8 weeks and 1,200 patients were monitored again at 24 weeks. Meaningful elevations of ALT and/or AST occurred in about 4% of patients and included marked elevations (i.e., more than 8 times the ULN) in about 1% of the 3,700 patients. In that open-label study, a higher incidence of borderline (less than 3 times the ULN), moderate (3-8 times the ULN), and marked (>8 times the ULN) elevations of ALT or AST was observed in patients receiving diclofenac when compared to other NSAIDs. Elevations in transaminases were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis.

Almost all meaningful elevations in transaminases were detected before patients became symptomatic. Abnormal tests occurred during the first 2 months of therapy with diclofenac in 42 of the 51 patients in all trials who developed marked transaminase elevations.

In postmarketing reports, cases of drug-induced hepatotoxicity have been reported in the first month, and in some cases, the first 2 months of therapy, but can occur at any time during treatment with diclofenac. Postmarketing surveillance has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted in fatalities or liver transplantation.

Physicians should measure transaminases periodically in patients receiving long-term therapy with diclofenac, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements are not known. Based on clinical trial data and postmarketing experiences, transaminases should be monitored within 4 to 8 weeks after initiating treatment with diclofenac. However, severe hepatic reactions can occur at any time during treatment with diclofenac.

If abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, abdominal pain, diarrhoea, dark urine, etc.), Diclofenac potassium immediate-release tablets should be discontinued immediately.

To minimize the possibility that hepatic injury will become severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhoea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms), and the appropriate action patients should take if these signs and symptoms appear. To minimize the potential risk for an adverse liver related event in patients treated with diclofenac potassium immediate-release tablets, the lowest effective dose should be used for the shortest duration possible. Caution should be exercised in prescribing diclofenac potassium immediate-release tablets with concomitant drugs that are known to be potentially hepatotoxic (e.g., antibiotics, anti-epileptics).

## Adverse reactions

**Cardiovascular System:** congestive heart failure, hypertension, tachycardia, syncope

**Digestive System:** dry mouth, esophagitis, gastric/peptic ulcers, gastritis, gastrointestinal bleeding, glossitis, hematemesis, hepatitis, jaundice

## Appendix 4: UK Summary of Product Characteristics for oral diclofenac potassium 50 mg tablet [Actavis]<sup>2</sup>

### 4.3 Contraindications

- Hypersensitivity to diclofenac or any of the excipients.
- Active, or history of recurrent peptic ulcer / haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- NSAIDs are contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema, or urticaria) in response to ibuprofen, aspirin, or other non-steroidal anti-inflammatory drugs.
- Severe heart failure, hepatic failure and renal failure (see section 4.4).
- History of gastro-intestinal bleeding or perforation, relating to previous NSAID therapy.
- During the last trimester of pregnancy (see section 4.6).
- This product contains soya. If you are allergic to peanut or soya, do not use this medicinal product

### 4.4 Special warnings and precautions for use

#### Warnings

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

The use of Diclofenac potassium with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

#### ***Elderly:***

The elderly have increased frequency of adverse reactions to NSAIDs especially gastro intestinal bleeding and perforation which may be fatal (see section 4.2).

#### ***Gastrointestinal:***

Close medical surveillance is imperative in patients with symptoms indicative of gastrointestinal disorders, with a history suggestive of gastric or intestinal ulceration, with ulcerative colitis, or with Crohn's disease as these conditions may be exacerbated (see section 4.8 Undesirable effects).

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding).

#### ***Gastrointestinal bleeding, ulceration and perforation:***

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

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<sup>2</sup> Updated 23/6/2011 accessed 3/1/14

<<http://www.medicines.org.uk/emc/medicine/24377/SPC/Diclofenac+Potassium+50+mg+Tablets/>>

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and section 4.5).

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving diclofenac potassium, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).

### ***Hepatic***

Close medical surveillance is imperative in patients suffering from severe impairment of hepatic function.

## **Precautions**

### ***Cardiovascular, renal and hepatic impairment:***

The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see also section 4.3).

### ***Hepatic***

If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), Diclofenac Potassium tablets should be discontinued. Hepatitis may occur without prodromal symptoms.

Use of Diclofenac Potassium tablets in patients with hepatic porphyria may trigger an attack.

### ***Long term treatment***

All patients who are receiving long term treatment with non-steroidal, anti-inflammatory agents should be monitored as a precautionary measure eg renal function, hepatic function (elevation of liver enzymes may occur) and blood counts. This is particularly important in the elderly.

### ***Cardiovascular and cerebrovascular effects:***

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of diclofenac, particularly at high dose (150mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with diclofenac after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking).

#### **4.8 Undesirable effects**

If serious side-effects occur, Diclofenac Potassium tablets should be withdrawn.

Clinical Trial and epidemiological data suggest that use of diclofenac, particularly at high doses (150 mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4)

*Gastrointestinal:* The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (See section 4.4) have been reported following administration. Less frequently, gastritis has been observed. Pancreatitis has been reported very rarely.

Other adverse reactions reported less commonly include:

*Hepatic:* abnormal liver function, hepatitis and jaundice.

*Cardiovascular system:* In isolated cases, Palpitations, chest pain, hypertension, congestive heart failure.

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## Appendix 5: Database search strategies

### Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search Strategy:

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1. Diclofenac/ (5892)
2. ortofen.ti,ab. (10)
3. 2,6-dichlorophenyl\*.rn. (3)
4. diclonate.ti,ab. (3)
5. diclofenac.ti,ab. (7620)
6. voltaren.ti,ab. (363)
7. diclophenac.ti,ab. (54)
8. orthophen.ti,ab. (7)
9. voltarol.ti,ab. (41)
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (8964)
11. (risk\* or tolera\* or adverse\* or toxic or toxicit\* or poison\* or safe\* or contraindicat\* or complicat\* or side).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (3872172)
12. 10 and 11 (3295)
13. diclofenac/pk, pd (1841)
14. 12 or 13 (4732)
15. limit 14 to "review articles" (449)
16. limit 14 to yr="1990 -Current" (4330)
17. adolescent/ or exp adult/ (5997225)
18. 16 and 17 (1771)
19. limit 18 to humans (1771)
20. limit 19 to "review articles" (81) Raymond: additional limits will also remove reviews from the results.
21. exp Tablets, Enteric-Coated/ or exp Tablets/ (19472)
22. 19 and 21 (56)
23. limit 22 to "review articles" (0)

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**Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search Strategy:**

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1. diclofenac/ae (1358)
2. exp Diclofenac/ (5892)
3. 2 not 1 (4534)
4. limit 3 to "review articles" (148)

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**Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search Strategy:**

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1. exp Diclofenac/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity] (3907)
2. limit 1 to yr="1990 -Current" (3350)
3. limit 2 to humans (2555)
4. limit 1 to "review articles" (258)
5. limit 3 to "review articles" (231)
6. 3 not (4 or 5) (2324)
7. 1 not (4 or 5) (3649)

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**Database: Embase <1980 to 2013 Week 26> Search Strategy:**

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1. exp diclofenac/ (27503)
2. ortofen.mp. (12)
3. diclonate.mp. (3)
4. 1 or 2 or 3 (27504)
5. 2, 6-dichlorophenyl\*.rn. (1)
6. tablet/ (21237)
7. capsule.mp. (58936)
8. exp suppository/ (4313)
9. topical gel.mp. (439)
10. 6 or 7 or 8 or 9 (83213)
11. 4 and 10 (765)
12. limit 11 to yr="1990 -Current" (716)
13. limit 12 to (adolescent <13 to 17 years> or adult <18 to 64 years>) (174)

14. exp adverse drug reaction/ (308222)
15. drug contraindication/ (26232)
16. (poison\$ or toxic\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (729978)
17. pharmacology/ (42664)
18. (safe\$ or risk\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (2670996)
19. 14 or 15 or 16 or 17 or 18 (3446038)
20. 13 and 19 (54)
21. 4 and 19 (10945)
22. limit 21 to (adolescent <13 to 17 years> or adult <18 to 64 years>) (2672)
23. limit 22 to yr="1990 -Current" (2635)
24. limit 23 to "review" (120)

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**Database: Ovid MEDLINE(R) <1946 to June Week 3 2013> Search Strategy:**

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1. exp Diclofenac/ (5759)
2. ortofen.mp. (11)
3. diclonate.mp. (3)
4. 2,6-dichlorophenyl\*.rn. (3)
5. 1 or 2 or 3 or 4 (5762)
6. adverse effect\$.mp. (91645)
7. (risk\$ or safe\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1854942)
8. exp Pharmacology/ (148930)
9. poison\$.mp. (98121)
10. contraindication\$.mp. (21031)
11. 6 or 7 or 8 or 9 or 10 (2146722)
12. 5 and 11 (1210)
13. limit 12 to yr="1990 -Current" (1159)
14. limit 13 to ("adolescent (13 to 18 years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") (616)

15. limit 14 to "review articles" (32)
16. exp tablets/ or exp tablets, enteric-coated/ (19092)
17. \*capsules/ or \*suppositories/ (2388)
18. 16 or 17 (21336)
19. 13 and 18 (69)
20. 14 and 19 (17)

## Appendix 6: Oxford Pain Group league table

Analgesic	Number of patients in comparison	Percent with at least 50% pain relief	NNT	Lower confidence interval	Higher confidence interval
Valdecoxib 40 mg	473	73	<b>1.6</b>	1.4	1.8
Ibuprofen 800	76	100	<b>1.6</b>	1.3	2.2
Ketorolac 20	69	57	<b>1.8</b>	1.4	2.5
Ketorolac 60 (intramuscular)	116	56	<b>1.8</b>	1.5	2.3
Rofecoxib 50	1900	63	<b>1.9</b>	1.8	2.1
Diclofenac 100	411	67	<b>1.9</b>	1.6	2.2
Piroxicam 40	30	80	<b>1.9</b>	1.2	4.3
Lumiracoxib 400 mg	252	56	<b>2.1</b>	1.7	2.5
Paracetamol 1000 + Codeine 60	197	57	<b>2.2</b>	1.7	2.9
Oxycodone IR 5 + Paracetamol 500	150	60	<b>2.2</b>	1.7	3.2
Diclofenac 50	738	63	<b>2.3</b>	2.0	2.7
Naproxen 440	257	50	<b>2.3</b>	2.0	2.9
Oxycodone IR 15	60	73	<b>2.3</b>	1.5	4.9
Ibuprofen 600	203	79	<b>2.4</b>	2.0	4.2
Ibuprofen 400	4703	56	<b>2.4</b>	2.3	2.6
Aspirin 1200	279	61	<b>2.4</b>	1.9	3.2
Bromfenac 50	247	53	<b>2.4</b>	2.0	3.3
Bromfenac 100	95	62	<b>2.6</b>	1.8	4.9
Oxycodone IR 10 + Paracetamol 650	315	66	<b>2.6</b>	2.0	3.5
Ketorolac 10	790	50	<b>2.6</b>	2.3	3.1
Ibuprofen 200	1414	45	<b>2.7</b>	2.5	3.1

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## **Appendix 7: Observational studies that do not show a significant difference between diclofenac and serious cardiovascular disease**

Cheetham et al. conducted a case control study examining the Kaiser Permanente insurance database to look at myocardial infarction and the association with traditional NSAIDs – 21 of the 1773 cases used diclofenac and 54 of the 6557 controls used diclofenac providing an adjusted odds ratio of 1.72 (95%CI 0.98-3.01)(34).

Solomon et al. conducted a retrospective cohort study of Medicare beneficiaries in the USA(35). There were 4141 diclofenac users and 46,558 non-users of any NSAID. The diclofenac group comprised 987 patient years and there were 92 events. The non-users comprised 27,844 patient years and there were 3107 events. The adjusted hazard ratio was 0.91 (95%CI 0.74-1.13).

Another study by Solomon et al. also conducted a retrospective cohort study of Medicare beneficiaries in the USA(36). The diclofenac group comprised 736 patient years and there were 86 events. The non-users comprised 17,067 patient years and there were 1847 events. The adjusted rate ratio was 1.10 (95%CI 0.89-1.37).

Garcia Rodriguez et al. conducted a case control study using the UK General Practice Research Database(37). For the outcome of myocardial infarction, there were 4795 cases of which 213 used diclofenac. Out of the control population of 20,000, 679 used diclofenac. The adjusted odds ratio was 1.18 (95%CI 0.99-1.40).

## Appendix 8: USA warnings and precautions for topical diclofenac

### USA product information Solaraze gel 3% [PharmaDerm]<sup>3</sup>

#### Contraindications

Solaraze® (diclofenac sodium) Gel is contraindicated in patients with a known hypersensitivity to diclofenac, benzyl alcohol, polyethylene glycol monomethyl ether 350 and/or hyaluronate sodium.

#### Adverse events

Cardiovascular: hypertension, congestive heart failure, palpitations, flushing, tachycardia, premature ventricular contractions, myocardial infarction, hypotension.

Digestive: diarrhoea\*, indigestion\*, nausea\*, constipation\*, flatulence\*, liver test abnormalities\*, PUB\*, i.e., peptic ulcer, with or without bleeding and/or perforation, or bleeding without ulcer, vomiting, jaundice, melena, oesophageal lesions, aphthous stomatitis, dry mouth and mucous membranes, bloody diarrhoea, hepatitis, hepatic necrosis, cirrhosis, hepatorenal syndrome, appetite change, pancreatitis with or without concomitant hepatitis, colitis, intestinal perforation.

### USA Voltaren gel 1% [Clinical Solutions Wholesale]<sup>4</sup>

#### Box warnings

##### **Warning: cardiovascular and gastrointestinal risk**

##### *Cardiovascular risk*

Nonsteroidal anti-inflammatory drugs (NSAIDs) may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk [see Warnings and Precautions (5.1)].

Voltaren® Gel is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery [see Contraindications (4)].

##### *Gastrointestinal risk*

NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events [see Warnings and Precautions(5.2)].

#### Contraindications

Use during the peri-operative period in the setting of coronary artery bypass graft (CABG) surgery. (4)

<sup>3</sup> Updated 12/12 accessed 6/1/14 <<http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=89a7bfbd-051f-4d87-a642-96b0df81b8e2>>

<sup>4</sup> Updated 11/13 accessed 6/1/14 <<http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=2280a305-34bd-4f9c-8f31-d6bb6fad90d5>>

## 5 warnings and precautions

### 5.1 Cardiovascular thrombotic events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with NSAIDs, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV toxicity and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAIDs use. The concurrent use of aspirin and NSAIDs such as diclofenac, does increase the risk of serious GI events [see *Warnings and Precautions (5.2)*].

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke [see *Contraindications (4)*].

### 5.2 Gastrointestinal effects – Risk of GI ulceration, bleeding, and perforation

NSAIDs, including diclofenac, can cause serious gastrointestinal (GI) events including bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAIDs therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration. Physicians and patients should remain alert for signs and symptoms of GI ulceration and bleeding during diclofenac therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

### 5.3 Hepatic effects

Elevations of one or more liver tests may occur during therapy with diclofenac sodium. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Borderline elevations (i.e. less than 3 times the ULN [ULN = the upper limit of normal range]) or greater elevations of transaminases occurred in about 15% of diclofenac-

treated patients. Of the markers of hepatic function, ALT (SGPT) is recommended for the monitoring of liver injury.

In clinical trials, meaningful elevations (i.e., more than 3 times the ULN) of AST (GOT) (ALT was not measured in all studies) occurred in about 2% of approximately 5,700 patients at some time during diclofenac treatment. In a large, open-label, controlled trial of 3,700 patients treated for 2-6 months, patients were monitored first at 8 weeks and 1,200 patients were monitored again at 24 weeks. Meaningful elevations of ALT and/or AST occurred in about 4% of patients and included marked elevations (i.e., more than 8 times the ULN) in about 1% of the 3,700 patients. In that open-label study, a higher incidence of borderline (less than 3 times the ULN), moderate (3-8 times the ULN), and marked (>8 times the ULN) elevations of ALT or AST was observed in patients receiving diclofenac when compared to other NSAIDs. Elevations in transaminases were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis.

Almost all meaningful elevations in transaminases were detected before patients became symptomatic. Abnormal tests occurred during the first 2 months of therapy with diclofenac in 42 of the 51 patients in all trials who developed marked transaminase elevations.

In postmarketing reports, cases of drug-induced hepatotoxicity have been reported in the first month, and in some cases, the first 2 months of therapy, but can occur at any time during treatment with diclofenac. Postmarketing surveillance has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted in fatalities or liver transplantation.

Physicians should measure transaminases periodically in patients receiving long-term therapy with diclofenac, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements are not known. Based on clinical trial data and postmarketing experiences, transaminases should be monitored within 4 to 8 weeks after initiating treatment with diclofenac. However, severe hepatic reactions can occur at any time during treatment with diclofenac.

If abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, abdominal pain, diarrhoea, dark urine, etc.), diclofenac sodium should be discontinued immediately. To minimize the possibility that hepatic injury will become severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhoea, pruritus, jaundice, right upper quadrant tenderness, and “flu-like” symptoms), and the appropriate action patients should take if these signs and symptoms appear.

To minimize the potential risk for an adverse liver related event in patients treated with diclofenac sodium, the lowest effective dose should be used for the shortest duration possible. Caution should be exercised in prescribing diclofenac sodium with concomitant drugs that are known to be potentially hepatotoxic (e.g., antibiotics, anti-epileptics).

## Appendix 9: Precaution/warnings UK

### UK SPC Solaraze 3% [Almirall]<sup>5</sup>

#### 4.3 Contraindications

Solaraze is contraindicated in patients with a known hypersensitivity to diclofenac, benzyl alcohol, macrogol monomethyl ether 350 and/ or sodium hyaluronate.

Because of cross-reactions, the gel should not be used by patients who have experienced hypersensitivity reactions such as symptoms of asthma, allergic rhinitis or urticaria, to acetylsalicylic acid or other non-steroidal anti-inflammatory agents.

The use of Solaraze is contraindicated during the third trimester of pregnancy (see Section 4.6).

#### 4.4 Special warnings and precautions for use

The likelihood of systemic side effects occurring following the topical application of Solaraze is very small compared to the frequency of side effects with oral diclofenac, owing to low systemic absorption with Solaraze. However, the possibility of systemic adverse events from application of topical diclofenac cannot be excluded if the preparation is used on large areas of skin and over a prolonged period (see product information on systemic forms of diclofenac). This product should be used with caution in patients with a history of and/or active gastrointestinal ulceration or bleeding, or reduced heart, liver or renal function, since isolated cases of systemic adverse reactions consisting of renal affection, has been reported with topically administered antiphlogistics.

### UK SPC Voltarol Emulgel P 1% Novartis<sup>6</sup>

#### 4.3 Contraindications

Patients with or without chronic asthma in whom attacks of asthma, urticaria or acute rhinitis are precipitated by acetylsalicylic acid (aspirin) or other non-steroidal anti-inflammatory drugs (NSAIDs).

- Hypersensitivity to diclofenac, acetylsalicylic acid, other non-steroidal anti-inflammatory drugs or any of the excipients.
- Third trimester of pregnancy.
- Hypersensitivity to any other ingredient of the gel.
- Concomitant use of other products containing diclofenac.
- Concomitant use of oral NSAIDs.
- The use in children and adolescents aged less than 14 years is contraindicated.

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<sup>5</sup> Updated 1/2/2012 accessed 6/1/14

<<http://www.medicines.org.uk/emc/medicine/21229/SPC/Solaraze/>>

<sup>6</sup> Updated 16/11/2012 accessed 6/1/14

<<http://www.medicines.org.uk/emc/medicine/21038/SPC/Voltarol+Emulgel+P/>>

#### **4.4 Special warnings and precautions for use**

The possibility of systemic adverse events from application of Voltarol Emulgel P cannot be excluded if the preparation is used on large areas of skin and over a prolonged period (see the product information on systemic forms of diclofenac).

Voltarol Emulgel P should be applied only to intact, non-diseased skin and not to skin wounds or open injuries. It should not be allowed to come into contact with the eyes or mucous membranes, and should not be ingested.

Discontinue the treatment if a skin rash develops after applying the product.

Patients with a history of, or active, peptic ulceration. Some possibility of gastro-intestinal bleeding in those with a significant history of this condition has been reported in isolated cases.

Like other drugs that inhibit prostaglandin synthetase activity, diclofenac and other NSAIDs can precipitate bronchospasm if administered to patients suffering from or with a previous history of, bronchial asthma.

Voltarol Emulgel P contains propylene glycol, which may cause mild localised skin irritation in some people.

Voltarol Emulgel P can be used with non-occlusive bandages but should not be used with an airtight occlusive dressing.

## Appendix 10: Australian Product Information sections discussing cardiovascular, gastrointestinal and hepatic risks

### Australian PI for Voltaren updated 20 April 2012

#### Tablets and suppositories:

##### *Contraindications*

Gastric or duodenal ulcer, gastro-intestinal bleeding or perforation.

Patients who are hypersensitive to the active ingredient, diclofenac, or any of the excipients contained in the tablets or suppositories.

Last trimester of pregnancy (see 'PRECAUTIONS - Use in Pregnancy').

Severe hepatic, renal or cardiac failure (see 'PRECAUTIONS').

Patients in whom diclofenac, aspirin or other NSAIDs induce asthma, urticaria or other allergic-type reactions, because severe, rarely fatal, anaphylactic type reactions to diclofenac have been reported in such patients.

##### *Precautions*

###### *Cardiovascular thrombotic events:*

Observational studies have indicated that non-selective NSAIDs may be associated with an increased risk of serious cardiovascular events including myocardial infarction and stroke, which may increase with dose or duration of use. Patients with cardiovascular disease or cardiovascular risk factors may also be at greater risk. To minimise the potential risk of an adverse cardiovascular event in patients taking an NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration (see 'DOSAGE AND ADMINISTRATION').

There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

###### *Hypertension:*

NSAIDs may lead to the onset of new hypertension or worsening of pre-existing hypertension and patients taking anti-hypertensives with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

###### *Heart failure:*

Fluid retention and oedema have been observed in some patients taking NSAIDs, including diclofenac, therefore caution is advised in patients with fluid retention or heart failure.

###### *Gastrointestinal effects:*

Close medical surveillance is imperative and particular caution should be exercised when prescribing NSAIDs, including diclofenac, in patients with symptoms indicative of gastrointestinal disorders (GI) or with a history suggestive of gastro-intestinal ulceration, bleeding or perforation (see 'ADVERSE REACTIONS').

Upper GI ulcers, gross bleeding or perforation caused by NSAIDs, including diclofenac, occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for one year. The risk of GI bleeding is higher with increasing NSAID doses, with increasing duration of use and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation and in the elderly.

Gastric or duodenal ulceration, perforation or gastrointestinal bleeding, which can be fatal, have been reported in patients receiving Voltaren. Studies to date have not identified any subset of patients who are not at risk of developing these problems.

Caution is advised in patients with risk factors for gastrointestinal events who may be at greater risk of developing serious gastrointestinal events, e.g. the elderly, those with a history of serious gastrointestinal events, smoking and alcoholism.

The concurrent use of aspirin and NSAIDs, including diclofenac, also increases the risk of serious gastrointestinal adverse events.

To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly, the treatment should be initiated and maintained at the lowest effective dose. Gastrointestinal bleeding, ulceration and perforation in general have more serious consequences in the elderly. They can occur at any time during treatment with or without warning symptoms or a previous history. In instances where gastrointestinal bleeding or ulcerations occur in patients receiving Voltaren, the drug should be withdrawn immediately. Physicians should warn patients about the signs and symptoms of serious gastrointestinal toxicity and what steps to take if they occur.

Combination therapy with protective agents (e.g. proton pump inhibitors or misoprostol) should be considered for these patients, and also for patients requiring concomitant use of medicinal products containing low-dose acetylsalicylic acid (ASA)/aspirin or other medicinal products likely to increase gastrointestinal risk.

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding). Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, anti-platelet agents or selective serotonin-reuptake inhibitors (see 'PRECAUTIONS - Interactions with other Drugs').

Close medical surveillance and caution should also be exercised in patients with ulcerative colitis, or with Crohn's disease, as well as in patients suffering from pre-existing

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dyshaemopoiesis or disorders of blood coagulation, as their condition may be exacerbated (see 'ADVERSE REACTIONS').

#### *Liver:*

Close medical surveillance is required when prescribing Voltaren to patients with impaired hepatic function, as their condition may be exacerbated (see 'CONTRAINDICATIONS').

As with other NSAIDs, including diclofenac, elevations of one or more liver enzymes may occur during Voltaren therapy. These laboratory abnormalities may progress, remain unchanged, or revert to normal despite continued therapy. Borderline elevations (i.e. 1.2 to 3 times the upper limit of normal (ULN), or greater elevations of transaminases occurred in about 15% of Voltaren-treated patients. In clinical trials, meaningful elevations (i.e. more than 3 times the ULN) of AST and/or ALT occurred in about 4% of patients treated for several months, including marked elevations (i.e. more than 8 times the ULN) in about 1% of patients. Transaminase elevations were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis (Refer to "ADVERSE REACTIONS").

Transaminase elevations were reversible on cessation of therapy, and even among patients with marked elevations, signs and symptoms of liver disease occurred only in isolated cases. Most patients with borderline elevations did not have therapy interrupted, and transaminase elevations in most of these cases disappeared or did not progress. There were no identifying features to distinguish those patients who developed marked elevations from those who did not.

In addition to the enzyme elevations seen in clinical trials, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, have been reported.

Severe hepatotoxicity may develop without prodromal symptoms, so transaminases should be measured periodically in patients receiving long-term therapy with Voltaren. The optimum times for making the measurements are not known. In most patients who have developed marked transaminase elevations, abnormal tests occurred during the first 2 months of therapy with Voltaren. Based on this experience the first transaminase measurement should be made no later than 8 weeks after the start of Voltaren treatment. As with other NSAIDs, including diclofenac, if abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), Voltaren should be discontinued.

To minimise the possibility of hepatic injury becoming severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritis, jaundice, abdominal tenderness in the right upper quadrant and "flu-like" symptoms) and the appropriate action to take should these signs and symptoms appear.

Caution should be exercised when using Voltaren in patients with hepatic porphyria, since Voltaren may trigger an attack.

### ***Adverse reactions***

#### *Cardiac disorders:*

Very rare: Palpitations, chest pain, cardiac failure, myocardial infarction.

#### *Vascular disorders:*

Very rare: Hypertension, vasculitis.

#### *Gastrointestinal disorders:*

Common: Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia.

Rare: Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer (with or without bleeding or perforation), proctitis (Voltaren suppositories).

Very rare: Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis, haemorrhoids aggravated (Voltaren suppositories).

#### *Hepatobiliary disorders:*

Common: Transaminases increased.

Rare: Hepatitis, jaundice, liver disorder.

## Appendix 11: Required Advisory Statements for Medicine Labels 2014 for diclofenac

Substance(s)	Conditions	Required statement(s)
Diclofenac <i>(Entry 1 of 4)</i>	In preparations for oral use when indicated exclusively for the treatment of dysmenorrhoea	<p>Do not use [this product/insert name of product] if you have a stomach ulcer.]</p> <p>Do not use [this product/insert name of product] if you are allergic to diclofenac or other anti-inflammatory medicines.</p> <p>Unless a doctor has told you to, do not use [this product/insert name of product] if you have asthma.]</p> <p>Unless advised by your doctor or pharmacist, do not use [this product/insert name of product] with other products containing diclofenac, aspirin or other anti-inflammatory medicines or with medicines that you are taking regularly.</p> <p>If you get an allergic reaction, stop taking and see your doctor immediately.</p> <p>Do not use for more than a few days at a time unless a doctor has told you to. Do not exceed the recommended dose. Excessive use can be harmful.</p> <p>Do not use if you have impaired kidney function.</p> <p>Do not use if you have heart failure.</p>

Substance(s)	Conditions	Required statement(s)
Diclofenac <i>(Entry 2 of 4)</i>	In preparations for oral use in adults when NOT indicated exclusively for the treatment of dysmenorrhoea	<p>Do not use [this product/<i>insert name of product</i>] if you have a stomach ulcer.</p> <p>Do not use [this product/<i>insert name of product</i>] if you are allergic to diclofenac or other anti-inflammatory medicines.</p> <p>Unless a doctor has told you to, do not use [this product/<i>insert name of product</i>] if you have asthma.</p> <p>Unless advised by your doctor or pharmacist, do not use [this product/<i>insert name of product</i>] with other products containing diclofenac, aspirin or other anti-inflammatory medicines or with medicines that you are taking regularly.</p> <p>If you get an allergic reaction, stop taking and see your doctor immediately.</p> <p>Do not use for more than a few days at a time unless a doctor has told you to. Do not exceed the recommended dose. Excessive use can be harmful.</p> <p>Do not use [this product/<i>insert name of product</i>] during the first 6 months of pregnancy, except on doctor's advice. Do not use at all during the last 3 months of pregnancy.</p> <p>Do not use if you have impaired kidney function.</p> <p>Do not use if you have heart failure.</p>

Substance(s)	Conditions	Required statement(s)
Diclofenac (Entry 3 of 4)	In preparations indicated for oral use in children	<p>Do not use [this product/<i>insert name of product</i>] if you have a stomach ulcer.</p> <p>Do not use [this product/<i>insert name of product</i>] if you are allergic to diclofenac or other anti-inflammatory medicines.</p> <p>Unless a doctor has told you to, do not use [this product/<i>insert name of product</i>] if you have asthma.</p> <p>Unless advised by your doctor or pharmacist, do not use [this product/<i>insert name of product</i>] with other products containing diclofenac, aspirin or other anti-inflammatory medicines or with medicines that you are taking regularly.</p> <p>If you get an allergic reaction, stop taking and see your doctor immediately.</p> <p>Do not use for more than a few days at a time unless a doctor has told you to. Do not exceed the recommended dose. Excessive use can be harmful.</p> <p>Ask your doctor or pharmacist before use of the medicine in children suffering from dehydration through diarrhoea and/or vomiting.</p> <p>Do not use if you have impaired kidney function.</p> <p>Do not use if you have heart failure.</p>
Diclofenac (Entry 4 of 4)	When the preparation is for dermal use	<p>Do not use [this product/<i>insert name of product</i>] if you are allergic to diclofenac or other anti-inflammatory medicines.</p> <p>If you get an allergic reaction, stop taking and see your doctor immediately.</p> <p>Unless a doctor or pharmacist has told you to, do not use [this product/<i>insert name of product</i>] with other medicines that you are taking regularly.</p>

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