Submission to the

Medicines Classification Committee

for the reclassification of Diclofenac from a

Restricted Medicine to a

Pharmacy Only Medicine for the following

Dose form and Strength:

- **In solid oral dose form containing 12.5 mg or less per dose form in packs of not more than 20 tablets or capsules**

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Note: References quoted throughout this submission are listed at the end of the Clinical Expert Report (Appendix II). The full reference document(s) are available on request.

INTRODUCTION

This submission contains data to support the reclassification of Diclofenac in solid oral dose forms, containing 12.5mg or less per dose form in packs of not more than 20 tablets or capsules, from Restricted Medicine to Pharmacy Only Medicine.

A New Medicine Application (NMA;TT50-6834) was submitted to Medsafe 19 December 2001 for an immediate release, film coated tablet formulation containing Diclofenac-K 12.5mg. The new medicine is proposed to be marketed in New Zealand under the trade name of **Voltaren Rapid 12.5**.

The low dose Diclofenac-K 12.5mg formulation has been developed for analgesic and antipyretic indications suitable for consumer self-medication use i.e. for the relief of the self-limiting indications. Diclofenac-K 12.5mg indicated for headaches, dental pain, period pain, rheumatic and muscular pain, backache, the symptoms of colds and flu and for fever reduction. Headache, the symptoms of colds and flu, and fever reduction are new indications for Diclofenac-K 12.5mg and are included in the NMA submitted 19 December 2001.

The recommended flexible low dosage regimen for Diclofenac-K 12.5mg tablets is 2 tablets (25mg) to start, followed by 1 or 2 tablets every 4 to 6 hours as needed. The maximum daily dosage is 6 tablets (75mg). In the context of self selection over-the-counter use, the product is to be taken for a maximum of 5 days for pain relief and 3 days for fever reduction.

The Novartis Expert Report on the Clinical documentation prepared for the EU dossier (*Appendix II*) evaluates the clinical data which justify approval of Diclofenac-K 12.5mg with regard to self-limiting indications. The Annex to the Expert Report on the Clinical documentation (*Appendix III*) was prepared for the dossier submitted in the EU and it contains the rationale for the application to change the legal status of Diclofenac-K 12.5mg tablets to non-prescription from prescription.

Diclofenac strength	Current Classification	Proposed Classification
25mg	Restricted Medicine	No change
12.5mg	Restricted Medicine	*Pharmacy Only Medicine*

Diclofenac is a well known NSAID with anti-inflammatory, analgesic and antipyretic properties. More than one billion patients world wide have been exposed over the last 25 years to diclofenac administered as Voltaren (diclofenac sodium) launched in 1974* or Cataflam (diclofenac potassium) launched in 1986*. The diclofenac safety profile is well established and no new or unknown adverse events are expected (safety data is described in the Clinical Expert report attached as *Appendix II*). The combined evidence from clinical trial data and from post-marketing experience shows that the lower daily dose and shorter treatment period proposed for Diclofenac-K 12.5mg, result in better tolerability and safety.

By lowering the maximum recommended daily dose of Diclofenac to half that currently recommended (75mg/day vs. 150mg/day) as a Restricted Medicine and by limiting its intake to no more than 5 days, it can be expected that Diclofenac-K 12.5mg is suitable and able to be well-tolerated as a Pharmacy Only Medicine for self-limiting indications.

* Novartis world-wide launch dates

PART A

1. International Non-proprietary Name of the medicine

Diclofenac

2. Proprietary name(s)

Voltaren Rapid 12.5

3. Name of company requesting reclassification

Novartis Consumer Health Australasia Pty Ltd
c/- Private Bag 19999
Avondale
Auckland

Contact Details:
Caroline Norwood
Pharmaceutical Solutions Ltd
15 Empire Road
Devonport
Auckland

Phone: 09 445 4260
Email: carolinenorwood@xtra.co.nz

4. Dose form(s) and strength(s) for which a change is sought

Dose form: solid oral dose, tablet or capsule
Strength: 12.5mg or less

5. Pack size and other qualifications

Pack size: 10 and 20 tablets (equivalent to a total of 125mg and 250mg Diclofenac-K per pack respectively)
The current pack sizes (as a Restricted Medicine) for 25mg diclofenac are 10, 20, 30 tablets (250mg, 500mg and 750mg diclofenac respectively)

Container: PVC/PE/PVDC aluminium blister in outer cardboard carton, containing a patient leaflet

Refer to *Appendix I*.

6. Indications for which change is sought

Relief of painful conditions such as headache, dental pain, period pain, rheumatic and muscular pain, backache. Relief of symptoms of cold and flu, including aches and pains and sore throat pain. Reduction of fever.

7. Present classification of medicine

Restricted Medicine

8. Classification sought

Pharmacy Only Medicine

9. Classification status in other countries

Please refer to *Appendix VII*.

Australia: Diclofenac 25mg or less per dosage unit (pack containing 30 or less units)
Schedule 3 (Pharmacist Only Medicine); included in Appendix H of the SUSDP on the following grounds:
Long history of safe use; well-characterised adverse effects and advertising would increase consumer awareness of the range of over-the-counter NSAIDs available.

10. Extent of usage in NZ and elsewhere (e.g. sales volumes) and dates of original consent to distribute

Please refer *to Appendix VII* for the dates of original approval for diclofenac potassium 12.5mg tablets.

Please note that the Diclofenac-K 12.5mg product is not yet approved in New Zealand and that there is no other 12.5mg diclofenac product on the New Zealand market. Consequently, we are unable to provide sales volumes.

Launch status around the world of Diclofenac-K 12.5mg tablets:

Country	Trade name	Launch date	Sales* (in packs of 10 and 20 tablets since launch, Norway and Switzerland sales combined)
Switzerland	Voltaren Dolo	September 2000	} 2000: 183,118 } 2001: 453,583 } 2002 – 30/6/02: 330,461
Norway	Otriflu	October 2001	
Hungary	Voltaren Dolo	May 2002	No sales data to date
Netherlands	TBA	Planned	N/A
Israel	TBA	Planned	N/A
Russia	TBA	Planned	N/A
Poland	TBA	Planned	N/A

* The sales data from Norway and Switzerland is only available as a combined sales figure per year.

11. Labelling or draft labelling for the proposed new presentation(s)

- Blister foil (primary packaging)
- Carton label (secondary packaging)
- Patient information leaflet (to be contained in the carton)

Refer to *Appendix I* for the draft text.

12. Proposed warning statements if applicable

Carton:
Keep out of the reach of children
Please read the enclosed leaflet carefully before taking the tablets
Do not take more than 6 tablets in 24 hours
Do not take for more than 5 days for pain or 3 days for fever
Not recommended for children under 14 years
CAUTION: Prolonged use could be harmful
Use only as directed
If symptoms persist or worsen, see your doctor.
WARNINGS: Do not exceed the stated dose. Do not take if you have a stomach or intestinal ulcer, if you are allergic to diclofenac or other pain relievers such as aspirin or ibuprofen. Do not use during the last 3 months of pregnancy.

Please refer to the proposed pack leaflet in *Appendix I* for further information available to the consumer.

13. Other products containing the same active ingredient(s) and which would be affected by the proposed change

To our knowledge there are no other Diclofenac-K 12.5mg (or other salt) tablets in registration.

PART B

1. A statement of the benefits to both the consumer and to the public expected from the proposed change
(*Appendix II* contains the references for claims)

The classification change to Pharmacy Only Medicine for the availability of diclofenac-K 12.5mg, offers the consumer a safe, more convenient dose strength of an effective, therapeutic medicine for relief of minor painful conditions, the symptoms of colds and flu and fever reduction. These common self-limiting indications are readily recognised by consumers. Consumers want to relieve their symptoms with self-selection medications and a low strength; low dose diclofenac will provide a safe and effective alternative to current Pharmacy Only products available such as ibuprofen and naproxen. The change is therefore expected to offer the consumer a more convenient dose of a proven therapeutic medicine (refer to the Diclofenac-K 12.5mg NMA) with no expected additional safety risks.

Diclofenac is comparable in safety to other non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen that are available as Pharmacy Only medicines. Therefore, availability of low dose Diclofenac-K 12.5mg should also be available to consumers under similar classification conditions.

There has already been considerable use of diclofenac on an OTC basis worldwide. Diclofenac-K 12.5mg tablets have been formulated for use by consumers who require self-selection medication for short term management and relief of minor painful conditions, and for fever reduction.

Currently diclofenac 25mg is only available over-the-counter in New Zealand as a Restricted Medicine (in a limited pack size). The maximum daily dose of diclofenac 25mg (eg Cataflam) is 6 tablets – equivalent to 150mg diclofenac-K / day.

The proposed Diclofenac-K 12.5mg flexible low dosage regimen has been proven to be effective and safe, similar to reference drugs ibuprofen and paracetamol, which allows ***consumers a minimum exposure to diclofenac with maximum benefit for relief of their symptoms***. Additionally, Diclofenac-K 12.5mg allows consumers to adjust their treatment according to the type, duration and severity of their symptoms which mirrors the in-use situation for these conditions.

Overall, Diclofenac-K 12.5mg / 2x12.5mg were equally effective to the established reference treatments ibuprofen 200mg / 2x200mg and paracetamol 500mg / 2x500mg and Diclofenac-K 75mg/day was equally effective to ibuprofen 1200mg/day and paracetamol 3g/day (*Appendix II*)**.**

The maximum daily dose of Diclofenac-K 12.5mg is 6 tablets (75mg):

Product	**mg diclofenac / tablet**	**Max tablets/day**	**Max dose/day**
Cataflam	25	6	150 mg
Diclofenac-K 12.5mg	12.5	6	75 mg

The overall safety profile of the diclofenac moiety has been confirmed in 18 post-marketing large scale field or multicentric studies in general practice setting. These studies involved more than 115 000 patients using prescribed diclofenac (all salts included) ranging from 75mg to 200mg/day (an average of 150mg/day) with most patients treated up to 2 weeks (*Voltaren 20 years of Clinical experience - an update, 1994*). The overall rate of adverse events was below 20% and the vast majority were not serious. The results of these studies consistently support the view that diclofenac is one of the safest NSAIDs available and predict a good safety profile for low dose Diclofenac-K 12.5mg in the general population.

The Clinical Expert Report and Annex (*Appendix II and III*) conclude that Diclofenac-K 12.5mg is suitable for consumer self-selection. Clear advice will be provided to the consumer (via the labelling) on the safe usage of the product and when medical referral is required. There are no data pointing to indirect hazards or a particular risk of abuse or misuse of diclofenac.

2. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated

A household survey was conducted in UK, France and Germany in 1995 to understand the self-medication habits of people who treat themselves with analgesics available over the counter when they suffer from minor pain or fever. A total of 1431 respondents revealed a user profile that is quite different from that of the average patient who receives a prescription for an NSAID (*Appendix II*; section 9).

- 75% treated only one episode per month (average 1.4 episodes)
- 82% of such episodes lasted only one day (average 1.9 days)
- 99% treated themselves for 1 to 5 days (average 1.9 days)
- 75% of episodes were treated with just 1 or 2 tablets (average 2.3)
- average number of tablets per dose was less than 2 (1.6)
- over half (54%) were less than 39 years of age, and only 13% were 59 years or older.

This survey revealed that compared to patients for whom an NSAID is prescribed, people taking OTC analgesics tend to be markedly younger and hence presumably healthier, two factors that speak in favour of better tolerability. There was one further reassuring finding, namely that users do not tend to be abusers, in that they treat themselves in a reasonable manner for a day or two, with a clearly limited number of tablets, be it per dose or per episode. All these observations are conducive to increased safety for a non-prescription / pharmacy medicine analgesic such as low-dose diclofenac.

Diclofenac-K 12.5mg tablets are for the relief of headaches, dental pain, period pain, rheumatic and muscular pain, backache, the symptoms of colds and flu and for fever reduction. These are common and well recognised symptoms of self-limiting conditions that are able to be self-diagnosed by the consumer with or without the assistance of a pharmacist. Consumers have a long history of self-diagnosis and self-medication of conditions such as those proposed to be indicated for Diclofenac-K 12.5mg.

There is no difference in the way Diclofenac-K 12.5mg should be used by consumers, compared to naproxen, ibuprofen (including ibuprofen plus codeine), paracetamol or aspirin, all of which are available Pharmacy Only or General Sale to consumers in New Zealand, without any requirements for pharmacist intervention.

3. Relevant comparative data for like compounds

Diclofenac-K 12.5mg (single dose) was equi-effective to ibuprofen 200mg and paracetamol 500mg, and diclofenac 75mg / day was equally effective to ibuprofen 1200mg / day and paracetamol 3g / day (refer to *Appendix II*).

The safety monitoring during the single-dose and multiple-dose clinical trials has shown that low-dose Diclofenac-K 12.5mg up to 75mg / day is safe and well tolerated; the safety profile is similar to that of low-dose ibuprofen and placebo (refer to *Appendix II*).

Diclofenac at currently recommended doses i.e. 25mg and above, and in current utilisation patterns is positioned in the medium to low risk category, immediately after ibuprofen, the “gold Standard” of NSAIDs safety (CSM/MCA 1994, Henry et al. 1996, Garcia Rodriguez 1997).

Also refer to Martindale monographs in *Appendix VI.*

Overdose (refer to *Appendix III*, section 2)

All NSAIDs share the same pharmacological mechanism of action; they inhibit cyclo-oxygenase, thus reducing the pain and inflammation associated with prostaglandin synthesis. This justifies the comparison between diclofenac and other NSAIDs with respect to the effects produced by acute overdose.
Despite the enormous popularity of NSAIDs, significant morbidity and mortality resulting from NSAID overdose is rare (*Smolinske et al. 1990*) and most NSAID overdoses result in a benign outcome. For example, of 50,614 NSAID exposures reported to Poison Control Centres in USA in a 2 year period, 131 (0.26%) had a major outcome, with 10 deaths (0.02%). NSAID poisoning represents only 6.3% of people presenting to emergency departments (in cases of poisoning) compared to 43% for paracetamol poisoning (*Thomas et al 1996*).

Three cases of overdose for Cataflam (worldwide) have been reported (*Appendix II*, safety summary section 3.3.1.2)

- 2 year old boy who took 100mg with no untoward effects
- unsuccessful suicide attempt with 1500mg (20 times higher than 75mg/day)
- 9 year old girl with 150mg who recovered completely.

A total of 87 cases of overdose were reported for Voltaren mostly in combination with other drugs in suicide attempts (*Appendix II*, safety summary section 3.3.2.3). The doses range from 200 to 5000mg.

- **Compared to Ibuprofen**

Limited information is available on the acute toxicity of diclofenac in humans because there have been few reports of overdose, despite having been so widely prescribed in more than 1 billion patients over 25 years. The literature suggest that diclofenac in acute overdose has a safety profile that compares favourably with ibuprofen, which is the agent with the most published data on overdose so far (*Hall et al 1992, Halpern et al 1993*). Ibuprofen has been shown to be safer in overdose than aspirin and paracetamol (*Smolinske et al. 1990, Thomas et al 1996, Veltri 1988).* The treatment of diclofenac overdose, as for other NSAIDs, is essentially supportive and symptomatic (*Smolinske et al. 1990, AHFS Drug Information 1999, Therapeutic Drugs 1999).*

- **Compared to Aspirin**

As for ibuprofen, the safety margin of diclofenac in overdose is larger when compared to salicylates.
In both chronic and acute intoxication with salicylates, intensive symptomatic and supportive therapy should be instituted. Treatment consists of removing the salicylates from the GI tract and prevention of further absorption; correction of fluid, electrolyte, and acid-base disturbances, and measures to enhance salicylate elimination.

- **Compared to Paracetamol**

As for ibuprofen, the safety margin of diclofenac is much larger when compared to paracetamol which is considered one of the safest and most widely used analgesic and antipyretic. Despite a good safety profile when used at recommended doses, paracetamol in acute or chronic overdose may result in irreversible liver toxicity and sometimes death (*AHFS Drug Information 1999, Medical letter 1996, Vale & Proudfoot 1995*). In addition to appropriate supportive therapy, liver injury may be minimised by administering oral methionine up to 10 hours and acetylcysteine up to 24 hours after dose (*Janes & Routledge 1992*). In the case of severe hepatic necrosis, liver transplantation could be envisaged.

Overdose Conclusion

Diclofenac in acute overdose compares favourably with other OTC NSAIDs, particularly with ibuprofen which has been shown to be safer than aspirin and paracetamol. Moreover, the risk of chronic overdose is reduced since diclofenac used at even a double dose of 150 to 200mg, is still within the safety margin. Such doses of diclofenac have been tested for long-term periods in the treatment of chronic ailments.

4. Local data or special considerations relating to NZ

Case reports were requested from the New Zealand Centre for Adverse Reaction Monitoring (CARM) for all reported adverse reactions for Cataflam and Nurofen for the time period ending 31 March 2002. The results of the search are as follows (full case reports are contained in *Appendix IV*):

Year of ADR	Cataflam (diclofenac 25mg)	Nurofen (ibuprofen 200mg)
1989		1
1990	-	-
1991	-	-
1992	-	-
1993	-	-
1994	2	-
1995	7	-
1996	2	-
1997	-	-
1998	1	1
1999	1	1
2000	1	1
2001	2	1
2002 up to 31/3	-	-

It is apparent from the above data, that spontaneous ADR reporting is similar for diclofenac 25mg (Restricted Medicine) and ibuprofen 200mg (Pharmacy Only Medicine). However it is recognised (*Appendix II*, section 7.2.1) that the relevance of spontaneous ADR reporting as a pharmacovigilance tool is limited.

5. Interactions with other medicines

Refer to *Appendix II*, section 4.4.
The known ability of NSAIDs to interact with other drugs is due in part to their high degree of binding with plasma albumin. The same interactions are to be expected for Diclofenac-K 12.5mg tablets as for Voltaren or Cataflam. Diclofenac may raise the plasma concentrations of lithium, digoxin and methotrexate. Like other NSAIDs, it may inhibit the activity of diuretics. There are isolated reports of an increased risk of haemorrhage with the combined use of anticoagulants. Co-administration may increase the nephrotoxicity of cyclosporine. Combined use of other NSAIDs may increase the frequency of side effects.

The influence of food on the absorption of diclofenac was investigated with Diclofenac-K 12.5mg tablets. Food intake reduced the absorption rate of diclofenac potassium (lower C_{max}, ⇩ 45%, and delayed t_{max} by ⇧ 35 min). The extent of absorption was reduced to a lower extent (15%), remaining entirely (AUC_t) or almost entirely ($AUC\infty$) included within the standard limits for confidence intervals. Therefore, for maximum efficacy, Diclofenac-K 12.5mg tablets should not be taken directly with or immediately after meals.

6. Contraindications

Contraindications are clearly communicated in the labelling and pack insert for the product, i.e.:

Stomach or intestinal ulcer
Known hypersensitivity to the active substance or to any of the excipients
Patients in whom attacks of asthma are precipitated by diclofenac or any other pain reliever/fever reducer such as aspirin or ibuprofen.

Refer to *Appendix I*.

7. Possible resistance

N/A

8. Adverse events - nature, frequency etc.

The first Diclofenac-K 12.5mg PSUR dated 22 February 2002 (for the period 01/8/00 to 31/1/02) is attached as *Appendix V*. Since the data-lock-point in the PSUR attached, only one further adverse event has been received (non-serious unlisted) and the CIOMS form is also included in *Appendix V*. The PSUR contains the data obtained after the Diclofenac-K 12.5mg launches in Norway and Switzerland. A crude estimate of the number of patients treated with Diclofenac-K 12.5mg has been calculated from the total number of tablets sold in Switzerland and Norway. It has been assumed that each patient has taken the maximum recommended dosage and duration of treatment (6 tabs/day during 3 days = treatment course). Thus it is estimated that around 600'000 patients have received Diclofenac-K 12.5mg during the period mentioned in the PSUR report.

Global analysis of safety in clinical trials (refer to *Appendix II*, section: 6)
NSAIDs as a class have the common potential of causing adverse reactions which result from their mechanism of action i.e. inhibition of prostaglandin synthesis. The most relevant are GI adverse reactions, resulting in gastric or duodenal ulcers, and depression of renal function, resulting in acute kidney insufficiency. Additional NSAID-associated adverse reactions include hepatotoxicity with or without symptoms of clinical liver disease, blood disorders and allergenic-type reactions. The incidence of serious adverse drug reactions associated with NSAIDs is however low and they can be regarded as a reasonable safe class of drugs (Carson & Willett 1993).

Safety in clinical trials (refer to *Appendix II*, section 6.3):
No differences between diclofenac potassium and ibuprofen in overall, and GI safety, treatment discontinuations due to AEs, AE severity, SAEs or death, were demonstrated at either dose level (low or high) in either category of duration (short-term or long-term) or in populations (otherwise healthy individuals or chronic users).

Spontaneous ADR reporting (refer to *Appendix II*, section 7.2):
Although it is universally considered the best method for recognising new or rare ADR's, the spontaneous reporting has some limits when estimating quantitatively and qualitatively the ADRs. Incidence rates and relative risks cannot be obtained from spontaneous ADR reports.
Diclofenac has been the most prescribed NSAID in the world. Over I billion patients were treated with Voltaren (launched 1974) or Cataflam (launched 1986). There is a huge amount of data, a wealth of experience and a well established safety profile with no unexpected trends.
Numerically the post-marketing surveillance experience is quite different with 16,539 ADRs reported for Voltaren (diclofenac sodium) vs. 348 for Cataflam (diclofenac potassium). The difference between the two products is related to different indications and different patients' profiles. Low dose Diclofenac-K 12.5mg is indicated for similar conditions as Cataflam, albeit of a lesser severity, generally in otherwise healthy individuals and duration of treatment is limited to a maximum of 5 days for self-selection Pharmacy Only Medicine use, thus increasing the overall safety.

Conclusion on ADRs:
The safety profile provided for both Voltaren and Cataflam by the spontaneous ADR reports corresponds to what can be expected for an NSAID. Cataflam, due to the shorter period of administration, results in a reduced incidence of ADRs in general and specifically, serious gastro-intestinal ADRs. Long-term animal studies have shown that the extent of GI damage is dose-dependent which suggests that with reduced dosage, as proposed in this application, one can expect fewer problems. In view of the long history of world-wide diclofenac use, it can be safely assumed that no new unexpected adverse events are likely to be reported. The data gathered support the safety of low-dose Diclofenac-K 12.5mg proposed for reclassification to Pharmacy Only Medicine.

Also refer to *Appendix IV* and Part B: 4 above.

9. Potential for abuse or misuse

Please refer to *Appendix II*, section 7.2.3; and *Appendix III,* section 2.

Diclofenac is in the same therapeutic category (NSAIDs) as substances such as naproxen and ibuprofen. Hence, if there is no evidence accumulating that Pharmacy Only availability of either of these substances has led to inappropriate patterns of medication use, the probability is that the Pharmacy Only availability of diclofenac likewise would not significantly affect patterns of use.

Diclofenac does not rank amongst substances known to be toxic in overdose or to be addictive. Diclofenac has a large safety margin in acute overdose. Overall, the clinical picture in overdose depends on the nature of the other drugs taken. The symptoms and signs correspond largely to those known with other NSAIDs. The safety margin is much greater than with paracetamol and than with aspirin.

The indications proposed for Diclofenac-K 12.5mg tablets are well known. Duration of use is limited to 5 days for relief of pain and 3 days for fever reduction. Clear instructions are given on the pack label as well as in the patient leaflet, and patients are advised to consult their doctor if symptoms persist. The pack sizes are limited to 10 or 20 tablets which makes overuse for long periods unlikely.

The absence of central nervous system effects makes the potential for abuse or addiction non-existent.