Novartis Consumer Health

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Submission to the Medicines Classification Committee

Classification of diclofenac (pharmacy only medicine) in solid oral dose form containing 12.5 mg or less per dose form

Increase in pack size limit from 20 dosage units to 40 dosage units

Prepared by: Novartis Consumer Health Australasia Pty Ltd
Date: 31 July 2009

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PART A:

1. International Non-proprietary Name of the Medicine

Diclofenac

2. Proprietary Name

Votlaren Rapid 12.5

3. Name of Company requesting reclassification

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

Dose Form: Solid oral dose

Strength: 12.5 mg or less.

No changes to the product dose or strength are being sought.

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5. Pack size and other qualifications

Pack Size:

Status	Dosage Unit per Pack (tablets)	Total active content (mg)	Max No. Days per pack
Current	10	125 mg	1.6
	20	250 mg	3.3
Proposed	**10**	**125 mg**	**1.6**
	20	**250 mg**	**3.3**
	30	**375 mg**	**5**
	40	**500 mg**	**6.6**

Container

PVC / PE / PVDC aluminium blister in outer cardboard carton, containing a patient leafet. This does not represent a change to the current container.

6. Indications for which change is sought

The approved indications are:

* 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).

* Reduction of fever.

No changes to the product indications are being sought.

7. Present Classification of Medicine

Pharmacy-only medicine

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8. Classification sought

Current Classification

Pharmacy-only medicine: diclofenac in solid dose form in medicines containing 12.5 milligrams or less per dose form in packs containing not more than 20 tablets or capsules and with a recommended daily dose of not more than 75 milligrams

Requested Classification:

Pharmacy-only medicine: diclofenac for oral use in solid dose form containing not more than 12.5 mg per dose form and with a recommended daily dose of not more than 75 mg per dose form and in packs containing not more than 40 dose units

Background:

In July 2002, Novartis submitted an application to the MCC requesting pharmacy-only medicine classification for diclofenac 12.5 mg in pack sizes of up to 20 tablets or capsules. This restriction on pack size was not one specifically imposed by the MCC. The maximum pack size was requested by Novartis to be in line with pack sizes proposed to be marketed worldwide for the product at that point in time.

At the 38th Meeting of the Medicines Classification Committee (the "Committee") held in December 2007, consideration was made of the submission by Novartis to increase the pack size restriction of diclofenac in solid oral dosage forms, containing 12.5 mg or less per dose, from 20 tablets or capsules to 40 tablets or capsules. This submission was based on updated safety data both globally, and within Australia and New Zealand. The committee rejected this application based on the following broad points:

(a) Larger pack sizes could lead to longer term usage, which could lead to more adverse effects.

(b) Concern about the potential for gastro-intestinal problems, hepatotoxicity and interactions with other medications

Purpose of current submission:

This application is seeking an increase in pack size limit of diclofenac in solid oral dosage forms, containing 12.5 mg or less per dose from pack sizes of 20 tablet or capsules to 40 dose units.

This application aims to specifically address the concerns raised by the Committee in December 2007 and to provide new data that supports the proposed re-classification.

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Overview of data in support of current submission:

Full details of the data that support the current submission are provided in Part B. Briefly, the data will demonstrate that:

(a) Diclofenac 12.5 mg is comparable in safety to ibuprofen 200 mg (currently Pharmacy Only Medicine with a pack size limitation of up to 100 dosage units when the recommended daily dose does not exceed 1200 mg, ie over 16 day's supply) [refer Section B, 3a and 3b].

(b) If a patient were to self-medicate with diclofenac continuously until the proposed 40-dosage unit pack is exhausted (equivalent to less than 7 days supply), data show that there are no increased safety concerns over the currently maximum pack size of 20 (equivalent to just over 3 days supply) [refer Section B, 3a] nor are there increased safety concerns compared to ibuprofen 200 mg.

(c) There is no data indicating that self-medicating patients would choose to medicate a single episode of pain for longer than is required for treatment of that pain (usually "a few days") [refer Section B, 4b and 4c].

(d) There are data indicating that the majority of patients will in fact follow dosage instructions on pack, rather than use an entire pack for the treatment of one episode of pain [refer Section B, 4b].

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9. Classification status in other countries

Below is the registration status of diclofenac potassium 12.5 mg tablets.

EU and EEA countries

EU & EEA Countries	Legal Status	Pack size
Denmark	OTC	40
Germany	OTC	30
Netherlands	OTC	24
Portugal	OTC	30

Other countries

Countries	Legal Status	Pack size
Mexico	OTC	40
South Africa	OTC (S2)	30
Venezuela	OTC	48

10. Extent of usage in NZ and elsewhere and dates of original consent to distribute

Voltaren Rapid 12.5 (TT50-6834) was given consent to distribute in New Zealand by Medsafe on 14 October 2004 as a pharmacy-only medicine.

Approximately 125,000 units of Voltaren Rapid 12.5 were sold in NZ in the previous 12 month period.

11. Labelling

Please refer to Appendix A for full labeling of Voltaren Rapid 12.5. No change is being made to the current labels apart from pack size descriptor. Please note that this labeling is consistent for packs of 10 and 20 tablets and is also intended for pack sizes up to 40 tablets.

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12. Proposed Warning Statements is applicable

Warning statements are as per current product labeling requirements, being:

- Keep out of reach of children
- Maximum 6 tablets in 24 hours
- Prolonged use could be harmful
- Do not exceed the stated dose
- Use only as directed
- If symptoms persist or worsen see your doctor
- Do not give to children under 14 years
- Contains lactose
- Do not take if the foil seal over tablets is broken
- Do not take if you have a stomach ulcer or other stomach disorders, impaired kidney function or heart failure.
- Do not take if you are allergic to diclofenac, aspirin or anti-inflammatory medicines
- Do not take if you are pregnant unless under medical advice
- Do not take during the last three months of pregnancy
- Do not take for more than a few days at a time, unless under medical advice
- Do not take if you have asthma, unless under medical advice
- Do not take with other medicines containing diclofenac, aspirin, other anti-inflammatory medicines, or other medicines you are taking regularly unless under medical advice.
- Store below 30°C.

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

Apart from a submission under Novartis Consumer Health Australasia (Ref TT50-8345a), we are unaware of any other diclofenac 12.5 mg oral dose form that would be affected by this change.

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PART B

1. Benefits to both Consumer and to the public expected from the proposed reclassification

The current classification pack size constraint (20 dosage units) for diclofenac 12.5 mg tablets and capsules restricts the consumer to purchase a new pack of Voltaren Rapid 12.5 for each bout of pain experienced. A pack of 20 tablets will last for approximately 3 days when used as directed (maximum of 6 tablets per 24 hour period). Certainly, 3 days is the accepted period for short-term treatment of self-limiting painful conditions.

However, comparable NSAIDs with similar safety profiles to diclofenac 12.5 mg (refer Section Part B, 3) such as ibuprofen 200 mg are currently available in larger pack sizes. Patients self-medicating with ibuprofen analgesics are hence provided with convenient access to treatment of up to 5 separate episodes of pain from the one purchase of a 100-dosage unit pack (based on 6 tablets per day for 3 days for each bout of pain). Labelling for ibuprofen tablets informs patients to use for only “a few days” at a time. As is seen in Appendix A, the proposed packaging artwork for 40-dosage unit packs of Votlaren Rapid 12.5 will reflect what is already considered adequate warnings for large pack sizes of ibuprofen.

Since patients self-medicating with diclofenac are required to re-purchase a new pack at each episode of pain (rather than reach for their chosen treatment via the convenience of their home supply) it is proposed in this submission that these patients are at a significant disadvantage when compared to patients using similar NSAIDs (with similar safety profiles) where each pack will last up to 5 episodes of pain.

We therefore believe that the benefits to consumers and to the public expected from the proposed change will provide equitable access to comparable NSAIDs for the short-term treatment of multiple episodes of pain.

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

Voltaren Rapid 12.5 is currently classified as a pharmacy-only medicine. There is no intention to modify the classification. As such, there is no impact on the diagnosis for the condition indicated as an outcome of this particular submission, and information submitted in the earlier re-classification application still holds.

3. Relevant comparative data for like comounds

The efficacy and safety of diclofenac 12.5mg has been previously evaluated by Medsafe in the New Medicines Application in 2004. The purpose of the current submission is to demonstrate that diclofenac 12.5mg has comparable safety to ibuprofen 200mg, and to hence demonstrate that there is no increased risk to public safety with the requested 40-pack of Voltaren Rapid 12.5.

In reviewing an earlier submission for a larger pack size of diclofenac 12.5mg, the Medicines Evaluation Committee outlined in the minutes of the December 2007 meeting concerns for "*the potential for gastro-intestinal problems, hepatoxoicity and interactions with other medicines".*

The current submission demonstrates that diclofenac 12.5mg has comparable safety to ibuprofen 200mg - an analgesic which, according to it's classification in New Zealand as both an unscheduled and a Pharmacy-only medicine, is already approved for sale to consumers from pharmacy in large pack sizes.

3a. Comparison of diclofenac potassium and ibuprofen over short term use

A meta-analysis has been published (Moore, 2007) which supports the contention that diclofenac 12.5 mg or 25 mg is just as effecitive as ibuprofen 200 mg or 400 mg in 'traditional' OTC indications such as acute lower back pain, tension-type headache, symptoms of cold and flu, and dysmenorrhoea.

In the meta-analysis, Table VIII (Page 181) showed the total adverse reaction rates in users of low-dose diclofenac (<75mg/day), ibuprofen (<1200mg/day) and placebo during short-term pain studies lasting 2-7 days (i.e. up to 40 tablets).

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Figure A: table VIII adapted from Moore (2007). Data on high-dose diclofenac has been removed as it is not relevant to the current submission on diclofenac 12.5mg.Frequency of adverse events (AEs) reported during short-term (<14d)multiple dose studies of diclofenac potassium (Diclo-K) vs ibuprofen (Ibu) and placebo.

Adverse event (frequency [%])	Low dose (≤7d)		
	Diclo-K ≤75mg (n = 610)	Ibu 1200mg (n = 523)	placebo (n = 599)
Any AE	13.9	13.0	10.5
Blood/lymphatic	0.2	0.2	0
Body as a whole	2.3	0.8	1.0
Cardiovascular	0.3	0.2	0.3
Gastrointestinal	6.7	6.5	4.2
Infections	0	0	0.2
Metabolic/ nutritional	0	0	0
Musculoskeletal	1.1	1.1	0.7
Nervous system	4.4	2.7	3.8
Respiratory system	1.0	1.5	1.3
Skin/appendages	1.0	1.0	0.3
Special senses	0.8	0.4	0.2
Urogenital system	0.8	0.6	0.7

In patients taking multiple doses of diclofenac (< 75mg/day) for up to 7 days, adverse events were most commonly related to GI and nervous system and were similar for patients taking multiple doses of ibuprofen (< 1200mg per day) or placebo for up to 7 days. The highest frequency of those experiencing a severe adverse event was actually seen in the placebo group in the short-term multiple dose studies. No serious adverse event or reaction occurred with low- dose diclofenac in any single-dose or short-term multiple dose trials up to 7 days duration. The current submission for a 40-tablet pack of diclofenac 12.5mg could allow for at most six and a half days of consecutive treatment. As the data above demonstration;

1. diclofenac potassium 12.5 mg has a similar safety profile to ibuprofen 200 mg over 7 days treatment

2. diclofenac potassium 12.5 mg taken over 7 days does not result in any significant increased risk of adverse events compared to placebo or ibuprofen 200 mg.

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3b. Comparison of diclofenac potassium and ibuprofen over longer term use.

To further demonstrate that diclofenac 12.5 mg (75mg maximum daily dose) has a similar safety profile to ibuprofen 200 mg, longer term studies (up to 30 continuous days for the treatment of osteoarthritis) show that the frequency of adverse events is no different to that of ibuprofen (1200mg max daily dose). This data is demonstrated in Figure B. Whilst it is acknowledged that the treatment of osteoarthritis is niether an OTC indication nor an OTC duration of treatment, the purpose of this data is to demonstrate the similarity in safety profiles between diclofenac and ibuprofen. Once again, the argument is made that if ibuprofen is considered safe to offer consumers pack sizes of up to 100 dosage units (within the pharmacy setting) than it should follow that diclofenac also be made available to consumers who choose to self medicate with an alternative NSAID to ibuprofen, as there is no evidence of increased risk.

Figure B: table IX adapted from Moore (2007). Data on high-dose diclofenac has been removed as it is not relevant to the current submission on diclofenac 12.5mg.Frequency of adverse events (AEs) reported in a 3 month study of diclofenac potassium vs low dose ibuprofen and placebo in patients with osteoarthritis.

Table IX. Frequency of adverse events (AEs) reported in a 3-month study of diclofenac potassium vs low-dose ibuprofen and placebo in patients with osteoarthritis[65]

Adverse event (frequency [%])	Diclofenac potassium ≤75mg (n = 687)	Ibuprofen 1200mg (n = 350)	Diclofenac potassium 150mg (n = 184)
Any AE	55	57.1	63.6
Blood/lymphatic	0.7	0.3	0.5
Body as a whole	13.0	15.4	16.3
Cardiovascular	2.9	3.1	2.2
Gastrointestinal	23.4	25.1	31.5
Laboratory abnormality	0.1	0.6	0.5
Metabolic/nutritional	0.3	0.6	0
Musculoskeletal	8.4	5.7	12.0
Nervous system	14.0	14.0	17.4
Respiratory system	16.4	16.9	18.5
Skin/appendages	5.8	8.3	1.6
Special senses	3.6	2.9	3.3
Urogenital system	5.2	8.0	7.6

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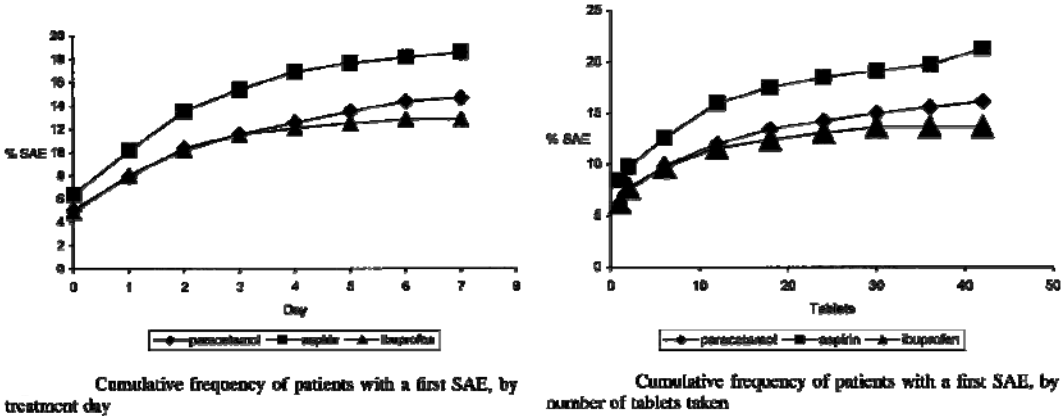
3c. Frequency of Adverse events over time: Short term use

Now that it has been established that the safety profile of low dose diclofenac and ibuprofen are similar, an analysis of the impact and timing of when any AEs are likely to occur if a consumer were to consume the entire 40 tablets of Voltaren Rapid 12.5 over 7 days is made. In answering the first half of this question, it is shown in Figure A that the frequency of AEs after consuming diclofenac (75 mg maximum daily dosage) is similar to that of placebo or ibuprofen (1200mg maximum daily dosage).

In answering the second half of this question, we refer to comparable NSAIDs. Whilst the Review article (Moore 2007) did not provide a breakdown of the events per study day, considering the pharmacological similarity of diclofenac to ibuprofen in terms of efficacy, and the similar total number of AE's in the clinical trials cited, it can be concluded that the adverse event rates with diclofenac or ibuprofen in these studies would follow the same timeframes as for ibuprofen (and aspirin and paracetamol) i.e. most of the adverse events occur early in the treatment (see figure C below taken from the PAIN study as referred to in Moore *et al* 1999).

Event rates did not change much between 20 and 40 tablets, or from the 3rd to the 7th day.



Cumulative frequency of patients with a first SAE, by treatment day

Cumulative frequency of patients with a first SAE, by number of tablets taken

Figure C, Time course of adverse event rates in the PAIN study, taken from Moore et al 1999.

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3d. Recent NSAID Review by Regulatory Authority

Sponsors of both prescription and OTC NSAID-containing products were invited by the TGA to submit all available safety data both published and 'in-house' to establish the safety profile of their respective NSAID in Australia during 2005. The review of NSAIDs was to asses their cardiovascular, gastrointestinal, and cuteneous safety, and the report was subsequently submitted to both the Australian Drug Evaluation Committee (ADEC) the Medicines Evaluation Committee (MEC) in 2006. The MEC concluded that in general, all NSAIDs reviewed at OTC doses were considered not to pose any increase in risk of serious adverse events, but however, all may pose some additional risks when used over long periods of time. This conclusion was not specific to any one NSAID. The outcome of this recent NSAID review by a regulatory authority of all available data confirms the position of the current submission that the safety profile of low dose diclofenac is similar to that of other NSAIDs such as ibuprofen 200 mg and does not warrant exceptional constraints to be placed on it.

3e. Summary

The above data demonstrates comparable AE rates between multiple dosing with diclofenac (75mg per day), ibuprofen (1200mg per day) or placebo, thus demonstrating that there is no increased risk of gastro-intestinal problems or hepetotoxicity with diclofenac.

The data demonstrate that the 40-dosage unit pack of diclofenac would not pose any increased safety risk (over an above ibuprofen or placebo) should the patient consume an entire pack continuously (up to seven consecutive days).

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4. Local data or special considerations relating to New Zealand

4a. World Wide Safety Data

Diclofenac products have been marketed since 1974, with more than one billion patients treated. Safety data are available from post-marketing surveillance studies, spontaneous ADR reports and pharmacoepidemiological studies (mainly from prescription products with high doses of diclofenac-K or diclofenac-Na). Attached in Appendix B is the latest Periodic Safety Update Report (PSUR) for diclofenac (both OTC and prescription).

4b. Local Consumer Research

Recent consumer research conducted in Australia by TNS Consultants has shown that consumers take OTC analgesics predominantly for conditions which are readily recognised and suitable for self-medication regardless of whether the analgesia was supplied in a small (10-12 tablets) or large (40-48 tablets) pack size. Moreover, consumers stated that the provision of larger pack sizes of OTC analgesia confered increased convenience ("available on-hand whenever I experience pain") and good value for money. Clearly, there is consumer demand for the convenience and value of larger pack sizes of OTC analgesia.

The study (refer to Appendix C for full details of study) found that consumers of OTC analgesics are compliant in reading the on-pack dosage and administration instructions. Regardless of whether the consumer was exposed to packs of low-dose diclofenac in either small or larger (10 or 40-tablets) pack sizes, the majority of consumers (85%) stated that they would use the medicine for 3 days or less.

The conclusions from the market research were that there was no significant difference in usage intention (i.e. smaller pack size versus larger pack size) which suggests that an increased pack size would not result in higher consumption levels or increased dosage for either diclofenac or ibuprofen brands

In addition to adhering to the maximum recommended duration of treatment, the consumer research demonstrated that when exposed to a larger pack of low-dose diclofenac, consumers would not exceed the recommended maximum number of tablets in any one day. The study found that only 3% of consumers would exceed the maximum daily intake of diclofenac tablets – however it should be pointed out that this figure was the same regardless of pack size the consumer was exposed to.

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Overall, the study showed:

* an increased pack size has the potential to fulfil consumer needs for household use, availability for specific pain episodes and value for money

* there were no significant differences in potential usage of smaller vs larger pack sizes, suggesting that an increased pack size would not result in higher consumption

* The study provided no evidence that a larger pack size would result in increased dosage for either brand (Voltaren Rapid or Nurofen)

* There were similar perceived dosage frequency use across all pack variants

In conclusion, it is considered that consumers are likely to be compliant with dosage, and frequency of dosage as well as duration of use irrespective of the pack size.

4c. Global Research in the Community and "clinical" setting

In its deliberations in 2007, the Committee concluded that "*"larger pack sizes could lead to longer periods of use…."*.

According to Professor Nicholas Moore (Department of Pharmacology, University Victor Segalen, Bordeau Cedex, France), who is a renowned epidemiologist, there is no indication from existing information including post-market surveillance studies concerning OTC diclofenac or other analgesics that the availability of a larger pack size changes the usage patterns for the self-medication of common pain, which is driven by the nature of the pain and the drug's efficacy, not by its availability. The studies discussed below show that specific duration of treatment is dependent on the type of pain. For instance, dental pain, dysmenorrhoea or a headache usually lasts less than "a few days", whereas acute lower back pain and acute tendonitis or other minor trauma may last "a few days" or, upon advice from a healthcare professional, could last a little more.

(i) <u>'Clinical' Evidence suggesting consumers will not consume entire packs of analgesics</u>

In the PAIN study (Moore et al 1999) the mean number of tablets (paracetamol, ibuprofen or aspirin) used was 20, despite patients being provided with 42 tablets for 7 days treatment with a recommended dose of 6 tablets per day. This would strongly support the view that even when given sufficient tablets for 7 days use, patients will use less than the full allowed dose daily after the first day or so.

Should this submission be successful, the benefit for patients using diclofenac will be that they will have the convenience of a pack size which allows treatment of multiple episodes of pain, so that treatment can commence immediately rather than having to suffer from their pain until they have purchased a new pack. This will also mean that patients using diclofenac are no longer disadvantaged versus those patients self-medicating with similar NSAID's such as ibuprofen that are available in larger pack sizes.

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(ii) Evidence from the "community setting" suggesting consumers will not consume entire packs of analgesics

The results from the PAIN study in relation to tablet usage were corroborated by data from a Norwegian OTC study in pharmacy (Hasford et al 2004). This study was a prospective, non-interventional cohort study with participants recruited from consumers presenting at 62 community based pharmacies in Norway 2002-2003. The design of this cohort study was to ensure that the real conditions of use ('community use') could be assessed.

In this study, the pack instructions for diclofenac were the same as currently registered dosage instructions for low-dose diclofenac (Voltaren Rapid 12.5). That is, an initial dose of 1-2 tablets followed by 1 or 2 tablets every 4-6 hours as needed with a maximum of 6 tablets/day for maximum 3 days.

More than 90% of the patients did not take more than 2 tablets at any dosing time or more than 6 tablets in a given day. In this community setting, it was noted that only a minority of patients took diclofenac for more than 3 days. As demonstrated in Section 3 of this submission, there is no increased risk of adverse event when diclofenac 12.5 mg is taken over 7 days (or even up to 30 days) compared to placebo or ibuprofen 200 mg.

4d. Summary

The data in this section would suggest that the usage pattern of analgesia for common mild to moderate pain indications is according to the pain type and relief experienced rather than continuing to take an entire packet until the pack is empty. The benefit to the patient is the possibility to have multiple episodes of pain treated readily from the one pack of medication.

5. Interactions with other medicines

Please refer to to previous MCC Application relating to drug interactions as the information remains valid and has not changed.

In its deliberations in 2007, the Committee raised a concern regarding "*the potential for gastro-intestinal problems, hepatoxoicity and interactions with other medicines".* Whilst the potential for gastro-intestinal problems and hepatotoxicity have been addressed in Section 3 above, it is argued that there is no scientific, clinical or theoretical basis for increased potential of interactions with other medicines due to increasing the pack size of Voltaren Rapid 12.5 from 20 to 40 tablets when the consumer follows the pack directions. And as outlined in Section 4b above, the majority of consumers adhere to the correct dosage regime outlined on the pack labeling regardless of pack size.

Information relating to interactions may also be located in the package leaflet (refer Appendix A).

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6. Contraindications

The current submission proposes no change to the contraindications for diclofenac 12.5mg. Please refer to the leaflet (Appendix A) for further details on existing contraindications.

7. Possible Resistance

As diclofenac 12.5 mg is for short term use in self-limiting pain conditions, resistance is not believed to be an issue.

8. Adverse events: Nature, frequency etc

Diclofenac products have been marketed since 1974, with more than one billion patients treated. For the purposes of this submission, we enclose a copy of the latest Periodic Safety Update Report (PSUR) in Appendix B which was released 16 November 2006. Please note that this report encompasses safety information for various dosage forms of the Voltaren and Cataflam products marketed worldwide.

As discussed previously in Section 3, the potential hazards for low-dose diclofenac are no different than those for low-dose ibuprofen. In the Moore (2007) review, no serious adverse events occurred with either low- or high-dose diclofenac in any single dose or short-term multiple dose trial up to 14 days duration. Likewise in the Hasford (2004) observational study in a pharmacy setting adverse events were minimal with the most commonly reported AEs being abdominal pain or discomfort, headache and nausea (consistent with the Product Information for Voltaren Rapid 12.5).

The availability of a pack of up to 40 tablets with a daily dose of <75 mg would provide less than 7 days continuous treatment, however as shown in the Moore (2007) and Hasford (2004) papers most patients do only take OTC analgesics for a ‘few days’ to treat their pain as the indication normally dictates the duration of treatment.

Reports for diclofenac potassium since its launch in the 1980’s are largely associated with prescription use, as Voltaren Rapid 50 (diclofenac potassium 50 mg) remains classified as a prescription only medicine while Voltaren Rapid 25 is now a restricted medicine. Diclofenac potassium products have been associated with 64 reports (a total of 201 reactions) over their period of availability in Australia (up to April 2007). This report was submitted previously to the Committee for the 38th Meeting. Please note that this report encompassed all products (including generics), all classifications and strengths and are not just limited to the 12.5 mg dose.

Note that Voltaren Rapid 12.5 has been available in New Zealand since 2006.

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9. Potential for abuse or misuse

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

Five reports of drug abuse were received during the PSUR 6 review period (Appendix B) and do not involve the non-prescription diclofenac dosage forms. The conclusion from the PSUR 6 is that the reports presented do not provide strong evidence indicating that diclofenac would induce drug dependency. Directions are provided that the dose should be individually adjusted and that the lowest effective dose should be given for the shortest possible duration. Warnings on the product labelling also state that concomitant use of Voltaren with systemic NSAIDs should be avoided.

Finally, many concerns relating to misuse are addressed in Sections 3 and 4 of the current submission.

Conclusions

The data collected on patient behavior from the studies discussed above show that overall, the vast majority of patients do not exceed the recommended doses and tend to only use the drug until their painful episode abates. Moreover, in the event that a patient not follow the dosage instructions, there are data that suggests that these patients would not be exposed to any increased risk versus those using currently available ibuprofen or even placebo (Moore, 2007; Figure 2).

The risks of a 40 tablet pack of diclofenac versus a 20 tablet pack (just over 6 days vs 3 days) would be minimal given that

1. AE rates are similar between diclofenac (75mg per day), ibuprofen (1200mg per day) and placebo for up to 7 days
2. AE's for similar NSAIDS (ibuprofen) mostly occur in the first few days of medication, meaning that risks are not substantially increased if a patient were to treat for more than a few days
3. the majority of patients only take sufficient medication according to the nature of the pain and the efficacy of the product and do not appear to use more medication simply because it is available
4. the issue of patient convenience in treating their episode of pain should not be underestimated

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The validity of these conclusions can be drawn from the similarity of the patient populations between the PAIN study and the Norwegian study - the first being a double blind randomised study and the latter a pharmacy study of OTC buyer behaviours. The age of the subjects were the same, predominantly female (respectively 58% versus 74%) with 49% and 50.4% using concomitant medication.

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