

# Submission for Reclassification of Aspirin for Prevention of Heart Disease

## Part A

### 1. International Non-proprietary Name (or British Approved Name or US Adopted Name) of the medicine

Aspirin

### 2. Proprietary name(s)

Aspirin 75mg, 100mg or 150mg is marketed in NZ under a variety of brand names such as Cartia®, Heartcare Aspirin®, Cardiprin® and Aspec®.

### 3. Name of company/organisation/individual requesting reclassification

Pharmacybrands Ltd, the parent company for Life, Unichem, Amcal and Care Pharmacies in New Zealand.

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

Solid dose preparations containing 150mg or less of aspirin

### 5. Pack size and other qualifications

No pack size qualifications

### 6. Indications for which change is sought

For the inhibition of blood clotting and to reduce the risk of heart attack and stroke (and similar indications)

### 7. Present classification of medicine

Ingredient	Conditions (if any)	Classification
Aspirin	except when specified in the First Schedule to the Medicines Regulations 1984	General Sale
Aspirin	in slow release forms; in enteric coated forms containing more than 300 milligrams per dose form; except when specified elsewhere in this Schedule	Restricted
Aspirin	for injection; when combined with caffeine, paracetamol or salicylamide	Prescription

## 8. Classification sought

### EITHER

Ingredient	Conditions (if any)	Classification
Aspirin	except when specified in the First Schedule to the Medicines Regulations 1984	General Sale
Aspirin	<u>when indicated for prevention of embolic phenomena associated with coronary artery disease, stroke and transient ischemic attacks; except when specified elsewhere in this Schedule</u>	Pharmacy-Only Medicine
Aspirin	in slow release forms; in enteric coated forms containing more than 300 milligrams per dose form; except when specified elsewhere in this Schedule	Restricted
Aspirin	for injection; when combined with caffeine, paracetamol or salicylamide	Prescription

### OR

Ingredient	Conditions (if any)	Classification
Aspirin	except when specified in the First Schedule to the Medicines Regulations 1984	General Sale
Aspirin	<u>In doses containing 150mg or less of aspirin</u>	Pharmacy-Only Medicine
Aspirin	in slow release forms; in enteric coated forms containing more than 300 milligrams per dose form; except when specified elsewhere in this Schedule	Restricted
Aspirin	for injection; when combined with caffeine, paracetamol or salicylamide	Prescription

## 9. Classification status in other countries (especially Australia, UK, USA, Canada)

Aspirin scheduling in Australia will be currently harmonised with NZ (i.e. unscheduled/general sales). The USA will have aspirin as a general sales medicine as they do not have the facility for intermediate pharmacy schedules.

In Canada aspirin is unscheduled in strengths of 325mg and 500mg per dosage unit, and schedule III (pharmacy-only) in strengths of 81mg per dosage unit and 650mg or

greater per dosage unit and in rectal preparations containing more than 150mg per dosage unit.<sup>1</sup>

In the UK, low dose aspirin appears to be unscheduled. However, it is not licensed for primary prevention of cardiovascular disease in the UK.<sup>2</sup>

#### **10. Extent of usage in New Zealand and elsewhere (e.g. sales volumes) and dates of original consent to distribute**

This information is not readily available to the submitter. These medicines have been available with this indication for some years now, and have high usage, nowadays pharmacist feedback indicates this is predominantly on prescription. Low dose aspirin has been marketed for some years now.

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

The only change to the current labelling (an example is supplied in Appendix 1) would be the addition of the words Pharmacy-Only Medicine.

#### **12. Proposed warning statements if applicable**

One example of the warning statements on the labelling is attached. It may be beneficial to include a recommendation that people seek advice from a doctor or pharmacist about whether they are likely to benefit from low dose aspirin.

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

Examples of brands are in (2) above. There may be other low dose aspirin products on the market in NZ also.

## Part B

### **1. A statement of the benefits to both the consumer and to the public expected from the proposed change**

Up-scheduling low dose aspirin for prevention of heart disease and stroke is likely to reduce inappropriate levels of risk in people who are using this for primary prevention or with a cardiovascular risk of less than 15% in 5 years when the risk-benefit equation does not recommend this usage (see below for evidence). Upscheduling also allows a triage by pharmacists such that people with potentially greater risk can be referred to a General Practitioner (GP) for further assessment and appropriate treatment, and/or be encouraged to make lifestyle changes such as stopping smoking. A healthcare professional is available during all opening hours in a community pharmacy in NZ, so is always on hand to advise if necessary, looking both at the individual's risk for a cardiovascular event and whether they are at increased risk of a bleed (for example are taking NSAIDs or warfarin, or have a history of previous gastro-intestinal bleeding or peptic ulcer).

There is already awareness amongst at least some community pharmacists of the BPAC advice<sup>3</sup> (for example through discussion this year on the Pharmacy Chat group subscribed to by over 600 NZ-registered pharmacists). However, upscheduling of this medicine would be followed by a concerted effort to ensure pharmacists are aware of the latest (2009) cardiovascular guidelines from the NZ Guidelines Group<sup>4</sup> and the BPAC document discussed below, as well as the website "know your numbers" from the Heart Foundation ([www.knowyournumbers.co.nz](http://www.knowyournumbers.co.nz)). Furthermore, pharmacists would be encouraged to prompt pharmacy assistants to ask people purchasing low dose aspirin if they have recently spoken to a pharmacist or doctor about their aspirin use and referring to the pharmacist for advice if not.

Financially consumers may be better off – if an analysis by the pharmacist suggests that the person is unlikely to benefit much from low dose aspirin, they will save the cost of future purchases of the product. The greater benefit is in the advisory role of the pharmacist which is likely to result in discussion of other lifestyle advice (particularly including smoking cessation if relevant) and referrals of people at risk who need appropriate further assessment and likely treatment. This is primary care screening at no cost to the government and with convenience for the consumer.

#### **The Evidence: Role of aspirin therapy in primary prevention of heart disease and stroke**

Recent papers have changed the view of aspirin therapy in primary prevention of heart disease and stroke.<sup>3</sup> At the end of 2009, the Best Practice Advocacy Centre in New Zealand summarised how this should change practice in primary prevention in practice in NZ as follows:<sup>3</sup>

"Primary prevention with aspirin therapy does not now appear justified in the majority of people with cardiovascular risk factors given the uncertain net absolute benefits."

BPAC went on further to say: “Patients without clinical CVD who have commenced themselves on over-the-counter aspirin, are often unaware of the risk of bleeding and should be advised to discontinue treatment.”

The final sentence clearly indicates that self-treatment by an individual over-the-counter without health professional advice is not appropriate.

BPAC is not alone in this regard. The British Medical Journal in April 2010 published an editorial titled “Don’t use aspirin for primary prevention of cardiovascular disease”. This article was published as a “Change Page” the intention of which is to “...alert clinicians to the immediate need for a change in practice to make it consistent with current evidence.” The authors noted that although low dose aspirin is unlicensed for primary prevention in the UK, use in primary prevention including over-the-counter usage may be widespread, and that therapy should be reviewed.<sup>2</sup>

Additionally the Scottish Intercollegiate Guidelines Network guideline on management of diabetes states that “low-dose aspirin is not recommended for primary prevention of vascular disease in patients with diabetes.”<sup>5</sup>

There have been multiple papers behind these recommendations. One in particular, a Lancet paper in 2009 was a collaborative meta-analysis between principal investigators of all large trials of primary prevention with aspirin using individual participant data.<sup>6</sup> A meta-analysis of 16 secondary prevention trials of aspirin (again using individual participant data) was used for comparative purposes. In total data from 95,000 participants was included. All trials included were randomised to aspirin compared with no aspirin, with other antiplatelet agents not used.

The authors found that the absolute reduction in events was considerably lower in primary prevention versus secondary prevention and was partly offset by increase in major gastro-intestinal and extracranial bleeds. In primary prevention results indicate that for 10,000 patients taking aspirin 51 would have serious vascular events in a year versus 57 without aspirin (net benefit of 6 per 10,000); 10 of the aspirin group would have major gastro-intestinal and extracranial bleeds versus 7 in the control group ( $p < 0.0001$ ). In comparison in secondary prevention for 10,000 patients taking aspirin 670 would have serious vascular events in the aspirin group versus 820 in the control group, a net benefit of 150 people per 10,000 treated (or 1.5 per 100) with a similar effect on major bleeds as seen in primary prevention. The authors concluded that their results “...do not seem to justify general guidelines advocating the routine use of aspirin in all apparently healthy individuals above a moderate level of risk of coronary heart disease.”

Also published in 2009, a BMJ paper presented a meta-analysis of trials looking at people with diabetes and no pre-existing cardiovascular disease, with a total of 10,117 participants.<sup>7</sup> There was no statistically significant reduction in the risk of major cardiovascular events nor in the risk of bleeding. The authors concluded that they “...cannot recommend using aspirin in the primary prevention of cardiovascular events in all patients with diabetes without additional evidence...”

There is a small discrepancy between the references above that state insufficient benefit in primary prevention and the NZ Cardiovascular Guidelines<sup>4</sup> which still

recommend usage in people with >15% cardiovascular disease risk. This has been usefully discussed in a recent paper which used modelling by risk category and age group to find that aspirin benefit outweighs harms in people with >15% cardiovascular disease risk under 80 years of age.<sup>8</sup> From 80 years of age risk probably outweighs harm.

Thus, a person purchasing aspirin in a supermarket is highly unlikely to understand the likely benefits versus harms of daily low dose aspirin for them. Of particular interest,

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

Self-diagnosis of a need for low dose aspirin for prevention of cardiovascular disease and stroke is probably beyond the ability of most consumers. Pharmacists are informed on risk factors (both for heart disease, and for aspirin itself) and understand primary prevention and secondary prevention.

Up-scheduling of this product would be associated with release of information to pharmacists and pharmacy assistants – through Pharmacy Brands Ltd and through trade journals and/or pharmacy organisations. This would assist pharmacists to recommend these products correctly, know when to refer for further treatment and encourage pharmacy assistants to question patients about whether their doctor or a pharmacist has recommended this product to them recently, and if not refer to the pharmacist. Additionally, pharmacy assistants are able to ask about allergy, asthma, gastro-intestinal disorders and other medicines and refer to the pharmacist as appropriate.

## **3. Relevant comparative data for like compounds**

There are no other registered medicines currently available in NZ for prevention of cardiovascular disease and stroke that are available through the supermarket.

It is uncommon for registered medicines to be available without prescription for preventative purposes. Folic acid for prevention of neural tube defects in a dose of 800 micrograms per day is a pharmacy-only medicine allowing pharmacist or pharmacy assistant advice. Simvastatin 10mg is available in the UK as a pharmacy-only medicine but in NZ is a prescription medicine.

## **4. Local data or special considerations relating to New Zealand**

There are no special considerations relating to New Zealand. Pharmacies are very accessible, with over 900 community pharmacies throughout the country, many of which are open at least six days per week. This allows more than adequate availability of low dose aspirin.

## **5. Interactions with other medicines**

One of the most important interactions is that of aspirin and warfarin. The addition of aspirin to warfarin has been estimated to increase risk of major bleed by 10-20/1000 treated per year, and death by 1-2 people per 1000 treated per year.<sup>9</sup> While sometimes these two medicines are deliberately used together for an individual, a warfarin patient should not use aspirin without advice from their cardiologist or GP. Screening by a pharmacist would recommend a referral where an individual was found to be on warfarin, potentially saving a serious hospitalisation and/or a life.

Some NSAIDs (e.g. ibuprofen) interact with low dose aspirin reducing the inhibition of thromboxane production.<sup>10</sup>

Use of corticosteroids or NSAIDs with aspirin increases the risk of gastric irritation and bleeding.<sup>11</sup>

## **6. Contraindications**

Contraindications include sensitivity to salicylates.<sup>11</sup> There is 90% cross-sensitivity across aspirin and NSAIDs, so avoidance of aspirin in hypersensitivity to an NSAID is recommended.

### **Precautions**

Caution is advised in patients prone to dyspepsia or with a lesion of the gastric mucosa, and patients with asthma or allergic disorders.<sup>11</sup> Aspirin should be stopped several days before scheduled surgery.

These contraindications and precautions for use suggests that healthcare professional input, particularly when initiating treatment, is appropriate for these medicines, particularly given the labelling (attached) of at least one of the products in the market only indicates that the product "...is not recommended for children, people allergic to salicylates or those taking anticoagulants".

## **7. Possible resistance**

Not applicable.

## **8. Adverse events - nature, frequency etc.**

The most concerning adverse events with low-dose aspirin are hypersensitivity (which can be fatal) and major bleeding including gastro-intestinal bleeding and extracranial bleeding.<sup>6, 11</sup> While major bleeding is rare, it reduces the overall benefit of low dose aspirin in primary prevention of cardiovascular disease to a level at which it is no longer recommended for use in this instance<sup>2</sup>, except where cardiovascular disease risk is above 15% in the next 5 years and the person is under 80 years of age.

Approximately a fifth of adult asthmatics have aspirin-induced asthma using provocation testing, and 2.5% of non-asthmatics report having aspirin-induced asthma.<sup>11</sup> The prevalence increases with age.

Rod Jackson, Professor of Epidemiology from the University of Auckland, was happy to be quoted for the purposes of this submission as saying “aspirin has the most serious side effect profile of the commonly used CVD risk management drugs”. The take-home message for consumers from the availability in supermarkets is likely to be that low-dose aspirin is safe for anyone to use for self-management.

The General Sales Category is not appropriate for a medicine with this adverse event profile for which consumers would have difficulty in assessing the likely benefit to themselves.

## 9. Potential for abuse or misuse.

Abuse is not expected to occur with low dose aspirin. The concern is the inability of consumers to appropriately decide whether low dose aspirin is appropriate for them or not without healthcare professional input, such as a pharmacist.

## Summary

In summary, recent publications have indicated the profile of aspirin is such that the risk-benefit for individuals needs assistance from a healthcare professional, such as a pharmacist or GP. While most aspirin is nowadays prescribed, given the funded status of low dose aspirin, the availability of aspirin in outlets that do not have a health professional available, such as supermarkets, is not in the best interests of consumers. Pharmacists should be used to triage those consumers who need further checks and advice from their GP, as well as dissuade consumers for whom low dose aspirin is unlikely to have a positive benefit-risk equation. This can be done through rescheduling low-dose aspirin for prevention of cardiovascular disease to a pharmacy-only medicine.

## References

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