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Dr Jane Cook
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Dear Dr Cook,

**Review of Cardiovascular Safety of Non-steroidal Anti-inflammatory Drugs
and Safety Review of Diclofenac**

ASMI (Australian Self Medication Industry) appreciates the opportunity to provide public comment in relation to The [Review of cardiovascular safety of non-steroidal anti-inflammatory drugs](#) and [Safety review of diclofenac](#) including the TGA's overall conclusions and four alternative options proposed to address the risks associated with the use of OTC non-steroidal anti-inflammatory drugs (NSAIDs) available in Australia.

ASMI is the peak body representing companies involved in the manufacture and distribution of consumer healthcare products (non-prescription medicines) in Australia. ASMI also represents related businesses providing support services to manufacturers, including advertising, public relations, legal, statistical and regulatory consultants.

ASMI is committed to expanding and promoting Quality Use of Medicines (QUM), which is central to the National Medicines Policy. Its goal is to make the best possible use of medicines by:

- Selecting management options wisely
- Choosing suitable medicines if a medicine is considered necessary
- Using medicines safely and effectively.

Mechanisms and initiatives that are supported by ASMI that contribute to QUM include:

- Development of criteria for consumer-focused labelling,
- Provision of information and education, in partnership with other key stakeholders
- Setting standards for promotional activities via the ASMI Code of Practice and participation in the co-regulatory arrangements for promotion of OTC medicines.

QUM requires a partnership approach, a close collaboration between consumers, health professionals and other relevant stakeholders in a consultative manner.

ASMI's response to this consultation is primarily focussed on the recommendations for OTC non-steroidal anti-inflammatory medicines.

The following is a summary of ASMI’s response to the options proposed to address the identified potential risks for OTC NSAIDs when not used according to the labelled instructions.

Oral dose OTC medicines

- For oral dose OTC medicines we support Option 4 – a combination of updated label information complemented by communication activities to raise awareness and educate health professionals and consumers.
- ASMI agree with the reviewer’s conclusion that *“Based on the current evidence, there are no major changes suggested to the availability and warnings on labels for OTC diclofenac, ibuprofen and naproxen. These drugs provide effective pain relief when used according to the label at recommended doses for short durations”*
- ASMI believe that with appropriate labelling statements and consumer awareness activities for OTC oral dose NSAIDs, the level of current consumer access to these medicines remains appropriate.
- ASMI does not support mandatory CMI as package inserts. ASMI advocates the availability of the necessary advisory statements on the label to inform consumers at the point of purchase to support appropriate selection.
- We have assessed recent updates to labelling statements on OTC NSAIDs in other comparable jurisdictions and have observed there is opportunity for harmonised labelling approaches to address cardiovascular (CV) risk following long term continuous or excessive use in contravention of existing label instructions and warnings. Wherever possible the imposition of uniquely Australian requirements should be avoided.
- We propose that labelling statements should be written in consumer-friendly language and should be action-oriented. (see [Labelling statement proposals](#))
- Getting the labelling statements right and having the appropriate statements to inform the purchase decision available on the carton (or primary pack) is critical. Therefore, regardless of the mechanism to impose the statements, either via the Required Advisory Statements for Medicine Labels (RASML) process or a Section 28 letter, the first step should be a RASML consultation. (see [Implementation Mechanism Options for Labelling Updates](#))
- ASMI support increasing consumer awareness of the importance of reading the medicine label, heeding warning statements and adhering to the instructions for use of all non-prescription medicines.
- We advise the importance of supporting the introduction of the new CV risk label warnings with communication materials to create broad awareness. A range of materials will be needed both to:
 - i. prepare and brief health professionals in readiness to inform and counsel consumers.
 - ii. inform consumers of the label changes, advise what to do, where to get more information generally and who to talk to for specific advice.
- ASMI recommend a collaborative approach in the development of the awareness materials as this is critical to ensure the appropriateness of communications, consistency of interpretation, avoidance of confusion and to maximize the reach and benefit of educational initiatives. ASMI would welcome the opportunity to be involved in this initiative. (see [Communication - Awareness and Education Initiatives](#))

Topical dose OTC medicines

- For OTC topical diclofenac (and all OTC topical NSAIDs) Option 1 of making no change to labels, nor any communication to awareness to health professionals and consumers, is the only viable option. We believe there is no basis to mitigate a theoretical risk for which there is no safety signal, either via labelling statements or awareness activities or more restrictive scheduling.

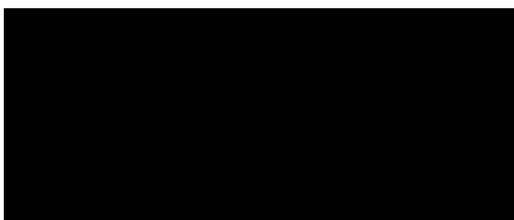
Implementation and next steps

- ASMI’s recommended option for OTC oral dose NSAIDs, Option 4, would require a transition timeframe for implementation on label of 12 months as a minimum.
- The consultation period time has been insufficient for ASMI and our members to consider the cost and timeframe implications of each combination of sub-options within the regulatory option. We therefore advise further detailed assessment would be required prior to implementation of other regulatory options.
- Given the number of pathways to implementation and possible next steps, ASMI request a clear statement of the outcomes of this consultation and an outline of the pathway for implementation prior to implementation commencing. (see [Next Steps and Transition Considerations](#))

The detail of ASMI’s consideration of the consultation follows.

We remain committed to work with the TGA and other key stakeholders to assist in the development of labelling statements and communication strategies to ensure the most appropriate approach to address the outcomes of these safety reviews and ensure the effective implementation of those approaches.

Yours sincerely



1. *The Conclusions and Recommendations of the Reviews*

ASMI have noted the recommendations arising from both the *Review of cardiovascular safety of non-steroidal anti-inflammatory drugs*, the subsequent *Safety review of diclofenac* and the *Summary and issues document* of the two reviews. ASMI found the last document somewhat confusing. Its purpose was to summarise the recommendations of the two reviews, provide relevant excerpts of the ACSOM advice to the TGA, and present the TGA's overall conclusions and the recommended options to mitigate the risks identified in the reviews. However, it lacked a clear set of statements of the final conclusions of the completed process, along with an explanation why these might differ from those of the review reports. Instead the conclusion appeared to merge the outcomes of the two reviews broadly back to NSAIDs, overlooking some recommendations altogether and without addressing the different scopes of the two reviews.

These things in turn, created ambiguity around the scope of the options in particular options 3 and 4. Of particular concern was the mis-match between the conclusions of the *Review of cardiovascular safety of non-steroidal anti-inflammatory drugs* in relation to OTC medicines and the options that were presented in the *Summary and issues document*, in particular Options 3 and 4.

In reviewing and assessing this consultation ASMI have been guided by the principles of:

- Quality Use of Medicines,
- Appropriate access to medicines,
- Self Care – the empowerment of consumers to actively participate in their health management,
- Harmonisation with comparable jurisdictions, and
- Minimum Effective Regulation

a. *Summary and Assessment of Options to address the Review of cardiovascular safety of non-steroidal anti-inflammatory drugs*

ASMI noted that the scope of this review was with regard to systemic adverse cardiovascular effects of NSAIDs via oral or rectal delivery forms.

ASMI's assessment of the options is as follows:

- Option 1 of maintaining status quo is not a viable option for OTC oral NSAID use.
- Option 2 of no changes to labelling and no changes to scheduling and instead using existing communication channels to raise awareness and educate health professionals on the risks associated with the use of NSAIDs would clearly be limited in its ability to reach consumers of OTC oral NSAID medicines and the likely effectiveness temporary in nature.
- Option 3 (a) of requiring sponsors of all OTC oral NSAIDs to update their labelling is an appropriate measure to ensure consumers have labelling statements at the point of purchase to prompt them to identify if they are at greater risk of adverse effects and to take the appropriate action.

ASMI does not support the proposal for mandatory CMI as package inserts. ASMI has always advocated having the necessary advisory statements available on the label to

inform consumers at the point of purchase. The majority of sponsors do not currently provide a package insert with the product. Additionally, OTC oral dose NSAIDs are a highly genericised category and therefore many sponsors do not currently have a PI/CMI as part of their product license.

Labelling alone cannot provide a comprehensive education program nor can it be used as a tool to create community awareness. However, on an individual level, labelling statements that are easily understood and action oriented can assist consumers with understanding whether a product is suitable for them, how to use a product appropriately and when they should seek advice. ASMI therefore recommend that labelling statements should be consumer-friendly and action oriented.

- Option 3 (b) of TGA referring all unscheduled and schedule 2 (Pharmacy Medicine) OTC oral NSAIDs to the Advisory Committee for Medicines Safety (ACMS) to be considered for rescheduling to Schedule 3 (Pharmacist Only Medicine), along with the labelling updates described in Option 3 (a), appears an excessive regulatory response, disproportionate to the potential risk being mitigated. It is inconsistent with the Review's findings "*Based on the current evidence, there are no major changes required to the availability and warnings on labels for over-the-counter (OTC) diclofenac, ibuprofen and naproxen*".

The review has not provided evidence of an emerging issue regarding long term, continuous use or excessive use of OTC NSAIDs in the Australian community. The potential risk posed is only in the event of inappropriate, unsafe or overuse of these OTC NSAIDs. This level of risk is already controlled by appropriate label warning statements: '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'.¹ The risk can be further mitigated by additional label statements as detailed in Section 2 below.

These medicines are regulated in comparable jurisdictions with similar market access arrangements however we note there is opportunity to consider harmonised labelling statements already included in these jurisdictions to mitigate the increased risk of CV events with prolonged use of OTC NSAIDs and the greater risk for those consumers with CV disease or risk factors for CV disease.

Currently, consumers can purchase up to 4 days' supply of ibuprofen 200 mg as unscheduled medicines. These are likely to be intermittent purchases for headaches, period pain, acute pain and sprains/strains/muscular pain (i.e. self-limiting conditions) rather than frequent and regular purchases for chronic problems of older people such as arthritic conditions. Unscheduled and Schedule 2 oral NSAIDs are not labelled for chronic conditions. Longer term users of NSAIDs are likely to source the NSAIDs via a doctor's prescription, as many NSAIDs are PBS listed, or within the pharmacy, where advice is readily available with purchase of larger pack sizes. Unscheduled ibuprofen products are required by RASML to carry an additional warning statement – *Unless a doctor has told you to, do not use this product if you are aged 65 years or over*.¹

¹ [Medicines Advisory Statements Specification 2014](#)

An education campaign involving health professionals and consumers would continue to empower consumers to identify if they are in an at risk group and be more effective in curbing inappropriate long-term use by consumers.

The review has not clearly demonstrated that short term, intermittent use of ibuprofen, naproxen and diclofenac carries the same cardiovascular risks as long term use at higher doses; these risks appear to have been extrapolated to short term intermittent use. Section 5.5.2 Benefit - risk assessment of cardiovascular safety of ibuprofen – Over-the-counter ibuprofen states that *“When used according to the label the benefit/risk profile of OTC ibuprofen is favourable.”* And *“At OTC doses over short duration, ibuprofen has a safety profile distinctly more positive than that associated with the use of ibuprofen in the prescription setting.”*

Therefore with appropriate labelling statements and consumer awareness activities ASMI believe that the current level of consumer access to these medicines remain appropriate.

- Option 4 of a combination of regulatory action, as described in Option 3 (a) and non-regulatory action, as described in Option 2, is supported by ASMI as the most appropriate response to the review outcomes.

This option provides the opportunity for a holistic and enduring approach to the outcomes of the Review. It will be very important to support the introduction of the new CV risk label warnings with communication materials to create broad awareness. A range of materials will be needed both to:

- prepare and brief health professionals in readiness to inform and counsel consumers.
- inform consumers of the label changes, advise what to do, where to get more information generally and who to talk to for specific advice.

However to be effective it needs to ensure that:

- i. Labelling statements are consumer-friendly and action oriented.
- ii. Awareness activities are developed and coordinated by the TGA with the collaborative involvement of key stakeholders.
- iii. Implementation of awareness activities is coordinated in a timely manner to coincide with the introduction of the updated labels.

We have assessed recent updates to labelling statements on OTC NSAIDs in other comparable jurisdictions and have observed there is opportunity for harmonised labelling approaches to address cardiovascular (CV) risk following long term continuous or excessive use in contravention of existing label instructions and warnings. Wherever possible the imposition of uniquely Australian requirements should be avoided.

ASMI have considered and propose additional labelling statements using the RASML labelling formats. (see [Labelling statement proposals](#)). We recommend TGA conduct public consultation of the labelling statements to ensure they are appropriate.

b. Summary and Assessment of Options to address the Safety Review of diclofenac

ASMI noted that, unlike the Review of cardiovascular safety of non-steroidal anti-inflammatory drugs, which was limited to systemic formulations, the scope of the diclofenac review also included topical forms and was a broad review of overall safety.

ASMI noted that the recommendations for cardiovascular safety for OTC diclofenac were consistent with the outcomes of those of the Review of CV Safety of NSAIDs.

ASMI noted that the Review also identified the rare idiosyncratic hepatotoxicity reaction already effectively described in the approved Australian Product Information for all oral NSAIDs and recommended the need for a RASML statement.

For topical diclofenac the Review recommendations note the “paucity of serious systemic side effects with topical diclofenac.” and “Despite this relative lack of evidence” recommended the CMI include warnings that systemic absorption is likely and that adverse CV events have been associated with oral diclofenac.

ASMI’s assessment of the options is as follows:

i. For OTC oral diclofenac:

- Cardiovascular side effects - ASMI’s assessment of all the options is as per our assessment of the *Review of CV Safety of NSAIDs* above. Option 4, a combination of regulatory action, as described in Option 3 (a) and non-regulatory action, as described in Option 2, is again supported by ASMI as the most appropriate response to the review outcomes.
- Rare idiosyncratic hepatotoxicity reaction – ASMI believe that the labelling statements already proposed as part of our response to the *Review of CV Safety of NSAIDs* will also mitigate risks for consumers with liver problems. Additionally RASML already requires a statement advising consumers “If you get an allergic reaction, stop taking and see your doctor immediately.” Therefore no additional action is required to address this issue on labelling. We consider Option 3 (b) requiring the intervention of a pharmacist in the sale of the product, unlikely to further mitigate this rare, idiosyncratic hepatotoxicity reaction. The risk should be mitigated by the minimal regulatory intervention necessary. (see [Labelling Statement Proposals](#))

ii. For OTC topical diclofenac:

- Option 1 of maintaining status quo is the only viable option in this scenario of mitigating a theoretical risk for which there is no safety signal. ASMI recommend no action is warranted. ASMI notes ACSOM’s advice:
 - “While the dosage of topical diclofenac is 10% of the dose of oral OTC diclofenac, safety is based on an assumed short term exposure and low bioavailability and therefore a theoretical risk exists with sustained exposure.” and
 - “that this theoretical risk should not be overplayed, as the exposure metrics of topical diclofenac are different to those for oral diclofenac, particularly high dose oral diclofenac and there is no evidence of a safety signal with topical diclofenac.”
- Option 2 of no changes to labelling and no changes to scheduling, instead using existing communication channels to raise general awareness of this speculative risk has not been justified. There is no safety signal in trial data or observational

research data to suggest an increased cardiovascular risk with topical diclofenac. Development of awareness and educational materials for health professionals and consumers should be based on a scientific foundation.

- Option 3 (a) requiring sponsors of OTC topical diclofenac to update their CMI or require them to have a CMI supplied with the product as a pack insert is an overly burdensome measure for advising consumers of a theoretical risk. Not all products will currently have a CMI. The safety of the product is promoted by detailed instructions on the carton explaining appropriate usage to minimise systemic exposure, such as limiting duration of use, ASMI therefore suggest that such regulatory measures in the absence of a safety signal would be unfounded.
- Option 3 (b) of TGA requiring all unscheduled and Schedule 2 (Pharmacy Medicine) OTC topical diclofenac products be considered for rescheduling to Schedule 3 (Pharmacist Only Medicine) to ensure the intervention of a pharmacist at the time of supply, along with the labelling updates described in Option 3 (a), would appear to be an extreme and disproportionate response in the absence of evidence of a safety risk and relative to the theoretical risk being mitigated.

Again ASMI note ACSOM advice that *“While the dosage of topical diclofenac is 10% of the dose of oral OTC diclofenac, safety is based on an assumed short term exposure and low bioavailability and therefore a theoretical risk exists with sustained exposure.”*

ASMI therefore believe that the outcomes of this Review has not changed the safety profile of these products and the current levels of consumer access to topical NSAIDs remains appropriate.

- Option 4 of a combination of regulatory action, as described in Option 3 (a) and non-regulatory action, as described in Option 2, also appears excessive.

2. Labelling Statement Proposals

Consumer comprehension is aided by clear easily understood and action-oriented statements. ASMI have assessed recent updates to labelling statements on OTC NSAIDs in other comparable jurisdictions and have observed there is opportunity for harmonised labelling approaches to address increased CV risk due to long-term continuous use. We have identified statements from other jurisdictions which address the Review recommendations and have rewritten them into the RASML statement formats for contraindications and precautions.

Review recommendation for OTC labelling	Labelling Statement Proposals (existing RASML statements in black, proposed additional statements in blue)
<p><i>“stronger reminders that patients with CV disease and/or CV risk factors should seek the advice of a physician before using these drugs,”</i></p> <p><i>“while a specific set of CV risk factors have not been determined it does identify that NSAIDs should be avoided in patients with: previous myocardial infarction (MI), angina, cardiac failure, hypovolemia, significant peripheral</i></p>	<ul style="list-style-type: none"> ● <i>Do not use if you have heart failure.</i> ● <i>Ask your doctor or pharmacist before use of the medicine if you have heart or circulatory problems, or any related risk factors.</i> ● <i>Do not use if you have impaired kidney function.</i>

<p><i>vascular disease and pre-existing significant renal/liver dysfunction.”</i></p>	<ul style="list-style-type: none"> • <i>Ask your doctor or pharmacist before use if you have liver disease.</i>
<p><i>“Stronger reminders about limiting the dose and duration of treatment in accordance with the package instructions unless otherwise advised by a health professional.”</i></p>	<ul style="list-style-type: none"> • <i>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.</i> <p>ASMI also advise that the ARGOM Dosing Instruction Requirements for analgesics already encourages a minimum dose be taken and to repeat dose only as necessary. This is reflected in the <i>Appendix 5 Guidelines on OTC applications for specific substances²</i> and <i>OTC Medicines Monographs³</i> for Analgesic products</p>
<p><i>“warnings that NSAIDs may cause an increased risk of serious CV thrombotic events, MI and stroke, which can be fatal, this risk may increase with duration of use, and consumers with CV disease or risk factors for CV disease may be at greater risk.”</i></p>	<ul style="list-style-type: none"> • <i>Long term continuous use may increase the risk of heart attack or stroke.*</i> <p>* We suggest that as this statement does not inform the purchase decision it may appear on pack insert where one is included.</p>
<p><i>“adding the following statement to convey the risk of hepatic injury: ‘Warning: In rare cases, diclofenac has been associated with serious liver injury.’”</i></p>	<p>ASMI recommend that the following existing RASML warning allows consumers to understand that adverse events may happen while taking the medicine, to be alert to them occurring and advises what action to take.</p> <ul style="list-style-type: none"> • <i>If you get an allergic reaction, stop taking and see your doctor immediately.</i>

It is not possible to identify all the risk factors for cardiovascular disease on a label. However ASMI believe there is already a high level of awareness of the risk factors for cardiovascular disease in the general community, for example:

- The explicit images and sad life stories featured in the Quit campaign and the graphic images smokers are forced to acknowledge on their cigarette packs.
- The impact of fast food and a sedentary lifestyle on the rapidly increasing in rates of obesity in the community is a constant subject of public debate, with concerns of health impacts and the costs to our health system.
- Blood pressure and cholesterol are understood by consumers as indicators of heart health regularly monitored by GPs.

It will be important for the awareness activities to link to the cardiovascular disease risk factors labelling statement and assist consumers to recognise their own general awareness of these factors and to consult a healthcare professional to confirm their status if they are unsure.

² [ARGOM Appendix 5: Guidelines on OTC applications for specific substances](#)

³ [OTC medicine monographs](#)

3. Implementation Mechanism Options for Labelling Updates

Getting the labelling statements right and having the appropriate statements to inform the purchase decision available on carton (or primary pack) is important. ASMI therefore propose that stakeholder consultation of the proposed statements should be conducted prior to them being imposed. Therefore, regardless of the mechanism to impose the statements, either via the Required Advisory Statements for Medicine Labels (RASML) process or a Section 28 letter, the first step should be a RASML consultation.

This would ensure appropriate crafting and confirmation of the statements which could then be included on both existing and new products via the RASML process or more immediately imposed on existing products via a Section 28 letter.

This approach avoids the need for sponsors to amend labels twice, first to comply with the statement imposed by TGA via a Section 28 letter, and second to amend to the final RASML approved statement determined after stakeholder consultation.

4. Communication - Awareness and Education Initiatives

ASMI believe a collaborative approach is critical to ensure the appropriateness of communications, consistency of interpretation, avoidance of confusion and to maximize the reach and benefit of educational initiatives.

ASMI would welcome the opportunity to represent the Industry in the development of the communication of OTC NSAID label changes and the education and awareness information for health professionals and consumers. Other key contributors for TGA and NPS to include would be the Pharmacy Guild, the PSA, non-pharmacy retailers and consumer advocacy groups.

ASMI also suggest that to maximize outreach and particularly to ensure the message reaches at-risk groups in the community, other relevant patient support groups might be included. For example Pain Australia, Arthritis Australia and the Heart Foundation.

Communication to health professionals should commence immediately, particularly with regards the importance of individualising NSAID prescribing based on likely benefits and risks to each patient, and assessing blood pressure, renal function and body weight, before and after starting treatment with a COX-2 inhibitor or non-selective NSAID, to allow for early detection of side effects. However, communication to consumers of the changes to labelling of OTC NSAIDs would be best timed to occur as the updated labelling is being introduced into the market.

By involving all key stakeholders a broad-reaching, effective awareness campaign could be cost-effectively developed. By first agreeing key core information, each stakeholder or smaller group of stakeholders, could develop the necessary materials. In this way, a coordinated campaign advising that the label statements have been updated and the reasons can be released.

One approach might include the development of statements and Q&A on the TGA and NPS website forming the core information pieces, with in-store shelf wobblers with a QR code linking to the TGA webpage with advice to the effect 'The warning statements on this product have been updated, is the medicine still right for you? Ask your pharmacist if you're unsure. More information is available at this website or scan this code.' Pharmacists could be briefed with the core information but also with a standard list of counselling information which might include, but not be limited to:

- Advice for consumers to follow the label instructions, to take the lowest necessary dose and repeat dose only if needed, and to seek advice from their doctor if the pain continues to persist after a few days.
- How to assist consumers to recognize if they have risk factors for cardiovascular disease and determine if the product is still appropriate for them.
- What the signs and symptoms are for serious CV toxicity.
- Advice to remain alert for CV events even in absence of previous CV symptoms.

5. Next Steps and Transition Considerations

a. Transition Considerations

ASMI recommends that a transition period of one year would be suitable to achieve compliance of product supplied to the market. This recommendation is based on implementation of Option 4 with labelling amendments similar to ASMI's proposals. We would hope that allowance would be made to ensure for appropriate overlap with the introduction of the revised labelling order, TGO 79, to reduce the need to update labels twice within the same period.

ASMI does not support mandatory CMI as package insert for OTC NSAIDs as stated above. However, we advise that the impact on timeframes and costs could be considerable and would need to be carefully assessed should this sub-option be proposed. There has been insufficient time allowed in the consultation to consider the cost and timeframe implications of each combination of sub-options within the regulatory option.

ASMI agrees with the findings of the Review that based on the current evidence, no major changes to the availability of ibuprofen, naproxen or diclofenac are suggested. However, we note that if this were to be contemplated, the regulatory impact would be considerable.

b. Importance of Transparency of Next Steps

ASMI have noted that the TGA will review and consider submissions made to the consultation. Any updates on proposed actions will be made available on the TGA's internet site.

ASMI would appreciate a transparent statement of outcome of this consultation and a clear outline of next steps. Previous reviews have lacked this transparency, and it has been uncertain for all involved.

6. Conclusions

OTC NSAIDs “provide effective relief when used according to the label at recommended doses for short durations.” They allow consumers to treat a wide range of self-limiting non serious pain events and contribute to the economy by reducing the burden to the health system and number of lost working days.

ASMI believe that the introduction of appropriate consumer-friendly, action-oriented label advisory statements supported by a coordinated consumer awareness campaign developed by TGA and NPS with key stakeholder involvement is the most appropriate option (Option 4) to address the recommendations arising from the Reviews for oral dose OTC NSAIDs.

We believe that no action is necessary for topical diclofenac, given there is no safety signal and the risk is theoretical (Option 1).