TGA response to recommendations arising from the Review of Non-prescription Analgesics

February 2000
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Background

The review was undertaken by the TGA to address public health and safety concerns surrounding the labelling and packaging of OTC analgesic products. It had been prompted by concerns about an apparent high level of childhood poisoning with paracetamol liquid products and the number and complexity of warning statements required on the labels of analgesic products in general. Copies of the Review were sent to a diverse group of stakeholders and extensive discussions were held with industry organisations. Final comments were received in January 2000.

This document summarises the comments received and sets out the TGA’s response to each of the recommendations of the Review. Responses have not been ascribed to particular persons or organisations except in the case of the Proprietary Medicines Association of Australia (PMAA) which provided detailed comments on all of the recommendations. Because of the extent of the PMAA’s comments, they have been quoted in full in many cases.

Comments received

The TGA wishes to thank the following individuals and organisations that have responded to the Review.

Ms Mary Davies Consumer Health Forum Representative
Professor Pierre Baume Central Sydney Area Health Services
Ms Rose-Marie Pennisi Regulatory Affairs Manager- Herron Pharmaceuticals
Professor H.A Kilham NSW PIC, New Childrens Hospital
Mr Brian Lilley Royal Childrens Hospital
Ms Elizabeth Hender Victorian PIC
Dr Annie Lim Consultant Paediatrician
Mr Kingsley Coulthard Director of Pharmacy – SA PIC
Mr Frank Shann Director of Intensive Care – Royal Childrens Hospital (VIC)
Ms Juliet Seifert The Proprietary Medicines Association of Australia Inc
Dr Ted O’Loughlin Paediatric Gastroenterologist - The New Children’s Hospital

Overview

The recommendations fall into three major categories:
1. Those that call for the communication of information to the public or to health professionals (e.g. 1.1, 2.5, 2.7, 3.1);
2. Those that call for a change to the TGA’s registration guidelines (e.g. 2.1, 2.2, 2.3, 2.6); and
3. Those that call for a change to the Labelling Order (TGO48) or to the SUSDP (e.g. 6.1.1, 6.4, 6.11).

The first category relates to the quality use of medicines. In most cases these matters have been referred to the Pharmaceutical Health and Rational Use of Medicines (PHARM) committee as the Department’s expert advisory committee on the quality use of medicines.

The second category is to be referred to the Medicines Evaluation Committee (MEC) which is the group responsible for advising the TGA on matters relating to the regulation of OTC medicines. While the *Australian Guidelines for Registration of Drugs, Volume 2* currently only applies to new products, the TGA has commenced discussions with the PMAA on a mechanism for making these guidelines apply to existing products as well.

The final category will be referred to the Therapeutic Goods Committee (TGC) or to the National Drugs and Poisons Schedule Committee (NDPSC). Both of these committees include representation from key stakeholders. In addition, proposed changes to the SUSDP go through a formal public consultation process before being accepted.

The TGA is aware of the need for careful consideration of all changes to standards, guidelines and the SUSDP and, in particular, the setting of implementation dates where changes are required to product labelling. These factors can be taken into account by the relevant committees in consultation with stakeholders.

Each of the committees will be provided with full copies of all comments from stakeholders. While some recommendations are referred to particular committees, all of the committees will be invited to comment on any of the recommendations in the Review.

The PMAA has proposed the formation of a ‘consultative forum’ which would involve all key stakeholders and necessary experts: government, industry, consumers, healthcare professionals and communication experts. The function of the forum would be to:

- agree measurable objectives (within an agreed timeframe);
- propose necessary modifications to existing guidelines and/or regulations;
- develop an agreed public communication strategy;
- coordinate implementation;
- evaluate results achieved; and
- plan any necessary further action.
The TGA does not support this proposal. Extensive consultation has already taken place and there are consultative mechanisms within each of the committees which will allow stakeholders to have input into the decision making process.

It is recognised, however, that the current requirements for labelling of medicines are complex, being spread across a number of different legislative documents and guidelines. To address this situation, the TGA will undertake a broad based project on the labelling of medicines in the near future. The project will involve extensive consultation with all stakeholders, including industry representative bodies.
Recommendation 1.1

Medical and pharmacy organisations remind their members of the toxicity of paracetamol in overdose with special reference to toxic doses and the delayed adverse effect on the liver.

Comments

Any dissemination of information to health care professionals should be coordinated with community service announcements arising from Recommendation 2.7 for maximum benefit and effect. This information must be consistent across organisations (perhaps by central coordination) and be aimed to reach as many individual healthcare professionals as possible.

Such bodies should also remind their members to exercise care when recommending doses to patient carers, and that where paracetamol is being used as an antipyretic there should be advice to seek medical attention if used for more than 48 hours.

It was also suggested that information specifically on hepatotoxicity in children be provided to remind GP’s of the potential problem of using large doses of paracetamol in this age group.

The PMAA’s comments follow.

Healthcare professionals, through their training, are clearly aware of the relative toxicity of analgesic substances that they recommend or prescribe. It is unclear therefore what this recommendation would effectively and efficiently achieve.

Unnecessary alarm and uncertainty within the community could result from the recommendation as phrased, unless consistency of messages being disseminated via individual healthcare professionals could be assured.

Industry has already produced many tools and healthcare aids, e.g. overdose charts (examples enclosed) that are routinely provided to relevant professionals. If any action is considered necessary arising from this recommendation, perhaps it could be that such tools be more widely disseminated. We would emphasise the need however for any dissemination of information to healthcare professionals to be centrally coordinated in concert with community messages arising from Recommendation 2.7.

TGA response

The TGA supports this recommendation. Paracetamol is a useful drug but it is not totally safe when used inappropriately. Pharmacists and doctors have a role to play in ensuring that patients do not inadvertently take more than the recommended dose and, if they do, that
treatment is sought promptly because of the delayed adverse effects on the liver.

The TGA agrees that these messages to health care professionals need to be coordinated with appropriate messages to consumers (see Recommendation 2.7) and will forward this recommendation to the Pharmaceutical Health and Rational Use of Medicines Committee (PHARM) for further consideration.

**Recommendation 2.1**

As a matter of TGA policy, strengths of uncompounded paracetamol oral liquids other than those containing 24mg/mL, 48mg/mL, 50mg/mL and 100mg/mL should not be placed on the Australian Register of Therapeutic Goods for supply in Australia. If necessary, the SUSDP should be amended accordingly.

**Comments**

Most respondents agreed with this recommendation. Some respondents believed that the number of strengths of uncompounded paracetamol oral liquids currently available should be reduced.

The PMAA’s comments follow.

The basis for this recommendation is apparently to avoid potential confusion within the community arising from the introduction of further alternative strengths of products. PMAA believes that the focus should be on overall label improvement to existing and new products, reinforced by agreed community messages about the importance of the label and the need to always read it.

We would suggest that the recommendation could be taken up within the Australian Guidelines for the Registration of Drugs, volume 2 – Non-prescription drugs registered via Compliance Branch (AGRD 2) as policy. Justification for any alternative strength could be made to the TGA (and/or the Medicines Evaluation Committee) as part of the review of the product’s safety, quality and efficacy. In this way, newer formulations with improved dosing and labelling (and hence improved compliance regimes) would not be prevented from entering the market in a timely fashion.

It would therefore appear unnecessary to change (and further complicate) the SUSDP entry for paracetamol as a substance.
**TGA response**

Any sponsor wishing to market a new strength of paracetamol oral liquid would have to apply to the TGA for registration of the product. This would require the submission of a detailed application, including a justification for the new strength, for evaluation by the Medicines Evaluation Committee (MEC). There is no need to change the SUSDP. The current registration system will allow rational and flexible consideration of any such submission.

The advice of the Medicines Evaluation Committee (MEC) will be sought as to whether the *Australian Guidelines for Registration of Drugs, Volume 2* (AGRD2) should be amended to make it clear to sponsors that any such application would be expected to include a detailed justification for the registration of new strengths or larger pack sizes (see Recommendation 2.2) of paracetamol oral liquid products.

**Recommendation 2.2**

*As a matter of TGA policy, packs of uncompounded paracetamol oral liquids containing volumes greater than those already on the market for each strength for supply in Australia should not be placed on the Australian Register of Therapeutic Goods. If necessary, the SUSDP should be amended accordingly.*

**Comments**

There was general agreement with this recommendation.

The PMAA’s comments follow.

*The availability of various pack sizes, e.g. 100mL, 200mL is a market driven issue, ie. larger packs are generally sold to families with more than one child for economic reasons. However, there is always an upper limit to this market equation and member companies have advised that it is unlikely that larger bottles would therefore be introduced.*

*The SUSDP is the current regulatory mechanism generally used for the restriction of pack sizes. These liquid paracetamol products are already confined to sale through pharmacy only and are all packaged with child-resistant closures. PMAA therefore believes the focus should be on the more fundamental issue, ie. appropriate storage of medicines within the home and the responsibility of the carer. We believe that the broad dissemination of agreed community messages regarding the proper storage of medicines generally (and the need to re-close child-resistant caps) would be more efficient and effective than simply limiting the pack size of a particular substance.*
TGA response

See the response to Recommendation 2.1 above.

The TGA agrees that it is important that the community be educated as to the proper storage of medicines and the correct use of child-resistant closures (see also Recommendation 2.7). Accordingly, this recommendation will be referred to the Pharmaceutical Health and Rational Use of Medicines (PHARM) Committee for further consideration of these important public health and communication issues.

Recommendation 2.3

Manufacturers of paracetamol oral liquids who wish to supply measuring devices with each bottle of a paracetamol oral liquid ensure that the calibrations correspond with the doses shown on the label to discourage calculation and guesswork.

Comments

There was general agreement with this recommendation.

The PMAA suggested that such a policy should be incorporated in the *Australian Guidelines for Registration of Drugs, Volume 2* (AGRD2) to allow transparency and flexibility and that an appropriate transitional period be agreed with industry.

TGA response

The advice of the Medicines Evaluation Committee (MEC) will be sought as to whether this recommendation should be implemented in AGRD2. Industry advice will be sought on a mechanism for applying changes to currently marketed products and an appropriate transitional period for those products.

Recommendation 2.4

The importation and manufacture (other than for export or re-export) of medicine measures for domestic use that are calibrated in other than metric units be prohibited.

Comments

The few comments that were made were in agreement with this recommendation.
The PMAA suggested that this issue be discussed with the Medical Industry Association of Australia (MIAA) whose members manufacture and/or import therapeutic devices.

**TGA response**

Medicine measures are “therapeutic goods” and, although exempt from registration or listing, must comply with Therapeutic Goods Order No. 37. This Order requires all labelling to be in the metric system. Other units of measurement can only be used where the TGA gives a specific exemption for the product.

The TGA will ask industry associations to remind their members of the requirements of TGO37 and take appropriate action against sponsors of products which do not comply with the Order. Exemptions will only be issued where a strong justification is present.

**Recommendation 2.5**

The Pharmaceutical Society of Australia request pharmacists and staff to:
(i) ensure that purchasers of paracetamol oral liquids have a suitable measuring device and;
(ii) demonstrate its use at the point of sale.

**Comments**

Strong agreement for this recommendation was received.

Any dissemination of information to health care personnel should be coordinated with community service announcements arising from Recommendation 2.7 for maximum benefit and effect. This information must be consistent (perhaps by central coordination) and be aimed to reach as many individual healthcare personnel as possible.

**TGA response**

The TGA agrees with this recommendation. It will be forwarded to the PHARM Committee for further consideration.

**Recommendation 2.6**

All doses of uncompounded paracetamol oral liquids containing 120 mg/5mL, 240 mg/5mL and 250 mg/5mL should (i) be in whole numbers of millilitres and (ii) omit the decimal point and the post-decimal zero (eg. 5 mL not 5.0 mL). Minor variations to the
15 mg/kg dose to be disregarded in the interests of safety and ease of administration.

Comments

In general this recommendation was supported, however it was noted that should this recommendation be accepted then the table on page 75 of the report would contradict the recommendation as it includes decimal places.

A suggestion that such a policy should be incorporated in the AGRD 2 to allow transparency and flexibility was also made.

TGA response

The TGA agrees with this recommendation. The advice of the Medicines Evaluation Committee (MEC) will be sought as to whether this recommendation should be implemented as part of a guideline in the Australian Guidelines for Registration of Drugs, Volume 2 (AGRD2) (see Recommendation 7.1). Industry advice will be sought on a mechanism for applying any changes to currently marketed products and an appropriate transitional period for those products.

Recommendation 2.7

Community service announcements sponsored by government, the professions and industry should (i) stress the importance of not leaving medicines in general and paracetamol in particular within reach of children; (ii) draw the public’s attention to the existence to different strengths of paracetamol; (iii) emphasise the need to read the label; and (iv) direct the public to seek the advice of a pharmacist or a doctor if they do not understand the label.

Comments

The comments made on this recommendation are to the effect that an educational program should be proposed not only for paracetamol but also for all analgesics.

This program should be a combined effort from industry, government and professional bodies, with guidance from recognised communication experts. The development of appropriate benchmark standards and measures would allow evaluation of the communication effectiveness.

With the recommendations given, concern was expressed that there are too many messages for one session, and that the information may need to be broken down in a piecemeal fashion.
In regard to the phrase: “... within reach of children,” a suggestion that an actual measurement be given of 1.5 metres off the floor and out of sight.

It was emphasised that a key reference point for safe and responsible use of medicines was understandable and actionable dosage instructions (ie. performance-based) on labels. This was identified as a pre-requisite to the extended messages recommended above.

PMAA’s comments

*Industry acknowledges the need for joint action in releasing appropriate community messages about the purpose, as well as the safe and responsible use of all medicines, including analgesics. (We note, however, the need to also include consumers in the planning and implementation of any such proposed activities). In this regard, it is noted that the goals of National Medicines Week (NMW) are consistent with this approach and that this activity in fact provides an opportunity for appropriately dealing with public communication on the issues raised in this recommendation.*

*Public education in this area needs to first clearly establish an understanding of the label of any medicine as a key reference point for safe and responsible use. This key message is a prerequisite to the extended messages recommended above. If appropriate behaviour is to be encouraged, attention must be given to the nature of ongoing public communication (following NMW), so as to ensure sustainable consumer behaviour based on understanding of the key messages.*

*Clearly this will have implications for the nature of any such communication approaches, in terms of structure, length, timing, cost effectiveness and funding.*

*The expertise required to produce effective communication messages and their delivery may lie in part within industry itself and in part within its links to recognised communication experts. It is crucial that such expertise be provided for, if the efforts and resources involved are to be cost effectively applied.*

*Such expertise will ensure development of appropriate benchmark standards and measures, enabling evaluation of the communication effectiveness as well as its demonstrability in applied behaviour.*

*The opportunity to build on existing industry information materials and to Co-ordinate key messages should not be overlooked. (This may apply equally to existing initiatives within each of the relevant sectors).*

*This points to the need to establish an appropriately representative forum to guide and plan*
the process, implement and jointly evaluate agreed activities and be accountable for resources expended and results achieved.

TGA response

This response to this recommendation is linked with responses to recommendations 1.1, 2.5, 2.8, 3.1, 4.1, and 4.2. The TGA agrees that these communication and education initiatives need to be a joint effort from industry, government, professional bodies and consumers and that they should form part of an overall strategy for the safe and responsible use of all medicines.

However, it should be recognised that some groups of medicines may warrant stronger, more targeted messages because of the serious consequences that may flow from inappropriate use in certain populations (e.g. analgesics in children).

The TGA’s role in this process is to ensure that OTC medicines are packed and labelled in a way that will enable safe use by consumers when used as directed.

Issues relating to the quality use of medicines are the responsibility of the Pharmaceutical Health and Rational Use of Medicines Committee (PHARM). This recommendation and others relating to education and communication initiatives will be sent to the PHARM committee for further consideration. See also the response to Recommendation 2.8.

Recommendation 2.8

The provision in Therapeutic Goods Order No.20 that enables dropper packs containing not more than 2 g of paracetamol to be exempted from the need to be fitted with a child resistant closure should be repealed.

Comments

There was very strong agreement for this recommendation.

It was noted that at a dose of 20 mg/kg, a 2 g amount would represent about 10 times the dose for an 18 month old child. Therefore this provision in TGO 20 should be repealed.

PMAA’s comments

Industry would agree with this recommendation, however PMAA would reiterate that the focus should continue to be on the more fundamental issue, ie. appropriate storage of medicines within the home. We believe that the broad dissemination of agreed community
messages regarding the proper storage of medicines generally and the need to re-close child-resistant caps in particular is necessary.

A transitionary period for existing paracetamol liquid products currently not compliant with the recommendation will need to be discussed between industry and TGA and agreed also with the consultative forum.

TGA response

The TGA supports this recommendation. It will be forwarded to the Therapeutic Goods Committee (TGC) for further consideration. The TGA also supports the PMAA’s call for a transitionary period for existing products provided that the period is the minimum possible to allow for an orderly change-over to child-resistant closures.

The TGA agrees with the PMAA’s comments with regard to community messages about the need to re-close child-resistant caps. The PHARM committee will be requested to consider this proposal in conjunction with Recommendation 2.7.

Recommendation 2.9

Age/weight range tables on labels should be uniform across the industry and be based on contemporary Australian figures.

Comments

There was strong agreement for this recommendation, however it was noted that the reference to “contemporary Australian figures” is problematic.

The data currently available (MIMS and 1997 ABS statistics) are stated to be neither up to date or comprehensive. The PMAA has suggested a three-stage strategy for addressing this problem:

a) The first stage should be a recommendation to make age/weight ranges, when appearing on a product label/information, consistent for all paracetamol liquid preparations. The most appropriate set of figures should be discussed by TGA with industry and a transitional period for existing products agreed.

b) The second stage should be a government-funded comprehensive study of the growth and therefore weight of Australian children. It is suggested that this would be supported by healthcare professionals working within this area, e.g. the children’s hospitals.
c) Stage three would then involve, upon finalisation of these figures, a further review of existing product labels. Any necessary agreed changes would then require the appropriate implementation strategy (to be discussed and agreed with industry)

TGA response

The TGA agrees that age / weight ranges on labels should be uniform across the pharmaceutical industry. This will be achieved, for new products, through acceptance of a guideline based on Appendix 4 in the *Australian Guidelines for Registration of Drugs, Volume 2* (AGRD2). Industry advice will be sought on a mechanism for applying these changes to currently marketed products and an appropriate transitional period for those products.

The age / weight data in MIMS appear to be the most commonly used reference for calculating doses of medicines. However, these are based on US data from the 1970’s and it appears from ABS data that contemporary Australian children (at least in the age range 2 to 12 years) may be marginally heavier. The consequence for parents administering paracetamol liquids to children based on age (not weight) is that children at the high end of the weight range may receive a slightly lesser dose per Kg than would otherwise be the case.

Doses of medicines derived from age alone can never be precise because of the wide variation in weights of children within each age group. The availability of more relevant age / weight information would enable a more accurate setting of dose ranges. This is an issue in terms of the quality use of medicines but it is not a safety issue. The TGA will refer this recommendation to PHARM for further consideration.

**Recommendation 2.10**

Dose tables on labels should preferably show age/weight/millilitre dose OR age/millilitre dose but not weight/millilitre dose to discourage the need for calculations by the carer.

**Comments**

There was general agreement with this recommendation. However there is again concern with the apparent contradiction to the table on page 75 of the report.

**PMAA’s comment**

*While industry agrees there is a need to minimise the need for calculations by the carer, weight/millilitre is the most accurate dosing mechanism, particularly in the absence of contemporary Australian weights (refer above to Recommendation 2.9).*
Pragmatically however, to minimise confusion and enhance ease of dosing of liquid paracetamol products, the recommendation is agreed to by industry and could be, for transparency, incorporated into the AGRD 2 policy section allowing flexibility as and when justified. For example, given the significance of dosage variations, it may be preferable for infant preparations to include age/weight/millilitre figures given the potential weight variation and its significance in appropriate dosing. For children’s preparations however, it may be appropriate to more simply include age/millilitre. Again, the focus should be on improvement to the label overall and of particular relevance here, the dosage instructions.

A transitional period for existing paracetamol liquid products currently not compliant with the recommendation will need to be discussed between industry and TGA and agreed by the consultative forum.

TGA response

The TGA agrees with this recommendation while recognising the need to maintain flexibility where a different approach can be justified.

The Medicines Evaluation Committee (MEC) will be requested to consider this issue in relation to the adoption of Appendix 4 in the Australian Guidelines for Registration of Drugs, Volume 2 (AGRD2) (Recommendation 7.1 refers)

Recommendation 2.11

A new paediatric dose for paracetamol based on 15 mg/kg should be referred to the Medicines Evaluation Committee for its consideration to replace the present dose based on 12.5 mg/kg.

Comments

General agreement for this recommendation was received, especially with different brands containing different doses.

PMAA’s comment

From our member company feedback, this recommendation would appear consistent with the current scientific literature. A carefully considered and timely transitional period for existing paracetamol liquid products will need to be agreed to avoid any exacerbation of confusion in the health professional and general community with regard to the correct dosages of paracetamol liquid preparations.
TGA response

The TGA agrees with this recommendation.

The Medicines Evaluation Committee (MEC) will be requested to consider this recommendation in relation to the adoption of Appendix 4 in the *Australian Guidelines for Registration of Drugs, Volume 2* (AGRD2). Industry advice will be sought on a mechanism for applying any changes to currently marketed products and an appropriate transitional period for those products.

Recommendation 2.12

In the event of the Medicines Evaluation Committee supporting a dose based on 15 mg/kg, the TGA and the industry agree on an implementation strategy.

Comments

Strong agreement for this recommendation was received. One respondent commented that it is not to say that a medical practitioner cannot give a higher dose where they feel it is required.

TGA response

As per Recommendation 2.11 above.

Recommendation 2.13

In the interests of paediatric health and safety, all labels for uncompounded paracetamol oral liquids, at next printing or before 1 January 2000, include statements to the effect that:

* Not more than 4 doses should be given in 24 hours.
* The medicine should not be administered for more than 48 hours without seeking medical advice.

Comments

Once again strong agreement was received, however, one respondent again stated that a medical practitioner could give a higher dose where they feel this is necessary.
The need for a warning statement that not more than 4 doses be given in 24 hours was queried as dosing every four hours would give a total daily dose of 90 mg/kg/day (an acceptable dose to the respondent). However another respondent stated that a safe upper limit of administration in the community would be 60 mg/kg/day, and that dosing children at 90 mg/kg/day would only be acceptable if the practitioner was prepared to monitor both LFT’s and paracetamol level? These responses reflect the diversity of views as to what is an acceptable paediatric dose of paracetamol.

A comment that “before 1 January 2000” seems a “long delay”, was also countered by the PMAA’s comment that such timing may or may not be appropriate in the context of other changes to be made to the labelling of existing paracetamol liquid preparations, including changes to signal headings by 30 June 2000.

**PMAA’s comment**

*Industry agrees with the label statements contained in this recommendation – they are consistent with those already detailed in the AGRD 2 policy section and therefore are currently applied to all new products. A transitional period for existing paracetamol liquid products currently not compliant with the recommendation will need to be discussed and agreed.*

*The suggestion of “at next printing or before 1 January 2000” may or may not be appropriate when considered in the context of all the other changes to be made to the labelling of existing paracetamol liquid preparations, including the change to the signal headings mandated by the SUSDP (the deadline for which is 30 June 2000).*

**TGA response**

The TGA agrees with this recommendation. The statements are consistent with current guidelines in AGRD2 and have been applied to new products for some time. The Medicines Evaluation Committee (MEC) will be requested to consider this issue in relation to the adoption of Appendix 4 in the *Australian Guidelines for Registration of Drugs, Volume 2* (AGRD2) Industry advice will be sought on a mechanism for applying these statements to currently marketed products and an appropriate transitional period for those products

**Recommendation 3.1**

**Professional organisations and departments of health**

(a) Remind medical practitioners, pharmacists and health centre sisters that:

(i) fever as such is not harmful;

(ii) paracetamol is not automatically indicated for fever;
(iii)  paracetamol is not indicated for sleeplessness and;
(b) Request practitioners to advise mothers and other carers accordingly.

Comments

One respondent commented that they were unclear as to the purpose of this recommendation, while another proposed it would more relevant to remind healthcare professionals of appropriate fever “strategy” of the different therapies available.

Another agreed with the recommendation, noting however that paracetamol is still the drug of choice for fever.

Comment was received that the medical profession in general considered current recommended therapeutic doses are too low and frequently advised patients to use quite large doses. In this context it was proposed that healthcare professionals be reminded that paracetamol is a potential hepatotoxin and it should not be administered in doses other than recommended unless they are prepared to closely monitor such patients.

PMAA’s comment

This recommendation needs to be carefully considered. Concern has been expressed about the effective and efficient implementation of this recommendation without unnecessarily alarming the community, sending mixed and therefore confusing messages to the carer with the possible withdrawal of medication when it is in fact necessary.

It may be more relevant to remind healthcare professionals of appropriate fever “strategy”, ie. the who, when, where, why and how of different therapies, whether that be paracetamol liquid or sponging

Industry may have already produced useful tools and healthcare aids that could be more widely disseminated to address messages about responsible use of these products and general fever “strategies”. If any additional action is considered necessary arising from this recommendation, we would reiterate the need for it to be centrally coordinated in concert with messages arising from Recommendation 2.7.

TGA response

The TGA agrees with this recommendation. It should be noted, however, that caution is required to avoid unduly alarming the community and to avoid drawing attention to the potential use of paracetamol for suicide attempts.

Because this recommendation relates to the quality use of medicines it will be forwarded to
the Pharmaceutical Health and Rational Use of Medicines Committee (PHARM) for further consideration.

Recommendation 3.2

The Medicines Evaluation Committee be asked to consider the appropriateness of limiting any antipyretic indications for paediatric paracetamol medicines in the Australian Register of Therapeutic Goods and in advertisements (including labels) to “reduces fever” or similar, without elaboration, except in the context of limits to the duration of treatment.

Comments

General support of this recommendation was received.

PMAA’s comment

The intent of this recommendation is unclear and industry requests further clarification and possibly justification. The recommendation would, for example, seem to preclude the use of paediatric paracetamol liquid preparations following immunisation. It should be noted that The Australian Immunisation Handbook, issued by the NH&MRC states

“The routine use of paracetamol to reduce unpleasant side-effects following DTP vaccination is recommended.”

TGA response

This recommendation will be discussed with the MEC and industry in conjunction with Recommendation 7.1. It should be noted that this recommendation is limited to “antipyretic indications” and would not prevent the inclusion on a product’s label of an indication for use following immunisation (which involves other side effects in addition to fever).

Recommendation 4.1

The editor of the Australian Prescriber be requested to arrange for, and publish, a review article about enhanced toxicity of paracetamol when it is taken by moderate to heavy habitual alcohol drinkers.

Comments

This recommendation was supported by one respondent.
PMAA’s comment

Again this recommendation needs to be carefully considered.

While it is agreed that health care professionals should understand the risks chronic alcoholics face when taking any medication, educating them through the Australian Prescriber as per this recommendation may not be the most appropriate mechanism.

This type of publication is regularly scanned for consumer press articles. If this occurred and the article focussed on paracetamol specifically, the outcome could be exactly the one the recommendation is endeavouring to avoid, ie. misuse and misunderstanding of the information.

We would recommend the need for information to be tailored specifically for healthcare professionals in the context of quality use of medicines and for it to be centrally coordinated in concert with messages arising from Recommendation 2.7.

Any information should be in the context of “chronic alcoholics”, not “moderate drinkers” as again this could be misused and/or misunderstood and create unnecessary alarm.

TGA response

The TGA agrees that this recommendation needs careful consideration, in conjunction with Recommendation 2.7. This is a quality use of medicines issue and will be forwarded, with the above comment, to the Pharmaceutical Health and Rational Use of Medicines (PHARM) committee for further consideration.

Recommendation 4.2

In the course of their detailing to medical practitioners and pharmacists, sponsors’ representatives mention that paracetamol dosages and the duration of treatment with it may need modification if the patient is a moderate to heavy habitual alcohol drinker.

Comments

Very few comments were received on this recommendation but those comments were supportive. The PMAA commented that any dissemination of information to health care professionals should be consistent and centrally coordinated with community service announcements arising from Recommendation 2.7 for maximum benefit and effect.
TGA response

The TGA recognises the important role that sponsor’s representatives have in disseminating information to health professionals and agrees that these activities should be coordinated with the education / communication issues identified in earlier recommendations.

This recommendation will be forwarded to the Pharmaceutical Health and Rational Use of Medicines (PHARM) committee and the PMAA for further consideration.

Recommendation 4.3

The TGA monitor the outcomes of the American labelling initiative concerning analgesics and alcohol drinking.

Comments

Very few comments were received on this recommendation but those comments were supportive. The PMAA stated that public health benefit and consumer research data should be requested as a measure of the effectiveness of the specific label warnings requested.

TGA response

The TGA will maintain a watching brief on the available literature concerning the American labelling initiative in relation to analgesics and alcohol consumption.

Recommendation 4.4

No warnings on the label of paracetamol, aspirin and the NSAIDs in relation to alcohol consumption should be required at present.

Comments

Very few comments were received on this recommendation but those comments were supportive. The PMAA commented that the relevance of the US information to the Australian setting could be assessed upon receipt of the above mentioned data. The relevance of the information to Australia, ie. through consideration of comparative drinking rates and use of analgesics will also need to be assessed at that time.
TGA response

The TGA agrees with this recommendation. It will be forwarded to the National Drugs and Poisons Committee (NDPSC) for information.

Recommendation 5.1

That paracetamol preparations should not be compulsorily co-formulated with methionine.

Comments

This recommendation was supported.

TGA response

The TGA accepts this recommendation.

Recommendation 5.2

The TGA monitor the UK data on morbidity and mortality following paracetamol poisoning after all of the UK legislative initiatives have been in operation for one year.

Comments

The PMAA suggested that upon receipt of requested public health benefit and consumer research data be collected as a measure of the effectiveness of the specific regulatory actions in the UK but that the relevance of this information to the Australian setting should be considered carefully through consideration of comparative suicide rates and comparable use and/or possible misuse of analgesics.

One respondent suggested that the following statement be added: “and compare these with data on trends in morbidity and mortality in Australia during the same period.”

Another respondent did not agree with the recommendation suggesting that instead a recommendation be included to monitor suicide deaths and attempts in Australia from paracetamol.
**TGA response**

The TGA agrees that information on the outcomes of the UK initiatives with regard to paracetamol may be of relevance in guiding future policy in Australia. A watching brief will be maintained on reported outcomes from the UK, noting that any consideration of UK data would need to be carefully considered in the Australian context.

Comprehensive data that incorporate outcomes of paracetamol poisoning do not seem to be available in this country. Accordingly, the National Injury Surveillance Unit will be requested to consider measures to monitor and report on morbidity and mortality from paracetamol ingestion (whether accidental or intentional) on a national basis.

**Recommendation 6.1.1**

**Warning statements for analgesics remain in the SUSDP for the time being.**

**Comments**

The PMAA commented on this recommendation as follows:

*The TGA legislation has effective and suitable mechanisms for the introduction and phase-in of new or revised mandatory label changes.*

*For example, the Therapeutic Goods Order 48 (TGO48) was introduced for all new products on or after 1 July 1994, and then made applicable to all existing products from 1 July 1996 (copy of the forward to the Order is attached for information).*

*An additional mechanism via the TGA legislation is to add a condition of registration for each affected product included on the Australian Register of Therapeutic Goods (ARTG). This was used in the application of warning statements on royal jelly (included in unscheduled and listable products).*

*While we acknowledge that the latter is extremely resource intensive, both examples are viable and legislatively possible alternatives to the application of mandatory statements through the SUSDP entry for the substance and/or Appendix F. Both TGA options also provide for a greater level of flexibility on a case by case basis (through a centralised exemption mechanism), therefore negating the need for consideration of Recommendation 6.1.3.*

*The review and its recommendations canvass an enormous range of possible label changes for analgesic products, the majority as part of the registration of product, others as part of the SUSDP entry for the substance and/or Appendix F. Further, Recommendation 6.2 calls*
for the warning labels to be tested for useability prior to adoption.

We would therefore suggest that it would be more appropriate to consider the most effective mechanism for legislative underpinning, once all the revised labelling and the implementation timetable have been agreed.

TGA response

The TGA supports this recommendation. Until complementary legislation is enacted in all States and Territories, persons who are not within the scope of Commonwealth legislation (e.g. a person manufacturing and selling therapeutic goods within State borders) would be able to sell products without warning statements even where these statements are specified in Commonwealth legislation. See also the response to Recommendation 6.1.2 (below).

Recommendation 6.1.2

When all States and Territories have legislation to complement the Therapeutic Goods Act 1989, warning statements applicable to any substance for therapeutic use should be transferred from Appendix F - Part 1 of the SUSDP to (a) a new Order under section 10 of the Act; or (b) a schedule to Therapeutic Goods Order No.48 “General requirements for labels of drug products”, or a succeeding corresponding order.

Comments

The PMAA commented on this recommendation as follows:

We would urge all States and Territories (that have not already done so) to implement complementary legislation as soon as possible. The previous “sunset” clause, ie. The deadline that was agreed upon with the introduction of the Commonwealth legislation was effectively 1993. To date, only Victoria and New South Wales have implemented such legislation.

We would respectfully remind the jurisdictions that the need for complementary legislation goes well beyond the regulation of analgesics and without it, the States and Territories are permitting loop holes in the therapeutic goods legislation for unincorporated bodies/sole traders and those only dealing intra-State. This creates a disturbing possibility for inconsistencies in the quality, safety and efficacy evaluation of medicines, potentially resulting in the distribution of unsafe products within States and Territories.

TGA response

The TGA agrees with this recommendation and will advise the NDPSC accordingly. See also
Recommendation 6.1.3

In the meantime, the NDPSC explore a means of granting exemptions to the application of warning statements in particular cases, based on the knowledge of its members, advice from evaluation committees, merit and commonsense. Such exemption to be applicable in all jurisdictions simultaneously.

Comments

General agreement with this recommendation however it should also involve consultation with industry, manufacturers, the Pharmacy Guild, Poisons Information Centres and Consumers.

The PMAA reiterated comments made under Recommendation 6.1.1.

TGA response

The TGA will refer this recommendation to the NDPSC for further consideration noting that a mechanism for granting exemptions from warning statements may be included in future amendments to the Therapeutic Goods Regulations associated with the establishment of the NDPSC under the Therapeutic Goods Act 1989.

Recommendation 6.2

The proposed new analgesic warning labels should be tested for useability before being written into the SUSDP.

Comments

This recommendation was generally supported.

PMAA’s comment

We would wholeheartedly agree with the prior testing of warning statements for useability however, there is a need for a fundamental change in the approach to the regulations pertaining to labelling for the concept of useability and performance-based labelling to be fully embraced. Copy of our submission to the IC Inquiry into Packaging and Labelling is attached for information.
TGA response

The TGA will refer this recommendation, together with the PMAA’s comments, to the NDPSC for further consideration.

Recommendation 6.3

Sponsors should be guided by publications such as “Writing about medicines for people: useability guidelines for consumer medicine information” by David Sless and Rob Wiseman (Department of Health and Family Services, Canberra, 1997) in drafting labels, package inserts and consumer medicine information text and “Designing better medicine labels. Report to PHARM” by D Rogers et al (Communication Research Institute of Australia, 1995) in drafting labels, package inserts and consumer medicine information text.

Comments

This recommendation was generally supported.

PMAA’s comments

We would agree that, notwithstanding our comments above, such useful guidance to sponsors of all medicines should be incorporated into the respective TGA guidelines as an initial step towards performance-based labelling.

TGA response

The TGA will include reference to these publications in the Australian Guidelines for the Registration of Drugs, Volume 2 (AGRD2).

Recommendation 6.4

The NDPSC consider a new warning statement [notionally numbered 99] applicable to paracetamol to read:

WARNING - Prolonged use of this medication without a doctor’s advice or in more than the recommended dose may be harmful.

Comments
One respondent suggested that the phrase: “without a doctor’s advice” be deleted as currently there is a perception in the medical profession that paracetamol is safe and can be used in much larger doses than what is currently recommended. The warning statement would then read: “Prolonged use of this medication in more than the recommended dose may be harmful.”

It was also suggested a warning statement that paracetamol can cause liver failure if used in excessive doses be on the container label of affected products.

The PMAA pointed out that the proposed statement should replace the current SUSDP statements 34 & 35 and reiterated previous comments with regard to performance-based labelling, Appendix F to the SUSDP and implementation timetables.

**TGA response**

The TGA supports this recommendation, noting that it should replace current SUSDP warning statements 34 and 35. The suggestion that a warning statement that paracetamol can cause liver damage in excessive doses is not supported because of the danger of drawing attention to the use of paracetamol in suicide attempts (see also Recommendation 3.1)

The TGA will refer this recommendation and associated comments to the NDPSC for further consideration.

**Recommendation 6.5**

The NDPSC consider the following new warning statements to apply to aspirin products for inclusion in Appendix F - Part 1 of the SUSDP.[note: the numbers assigned to the proposed warnings are notional only]

100. WARNING - Unless a doctor has told you to, do not use [this product]/[name of product]
    - for a long time;
    - in the last 3 months of pregnancy;
    - if you have asthma or a stomach ulcer;
    - if you are allergic to aspirin or anti-inflammatory medicines;
    - in children under 2 years of age or in older children or teenagers with chickenpox, influenza or fever.
    See a doctor before taking [this product]/[name of product] for thinning the blood or for your heart.

101. WARNING - Unless a doctor has told you to, do not use [this product]/[name of product]...
product]  
• for a long time;
• in the last 3 months of pregnancy;
• if you have asthma or a stomach ulcer;
• if you are allergic to aspirin or anti-inflammatory medicines;
• in children under 2 years of age or in older children or teenagers with chickenpox, influenza or fever.

Comments

One respondent questioned the relevance of “for a long time” in these warning statements. It was proposed that a more descriptive measure of time be given.

The other concern with these warning statements was the statement “in children under 2 years of age or in children or teenagers with chickenpox, influenza or fever.” It was suggested that this statement could be broken into two statements to prevent ambiguity.

It was also noted that children under the age of 15 years should not be taking aspirin.

The PMAA reported that concern has been raised and clarification sought in regards to the use of the following terms:
- “unless a doctor has told you to… do not use” (negative);
- “if you have asthma” (implies absolute contraindication);
- “thinning the blood or for your heart” (confusing); and
- “older children” (ambiguous).

The Association suggested that these terms should be investigated in useability testing and pilot performance-based labelling of analgesics.

Apart from changes to the wording of the warning statements most respondents agreed that this recommendation was acceptable.

TGA response

The TGA accepts this recommendation in principle. It will be referred, together with associated comments, to the NDPSC for further consideration.

Recommendation 6.6

Subject to proposed SUSDP warning statement no.100 being adopted, clause 4 of the Therapeutic Goods Advertising Code should be amended by adding the following
exception to the entry for cardiovascular system diseases; “(v) when prescribed in the Standard for the Uniform Scheduling of Drugs and Poisons for aspirin”.

Comments

The PMAA noted that further discussion of this recommendation would be required subject to finalisation of Recommendation 6.5 and then, if necessary, referral to the Therapeutic Goods Advertising Code Council.

TGA response

The TGA accepts this recommendation in principle. It will be referred to the Therapeutic Goods Advertising Code Council for further consideration following finalisation of Recommendation 6.5.

Recommendation 6.7

The NDPSC consider the use of warning statement no.102 to replace those currently used for ibuprofen:

102. WARNING - Unless a doctor has told you to, do not use [this product]/[name of product]
    • for a long time;
    • in the last 3 months of pregnancy;
    • if you have asthma or a stomach ulcer;
    • if you are allergic to aspirin or anti-inflammatory medicines.

Comments

Once again the issue of the ambiguity of the statement “for a long time” was raised as a concern with warning statement 102. It was also suggested that warning statement 102 should be worded more clearly as to whether the warning refers to frequent/ regular dosing over a long period or occasional dosing over a period of time.

The PMAA drew attention to their earlier comments regarding Recommendation 6.5, performance-based labelling, SUSDP Appendix F, layout and implementation timetables.

TGA response

The TGA accepts this recommendation in principle. It will be referred, together with associated comments, to the NDPSC for further consideration.
Recommendation 6.8

The NDPSC consider the use of warning statement no.103 replacing those currently used for naproxen and mefenamic acid.

103. WARNING - Unless a doctor has told you to, do not use [this product]/[name of product]
  • for a long time;
  • if you have asthma or a stomach ulcer;
  • if you are allergic to aspirin or anti-inflammatory medicines.

Comments

As for 6.7 with regards the statement: “for a long time.”

It was also suggested that “in the last 3 months of pregnancy” be included on naproxen and mefenamic acid products indicated for spasmodic dysmenorrhoea, as patients may take these products for off-label indications.

PMAA’s comment

No further objections have been raised to this recommendation. However it has been suggested that when approved with expanded indications (recognising there would need to be a consequential change to the schedule 2 entries themselves), that similar warnings as applicable for ibuprofen be required for these substances.

TGA response

The TGA will refer this recommendation to the NDPSC for further consideration.

Recommendation 6.9

Following consultation with industry, sufficient time should be allowed for replacement of the old warning labels by the new and provision be made for either format to be used for an agreed period.

Comments

This recommendation was supported. The PMAA drew attention to their earlier comments
regarding implementation timetables.

**TGA response**

The TGA accepts this recommendation in principle and will refer it to the NDPSC, TGC and MEC for consideration in relation to other recommendations which may require changes to labelling.

**Recommendation 6.10**

The NDPSC consider amending the entry in Schedule 2 for paracetamol under sub-paragraph (c)(i) by deleting the words “or in a container with a child-resistant closure.”

**Comments**

The PMAA commented as follows.

*Concern has been expressed regarding the evidential basis of this recommendation. It is suggested within the review that such a restriction on packaging would be “prudent” in light of the UK experience but in other parts of the review, the relevance of the UK experience to Australia is questioned. Indeed Recommendation 5.2 calls for the monitoring of the impact of the UK regulatory action prior to any similar action being taken in Australia.*

*Concern has also been expressed regarding the regulatory impact of this recommendation, ie. about removing the option to package in child-resistant closures and mandating only blister or strip packaging. It has been suggested that this would potentially limit innovative packaging developments and may not be justifiable in the future.*

*Therefore, until satisfactory evidence to justify this recommendation is provided, industry cannot support it.*

*Given that the Therapeutic Goods Orders 20 and 33 (TGO 20 & 33) require child-resistant closures on all paracetamol solid dosage forms and liquid preparations (irrespective of the scheduling of the products), why do such packaging provisions still remain in the SUSDP schedule entries for paracetamol? Furthermore, the TGOs specify the types of the acceptable child-resistant closures following a review process of the closures by the relevant subcommittee of the Therapeutic Goods Committee (TGC).*

**TGA response**

The TGA does not support this recommendation. Child resistant closures are widely accepted
as being an effective means of reducing the risk of poisoning in children. It would be inconsistent to remove the option to use a child resistant closure on tablets or capsules of paracetamol while retaining it on liquid preparations. See also the responses to Recommendations 2.7 and 6.11.

In relation to the duplication of requirements for child resistant closures in the SUSDP and TGO 20 and 33, it is necessary to retain both references until complementary legislation is adopted in all States and Territories to avoid creating a gap in the legislation for sole traders operating within State borders (see also Recommendations 6.1.1 and 6.1.2).

**Recommendation 6.11**

**Therapeutic Goods Order No.20 be amended to require solid dose forms of paracetamol when present as either (a) the only therapeutically active substance or; (b) when combined with codeine or dihydrocodeine, to be packed exclusively in blister or strip packaging, subject to clause 6 of the Order.**

**Comments**

This recommendation was not supported by the PMAA for the reasons stated under Recommendation 6.10.

**TGA response**

The TGA does not support this recommendation for the reasons set out in the response to Recommendation 6.10 above.

**Recommendation 7.1**

**The Medicines Evaluation Committee give consideration to the content of Appendix 4 as the basis for a guideline on paracetamol.**

**Comments**

The PMAA commented as follows.

*This and the following recommendation propose expanded and comprehensive monograph-style guidelines for analgesic substances. This concept is supported for incorporation in the AGRD 2 and industry is proactively developing a similar appendix for ibuprofen (to be provided under separate cover).*
Effective implementation and appropriate phase in periods will need to be discussed and agreed. The following specific comments on the content of Appendix 4 have been received:

Indications
Osteoarthritis and tension headache should be specifically listed as the efficacy of paracetamol in the temporary relief of pain associated with this condition has been proven.

Dose
It is apparently now recognised that the minimum effective dose of paracetamol is around 650mg and that the optimal dose is 1000mg every 4 hours. The adult dose recommendation in single active ingredient products should reflect this. (This change will also remove the previous conflict between the single and combination dosage guidelines.)

(References are available upon request.)

We note that upon finalisation of the preceding recommendations, significant revision of these appendices will be required. We have therefore not endeavoured to incorporate such further amendment at this stage. For example, in light of recommendation 2.12, ie. To increase to a 15mg/kg dosage rate for liquid paracetamol, the proposed children’s dosage recommendations should be reviewed. Also, we recommend the inclusion of all warning statements and labelling requirements in these proposed AGRD 2 guidelines.

TGA response

The TGA will request the MEC to advise on the adoption of Appendix 4 as the basis for a guideline on paracetamol noting the specific issues that the PMAA has raised. The draft guideline on products containing ibuprofen to be developed by the PMAA will also be referred to the MEC when it becomes available.

Recommendation 7.2

The Medicines Evaluation Committee give consideration to the content of Appendix 5 as the basis for a guideline on aspirin.

Comments

The PMAA’s comments follow.
In general industry agrees with the content of Appendix 5 as a guideline on aspirin. However, the recommendation to remove children’s dosage is rejected. The review has not provided any evidence that the inclusion of appropriate dosage instructions for children who do not suffer the contraindicated conditions, has led to any compromise of safety.

We believe that the inclusion of relevant dosage information for children will assist healthcare professionals and/or adult carers in choosing a correct dose on the occasions where aspirin is considered appropriate.

This approach is consistent with harm minimisation principles.

Industry would support the inclusion of the term ‘on medical advice’ for children’s dosages providing the appropriate dosage levels are retained on the label after this statement.

As already noted, significant revision of the appendix will be required upon finalisation of the preceding recommendations.

TGA response

The TGA will request the MEC to advise on the adoption of Appendix 5 as the basis for a guideline on aspirin noting the specific issues that the PMAA has raised.

Recommendation 7.3

Subject to Recommendation 7.2 being agreed to, the TGA notify sponsors of aspirin products to remove specific doses of aspirin for children from labels when revised styles of SUSDP warning statements are in operation or earlier at the discretion of the sponsor with the words “on medical advice” to replace the children’s doses.

Comments

The PMAA rejected this recommendation. Refer to comments under Recommendation 7.2.

TGA response

The TGA notes the PMAA’s rejection of this recommendation. The advice of the MEC will be requested in conjunction with consideration of Appendix 5.