5 May 2014

ASMI Response to TGA Consultation: OTC nasal decongestants for topical use
Proposed advisory statements for labelling

ASMI (Australian Self Medication Industry) is the peak body representing companies involved in the manufacture and distribution of consumer health care 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 appreciates the opportunity to respond to the consultation paper on the proposed advisory statements for OTC nasal decongestant preparations for topical use, intended to be included in the next update of the Required Advisory Statements for Medicine Labels (RASML) when next updated.

It is noted that currently, Appendix 5 of ARGOM requires a statement advising against prolonged use, such as:
“If congestion persists for more than a few days, seek medical or pharmacist advice”.

The TGA consultation document details two proposed additional warning statements for OTC topical nasal decongestant preparations for topical use. ASMI wishes to provide comment on each statement, separately.

TGA proposed warning statement – “Frequent or prolonged use may cause nasal congestion to recur or worsen”

ASMI supports the inclusion of the above statement in RASML. It is important for consumers to understand the safety implications of frequent or prolonged use of OTC topical nasal decongestants.

TGA proposed warning statement – “Do not use for more than three days at a time unless advised by a doctor or pharmacist”

ASMI accepts that consumers require useful and clear information on the safe duration of use for OTC topical nasal decongestants and for this reason we agree in principle that a warning statement which contains advice on duration of use is required. ASMI also accepts that there should be consistency on duration of use statements between the labelling of products that contain the same active ingredient as well as those containing different OTC topical nasal decongestant active ingredients, unless there is evidence to indicate that different OTC topical nasal decongestants vary in their effects on the nasal mucosa. An evidence based approach should be followed when deciding on proposed warning statements.

Currently, the labels of OTC topical nasal decongestants contain recommended treatment durations that vary in wording, from “a few days”; “three days” and “five to seven days”. Despite this variation, we do not believe that there is any evidence of widespread misuse or overuse and rebound congestion, and it has been the development of the TGA OTC Medicine Monographs which has triggered the consideration or examination of the warning statements on labelling of these medicines, rather than any new safety concerns or safety signals.

The rationale for the TGA’s proposed three day duration, as presented in the RASML consultation, focuses on a fairly limited set of data. The literature on rebound congestion or rhinitis medicamentosa shows...
discordant results. The terms “rebound congestion” and “rhinitis medicamentosa” are considered by some researchers to be quite vague and may present diagnostic challenges.

Data on the recommended duration of use also varies considerably, from animal studies to clinical studies, using different evaluation and diagnostic techniques. The duration of use of topical nasal decongestants to cause rhinitis medicamentosa has been widely debated, and there is a range of studies showing results ranging from 3 days to 8 weeks. However as stated in two comprehensive reviews of the literature on balance, the risk of the condition is accepted to be greater following 10 days’ use.

While ASMI acknowledges that a duration of use statement is required, we have some concerns around the TGA’s proposed duration of use of three days, and suggest that the proposed three day duration should be amended to a longer timeframe. ASMI believes that the evidence base supports a longer duration than that proposed by the TGA.

ASMI notes that there is an inconsistent approach to duration of treatment globally, and different agencies have adopted different duration statements. Some sponsors also hold data to support treatment durations of 7 days or even longer. TGA therefore ought to examine the broad body of evidence and not necessarily simply adopt the most conservative treatment duration.

Australian standard reference texts

Australian healthcare professionals will generally refer to either the Australian Medicines Handbook (AMH), the Australian Pharmaceutical Formulary and Handbook (APF) or the PSA’s Non-Prescription Medicines in the Pharmacy, and the Australian Therapeutic Guidelines (TG) or electronic Therapeutic Guidelines (eTG). In particular, the AMH and APF are standard texts required to be kept in pharmacies as per the Pharmacy Board practice standards and these are the references used by the majority of practicing pharmacists.

ASMI notes that each of the above references recommends a treatment duration of no more than 5 days, due to the risk of rebound congestion (rhinitis medicamentosa):

Australian Medicines Handbook4: “Do not use this medicine more than recommended or for more than 5 days at a time as it can worsen your symptoms when you stop using it.”

Australian Pharmaceutical Formulary & Handbook5: “Topical decongestants should not be used for more than 5 days: prolonged use causes rebound congestion”

PSA’s Non-Prescription Medicines in the Pharmacy6: “Nasal decongestants should not be used for longer than 5 days at a time”

Australian Therapeutic Guidelines7: “maximum of 5 days” for oxymetazoline, tramazoline and xylometazoline.

The American Hospital Formulary Service Drug Information (AHFS)8 and the American Handbook of Non-Prescription Drugs9 recommend a duration of use of 3 to 5 days. While these references provide accurate and authoritative drug information, they are not used in Australian medical and pharmacy practices.

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4 Australian Medicines Handbook
5 Australian Pharmaceutical Formulary and Handbook 2012
6 PSA Non-prescription medicines in the pharmacy 2012
7 E-Therapeutic Guidelines - Respiratory
8 American Hospital Formulary Service Drug Information – EENT Preparations - Vasoconstrictors
ASMI does not believe that it is necessary to adopt the most stringent statement contained in US reference texts. The guiding principle should be that the statements on labelling are evidence based. On this basis, it may be appropriate to adopt labelling warning statements that are consistent with the Australian commonly used references, for example:

“Do not use for more than five days at a time unless advised by a doctor or pharmacist”

Global approach

ASMI accepts that where possible, Australian warning statements ought to be harmonised with equivalent regulatory bodies. In the case of OTC nasal decongestants, it is noted that there is no consistent approach to a duration of use warning statement.

The UK allows a 7 day duration of use statement on most products, as shown the SPC documents for these active ingredients. The US Monograph (1994) recommends a three day duration of use statement on labelling. Canada, in order for their market to deliberately align with the USA has proposed a three day duration statement in their draft Monograph but this has not yet been finally adopted. The Medsafe Label Statements Database does not contain any duration of use statement for OTC nasal decongestants, therefore it is likely that New Zealand products will reflect a similar variation as found currently in Australia. We also note that the recent TGA and Medsafe review of cough and cold medicines in children also considered OTC nasal decongestants and the review did not comment on the adequacy or otherwise of the existing labelling statements.

ASMI therefore sees no clear reason for harmonising with the US Monograph’s three day duration statement, in preference to any other warning statements currently used by other agencies or by Australian reference texts.

As an alternative, the TGA could also consider harmonising with the UK, by adopting the following statement:

“Do not use for more than 7 days at a time unless advised by a doctor or pharmacist”

As some Australian sponsors already have labelling that has a 7 day duration statement, this would allow those sponsors to continue using this statement on their labelling. This statement is supported by the reviews into rhinitis medicamentosa, which generally state that rebound congestion develops after 10 days’ use.

Individual Sponsor Data

Some sponsors have already included a duration of use warning on labels of products marketed in Australia. Individual sponsors have advised that they hold clinical data that justifies longer duration of action compared to the proposed three day statement - in some cases up to 7 or 10 days. These members will make separate submissions to this consultation.

The TGA may also want to give consideration to a mechanism regarding the RASML labelling statement if or when sponsors supply data that can support a longer duration than that finally adopted the TGA. For example, could a Section 14 exemption be issued to allow a longer duration statement, e.g. 7 days? If this is granted, could generics registered via the N2 OTC Monograph route subsequently apply or be allowed a longer duration? Or would an approval to use a longer duration be granted, which would result in a RASML amendment?
Conversely, some multi-national sponsors’ head office / global policies require that all affiliates adopt a single more restrictive label statement. While this may not pose regulatory problems, it may still lead to inconsistency among product labels, despite RASML requirements.

ASMI recommendations

ASMI understands that it will be difficult for all stakeholders to agree on the exact wording for a duration of use statement given that there is variation between other regulatory agencies’ requirements, there is variation between different sponsors’ positions and data, and there are differences between Australian standard texts and US standard texts. These different views make it difficult to reach universal agreement.

We also acknowledge that consumers require clear guidance on how long these products may be safely used, and that this should be conveyed on labelling. Given that a TGA OTC Monograph for these products is being proposed, it is important for some consistency among labels so that products containing OTC topical nasal decongestant active ingredients may have similar warning statements irrespective of their regulatory pathway for registration.

In order to achieve a “consensus” approach, ASMI recommends that the RASML statement:

- should not necessarily reflect the most stringent of all regulatory agencies or reference texts
- should reflect the overall evidence base
- should be consistent with current Australian standard health care professional recommendations
- should be able to co-exist with scenarios where sponsors may apply to use longer duration of use statements, should data be submitted to the TGA, or shorter statements due to corporate policy requirements

ASMI believes that two different approaches to a warning statement could be supported, for different reasons:

1. “Do not use for more than five days at a time unless advised by a doctor or pharmacist”
2. “Do not use for more than a few days at a time unless advised by a doctor or pharmacist”

Statement 1
The statement “Do not use for more than five days at a time unless advised by a doctor or pharmacist” is consistent with Australian recommended reference texts and Therapeutic Guidelines. Australian healthcare professionals would be familiar with this duration. It also provides a good margin of safety for consumers by being well below the 10 day duration that presents increased risk.

In ASMI’s view, this statement represents the most appropriate balance between assisting consumers, allowing a safety margin, and reflecting the body of evidence, and is therefore suitable as a default statement.

If this statement is adopted, individual sponsors should then also have the option of providing clinical data to justify use of a longer duration statement on their labelling. ASMI is aware that some sponsors would like to provide such data to justify a longer duration, such as “Do not use for more than 7 days at a time, unless advised by a doctor or pharmacist”. The 7 day statement is consistent with the UK approach, is within the general 10 day duration stated in the literature, and would allow some sponsors who currently have a 7 day duration to continue using their labelling.

Statement 2
The alternative of “a few days” could be useful as a general statement, that could co-exist alongside some products carrying a longer durations (e.g. 7 days, or 5 days, if data is provided to support this duration) or even shorter durations (due to restrictive corporate policies, where applicable) without the various labels appearing grossly inconsistent. A more general statement is more accommodating of variation than a specific statement.
A duration statement of “a few days at a time” is already used by some sponsors on OTC topical nasal decongestants and is consistent with an existing statement in RASML for paracetamol and ibuprofen (for example). ASMI notes that Appendix 5 of ARGOM states that sponsors require a statement on labelling with words to the effect of “If congestion persists for more than a few days, seek medical or pharmacist advice.”

This could provide a useful consensus that allows some labels to carry a different statement, if approved. It could also be suitable for applicants who use the TGA OTC Monograph route, as a default statement.

**Transitional arrangements**

ASMI requests a 2 year transitional period, or alternately allow these changes to be introduced together with the proposed updates to the Therapeutic Goods Order for labelling & packaging, as cough and cold products have recently had label changes following the TGA’s review of children’s cough & cold medicines in 2012. This will mean that sponsors would require one set of labelling changes rather than two. Sponsors will incur significant costs by requiring an additional two rounds of labelling changes resulting from this consultation together with changes to the TGO 69.

Some sponsors market many different OTC cough medicine brands, in a number of pack sizes. These sponsors in particular will incur additional, unexpected costs as a result of labelling changes following changes to RASML.

**Sponsor applications to TGA to update labels to new RASML statements**

Given the number of labelling changes that have been made recently to cough and cold products, ASMI considers that the TGA should allow all affected sponsors to use change code LLO – C1 application for all updates to labelling, irrespective of whether a sponsor’s existing (current) labels have a stricter warning statement than that which may be proposed in any changes to RASML. A C2 change should not be required to delete an existing warning statement that will be replaced by any new RASML statement.

**Conclusion**

ASMI thanks the TGA for the opportunity to comment on this consultation paper. ASMI supports the statement “Frequent or prolonged use may cause nasal congestion to recur or worsen”. However, we acknowledge that it will be difficult for all stakeholders to agree on a duration of use statement due to inconsistencies between global regulatory agency approaches, different corporate policies, and variation that appears in the medical literature itself.

ASMI has therefore recommended two possible approaches to a duration of use statement, namely either a “five day” or a “few days” duration, as we believe that these offer a suitable balance that does not reflect the most conservative duration, is consistent with recommendations in the Australian reference texts and guidelines, and still allows a margin of safety well within that which is associated with increased risk of rebound congestion in the literature.

Irrespective of which duration statement is eventually adopted by TGA, some sponsors will want to apply to the TGA for a longer duration statement, for example 7 days, which is consistent with the UK. The TGA should provide a mechanism for industry to make such applications and allow these longer duration statements on a case by case basis.