

A meeting of the National Drug Scheduling Advisory Committee (NDSAC) was held on Sunday, December 6 and Monday, December 7, 2015 at the Lord Elgin Hotel, Ottawa.

Present:

NDSAC members:

Dr. Carlo Marra (Chair); Dr. Tom Bailey (Vice Chair); Dr. Murray Brown, Ms. Drena Dunford; Dr. Melanie Johnson, Dr. Deborah Kelly, Ms. Judy McPhee, Ms. Kendra Townsend

Observers:

Dr. Ratna Bose – Natural and Non-prescription Health Products Directorate, Health Canada
Ms. Joan Sayer – Consumers Association of Canada

NAPRA Staff:

Carole Bouchard – Executive Director
Sarah Marshall – Manager, Professional and Regulatory Affairs, Committee Secretary

1.0 Call to order

1.1 Opening remarks

C. Marra welcomed everyone and called the meeting to order at 9:32 a.m. (ET) on December 6, 2015.

1.2 Conflict of interest declarations

C. Marra called for conflict of interest declarations. Dr. Murray Brown declared that he might be in a perceived conflict of interest for both submissions, since he worked for the applicant pharmaceutical company in the past. However, his employment with the company ended over 3 years ago and he did not work on any of the drug files under review at this meeting. The committee agreed that this did not represent an actual conflict of interest. Nevertheless, Dr. Brown felt more comfortable abstaining from the votes. The Chair agreed to proceed in this manner.

2.0 Approval of the agenda

A motion to approve the agenda as presented was put forward by K. Townsend, seconded by D. Dunford and approved by consensus.

3.0 Approval of minutes

3.1 Approval of the minutes from the September 7, 2014 meeting

A motion to approve the minutes from the NDSAC meeting of September 7, 2014 as posted on the NAPRA website was put forward by T. Bailey, seconded by J. McPhee and approved by consensus.

4.0 New Business

4.1 Request for :

- Schedule III status for a modified-release oral dosage form that provides 600 milligrams of ibuprofen (200mg Immediate Release(IR)/400mg Extended Release(ER)) or less per dosage unit for package sizes containing more than 31,200 milligrams of ibuprofen.

- Unscheduled status for a modified-release oral dosage form that provides 600 milligrams of ibuprofen (200mg Immediate Release(IR)/400mg Extended Release(ER)) or less per dosage unit for package sizes containing 31,200 milligrams or less of ibuprofen .

The committee reviewed and considered the application for drug scheduling. One request for interested party status was granted to Bayer Inc., Consumer Care. Three interrogatories were completed during the interrogatory process. One set of comments was received via the alternate method of participation.

At 11:00 a.m. on December 6, 2015, C. Marra welcomed representatives from Bayer Inc., Consumer Care: Dr. Wendy Arnott, Head, Global Regulatory Affairs Canada and Mr. Joseph Chan, Regulatory Affairs Manager. The Bayer representatives gave a short slide presentation to the committee, which was followed by a question and answer period.

At 1:00 p.m. on December 6, 2015, C. Marra welcomed representatives from Pfizer Consumer Healthcare: Mr. James Johnson, Regulatory Affairs Manager; Ms. Hilary Orr, Director of Regulatory Affairs and Mr. David Kellstein, Senior Director, Global Pain Management Franchise Team. The Pfizer representatives gave a short slide presentation to the committee, which was followed by a question and answer period.

The committee then discussed the information previously provided to them for review and consideration, as well as the information received during the company presentations and the subsequent question and answer periods.

The committee discussed the particularities of the modified-release formulation. There was concern that the introduction of this new drug delivery system for ibuprofen might lead to confusion in product selection. The committee agreed that a pharmacist should be available to help the patient with self-selection based on duration of pain, which was not well understood in the actual use and label comprehension studies provided by the applicant. Most importantly, members agreed that a pharmacist should be available to clarify the release properties of the modified-release product. The committee noted that the product labelling does not provide any information about the actual dose patients will receive over a 12 hour period. It was determined that accessibility to a pharmacist would help clarify that the modified-release formulation delivers the equivalent of 200 mg every 4 hours. Patients may see the mention of 600 mg on the label of the modified-release product and assume that it provides greater and faster pain relief than a 300mg or 400mg immediate release product, which could result in users taking more than recommended in order to receive adequate pain control, as seen in the actual use study.

Members concurred that a pharmacist should be available to reinforce and expand on product labelling. They noted that the allergy warnings were not well understood in the label comprehension study and that there is no information in the product labelling about whether the product can be chewed or crushed. In addition, members agreed that a pharmacist should be available to answer questions about the recommended age range for the product, which differs from that of the immediate release products. The committee noted that non-compliance in the actual use study was disproportionately higher in the low literacy groups and agreed that a pharmacist should be available to help these individuals. It was noted that a few drug interactions were missing from the

package insert and that the majority of drug interactions were missing from the outer labelling. Members also pointed out concerns with the possibility of patients inadvertently combining multiple ASA and NSAID products. Therefore, the committee agreed that a pharmacist should be available to answer patient questions about drug interactions. It was further noted that non-compliance in the actual use study was attributed to users voluntarily overriding directions, rather than to any difficulties with label comprehension. The committee saw this as evidence of the need for intervention beyond labelling and the need for accessibility to a pharmacist to promote appropriate use. These concerns were compounded by the fact that there is some evidence to support the fact that users of non-prescription drugs do not always consult the package directions, particularly if they are familiar with the drug. There was concern that patients might feel familiar with ibuprofen and therefore not consult the labelling and not identify important differences between the modified release and immediate release product.

Members then discussed concerns regarding the risk that patients will exceed the recommended duration of use, given the fact that the maximum duration of use was not well understood in the label comprehension study and actual use study. It was also noted that there is evidence in the literature supporting the fact that non-steroidal anti-inflammatory drugs (NSAIDs) are often used inappropriately in the non-prescription setting. The committee noted that a recommended frequency of re-treatment is not indicated in the product labelling and therefore patients could be following the directions on the label and still be taking the product on a regular basis long-term. The committee expressed concern about the serious adverse events that are known to occur with NSAIDs such as ibuprofen, particularly as dose and duration of use increase. It was agreed that a pharmacist should be available to reinforce the appropriate duration of use, with the goal of reducing the risk of patients experiencing serious adverse events. The committee acknowledged that the possibility of serious adverse events is not unique to the modified-release formulation and also applies to immediate release products. However, the committee was of the opinion that the results of the user testing for the modified-release product further confirm this possibility.

C. Marra led the group in a review of the applicability of the National Drug Scheduling Factors. It was agreed that the following scheduling factors were applicable to ibuprofen when sold in a modified-release oral dosage form that provides 600mg or less per dosage unit:

- #I-4, I-6, II-2, II-10, III-3 and III-5

The committee discussed the overall best fit for the scheduling of this substance. While the concerns related to the risks of long-term use of ibuprofen in a non-prescription setting and the need for a pharmacist to be available to expand on adverse drug reaction and drug interaction information are common for all ibuprofen products, the committee noted a number of concerns specific to the modified release product. In particular, the need to help patients select the most appropriate product based on duration of pain, to help patients understand the actual dose received over a 12 hour period from the modified release product and to reemphasize the recommended age range for this product, led the committee to determine that a pharmacist should be available to assist patients in their selection of the modified release product. It was agreed that the best placement for this drug would be Schedule III for all package sizes.

The committee did not want to finalize its recommendation until it receives confirmation of Health Canada's final decision regarding the removal of this substance from the Prescription Drug List and has the opportunity to review the final Health Canada approved product monograph and product labelling. However, members agreed that a draft motion could be made pending Health Canada's final decision.

A draft motion was put forward:

It was moved by D. Kelly, seconded by D. Dunford: **to recommend that ibuprofen or its salts, when sold in a modified-release oral dosage form that provides 600mg or less per dosage unit - be granted Schedule III status, subject to verification of the final approved labelling and removal from the Prescription Drug List**

Motion carried. All members agreed to the above noted motion with one abstention as explained in section 1.2.

It was further moved by K. Townsend, seconded by J. McPhee: **to recommend that the current National Drug Schedules listings for ibuprofen be amended for clarity once the modified release product becomes listed, to specify that they only apply to immediate release products.**

Motion carried. All members agreed to the above noted motion

The 30-day consultation period will not begin until the committee has reviewed the final approved product monograph and product labelling following Health Canada's final decision regarding the removal of this substance from the Prescription Drug List. Once this occurs, the committee will finalize its draft recommendation and forward it to the NAPRA Executive Committee, which will trigger the start of the 30-day consultation period.

4.2 Request for Schedule III status for esomeprazole 20mg (as esomeprazole magnesium trihydrate) when sold for the 14-day treatment for frequent heartburn at a daily dose of 20 milligrams in package sizes containing up to 840 milligrams of esomeprazole

The committee reviewed and considered the application for drug scheduling. No requests for interested party status were received for this review. One set of comments was received via the alternate method of participation.

At 10:00 a.m. on December 7, 2015, C. Marra welcomed representatives from Pfizer Consumer Healthcare: Ms. Turkan Akturk, Senior Regulatory Affairs Manager; Ms. Hilary Orr, Director of Regulatory Affairs and Dr. Charles Pollack, Senior Director, Global R&D. The Pfizer representatives gave a short slide presentation to the committee regarding the request for Schedule III status for esomeprazole 20mg (as esomeprazole magnesium trihydrate) when sold for the 14-day treatment for frequent heartburn at a daily dose of 20 milligrams in package sizes containing up to 840 milligrams of esomeprazole, which was followed by a question and answer period. The committee then discussed the information previously provided to them for review and consideration, as well as the information received during the company's presentation and the subsequent question and answer period.

The committee recognized the efforts of the applicant to add additional drug interaction and warning information to the outer label of their product based on concerns noted in the minutes of the June 2014 NDSAC meeting for the review of omeprazole. The committee noted that the drug interaction information in the product monograph and product labelling is nevertheless incomplete. A number of serious or contraindicated drug interactions highlighted in references consulted by the committee, such as rilpivavine, risedronate DR and citalopram, are missing from the product monograph and labelling. The committee was concerned that the process for updating drug interaction information in the product information cannot occur quickly enough to capture new drug interaction information. In addition, the committee noted that some of the information in the drug interaction section of the labelling could be misleading or confusing for the patient. Members agreed that the wording and organization of the warnings section of the labelling may make it difficult for patients to fully understand when it is appropriate for them to use the product. Furthermore, the labelling does not provide information to patients on how long before eating the product should be taken. Therefore, the committee concurred that a pharmacist is required to expand on drug interaction information and clarify information in the directions for use and warnings sections of the product labelling.

Members discussed the possible use of esomeprazole 20 mg in a chronic, persistent or recurrent fashion exceeding the recommended re-treatment interval, due to the episodic and recurring nature of heartburn in those prone to the condition. The literature describes the recurring and episodic nature of heartburn and problems with the inappropriate use of proton pump inhibitors. Furthermore, it is noted that clinical studies with esomeprazole 20mg indicate that symptoms might return within 7 days in up to one quarter of patients. In addition, the duration of use and appropriate interval for re-treatment were some of the least well understood information, particularly in subpopulations, in the label comprehension study provided by the applicant. Members indicated that due to the fact that proton pump inhibitors are used for frequent heartburn and the literature shows that they are more effective than histamine receptor blockers, patients may be more likely to continue to use them for more severe symptoms without consulting a healthcare professional. Therefore, it was seen as important to have esomeprazole 20 mg provided to patients in quantities that are appropriate for the recommended dose and duration of use of 14 days.

Members noted that even if used according to the labelling, if used recurrently every 4 months, the patient could benefit from discussion with the pharmacist prior to re-treatment. The patient's overall condition could change within the 4 months between treatments, yet there is evidence to support the fact that users of non-prescription drugs do not always consult the package directions, particularly if they are familiar with the drug. A pharmacist could assess the patient to determine if the product is still appropriate.

The committee was concerned with the potential for long-term use, as use beyond 14 days could mask the symptoms of serious disease such as ulcers, erosive esophagitis and malignancies and could lead to serious adverse effects such as infections or fractures. The committee was concerned that such adverse events would be under-reported in a non-prescription setting. Committee members agreed that a pharmacist is required to reinforce the appropriate duration of use and re-treatment schedule and refer the

patient for further investigation if symptoms persist beyond 14 days, particularly for a drug that is new to the non-prescription setting.

C. Marra led the group in a review of the applicability of the National Drug Scheduling Factors. It was agreed that the following scheduling factors were applicable to esomeprazole when sold for the 14-day treatment for frequent heartburn at a daily dose of 20mg

- #I-6, II-2, II-7, II-8, II-9, II-10, III-1, III-2, III-3 and III-5

The committee discussed the overall best fit for the scheduling of this drug in view of the drug profile and the need for a limited duration of use as a non-prescription product. Members agreed that Schedule II would be the best fit for esomeprazole 20mg in package sizes that match the recommended dose and duration of use of the product of 14 days. Furthermore, the committee agreed that, independently of how they are presented, package sizes that may contain more than one course of treatment would reduce the opportunity for pharmacist intervention and should remain in Schedule I to ensure that patients receive appropriate monitoring and follow-up to mitigate the increased risks of long-term use.

The committee did not want to finalize its recommendation until it receives confirmation of Health Canada's final decision regarding the removal of this substance from the Prescription Drug List and has the opportunity to review the final Health Canada approved product monograph and product labelling. However, members agreed that a draft motion could be made pending Health Canada's final decision.

A draft motion was put forward:

It was moved by D. Kelly, seconded by D. Dunford: **to recommend that**

- **esomeprazole or its salts, when sold for the 14-day treatment for frequent heartburn at a daily dose of 20mg, in package sizes of no more than 280 mg of esomeprazole - be granted Schedule II status, subject to verification of the final approved labelling and removal from the Prescription Drug List and**
- **esomeprazole or its salts, EXCEPT when sold for the 14-day treatment for frequent heartburn at a daily dose of 20mg in package sizes of no more than 280 mg of esomeprazole - be retained in Schedule I, subject to verification of the final approved labelling and removal from the Prescription Drug List**

Motion carried. All members agreed to the above noted motion with one abstention as explained in section 1.2.

The 30-day consultation period will not begin until the committee has reviewed the final approved product monograph and product labelling following Health Canada's final decision regarding the removal of this substance from the Prescription Drug List. Once this occurs, the committee will finalize its draft recommendation and forward it to the NAPRA Executive Committee, which will trigger the start of the 30-day consultation period.

5.0 Updates

5.1 Natural and Non-prescription Health Products Directorate

Dr. R. Bose provided an update on the acetaminophen 2nd technical discussion that took place on November 24, 2015.

Dr. R. Bose also shared information on the risk assessment that is currently on-going internationally regarding the cardiovascular risks with the use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).

Regulatory requirements with respect to the Plain Language Labelling that will be coming into force on June 13, 2017 for non-prescription drugs were also discussed. These requirements will require the presence of a Product Facts Table on the outer product labels. This will provide safety information in an easy-to-read format using plain language; so that consumers can more easily identify products, understand the risks associated with the drug and use the products as directed.

5.2 NAPRA Strategic Plan 2016-2017

C. Bouchard provided an update on NAPRA's Strategic plan for 2016-2017, including plans to continue the second phase of the review of the National Drug Schedules.

6.0 Next meeting

Tentatively set for March 7-8, 2016.

7.0 Adjournment

The meeting was adjourned Monday, December 7, 2015 at 12:21 p.m.