A meeting of the National Drug Scheduling Advisory Committee (NDSAC) was held on Sunday, September 9, 2018 at the Lord Elgin Hotel, Ottawa.

Present:

NDSAC members:

Dr. Tom Bailey (Chair); Ms. Kendra Townsend (Vice Chair); Dr. Murray Brown; Dr. Drena Dunford; Dr. Melanie Johnson; Dr. Deborah Kelly; Dr. Jason Kielly (via teleconference)

Observers:

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

NAPRA Staff:

Sarah Marshall – Manager, Professional and Regulatory Affairs, Committee Secretary

Regrets:

Ms. Judy McPhee

1.0 Call to order

1.1 Opening remarks

T. Bailey welcomed everyone and called the meeting to order at 9:01 a.m. (ET) on Sunday, September 9, 2018.

1.2 Conflict of interest declarations

T. Bailey called for conflict of interest declarations. Three members indicated a potential conflict of interest. K. Townsend is involved in research trials that are funded by Astra Zeneca, who markets a prescription-only esomeprazole product, but there is no link to Pfizer and Astra Zeneca does not market any competing non-prescription products. M. Brown worked for Astra Zeneca and Pfizer in the past, but was not involved in any of the files related to acid reduction treatments. Furthermore, he has had no interest in these companies, financial or otherwise, for more than 6 years. D. Kelly is involved in a de-prescribing project, which includes de-prescribing of long-term use of prescription proton pump inhibitors as well as other medications, but which evaluates use on a population basis and is not related to scheduling status. The committee discussed these cases and determined that they did not present a real conflict of interest. The committee agreed that each could participate in the meeting. The appropriate conflict of interest documentation was collected by NAPRA staff.

2.0 Approval of the agenda

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

3.0 Approval of the minutes from the June 11, 2017 NDSAC meeting

A motion to approve the minutes from the NDSAC meeting of June 11, 2017 as posted on the NAPRA website was put forward by M. Brown, seconded by M. Johnson and approved by consensus.

4.0 New Business

4.1 Request for Schedule III status for esomeprazole magnesium trihydrate 20 mg delayed release capsules when sold for the 14-day treatment for frequent heartburn for the following package sizes: 280 mg (14 capsules), 560 mg (28 capsules), 840 mg (42 capsules)

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

At 10:15 a.m., T. Bailey welcomed representatives from Pfizer Consumer Healthcare: Dr. Nardine Nakhla, Dr. David Johnson and Ms. Anjali Newman. 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, including the Pfizer submission and the Alternate Method of Participation submissions, as well as the information received during the presentation and the subsequent question and answer period.

The committee remained concerned about the risks of long-term use of esomeprazole in a chronic, persistent or recurrent fashion that exceeds the recommended duration of use and re-treatment interval. The literature provides evidence of the recurring nature of heartburn and there is evidence to suggest that heartburn is likely to return before the approved re-treatment interval of 4 months. It was noted that the re-treatment interval was not well understood by sub-populations in the label comprehension study. In addition, significant changes to the labelling have occurred since the study without a repeat label comprehension study being conducted. The committee noted a risk that patients will continue to self-treat with esomeprazole if it was effective for them in the past and indeed are seeing such cases in practice. Members agreed that this risk is increased with package sizes that exceed the recommended duration of use, as such package sizes imply that this amount of medication is safe to take without the intervention of a healthcare professional.

Additional evidence provided since the last NDSAC review of this molecule demonstrated that esomeprazole is unlikely to cause serious adverse effects or mask the symptoms or delay the diagnosis of serious disease when used appropriately for 14 days. However, although the evidence is conflicting and causality has not been established, members agreed that there is a possible association between the long-term use of esomeprazole and serious adverse effects such as infections, fractures and kidney problems, among others. Members also agreed that, although the risk is low, long-term self-treatment with esomeprazole may mask the symptoms or delay the diagnosis of serious conditions. Therefore, the committee agreed that a pharmacist should be available to reinforce the appropriate duration of use and re-treatment schedule, assess the continued appropriateness of self-treatment, refer patients to a physician or other healthcare provider when appropriate and ensure that patients using the product long-term are monitored for potential serious adverse effects. The committee also agreed that package sizes exceeding the recommended duration of use are not appropriate as they are not consistent with the Health Canada approved duration of use for the non-prescription environment and could contribute to long-term use and its associated risks.

Members were concerned that the drug interaction information in the product labelling remained incomplete, despite the committee having noted similar concerns in 2015. The committee acknowledged that some of the potential pharmacokinetic interactions with esomeprazole have not been found to be clinically significant. However, the NDSAC was

particularly concerned with the lack of warning about the potentially serious drug interactions with rilpivirine and selective serotonin re-uptake inhibitors, particularly citalopram and escitalopram, which are supported by numerous references. During the meeting, the Pfizer representatives indicated that they have submitted a labelling change to Health Canada to update the product monograph (including the patient information leaflet) and product labels to include information on these two interactions. The committee agreed that, should these changes be made as indicated, it would alleviate a number of their concerns regarding the need for a pharmacist to expand on limited information in the product labelling.

The committee was concerned about extending the results of the Canadian label comprehension study provided to the current labelling, given the large number of changes that have been made to the labelling since the time of the study. The committee decided that a pharmacist should be available to clarify the labelling, given the lack of evidence to support comprehension of the current labelling. A pharmacist could also assist patients with self-assessment and identification of alarm symptoms or other situations in which they should not take the product and reinforce the appropriate duration of use and re-treatment interval to minimize the risks of long-term use. However, given the additional post-market safety data for esomeprazole in self-selection environments in other jurisdictions since the previous NDSAC review, members agreed that pharmacist intervention would not be required in all cases. The committee noted that this decision is dependent on the proposed labelling changes. Should the drug interaction information remain incomplete, members agreed that the safety risks would require the intervention of a pharmacist.

T. Bailey led the group in a review of the applicability of the National Drug Scheduling Factors. It was determined that, should the product monograph and drug labels be updated as indicated by Pfizer, the following scheduling factors were applicable to esomeprazole magnesium trihydrate 20 mg delayed release capsules when sold for the 14-day treatment for frequent heartburn:

- #I-6, II-2, III-1, III-2, III-3, III-5.

The committee discussed the overall best fit for the scheduling of this drug. The committee noted that, with the exception of the concerns regarding limited drug interaction information in the labelling, many of its concerns were related to the risks of long-term self-treatment with esomeprazole. As such, the NDSAC determined that, should the product monograph and labelling be updated as indicated, Schedule III would be the best fit for package sizes consistent with the Health Canada approved duration of use of 14 days for the non-prescription setting.

The committee did not want to finalize its recommendations until it has the opportunity to review the final revisions to the product monograph and labelling regarding drug interactions. However, members agreed that a draft motion could be made pending receipt and review of the updated product monograph and labelling.

A draft motion was put forward:

It was moved by K. Townsend, seconded by D. Kelly: to recommend that **esomeprazole or its salts, when sold for the 14-day treatment for frequent heartburn at a daily dose of 20 mg, in package sizes of no more than 280 mg of esomeprazole, be granted Schedule III status, and esomeprazole or its salts, EXCEPT when sold for the 14-day treatment for frequent heartburn at a daily dose of 20 mg in package sizes of no more than 280 mg of esomeprazole, be retained in Schedule I; subject to verification of the final revisions to the Health Canada approved product monograph and labelling regarding drug interactions.**

Draft Motion carried. All members agreed to the above noted draft motion.

The 30-day consultation period will not begin until the committee has reviewed the final revisions to the Health Canada approved product monograph and labelling regarding drug interactions. Once this occurs, the committee will finalize its draft recommendations and forward them to the NAPRA Board of Directors, which will trigger the start of the 30-day consultation period.

5.0 Updates

5.1 Natural and Non-prescription Health Products Directorate

S. Ghimire provided an update on the activities of the Natural and Non-Prescription Health Products Directorate and Health Canada.

The Plain Language Labelling (PLL) requirements for non-prescription drugs came into effect on June 13, 2017. During the first year of its implementation Health Canada received approximately 400 PLL submissions. These submissions have used a variety of flexibilities available within the *Good Label and Package Practices Guide* (GLPPG) for non-prescription drugs and natural health products. Also, Health Canada held a "Lessons Learned" session with stakeholders in May 2018 to identify issues or concerns with the implementation of the PPL regulations. Based on the feedback, the guidance is being revised to provide more clarity to the stakeholders.

In February 2018, Health Canada published Next Steps on the self-care framework whereby a phased approach was proposed. The first phase (Fall 2018) will introduce, for consultation, targeted amendments to the *Natural Health Products Regulations* to improve labelling of natural health products. Phase 2 (early 2019) will introduce, for consultation, targeted amendments to the *Food and Drug Regulations* to introduce a risk-based approach to regulatory oversight for non-prescription drugs. Phase 3 (2020) will introduce, for consultation, regulatory amendments to address evidence standards for similar health claims, extending risk-based regulatory oversight, and seeking additional powers for Health Canada (e.g., recall or label change).

Health Canada published (July, 2018) a Notice of intent to amend the Prescription Drug List to include phytocannabinoids produced by, or found in, the cannabis plant and substances that are duplicates of such phytocannabinoids. This will be effective when the *Cannabis Act* and Regulations come into force. Health Canada also consulted on a new cost-recovery framework for drugs and medical devices. The revised fee proposal will be effective April 1, 2019.

5.2 NAPRA Strategic Plan 2019-2023

S. Marshall provided an update on the development of the NAPRA Strategic Plan for 2019-2023, including plans to continue moving forward on the review of the NDS program.

6.0 Next meeting

Tentatively scheduled for December 2-3, 2018.

7.0 Adjournment

The meeting was adjourned at 1:47 p.m (ET).