

## Minutes - National Drug Scheduling Advisory Committee Meeting – December 3-4, 2023

A meeting of the National Drug Scheduling Advisory Committee (NDSAC) was held on Sunday, December 3, 2023 and Monday, December 4, 2023 at the Lord Elgin Hotel, Ottawa.

### **Present:**

#### **NDSAC members:**

Jason Kielly (Chair); Vaughn Chauvin; Michael Hamilton; Husayn Kassam; Carole Kierstead (virtual attendance); Kevin Pothier; Marjorie Rempel Friesen

#### **Observers:**

Joan Sayer – Consumers Association of Canada (virtual attendance)  
Michel Ntemgwa - Natural and Non-prescription Health Products Directorate, Health Canada  
Kevin Bernardo – Marketed Health Products Directorate, Health Canada (virtual attendance on Dec 3)

#### **NAPRA Staff – Committee Secretariat:**

Sarah Marshall – Manager, Professional and Regulatory Affairs  
Sarah ter Huurne – Senior Pharmacist Specialist, Professional and Regulatory Affairs  
Krista Jajko – Project and Policy Advisor, Professional and Regulatory Affairs (virtual attendance)

### **1.0 Call to order**

#### **1.1 Opening remarks**

J. Kielly welcomed everyone and called the meeting to order at 9:10 a.m. (ET) on Sunday, December 3, 2023. The meeting recessed at 4:06 p.m. (ET) on December 3, 2023 and resumed again at 9:05 a.m. (ET) on December 4, 2023.

#### **1.2 Roll call and declaration of quorum**

J. Kielly noted the members in attendance and declared quorum.

#### **1.3 Conflict of interest declarations**

J. Kielly called for conflict-of-interest declarations. None of the members had any conflicts of interest to declare.

#### **1.4 Confidentiality Reminder**

J. Kielly reminded participants and observers of the confidentiality policies in effect.

### **2.0 Approval of the agenda**

A motion to approve the agenda as presented was put forward by M. Hamilton, seconded by V. Chauvin and approved by consensus.

### **3.0 Confirmation of approval of the minutes from the March 5, 2023 NDSAC meeting**

The minutes of this meeting had previously been approved by the NDSAC members via email. A motion to formally confirm approval of the minutes from the NDSAC meeting of March 5, 2023 as posted on the NAPRA website was put forward by V. Chauvin, seconded by H. Kassam, and approved by consensus.

**4.0 New Business**

**4.1 Request for Schedule III status for acetaminophen and ibuprofen, when sold in oral, fixed-dose combinations, in package sizes containing either more than 36,000 mg of acetaminophen or more than 18,000 mg of ibuprofen**

and

**Unscheduled status for acetaminophen and ibuprofen, when sold in oral, fixed-dose combinations, in package sizes containing 36,000 mg or less of acetaminophen and 18,000 mg or less of ibuprofen**

The committee reviewed and considered the application for drug scheduling, as well as additional information submitted through the Interested Party process and the Alternate Method of Participation. BioSyent Pharma Inc. (BioSyent) was granted interested party status. No interrogatories were completed during the interrogatory process. The committee received two submissions via the alternate method of participation.

At 9:45 a.m., J. Kielly welcomed the representative from BioSyent: Navid Ashrafi. The BioSyent representative gave a concise slide presentation to the committee, which was followed by a question-and-answer period.

At 10:45 a.m., J. Kielly welcomed representatives from Haleon: Chanbin Kim, Peter Gao, and Stella Chan. The Haleon representatives gave a concise slide presentation to the committee, which was followed by a question-and-answer period.

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

Members were concerned about the potential risks to consumers of fixed dose combinations (FDCs) of acetaminophen and ibuprofen, particularly from off-label use in high doses or on a long-term basis. While the safety profile of FDCs of acetaminophen and ibuprofen appears to be consistent with that of the individual ingredients, the individual ingredients are known to cause serious adverse events which are documented in the product monographs, post-market surveillance, and in the literature. For example, ibuprofen may increase the risk of cardiovascular events, renal toxicity and gastrointestinal toxicity including stomach bleeding. Acetaminophen may cause liver toxicity, especially when used off-label in high doses. While there is no evidence of a pharmacokinetic interaction between acetaminophen and ibuprofen, both drugs can cause serious drug interactions. For example, both drugs interact with warfarin, as well as many other medications. Although serious adverse effects and interactions with ibuprofen and acetaminophen are uncommon at the non-prescription dose and duration of use, the committee noted that patients with risk factors are more susceptible to experiencing serious adverse events, even at normal therapeutic dosage levels, and that the risks have been shown to augment with increased dose and duration of use.

The committee discussed concerns with long-term use, given the increased risks of adverse effects with increased duration of use. Additionally, although taking a FDC of acetaminophen and ibuprofen for the non-prescription duration of use of 3-5 days is not expected to significantly delay recognition or mask the symptoms of serious disease, longer treatment could potentially cause issues in this regard. While FDCs of acetaminophen and ibuprofen are only indicated for short-term use, there is evidence that acetaminophen and ibuprofen are used on a persistent, chronic or recurrent basis. In addition, the labels submitted in this review included mention of chronic or recurring conditions such as arthritis, backache and menstrual pain. Given the risks of serious adverse events, the committee agreed that patients using the drug on a chronic, persistent or recurring basis should consult with a pharmacist to determine appropriateness, monitor for adverse events, and determine whether further health professional intervention is required.

Members also discussed the risks of high doses leading to acetaminophen-induced liver toxicity. Misuse of acetaminophen resulting in overdose, including inadvertent duplication of treatment linked to confusion in product selection, has been well documented in the literature. New evidence in this review indicated that labelling is not sufficient to prevent the risks of unintentional acetaminophen overdose. As one example, in the new label comprehension study included in this review, the two endpoints on understanding not to use this product with other drugs containing acetaminophen failed to meet the pre-defined success criteria. Given the large number of warnings required for each component on the labelling of FDCs of acetaminophen and ibuprofen, the committee determined that a pharmacist should be available to provide education on the potential risks of acetaminophen-induced liver toxicity and to reinforce the appropriate dose and duration of use, especially with the purchase of large quantities.

Further, the committee noted that a pharmacist should be available to reinforce or expand on product labelling and assist with product selection. As noted earlier, the labelling for FDCs of acetaminophen and ibuprofen can be complex and overwhelming due to the many warnings required for each component. Many of these warnings on the outer label are therefore very general and non-specific statements, providing patients with minimal information to assist with self-selection. The committee determined that the availability of a pharmacist could help patients interpret the label and determine which warnings may apply to them. In addition, the label comprehension study submitted by the applicant indicated that a significant number of patients may need pharmacist support to find and understand relevant information among the large amount of label information, especially since the endpoints that did not meet pre-defined success criteria were some of the most important safety considerations for FDCs of acetaminophen and ibuprofen. There was agreement that a pharmacist could assist patients in determining when the FDC of acetaminophen and ibuprofen might be appropriate for them, amongst the vast number of products available to treat pain and fever, as well as educate on the risks of overdose and long-term use of acetaminophen and ibuprofen outlined above.

J. Kielly 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 fixed-dose combinations of acetaminophen and ibuprofen:

- #I-4, I-6, II-2, II-8, III-1, III-3, III-5

The committee discussed the overall best fit for the scheduling of FDCs of acetaminophen and ibuprofen. The committee agreed that a pharmacist must be available to reinforce or expand on complex product labelling and assist with product selection, especially given the potentially confusing and overwhelming amount of warnings and information on the labels of FDCs of acetaminophen and ibuprofen and the fact that patients with risk factors are more susceptible to experiencing serious adverse events, even at normal therapeutic dosage levels. Therefore, the committee agreed that an Unscheduled environment was not appropriate.

Members agreed that the greatest potential risks to consumers of FDCs of acetaminophen and ibuprofen are the risks of acetaminophen overdose and of long-term use, which can both result in serious adverse effects, including liver toxicity, cardiovascular events, renal toxicity and gastrointestinal toxicity including stomach bleeding. Therefore, the committee determined that package sizes above the maximum duration of use approved for the non-prescription setting should be Schedule II, to ensure the opportunity to reinforce the appropriate dose and duration of use and ensure assessment and monitoring, to reduce the associated risks of high doses and chronic, persistent or recurrent use.

**MOTION:** It was moved by J. Kielly, seconded by M. Hamilton to recommend that:

Acetaminophen and ibuprofen in oral, fixed-dose combinations, in package sizes containing 20,000 mg or less of acetaminophen and 6,000 mg or less of ibuprofen, remain in Schedule III and

Acetaminophen and ibuprofen in oral, fixed-dose combinations, in package sizes containing either more than 20,000 mg of acetaminophen or more than 6,000 mg of ibuprofen, remain in Schedule II

**Motion carried.** All members agreed to the above noted motion.

This recommendation will be reported to the NAPRA Board of Directors.

**4.2 Request for Unscheduled status for brimonidine tartrate ophthalmic solution in concentrations up to and including 0.025%, used for the relief of redness of the eye due to minor eye irritations caused by environmental allergies, dryness and fatigue for adults of 18 years and older**

The committee reviewed and considered the application for drug scheduling. The committee noted the new information (post-market safety data) provided since the last review. No requests for interested party status and no comments via the alternate method of participation were received for this review.

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At 9:30 a.m. on December 4, 2023, J. Kielly welcomed representatives from Bausch + Lomb: Gaganpreet Bassi, Melinda DiVito, and Michelle Baron. The Bausch + Lomb representatives gave a concise slide presentation to the committee, which was followed by a question-and-answer period.

The committee then discussed all the information previously provided to them for review and consideration, as well as the information received during the presentation and the subsequent question-and-answer period.

The committee discussed the relative newness of ophthalmic brimonidine 0.025% in the self-selection environment in Canada. It was noted that ophthalmic brimonidine has been available at higher concentrations in prescription products for decades, therefore a lot is known about the safety of the ingredient. Low-dose ophthalmic brimonidine has now been available in Canada in the self-selection environment for approximately 17 months and has been available in the United States for over five years. While post-market data on the 0.025% concentration is still limited, the data is increasing and continues to show an absence of any significant safety signals.

Members discussed the fact that redness of the eye can be a recurring condition and the product labelling does not provide information on appropriate retreatment intervals. The information about when to stop use and seek medical attention was not tested in a label comprehension study. Therefore, a pharmacist could help to promote appropriate duration of use of this product. However, it was noted that the information to date has not shown any evidence of tachyphylaxis and only minimal rebound redness with brimonidine 0.025% ophthalmic drops. Clinical trials have demonstrated safety up to four weeks and post-market safety data to this point, while limited, has not identified any significant safety signals.

In addition, while the product is indicated for relief of redness of the eye due to minor irritations caused by environmental allergies, dryness and fatigue, there can be many causes or conditions that may lead to eye redness. There are currently many marketed products for the treatment of eye redness and other eye conditions available in the non-prescription market, and therefore the place in therapy of this particular product may not be clear. A pharmacist could provide advice on appropriate symptoms management, assist with product selection, and advise on place in therapy of this product amongst the many other potential ophthalmic treatments. However, the lack of significant safety signals to date was again acknowledged.

The committee was also concerned about the potential for use in children, as this drug is only indicated for individuals 18 years of age and older since safety in children has not been established. The wording of the age range in the product insert could be confusing and this drug has a different age range than other eye redness relievers. However, after a thorough examination, it was determined that the evidence showed that the risks to children of 0.025% ophthalmic brimonidine would be low.

J. Kielly 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 brimonidine tartrate ophthalmic solution in concentrations up to and including 0.025%, used for the relief of redness

of the eye due to minor eye irritations caused by environmental allergies, dryness and fatigue for adults of 18 years and older:

- #III-3 and III-5

The committee discussed the overall best fit for the scheduling of brimonidine tartrate ophthalmic solution in concentrations up to and including 0.025%, used for the relief of redness of the eye due to minor eye irritations caused by environmental allergies, dryness and fatigue for adults of 18 years and older. Overall, the committee agreed that while a pharmacist could be helpful to promote appropriate use, including appropriate indications, age and duration of use, the evidence to date has demonstrated safety up to four weeks and has not identified any significant safety signals. There is no indication that use of this product would delay recognition or mask the symptoms of serious disease and the risks to children of the amount of brimonidine in a 7.5mL bottle would be low. Therefore, there was no evidence to suggest that this drug could not be sold in an Unscheduled environment.

**MOTION:** It was moved by J. Kielly, seconded by M. Hamilton to recommend that:

- Brimonidine tartrate ophthalmic solution in concentrations up to and including 0.025%, used for the relief of redness of the eye due to minor eye irritations caused by environmental allergies, dryness and fatigue for adults of 18 years and older be granted Unscheduled status
- Brimonidine or its salts, **except** when sold as brimonidine tartrate ophthalmic solution in concentrations up to and including 0.025%, used for the relief of redness of the eye due to minor eye irritations caused by environmental allergies, dryness and fatigue for adults of 18 years and older, will remain in Schedule I (as per the Prescription Drug List)

**Motion carried.** All members agreed to the above noted motion.

This recommendation will be reported to the NAPRA Board of Directors.

## **5.0 Updates**

### **5.1 Natural and Non-prescription Health Products Directorate**

M. Ntemgwa provided an update on recent activities of the Natural and Non-prescription Health Products Directorate of Health Canada.

### **5.2 Marketed Health Products Directorate**

K. Bernardo provided an update on recent activities of the Marketed Health Products Directorate of Health Canada.

### **5.3 NDS Modernization**

K. Jajko provided an update on NAPRA's NDS modernization project.

## **6.0 Next meeting**

Tentatively scheduled for March 3-4, 2024.

**7.0 Adjournment**

The meeting was adjourned at 2:21 p.m. (ET) on December 4, 2023.