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April 7, 2023

VIA ECF

The Honorable Denise L. Cote
United States District Court Judge
Southern District of New York
500 Pearl Street, Room 1910
New York, New York 10007

Re. *In Re: Acetaminophen – ASD–ADHD Products Liability Litigation*, Case No. 1:22-md-03043 (S.D.N.Y.) – Plaintiffs' Proposed Language for Acetaminophen Labels
This Document Relates To: All Cases

Dear Judge Cote:

Pursuant to the Court's January 13, 2023 Order, Dkt. 343 ("Order"), Plaintiffs submit the following language that Defendants could have included on the labels of the acetaminophen products pleaded in the Master Complaints:

> **Autism/ADHD**: Some studies show that frequent use of this product during pregnancy may increase your child's risk of autism and attention deficit hyperactivity disorder. If you use this product during pregnancy to treat your pain and/or fever, use the lowest effective dose for the shortest possible time and at the lowest possible frequency.

The final clause, "use the lowest effective dose for the shortest possible time and at the lowest possible frequency," is taken from the European Union's label for paracetamol, which is the name for acetaminophen in Europe. *See* **Exhibit 1** at § 4.6.

Plaintiffs do not suggest that the language they propose is the only way Defendants could have satisfied their state-law duties to warn. Defendants could have used different words to apprise pregnant women of acetaminophen's risks. [redacted]

Finally, while Plaintiffs submit this proposed language at the Court's direction and hope it is helpful to the Court, Plaintiffs respectfully point out a critical aspect regarding the law that governs these claims. In almost every state whose courts have considered the question, plaintiffs pursuing failure-to-warn claims need not provide the fact finder with specific, alternative language

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for the label. *See, e.g.*, *Motor Coach Indus. Inc. v. Khiabani*, 493 P.3d 1007, 1012 (Nev. 2021) ("[P]laintiffs do not need to provide the jury with a specific proposed warning in failure-to-warn cases.").[1] The only potential counterexample is Indiana, where the case law is mixed but recent authority conforms to the general rule. *Compare Nissen Trampoline Co. v. Terre Haute First Nat'l Bank*, 358 N.E.2d 974, 978 (Ind. 1976) (finding that "evidence relevant to a determination of what a proper warning should state . . . [is] indispensable to a rational conclusion that the product was defective . . ."), *and Morgen v. Ford Motor Co.*, 797 N.E.2d 1146, 1152 (Ind. 2003) (same), *with Barton v. Gella*, No. 2:21-CV-00319-JRS-MG, 2022 WL 10077734, at *5 (S.D. Ind. Oct. 17, 2022) ("The IPLA does not mention or otherwise require 'proposed warnings' to proceed on a failure to warn theory . . . . At no point will Plaintiffs themselves need to invent a hypothetical sufficient warning."). Therefore, by filing this letter, Plaintiffs do not concede that Plaintiffs' proposed label change is a required element of their claims.

If the Court has any questions about Plaintiffs' language or the other points raised, we are of course at your Honor's disposal.

Respectfully submitted,

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[1] *See also Moore v. Ford Motor Co.*, 332 S.W.3d 749, 759–61 (Mo. 2011) (en banc) (holding that plaintiffs are not required to propose an alternative warning to prove a failure-to warn-claim); *Ayers v. Johnson & Johnson Baby Prods. Co.*, 818 P.2d 1337, 1341–42 (Wash. 1991) (en banc) (same); *Soucy v. Briggs & Stratton Corp.*, No. 1:13-CV-00068-NT, 2014 WL 794570, at *4 (D. Me. Feb. 27, 2014) (same, applying Maine law); *Goyal v. Thermage, Inc.*, No. 08-0020, 2012 WL 3240381, at *11 (D. Md. Aug. 2, 2012) (same, applying Maryland law).

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Exhibit 1

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

8 April 2019[1]
EMA/PRAC/157165/2019
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 12-15 March 2019 PRAC meeting

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 12-15 March 2019 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT][2] reference numbers).

PRAC recommendations to provide supplementary information are directly actionable by the concerned marketing authorisation holders (MAHs). PRAC recommendations for regulatory action (e.g. amendment of the product information) are submitted to the Committee for Medicinal Products for Human Use (CHMP) for endorsement when the signal concerns Centrally Authorised Products (CAPs), and to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) for information in the case of Nationally Authorised Products (NAPs). Thereafter, MAHs are expected to take action according to the PRAC recommendations.

When appropriate, the PRAC may also recommend the conduct of additional analyses by the Agency or Member States.

MAHs are reminded that in line with Article 16(3) of Regulation No (EU) 726/2004 and Article 23(3) of Directive 2001/83/EC, they shall ensure that their product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations published on the European Medicines Agency (EMA) website (currently acting as the EU medicines webportal).

For CAPs, at the time of publication, PRAC recommendations for update of product information have been agreed by the CHMP at their plenary meeting (25-28 March 2019) and corresponding variations will be assessed by the CHMP.

For nationally authorised medicinal products, it is the responsibility of the National Competent Authorities (NCAs) of the Member States to oversee that PRAC recommendations on signals are adhered to.

Variations for CAPs are handled according to established EMA procedures. MAHs are referred to the available guidance. Variations for NAPs (including via mutual recognition and decentralised procedures) are handled at national level in accordance with the provisions of the Member States.

[1] Intended publication date. The actual publication date can be checked on the webpage dedicated to PRAC recommendations on safety signals.
[2] The relevant EPITT reference number should be used in any communication related to a signal.

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Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

The timeline recommended by PRAC for submission of variations following signal assessment is applicable to both innovator and generic medicinal products, unless otherwise specified.

For procedural aspects related to the handling of PRAC recommendations on signals (e.g. submission requirements, contact points, etc.) please refer to the Questions and Answers on signal management.

1. Recommendations for update of the product information[3]

1.1. Nivolumab – Hypoparathyroidism

Authorisation procedure	Centralised
EPITT No	19310
PRAC rapporteur(s)	Brigitte Keller-Stanislawski (DE)
Date of adoption	15 March 2019

Recommendation

Having considered the available evidence from the cumulative review provided by the MAH for Opdivo (Bristol-Myers Squibb Pharma), including the recent comments from the MAH, the PRAC has agreed that there is a reasonable suspicion of a causal link between nivolumab and hypoparathyroidism and that clinicians should be aware of the potential risk for hypocalcaemia and other symptoms of hypoparathyroidism that may be associated with the use of nivolumab. Therefore, the PRAC agreed that the MAH for Opdivo (Bristol-Myers Squibb Pharma) should submit a variation within 2 months, to amend the product information as described below (new text underlined):

Summary of product characteristics

4.4. Special warnings and precautions for use

Other immune-related adverse reactions: […] Cases of Vogt-Koyanagi-Harada syndrome and hypoparathyroidism have been reported post-marketing (see section 4.8).

4.8. Undesirable effects

Hypoparathyroidism[h]
Frequency: Not known for nivolumab monotherapy / nivolumab in combination with ipilimumab
[Table key: [h] Post-marketing event (also see section 4.4)]

Package Leaflet

2. What you need to know before you use OPDIVO

Warnings and precautions

[…]

Problems with your hormone producing glands (including the pituitary, the thyroid, the parathyroid and adrenal glands) that may affect how these glands work. Signs and symptoms that these glands are not working properly may include fatigue (extreme tiredness), weight change or headache, decreased blood levels of calcium and visual disturbances.

[3] Translations in all official EU languages of the new product information adopted by PRAC are also available to MAHs on the EMA website.

4. Possible side effects

[...]

Other side effects that have been reported (frequency not known) with nivolumab alone and nivolumab in combination with ipilimumab include:

- Solid organ transplant rejection
- A group of metabolic complications occurring after cancer treatment characterised by high blood levels of potassium and phosphate, and low blood levels of calcium (tumour lysis syndrome)
- An inflammatory disorder (most likely of autoimmune origin) affecting the eyes, skin and the membranes of the ears, brain and spinal cord (Vogt-Koyanagi-Harada syndrome)
- Inflammation of the covering of the heart and accumulation of fluid around the heart (pericardial disorders)
- Decreased function of the parathyroid gland

1.2. Paracetamol – Paracetamol use in pregnancy and child neurodevelopment and effects on the urogenital apparatus

Authorisation procedure	Non-centralised
EPITT No	17796
PRAC rapporteur(s)	Laurence de Fays (BE)
Date of adoption	15 March 2019

Recommendation

Having considered the available evidence from literature, including non-clinical and epidemiological studies, regarding the signal of prenatal exposure to paracetamol and the impact on the urogenital apparatus or neurodevelopmental disorders in offspring, and the comments received from the MAHs, the PRAC concluded that the studies are inconclusive, but nevertheless, the summary of product characteritics (SmPC) of paracetamol containing medicinal products should be amended in order to reflect the current state of scientific knowledge, as detailed below. The SmPC update applies to all paracetamol containing products independently of the route of administration/formulation and supersedes any pre-existing wording in these sections on the subject.

The wording applies as well to all paracetamol-containing combination products, unless a more stringent restriction and wording is in place in the product information (PI) because of the presence of another active substance in the combination product with restriction for use in pregnancy. In such case, in the relevant sections, the more stringent wording already in place in the PI would supersede the proposed wording below.

The MAHs should submit a variation within 3 months.

Summary of product characteristics

4.6. Fertility, pregnancy and lactation

A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

5.3. Preclinical safety data

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

Package leaflet

2. What you need to know before you use [product name]

Pregnancy and breast-feeding

If necessary, <Product name> can be used during pregnancy. You should use the lowest possible dose that reduces your pain and/or your fever and use it for the shortest time possible. Contact your <doctor><midwife> if the pain and/or fever are not reduced or if you need to take the medicine more often.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Levomethadone; methadone	Opioid toxicity in infants exposed to levomethadone and/or methadone via breast milk (19372)	Ronan Grimes (IE)	Assess in the next PSUR (submission by 30 July 2019)	Takeda Pharma, Sanofi-Aventis Deutschland GmbH
Natalizumab	Psoriasis (19365)	Brigitte Keller-Stanislawski (DE)	Supplementary information requested (submission by 7 May 2019)	Biogen Netherlands B.V.
Ondansetron	Birth defects following in-utero exposure during the first trimester of pregnancy arising from recent publications (19353)	Gabriela Jazbec (SI)	Supplementary information requested (submission by 11 April 2019)	Novartis
Pirfenidone	Herpes viral infections (19374)	Rhea Fitzgerald (IE)	Assess in the next PSUR (submission by 8 May 2019)	Roche Registration GmbH
Pirfenidone	Hyponatraemia (19373)	Rhea Fitzgerald (IE)	Assess in the next PSUR (submission by 8 May 2019)	Roche Registration GmbH
Sodium-glucose co-transporter 2 inhibitors: canagliflozin; canagliflozin, metformin; dapagliflozin; dapagliflozin, metformin; empagliflozin; empagliflozin, metformin; ertugliflozin; ertugliflozin, metformin	New information on the known association between sodium-glucose co-transporter 2 (SGLT2) inhibitors and diabetic ketoacidosis (DKA) in surgical patients (19355)	Martin Huber (DE)	Supplementary information requested (submission by 13 May 2019)	MAHs of SLGT-2 inhibitors containing products

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Tocilizumab	Drug reaction with eosinophilia and systemic symptoms (19360)	Brigitte Keller-Stanislawski (DE)	Supplementary information requested (submission by 7 May 2019)	Roche Registration GmbH
Tofacitinib	Increased risk of pulmonary embolism and overall mortality arising from a post-authorisation safety study in patients with cardiovascular risk factors treated for rheumatoid arthritis with tofacitinib 10 mg twice daily (19382)	Liana Gross-Martirosyan (NL)	Supplementary information (submission by 5 April 2019) and Direct Healthcare Professional Communication (DHPC) requested	Pfizer Europe MA EEIG

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Apixaban	Pancreatitis (19265)	Menno van der Elst (NL)	Monitor in PSUR	Bristol-Myers Squibb / Pfizer EEIG
Belimumab	Lupus nephritis (19174)	Ulla Wändel Liminga (SE)	Routine pharmacovigilance	GlaxoSmithKline (Ireland) Limited
Paracetamol	Paracetamol use during pregnancy and premature ductus arteriosus closure in offspring (19297)	Laurence de Fays (BE)	Monitor in PSUR	MAHs of paracetamol-containing products
Tocilizumab	Psoriasis (19273)	Brigitte Keller-Stanislawski (DE)	Routine pharmacovigilance	Roche Registration GmbH

Exhibit 2

Under Seal