Provepharm wishes to inform the Chairperson and members of the Medical Association about the potential safety risks associated with the off-label use of methylene blue as a visualization aid during ureteral patency assessment via cystoscopy.

Methylene Blue (ProvayBlue® -- Provepharm SAS) has been approved by the FDA since 2016 as an intravenous treatment for patients with acquired methemoglobinemia. In addition to its approved indication, methylene blue (including ProvayBlue® - Provepharm SAS) is widely used off-label as a blue dye for cystoscopic ureteral patency assessments in complex abdominal pelvic surgical procedures[1]. It is also frequently employed off-label to detect vesicoureteral injury during cystocele repair and a variety of other clinical indications[2-5].

In 2011, the FDA issued a drug safety announcement for methylene blue after receiving reports of serious central nervous system reactions. These reactions occurred in patients taking psychiatric medications that can over activate both peripheral and central postsynaptic 5HT-1A and 5HT-2A receptors.[6,7] While the exact mechanism of this drug interaction was not fully understood in 2011, it was suspected that methylene blue's inhibition of monoamine oxidase was a key factor. This enzyme is involved in the breakdown of serotonin in the brain and its inhibition in combination with serotonergic psychiatric medications can lead to serotonin syndrome. The FDA requested Provepharm to add this contraindication to the prescribing information as a black box warning when ProvayBlue® was approved in 2016.[8]

More recently, in 2020, concomitant treatment with opioids was also identified as a risk factor of serotonin syndrome[9]. Based on a literature review of signal detection, Provepharm updated its prescribing information to include opioids in the black box warning for serotonin syndrome[8]. In collaboration with American Regent, the product distributor, Provepharm prepared a Health Care Provider Important Drug Warning Letter that was issued January 10, 2024[10].

The true incidence of serotonin syndrome remains unknown, and the actual number of cases is likely higher than reported. The clinical presentation varies widely, with symptoms that can resemble several other medical conditions. As a result, mild cases are frequently overlooked or misdiagnosed in clinical practice.[11] The FAERS database has 558 case reports of serotonin syndrome associated with methylene blue from 2007-2024 (Attachment 1). It is likely that some cases are underreported, particularly mild to moderate cases that are difficult to diagnose or are not anticipated by specialists who are unfamiliar with this risk.[11]

In the United States, there is an increasing trend for the use of antidepressants. During the time between 2009 and 2018, antidepressant use increased from 10.6% to 13.8%.[12] This rise was significant among women (from 13.8% to 18.6%) but less pronounced in men (from 7.1% to 8.7%). Nearly one-quarter of women aged 60 and over (24.3%) used antidepressants during this period. [12] Prescription opioid use remained stable overall. Between 2015 and 2018, the use of one or more prescription opioids remained at 5.7%. Usage was higher in women (6.4%) than in men (4.9%) and use increased with age, from 2.8% among adults aged 20–39 to 6.6% for those aged 40–59 and 8.2% for those aged 60 and older.[13]

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From our clinical trial experience with patients undergoing ureteral patency assessment, we observed an even higher percentage of patients taking either antidepressants or opioids. Provepharm performed a retrospective analysis of data from a phase 3 clinical trial involving patients undergoing ureteral patency assessment using indigo carmine (Bludigo©) as part of their procedure, enrolled between 2020 and 2021. Concomitant medications were reviewed for the presence of contraindicated medications for methylene blue that were taken concurrently with the procedure (SSRIs, SNRIs, MAOIs, or opioids). Among the 118 patients, 65 (55%) were taking at least one contraindicated medication, and 28 patients (23.7%) were taking multiple contraindicated medications. Additionally, 37 patients (33%) were taking contraindicated antidepressants.[14] A separate observational study of patients undergoing procedures with a ureteral patency assessment evaluated the use of medications contraindicated with methylene blue administration. During the enrollment period from 2024 to 2025, 29 patients (39.7%) screened were on SSRIs, SNRIs, MAOIs, or opioids, all contraindicated for use with methylene blue.[14]

Methylene blue usage increased after indigo carmine, the standard of care, became unavailable in 2014, prompting physicians to seek alternative methods for evaluating ureteral patency.[1] As of 2022, indigo carmine is available as an FDA approved product under the trade name Bludigo® (indigotindisulfonate sodium injection) for use as a visualization aid in the cystoscopic assessment of the integrity of the ureters in adults. The safety and efficacy of indigo carmine has been demonstrated in over 7,000 patients[15,16]. In contrast, only two studies have been published using methylene blue for ureteral patency evaluation: one retrospective cohort and one a case series, totaling 36 patients; neither were randomized clinical trials.[15]

Both methylene blue (trade name Provayblue®, distributed by American Regent) and indigo carmine (Bludigo®, distributed by Provepharm) are products of Provepharm Inc. It is important for physicians to recognize that, unlike indigo carmine, methylene blue is metabolically active and has a different safety profile. We are concerned about the risk of serotonin syndrome in patients undergoing cystoscopic ureteral patency assessments with methylene blue. Physicians should be aware of the risk-benefit profile of methylene blue for this off-label use. Provepharm field representatives (commercial and medical science liaisons) are educating health care practitioners about the differences and indicated uses of these two products.

Provepharm would greatly appreciate your Medical Association's support in raising healthcare provider awareness of the risks associated with the off-label use of methylene blue and highlighting the availability of an FDA-approved product for ureteral patency assessments.

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MRC02212025

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Attachment 1

Search Term: Methylene Blue (G) | Reaction Group: Nervous System Diso... | Reaction Term: Serotonin Syndrome

FDA Adverse Events Reporting System (FAERS) Public Dashboard

U.S. FOOD & DRUG ADMINISTRATION

Home | Demographics | Reaction Group | Reaction | Listing of Cases | Disclaimer | Report a Problem | FAQ | Site Feedback | Search by Product

METHYLENE BLUE (G)

Total Cases: 558

Serious Cases (including deaths): 558

Death Cases: 16

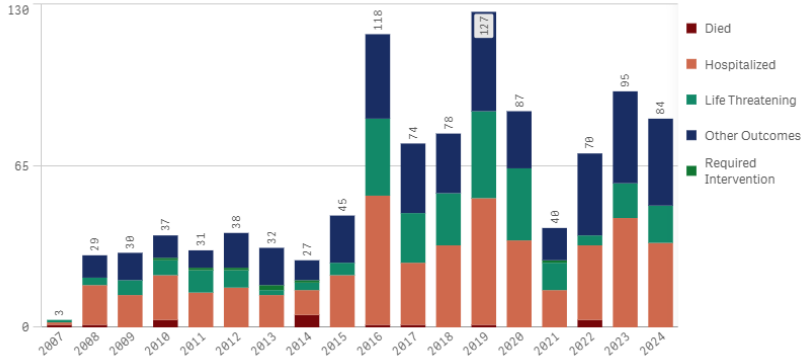
Outcome counts by Received Year | **Case counts by Age Group and Sex**

Reaction Group and Reaction

Reaction Group | Reaction

		Number of Cases
Total Cases		**558**
Nervous System Disorders	**Number of Cases**	**558**
	Serotonin Syndrome	558

Outcome counts by Received Year



Data as of December 31, 2024

Vulnerability Disclosure Polic

This page displays the number of cases identified for the product/reaction term of interest by "Reaction Group", "Reaction", patient age and sex, and report outcome. A case may describe one or more "Reaction Group", "Reaction", or outcome. "Reaction Groups" are based on a classification of the side effect (also known as "Reaction" or adverse event or adverse drug reaction), using the MedDRA dictionary of adverse event terms. For example, "Cardiac Disorders" is one of the "Reaction Groups" defined by the MedDRA dictionar as a grouping of several related "Reactions" such as "Cardiac Arrest", and "Cyanosis". "Reaction" corresponds to the suspected reaction reported by the Reporter. The "Reaction" is based on the MedDRA dictionary Preferred Term (PT). Including one or more of these outcomes or reported reactions in a report does not necessarily mean that the suspect product of interest was the cause of the reported outcomes or reactions. A case may have one or more reported outcomes.