January 10, 2024

IMPORTANT DRUG WARNING

Subject: PROVAYBLUE® (methylene blue) injection USP, for intravenous use

- **Serotonin Syndrome with concomitant use of Serotonergic drugs (drugs producing serotonergic effects) and Opioids**

Dear Health Care Provider:

This letter aims to inform you of important safety information for PROVAYBLUE® (methylene blue 0.5%) injection USP, approved for treating pediatric and adult patients with acquired methemoglobinemia.

Serious risks with concomitant use of PROVAYBLUE® and Serotonergic drugs, and Opioids.

Provayblue® (methylene blue 0.5%) injection is a reversible monoamine oxidase inhibitor (MAOI). As indicated in its Black Box Warning, concomitant use of methylene blue and serotonergic drugs and opioids has the potential for a serious or fatal serotonergic syndrome.

Prescriber Action

Concomitant use of multiple classes of serotogenic drugs has resulted in serotonin syndrome. Although the mechanism is not clearly understood, literature reports suggest that methylene blue is a potent reversible inhibitor of monoamine oxidase.

Methylthioninium chloride should be avoided in patients receiving medicinal products that enhance serotonergic transmission because of the potential for serious CNS reactions, including potentially fatal serotonin syndrome. These include SSRIs (selective serotonin reuptake inhibitors), bupropion, buspirone, clomipramine, mirtazapine, and venlafaxine. Opioids, for example, tramadol, pethidine, and dextromethorphan, may also increase the risk of developing serotonin syndrome, when used in combination with methylthioninium chloride.

If the intravenous use of methylene blue for the treatment of acquired methemoglobinemia cannot be avoided in patients concomitantly treated with serotonergic medicinal products, choose the lowest possible dose/concentration of methylene blue, and observe the patient closely for CNS effects for up to 4 hours after administration.

The use of any available methylene blue product as a visualization aid during or after surgery, or as a dye for the visualization of lymphatic or other tissues is not FDA-approved and may also involve a heightened risk of adverse events. Healthcare providers are encouraged to use only FDA-approved products for such indications that are not associated with life-threatening serotonin syndrome.

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Reporting Adverse Events
Healthcare providers and patients are encouraged to report adverse events in patients receiving PROVAYBLUE® to American Regent at 1-800-734-9236. You are encouraged to report the negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA- 1088.

You may also contact the American Regent medical information department at 1-888-354-4855 if you have any questions about the information contained in this letter or the safe and effective use of PROVAYBLUE®.

This letter is not intended as a complete description of the benefits and risks related to the use of PROVAYBLUE®. Please refer to the enclosed full prescribing information.

Enclosure(s): PROVAYBLUE® Full Prescribing Information

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