methemoglobinemia. If methemoglobinemia does not respond to 2 doses of PROVAYBLUE™ or if methemoglobinemia rebounds after a
• Inaccurate Pulse Oximeter Readings
• Interference with Laboratory Tests
• Effects on Ability to Drive and Operate Machinery
• Interference with In-Vivo Monitoring Devices

Use the lowest effective dose. (2.1)

Each mL of PROVAYBLUE™ contains 5 mg methylene blue (methylene blue) is an oxidation-reduction agent indicated for the treatment of pediatric and adult patients with acquired methemoglobinemia. This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon clinical

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Product Information</th>
<th>All Grades</th>
<th>Severe Grades</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsening of pre-existing psychiatric disorder</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Cold sweat</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Gastritis</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Phlebitis</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Mucosal edema</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Pallor</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Dermatitis contact</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Feeling hot</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Cold sweat</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Mucosal edema</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Pallor</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Dermatitis contact</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Feeling hot</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Cold sweat</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Mucosal edema</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Pallor</td>
<td>57.4%</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>
conjugation by multiple UGT enzymes, including UGT1A4 and UGT1A9. Methylene blue is metabolized by CYPs 1A2, 2C19 and 2D6 in vitro; however, the predominant in vitro pathway appears to be UGT-mediated.

Elimination

transporter, but not for BCRP or OCT2 in vitro.

8.6 Renal Impairment

patients should use the lowest number of doses needed to achieve a response. This drug is known to be substantially excreted by the kidney, so the risk of adverse reactions to this drug may be greater in patients with renal impairment (see Clinical Pharmacology (12.3)).

Changes (T-wave flattening or inversion). These effects lasted 2-12 hours following administration.

Administration of large intravenous doses (cumulative dose ≥ 7 mg/kg) of a methylene blue class product caused nausea, vomiting, precordial pain, hypotension, wheezing and reduced oxygenation have been reported in patients who received methylene blue class products in single doses of at least 3 mg/kg or more.

Hypotension, wheezing and reduced oxygenation have been reported in patients who received methylene blue class products in single doses of at least 3 mg/kg or more.

The mean± standard deviation steady state volume of distribution of a 2 mg/kg dose of PROVAYBLUE™ was 255 L ± 58. The mean plasma half-life was 6 h ± 1.5. The mean cumulative percentage of the administered dose excreted in urine was 2-4% and 20%, respectively, the clinical dose of 1 mg/kg (see Data).

N

CH3Cl-