MIRVASO® topical gel is for use on your skin only. Do not use MIRVASO topical gel in your eyes, mouth, or vagina.

8.1 Pregnancy

8.2 Lactation

8.3 Pediatric Use

8.4 Carcinogenesis, Mutagenesis, Impairment of Fertility

8.5 Animal Data

8.6 Clinical Pharmacology

8.7 Pharmacokinetics

8.8 Overdose

9 CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

9.2 Clinical Studies

9.3 Postmarketing Experience

9.4 Antihypertensives/Cardiac Glycosides

10 ADVERSE REACTIONS

10.1 General Adverse Reactions

10.2 Severe Cardiovascular Disease

10.3 Potentiation of Vascular Insufficiency

10.4 Hypersensitivity

10.5 Local Vasculitis Adverse Reactions

10.6 Systemic Vasculitis Adverse Reactions

10.7 MIRVASO topical gel (5.3) [See Warnings and Precautions (5.3)]

10.8 Potentiation of Vascular Insufficiency

10.9 MIRVASO topical gel (5.1) [See Warnings and Precautions (5.1)]

10.10 Antihypertensives/Cardiac Glycosides

10.11 MIRVASO topical gel (5.4) [See Warnings and Precautions (5.4)]

10.12 CNS Depressants

10.13 Monoamine oxidase (MAO) inhibitors

10.14 MIRVASO topical gel (5.2) [See Warnings and Precautions (5.2)]

10.15 MIRVASO topical gel (5.6) [See Warnings and Precautions (5.6)]

11 DESCRIPTION

12 CLINICAL STUDIES

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Studies

13.3 Preclinical Safety Studies

14 CLINICAL STUDIES

15 MIRVASO topical gel (4.3) [See Warnings and Precautions (4.3)]

15.1 Potentiation of Vascular Insufficiency

15.2 Hypersensitivity

15.3 Local Vasculitis Adverse Reactions

15.4 Systemic Vasculitis Adverse Reactions

15.5 MIRVASO topical gel (4.5) [See Warnings and Precautions (4.5)]

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

18 PATIENT INFORMATION

19 PATIENT INFORMATION

20 PATIENT INFORMATION

21 PATIENT INFORMATION

22 PATIENT INFORMATION

23 PATIENT INFORMATION

24 PATIENT INFORMATION

25 PATIENT INFORMATION

26 PATIENT INFORMATION

27 PATIENT INFORMATION

28 PATIENT INFORMATION

29 PATIENT INFORMATION

30 PATIENT INFORMATION

31 PATIENT INFORMATION

32 PATIENT INFORMATION

33 PATIENT INFORMATION

34 PATIENT INFORMATION

35 PATIENT INFORMATION

36 PATIENT INFORMATION

37 PATIENT INFORMATION

38 PATIENT INFORMATION

39 PATIENT INFORMATION

40 PATIENT INFORMATION

41 PATIENT INFORMATION

42 PATIENT INFORMATION

43 PATIENT INFORMATION

44 PATIENT INFORMATION

45 PATIENT INFORMATION

46 PATIENT INFORMATION

47 PATIENT INFORMATION

48 PATIENT INFORMATION

49 PATIENT INFORMATION

50 PATIENT INFORMATION

51 PATIENT INFORMATION

52 PATIENT INFORMATION

53 PATIENT INFORMATION

54 PATIENT INFORMATION

55 PATIENT INFORMATION

56 PATIENT INFORMATION

57 PATIENT INFORMATION

58 PATIENT INFORMATION

59 PATIENT INFORMATION

60 PATIENT INFORMATION

61 PATIENT INFORMATION

62 PATIENT INFORMATION

63 PATIENT INFORMATION

64 PATIENT INFORMATION

65 PATIENT INFORMATION

66 PATIENT INFORMATION

67 PATIENT INFORMATION

68 PATIENT INFORMATION

69 PATIENT INFORMATION

70 PATIENT INFORMATION

71 PATIENT INFORMATION

72 PATIENT INFORMATION

73 PATIENT INFORMATION

74 PATIENT INFORMATION

75 PATIENT INFORMATION

76 PATIENT INFORMATION

77 PATIENT INFORMATION

78 PATIENT INFORMATION

79 PATIENT INFORMATION

80 PATIENT INFORMATION

81 PATIENT INFORMATION

82 PATIENT INFORMATION

83 PATIENT INFORMATION

84 PATIENT INFORMATION

85 PATIENT INFORMATION

86 PATIENT INFORMATION

87 PATIENT INFORMATION

88 PATIENT INFORMATION

89 PATIENT INFORMATION

90 PATIENT INFORMATION

91 PATIENT INFORMATION

92 PATIENT INFORMATION

93 PATIENT INFORMATION

94 PATIENT INFORMATION

95 PATIENT INFORMATION

96 PATIENT INFORMATION

97 PATIENT INFORMATION

98 PATIENT INFORMATION

99 PATIENT INFORMATION

100 PATIENT INFORMATION

101 PATIENT INFORMATION

102 PATIENT INFORMATION

103 PATIENT INFORMATION

104 PATIENT INFORMATION

105 PATIENT INFORMATION

106 PATIENT INFORMATION

107 PATIENT INFORMATION

108 PATIENT INFORMATION

109 PATIENT INFORMATION

110 PATIENT INFORMATION

111 PATIENT INFORMATION

112 PATIENT INFORMATION

113 PATIENT INFORMATION

114 PATIENT INFORMATION

115 PATIENT INFORMATION

116 PATIENT INFORMATION

117 PATIENT INFORMATION

118 PATIENT INFORMATION

119 PATIENT INFORMATION

120 PATIENT INFORMATION

121 PATIENT INFORMATION

122 PATIENT INFORMATION

123 PATIENT INFORMATION

124 PATIENT INFORMATION

125 PATIENT INFORMATION

126 PATIENT INFORMATION

127 PATIENT INFORMATION

128 PATIENT INFORMATION

129 PATIENT INFORMATION

130 PATIENT INFORMATION

131 PATIENT INFORMATION

132 PATIENT INFORMATION

133 PATIENT INFORMATION

134 PATIENT INFORMATION

135 PATIENT INFORMATION

136 PATIENT INFORMATION

137 PATIENT INFORMATION

138 PATIENT INFORMATION

139 PATIENT INFORMATION

140 PATIENT INFORMATION

141 PATIENT INFORMATION

142 PATIENT INFORMATION

143 PATIENT INFORMATION

144 PATIENT INFORMATION

145 PATIENT INFORMATION

146 PATIENT INFORMATION

147 PATIENT INFORMATION

148 PATIENT INFORMATION

149 PATIENT INFORMATION

150 PATIENT INFORMATION

151 PATIENT INFORMATION

152 PATIENT INFORMATION

153 PATIENT INFORMATION

154 PATIENT INFORMATION

155 PATIENT INFORMATION

156 PATIENT INFORMATION

157 PATIENT INFORMATION

158 PATIENT INFORMATION

159 PATIENT INFORMATION

160 PATIENT INFORMATION

161 PATIENT INFORMATION

162 PATIENT INFORMATION

163 PATIENT INFORMATION

164 PATIENT INFORMATION

165 PATIENT INFORMATION

166 PATIENT INFORMATION

167 PATIENT INFORMATION

168 PATIENT INFORMATION

169 PATIENT INFORMATION

170 PATIENT INFORMATION

171 PATIENT INFORMATION

172 PATIENT INFORMATION

173 PATIENT INFORMATION

174 PATIENT INFORMATION

175 PATIENT INFORMATION

176 PATIENT INFORMATION

177 PATIENT INFORMATION

178 PATIENT INFORMATION

179 PATIENT INFORMATION

180 PATIENT INFORMATION

181 PATIENT INFORMATION

182 PATIENT INFORMATION

183 PATIENT INFORMATION

184 PATIENT INFORMATION

185 PATIENT INFORMATION

186 PATIENT INFORMATION

187 PATIENT INFORMATION

188 PATIENT INFORMATION

189 PATIENT INFORMATION

190 PATIENT INFORMATION

191 PATIENT INFORMATION

192 PATIENT INFORMATION

193 PATIENT INFORMATION

194 PATIENT INFORMATION

195 PATIENT INFORMATION

196 PATIENT INFORMATION

197 PATIENT INFORMATION

198 PATIENT INFORMATION

199 PATIENT INFORMATION

200 PATIENT INFORMATION
Instructions for Use

MIRVASO® topical gel is for use on the face only. Do not use MIRVASO topical gel in the eyes, mouth, or vagina.

Keep MIRVASO topical gel out of the reach of children.

If anyone, especially a child, accidentally swallows MIRVASO topical gel, they may have serious side effects and need medical care immediately. Call your doctor right away if any of the following occur:

• lack of energy, trouble breathing or stops breathing, a slow heart beat, confusion, sweating, or dizziness. This may be a sign of a more serious side effect that requires medical care immediately.

Note: 1. Push the cap down and turn it counter-clockwise until the cap can be removed. See Figures A and B. The clear, airtight pump is child-resistant again. See Figure D.

Note: 2-grade Composite Success: 2-grade improvement on CEA and 2-grade improvement on PSA.

Table 2: Summary of 2-grade Composite Success on Day 29

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>MIRVASO Topical Gel 5% (N=129)</th>
<th>Vehicle Gel 5% (N=131)</th>
<th>MIRVASO Topical Gel 1% (N=148)</th>
<th>Vehicle Gel 1% (N=145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hour 3</td>
<td>31%</td>
<td>31%</td>
<td>25%</td>
<td>32%</td>
<td>25%</td>
</tr>
<tr>
<td>Hour 6</td>
<td>35%</td>
<td>35%</td>
<td>25%</td>
<td>36%</td>
<td>25%</td>
</tr>
<tr>
<td>Hour 9</td>
<td>28%</td>
<td>31%</td>
<td>25%</td>
<td>28%</td>
<td>25%</td>
</tr>
<tr>
<td>Hour 12</td>
<td>22%</td>
<td>22%</td>
<td>25%</td>
<td>21%</td>
<td>25%</td>
</tr>
</tbody>
</table>

2-grade Composite Success: 2-grade improvement in CEA and 2-grade improvement on PSA.

Figure 1: 2-grade Composite Success by Hour and Day for Study 1

Figure 2: 2-grade Composite Success by Hour and Day for Study 2

Figure 3: Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

12.1 Mechanism of Action

Brimonidine is a relatively selective alpha-2 agonist. Topical application of MIRVASO topical gel may reduce erythema through direct vasoconstriction.

12.2 Pharmacokinetics

Absorption

The absorption of brimonidine from MIRVASO topical gel was evaluated in a clinical trial in 24 adult subjects with facial erythema associated with rosacea. All enrolled subjects received the same total topical application of MIRVASO topical gel given in the order for 28 days.

Pharmacokinetic assessments were performed on Days 1, 3, 15, and 29. Mean plasma minimum concentration (Cmin) occurred at 3 hours post-dose. Plasma exposure (AUC) increased with dose, approximately 1.5-fold at 3 hours post-dose (Day 1) and 1.8-fold at 3 hours post-dose (Day 29) indicating in further drug accumulation.

Metabolism

Brimonidine is extensively metabolized by the liver.

Excretion

Urinary excretion is the major route of elimination of brimonidine and its metabolites.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In 12-month oral (diet) mouse carcinogenicity study and a 24-month oral (diet) carcinogenicity study, no drug-related tumors were observed in mice or rats in any of these studies at doses of brimonidine tartrate up to 3 mg/kg/day.

In a 2-year tumor incidence study in rats with MIRVASO topical gel, brimonidine was administered subcutaneously at dose levels of 3.3 mg/kg/day (1% gel) and 10 mg/kg/day (3% gel) for 26 months, and 0.1 mg/kg/day (0.03% gel) and 0.3 mg/kg/day (0.1% gel) for 24 months. No drug-related tumors were observed in this study.

Pharmacokinetics in rats were similar to those observed in mice. Whole body autoradiograms in mice showed that brimonidine tartrate was biotransformed to its glucuronide and sulfonate conjugates. The mutagenic activity of brimonidine tartrate was tested in a series of in vitro assays, including the Ames test, a chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, and three studies in C57B1 mice using the micronucleus test. No increase in spontaneous or drug-induced micronucleated erythrocytes was observed in any assay, and no bone marrow or thymus lymphocyte analysis was conducted in this study.

Impairment of Fertility

Pharmacokinetic and fertility studies in rats with brimonidine demonstrated no adverse effects on male or female fertility and no deviation from control in this study.

14 CLINICAL STUDIES

MIRVASO topical gel was evaluated for the treatment of moderate to severe, persistent (continuous) facial erythema of rosacea in 3 pivotal, double-blind, vehicle-controlled clinical trials, which were identical in design. The trials were conducted in US subjects aged 18 years and older who were treated daily for 4 weeks with either MIRVASO topical gel or vehicle. Overall, 958 subjects across these 3 studies were entered, 553 in the pivotal trials, and 405 in a Phase II study. Baseline disease severity was assessed using the Global Erythema Score (GES) and the 4-item modified Rose scale. Disease activity was measured using the Global Erythema Score (GES), a 4-item modified Rose scale, a 7-point (0-6) Global Improvement Score, and a 7-point (0-6) Physician Global Assessment (PGA) scale, on which subjects scored the "worst/least" (1-7) or "best/least" (7-1).

Primary efficacy endpoints included a 2-grade improvement in facial redness in a composite of 2-visit assessment in skin sites, including the Area Rosacea, a chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, and three studies in C57B1 mice using the micronucleus test. In a study conducted in hairless albino mice, a once-daily topical application of MIRVASO topical gel was administered to hairless albino mice once a day, five days per week, with concurrent exposure to simulated sunlight. No drug-related adverse effects were observed in this study. The results of this study suggest that topical treatment with MIRVASO topical gel would not enhance photos-carcinogenesis.

Brimonidine tartrate was not mutagenic or clastogenic in a series of in vitro studies, including the Ames test, a chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, and three studies in C57B1 mice using the micronucleus test. No increase in spontaneous or drug-induced micronucleated erythrocytes was observed in any assay, and no bone marrow or thymus lymphocyte analysis was conducted in this study.

15 NONCLINICAL TOXICOLOGY

15.1 Metabolism

The molecular formula of brimonidine tartrate is C21H19BrN2O5. Brimonidine tartrate has a molecular weight of 442.24 and appears as a white to slightly yellowish powder.

Chemically, brimonidine tartrate is 5-Bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate. Brimonidine tartrate has a molecular weight of 442.24 and appears as a white to slightly yellowish powder.

16 HOW SUPPLIED/STORAGE AND HANDLING

MIRVASO (brimonidine topical gel, 0.33%) is a white to light yellow opaque gel, supplied in a laminated foil or pump with a child-resistant cap in the following sizes:

30 gram tube NDC 0299-5980-30
30 gram pump NDC 0299-5980-45
45 gram pump NDC 0299-5980-46

Store at 20°C to 25°C (68°F to 77°F) except as permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See 15.1 Metabolism (a summary of the absorption, distribution, and excretion of brimonidine tartrate from the gel) 

Patients using MIRVASO topical gel may experience erythema, flushing or excessive whitening.

Patients should report any adverse reactions to their physician.

Keep out of reach of children.