

1 07-24-04-Final Draft sent to the sponsor

2 **SYNAGIS® (PALIVIZUMAB)**
3 **for Intramuscular Administration**

4 **DESCRIPTION:** Synagis® (palivizumab) is a humanized monoclonal antibody (IgG1 κ) produced by
5 recombinant DNA technology, directed to an epitope in the A antigenic site of the F protein of respiratory
6 syncytial virus (RSV). Synagis® is a composite of human (95%) and murine (5%) antibody sequences.
7 The human heavy chain sequence was derived from the constant domains of human IgG1 and the
8 variable framework regions of the V_H genes Cor (1) and Cess (2). The human light chain sequence was
9 derived from the constant domain of C κ and the variable framework regions of the V_L gene K104 with J κ -
10 4 (3). The murine sequences were derived from a murine monoclonal antibody, Mab 1129 (4), in a
11 process that involved the grafting of the murine complementarity determining regions into the human
12 antibody frameworks. Synagis® is composed of two heavy chains and two light chains and has a
13 molecular weight of approximately 148,000 Daltons.

14 Synagis® is available in two formulations: a lyophilized powder and a liquid solution.

15 **Lyophilized Powder:** Synagis® is supplied as a sterile lyophilized product for reconstitution with sterile
16 water for injection. Reconstituted Synagis® (100 mg/mL) is to be administered by intramuscular injection
17 (IM) only. The reconstituted solution should appear clear or slightly opalescent with pH of 6.0.

18 Each 100 mg single-use vial of Synagis® lyophilized powder is formulated in 67.5 mg of mannitol, 8.7 mg
19 histidine and 0.3 mg of glycine and is designed to deliver 100 mg of Synagis® in 1.0 mL when
20 reconstituted with 1.0 mL of sterile water for injection.

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22 Each 50 mg single-use vial of Synagis® lyophilized powder is formulated in 40.5 mg mannitol, 5.2 mg of
23 histidine and 0.2 mg of glycine and is designed to deliver 50 mg of Synagis® in 0.5 mL when reconstituted
24 with 0.6 mL of sterile water for injection.

25 **Liquid Solution:** Synagis® (100 mg/mL) is supplied as a sterile, preservative-free solution to be
26 administered by intramuscular injection (IM) only. The solution should appear clear or slightly opalescent
27 with pH of 6.0.

28 Each 100 mg single-use vial of Synagis® liquid solution is formulated in 4.7 mg of histidine and 0.1 mg of
29 glycine in a volume of 1.2 mL to and is designed to deliver 100 mg of Synagis® in 1.0 mL.

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31 Each 50 mg single-use vial of Synagis® liquid solution is formulated in 2.7 mg of histidine and 0.08 mg of
32 glycine in a volume of 0.7 mL to and is designed to deliver 50 mg of Synagis® in 0.5 mL.

33 **CLINICAL PHARMACOLOGY:** *Mechanism of Action:* Synagis® exhibits neutralizing and fusion-
34 inhibitory activity against RSV. These activities inhibit RSV replication in laboratory experiments.
35 Although resistant RSV strains may be isolated in laboratory studies, a panel of 57 clinical RSV isolates
36 were all neutralized by Synagis® (5). Synagis® serum concentrations of = 40 μ g/mL have been shown to
37 reduce pulmonary RSV replication in the cotton rat model of RSV infection by 100-fold (5). The *in vivo*
38 neutralizing activity of the active ingredient in Synagis® was assessed in a randomized, placebo-
39 controlled study of 35 pediatric patients tracheally intubated because of RSV disease. In these patients,

40 Synagis[®] significantly reduced the quantity of RSV in the lower respiratory tract compared to control
41 patients (6).

42 *Pharmacokinetics:* In pediatric patients less than 24 months of age without congenital heart disease, the
43 mean half-life of Synagis[®] was 20 days and monthly intramuscular doses of 15 mg/kg achieved mean
44 \pm SD 30 day trough serum drug concentrations of 37 ± 21 μ g/mL after the first injection, 57 ± 41 μ g/mL
45 after the second injection, 68 ± 51 μ g/mL after the third injection and 72 ± 50 μ g/mL after the fourth
46 injection (7). Trough concentrations following the first and fourth Synagis[®] dose were similar in children
47 with congenital heart disease and in non-cardiac patients. In pediatric patients given Synagis[®] for a
48 second season, the mean \pm SD serum concentrations following the first and fourth injections were 61
49 ± 17 μ g/mL and 86 ± 31 μ g/mL, respectively.

50 In 139 pediatric patients \leq 24 months of age with hemodynamically significant congenital heart disease
51 (CHD) who received Synagis[®] and underwent cardio-pulmonary bypass for open-heart surgery, the mean
52 \pm SD serum Synagis[®] concentration was 98 ± 52 μ g/mL before bypass and declined to 41 ± 33 μ g/mL after
53 bypass, a reduction of 58% (see *DOSAGE AND ADMINISTRATION*). The clinical significance of this
54 reduction is unknown.

55 Specific studies were not conducted to evaluate the effects of demographic parameters on Synagis[®]
56 systemic exposure. However, no effects of gender, age, body weight or race on Synagis[®] serum trough
57 concentrations were observed in a clinical study with 639 pediatric patients with congenital heart disease
58 (\approx 24 months of age) receiving five monthly intramuscular injections of 15 mg/kg of Synagis[®].

59 Trough serum Synagis[®] concentrations were comparable between the Synagis[®] liquid and
60 Synagis[®] lyophilized formulations administered IM at 15 mg/kg in a cross-over trial in 153
61 pediatric patients \leq 6 months of age with a history of prematurity.

62 **CLINICAL STUDIES:** The safety and efficacy of Synagis[®] (palivizumab) were assessed in two
63 randomized, double-blind, placebo-controlled trials of prophylaxis against RSV infection in pediatric
64 patients at high risk of an RSV-related hospitalization. Trial 1 was conducted during a single RSV
65 season and studied a total of 1,502 patients = 24 months of age with bronchopulmonary dysplasia
66 (BPD) or infants with premature birth (\approx 35 weeks gestation) who were = 6 months of age at study entry
67 (7). Trial 2 was conducted over four consecutive seasons among a total of 1287 patients = 24 months
68 of age with hemodynamically significant congenital heart disease. In both trials participants received 15
69 mg/kg Synagis[®] or an equivalent volume of placebo IM monthly for five injections and were followed for
70 150 days from randomization. In Trial 1, 99% of all subjects completed the study and 93% completed
71 all five injections. In Trial 2, 96% of all subjects completed the study and 92% completed all five
72 injections. The incidence of RSV hospitalization is shown in Table 1.

73 **Table 1: Incidence of RSV Hospitalization by Treatment Group**

Trial		Placebo	Synagis	Difference between groups	Relative Reduction	p-Value
Trial 1 Impact-RSV	N	500	1002			
	Hospitalization	53 (10.6%)	48 (4.8%)	5.8%	55	<0.001
Trial 2 CHD	n	648	639			
	Hospitalization	63 (9.7%)	34 (5.3%)	4.4%	45%	0.003

74
75 In Trial 1, the reduction of RSV hospitalization was observed both in patients with BPD (34/266 [12.8%]
76 placebo vs. 39/496 [7.9%] Synagis[®]), and in premature infants without BPD (19/234 [8.1%] placebo vs.
77 9/506 [1.8%] Synagis[®]). In Trial 2, reductions were observed in acyanotic (36/305 [11.8%] placebo

78 versus 15/300 [5.0%] Synagis[®] and cyanotic children (27/343 [7.9%]) placebo versus 19/339 [5.6%]
79 Synagis[®].

80 The clinical studies do not suggest that RSV infection was less severe among RSV hospitalized patients
81 who received Synagis[®] compared to those who received placebo.

82 **INDICATIONS AND USAGE:** Synagis[®] is indicated for the prevention of serious lower respiratory tract
83 disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease.
84 Safety and efficacy were established in infants with bronchopulmonary dysplasia (BPD), infants with a
85 history of premature birth (= 35 weeks gestational age), and children with hemodynamically significant
86 CHD. (See *CLINICAL STUDIES*)

87 **CONTRAINDICATIONS:** Synagis[®] should not be used in pediatric patients with a history of a severe
88 prior reaction to Synagis[®] or other components of this product.

89 **WARNINGS:** Very rare cases of anaphylaxis (<1 case per 100,000 patients) have been reported
90 following re-exposure to Synagis[®] (see *ADVERSE REACTIONS, POSTMARKETING EXPERIENCE*).
91 Rare severe acute hypersensitivity reactions have also been reported on initial exposure or re-exposure
92 to Synagis[®]. If a severe hypersensitivity reaction occurs, therapy with Synagis[®] should be permanently
93 discontinued. If milder hypersensitivity reactions occur, caution should be used on readministration of
94 Synagis[®]. **If anaphylaxis or severe allergic reactions occur, administer appropriate medications**
95 **(e.g., epinephrine) and provide supportive care as required.**

96 **PRECAUTIONS: General:** Synagis[®] is for intramuscular use only. As with any intramuscular injection,
97 Synagis[®] should be given with caution to patients with thrombocytopenia or any coagulation disorder.

98 The safety and efficacy of Synagis[®] have not been demonstrated for treatment of established RSV
99 disease.

100 The single-use vial of Synagis[®] (palivizumab) does not contain a preservative. Lyophilized Synagis[®]
101 must be used within 6 hours of reconstitution. Administration of either reconstituted Synagis[®] or
102 liquid Synagis[®] should occur immediately after withdrawal from vial. The vial should not be re-
103 entered. Discard any unused portion.

104 *Drug Interactions:* No formal drug-drug interaction studies were conducted. In Trial 1, the proportions of
105 patients in the placebo and Synagis[®] groups who received routine childhood vaccines, influenza vaccine,
106 bronchodilators or corticosteroids were similar and no incremental increase in adverse reactions was
107 observed among patients receiving these agents.

108 *Carcinogenesis, Mutagenesis, Impairment of Fertility:* Carcinogenesis, mutagenesis and reproductive
109 toxicity studies have not been performed.

110 *Pregnancy:* Pregnancy Category C: Synagis[®] is not indicated for adult usage and animal reproduction
111 studies have not been conducted. It is also not known whether Synagis[®] can cause fetal harm when
112 administered to a pregnant woman or could affect reproductive capacity.

113 **ADVERSE REACTIONS:**

114 The most serious adverse reactions occurring with Synagis[®] treatment are anaphylaxis and other acute
115 hypersensitivity reactions (see *WARNINGS*). The adverse reactions most commonly observed in
116 Synagis[®]-treated patients were upper respiratory tract infection, otitis media, fever, rhinitis, rash, diarrhea,
117 cough, vomiting, gastroenteritis, and wheezing. Upper respiratory tract infection, otitis media,
118 fever, and rhinitis occurred at a rate of 1% or greater in the Synagis[®] group compared to placebo (Table
119 2).

120 Because clinical trials are conducted under widely varying conditions, adverse event rates observed in
121 the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and
122 may not reflect the rates observed in practice. The adverse reaction information does, however, provide a
123 basis for identifying the adverse events that appear to be related to drug use and a basis for
124 approximating rates.

125 The data described reflect Synagis[®] exposure for 1641 pediatric patients of age 3 days to 24.1 months in
126 Trials 1 and 2. Among these patients, 496 had bronchopulmonary dysplasia, 506 were premature birth
127 infants less than 6 months of age, and 639 had congenital heart disease. Adverse events observed in the
128 153 patient crossover study comparing the liquid and lyophilized formulations were similar between the
129 two formulations, and similar to the adverse events observed with Synagis[®] in Trials 1 and 2.

130

131 **Table 2 - Adverse events occurring at a rate of 1% or greater more frequently in**
132 **patients[†] receiving Synagis[®]**

Event	Synagis [®] (n=1641) n (%)	Placebo (n=1148) n (%)
Upper respiratory infection	830 (50.6)	544 (47.4)
Otitis media	597 (36.4)	397 (34.6)
Fever	446 (27.1)	289 (25.2)
Rhinitis	439 (26.8)	282 (24.6)
Hernia	68 (4.1)	30 (2.6)
SGOT Increase	49 (3.0)	20 (1.7)
†Cyanosis (Synagis [®] [9.1%]/ placebo [6.9%]) and arrhythmia (Synagis [®] [3.1%]/placebo [1.7%]) were reported during Trial 2 in congenital heart disease patients.		

133

134 *Immunogenicity*

135 In the Trial 1, the incidence of anti-Synagis[®] antibody following the fourth injection was 1.1% in the
136 placebo group and 0.7% in the Synagis[®] group. In pediatric patients receiving Synagis[®] for a second
137 season, one of the fifty-six patients had transient, low titer reactivity. This reactivity was not associated
138 with adverse events or alteration in serum concentrations. Immunogenicity was not assessed in Trial 2.

139 These data reflect the percentage of patients whose test results were considered positive for antibodies
140 to Synagis[®] (palivizumab) in an ELISA assay, and are highly dependent on the sensitivity and specificity
141 of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by
142 several factors including sample handling, concomitant medications, and underlying disease. For these
143 reasons, comparison of the incidence of antibodies to Synagis[®] with the incidence of antibodies to other
144 products may be misleading.

145 *Post-Marketing Experience*

146 The following adverse reactions have been identified and reported during post-approval use of
147 Synagis[®]. Because the reports of these reactions are voluntary and the population is of uncertain size,
148 it is not always possible to reliably estimate the frequency of the reaction or establish a causal
149 relationship to drug exposure.

150 Based on experience in over 400,000 patients who have received Synagis[®] (>2 million doses), rare severe
151 acute hypersensitivity reactions have been reported on initial or subsequent exposure. Very rare cases of
152 anaphylaxis (<1 case per 100,000 patients) have also been reported following re-exposure
153 (See **WARNINGS**). None of the reported hypersensitivity reactions were fatal. Hypersensitivity

154 reactions may include dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia and
155 unresponsiveness. The relationship between these reactions and the development of antibodies to
156 Synagis[®] is unknown.

157 Limited information from post-marketing reports suggests that, within a single RSV season, adverse
158 events after a sixth or greater dose of Synagis[®] are similar in character and frequency to those after the
159 initial five doses.

160 **OVER DOSAGE:** No data from clinical studies are available on over dosage. No toxicity was observed
161 in rabbits administered a single intramuscular or subcutaneous injection of Synagis[®] at a dose of 50
162 mg/kg.

163 **DOSAGE AND ADMINISTRATION:** The recommended dose of Synagis[®] is 15 mg/kg of body weight.
164 Patients, including those who develop an RSV infection, should continue to receive monthly doses
165 throughout the RSV season. The first dose should be administered prior to commencement of the RSV
166 season. In the northern hemisphere, the RSV season typically commences in November and lasts through
167 April, but it may begin earlier or persist later in certain communities.

168 Synagis[®] serum levels are decreased after cardio-pulmonary bypass (See *CLINICAL*
169 *PHARMACOLOGY*). Patients undergoing cardio-pulmonary bypass should receive a dose of Synagis[®] as
170 soon as possible after the cardio-pulmonary bypass procedure (even if sooner than a month from the
171 previous dose). Thereafter, doses should be administered monthly.

172 Synagis[®] should be administered in a dose of 15 mg/kg intramuscularly using aseptic technique,
173 preferably in the anterolateral aspect of the thigh. The gluteal muscle should not be used routinely as an
174 injection site because of the risk of damage to the sciatic nerve. The dose per month = patient weight
175 (kg) x 15 mg/kg ÷ 100 mg/mL of Synagis[®]. Injection volumes over 1 mL should be given as a divided
176 dose.

177 *Preparation of Lyophilized Product for Administration:*

- 178 • To reconstitute, remove the tab portion of the vial cap and clean the rubber stopper with 70% ethanol or
179 equivalent.
- 180 • Both the 50 mg and 100 mg vials contain an overfill to allow the withdrawal of 50 milligrams or 100 milligrams
181 respectively when reconstituted following the directions described below.
- 182 • SLOWLY add 0.6 mL of sterile water for injection to the 50 mg vial or add 1.0 mL of sterile water for injection
183 to the 100 mg vial. The vial should be tilted slightly and gently rotated for 30 seconds to avoid foaming. DO
184 NOT SHAKE or VIGOROUSLY AGITATE the VIAL. This is a critical step to avoid prolonged foaming.
- 185 • Reconstituted Synagis[®] should stand undisturbed at room temperature for a minimum of 20 minutes until the
186 solution clarifies.
- 187 • Reconstituted Synagis[®] (palivizumab) should be inspected visually for particulate matter or discoloration prior to
188 administration. The reconstituted solution should appear clear or slightly opalescent (a thin layer of micro-
189 bubbles on the surface is normal and will not affect dosage). Do not use if there is particulate matter or if the
190 solution is discolored.
- 191 • Reconstituted Synagis[®] does not contain a preservative and should be administered within 6 hours of
192 reconstitution. Administer immediately after withdrawal from vial. Synagis[®] is supplied in single-use vials DO
193 NOT re-enter the vial. Discard any unused portion.

194 *Preparation of Liquid Product for Administration:*

- 195 • Remove the tab portion of the vial cap and clean the rubber stopper with 70% ethanol or equivalent.
- 196 • Both the 50 mg and 100 mg vials contain an overfill to allow the withdrawal of 50 milligrams or 100 milligrams.
- 197 • Synagis[®] does not contain a preservative and should be administered immediately after withdrawal from
198 vial. Synagis[®] is supplied in single-use vials. DO NOT re-enter the vial. Discard any unused portion.

199

200 To prevent the transmission of hepatitis viruses or other infectious agents from one person to another,
201 sterile disposable syringes and needles should be used. Do not reuse syringes and needles.

202
203 **HOW SUPPLIED:** Synagis[®] is available in two formulations: a lyophilized powder and liquid
204 solution.

205 **Lyophilized Powder:** Synagis[®] is supplied in single-use vials as lyophilized powder to deliver either 50
206 milligrams or 100 milligrams when reconstituted with sterile water for injection.

207 50 mg vial NDC 60574-4112-1

208 Upon reconstitution the 50 mg vial contains 50 milligrams Synagis[®] in 0.5 mL.

209 100 mg vial NDC 60574-4111-1

210 Upon reconstitution the 100 mg vial contains 100 milligrams Synagis[®] in 1.0 mL.

211 **Liquid Solution:** Synagis[®] is supplied in single-use vials as a preservative free, sterile solution at 100
212 mg/mL in 0.5 mL and 1.0 mL to deliver either 50 milligrams or 100 milligrams, respectively for IM injection.

213 50 mg vial NDC [60574-4114-1](#)

214 The 50 mg vial contains 50 milligrams Synagis[®] in 0.5 mL.

215 100 mg vial NDC [60574-4113-1](#)

216 The 100 mg vial contains 100 milligrams Synagis[®] in 1.0 mL.

217 Upon receipt and until use, Synagis[®] should be stored between 2 and 8°C (35.6° and 46.4°F) in its
218 original container. Do not freeze. Do not use beyond the expiration date.

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Co-Marketed by:



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