

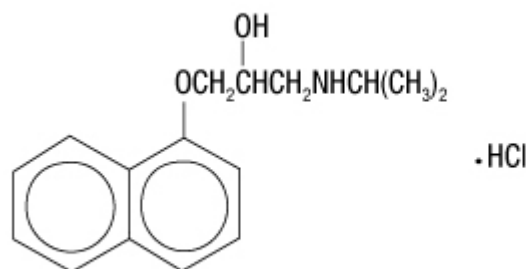
PRESCRIBING INFORMATION

InnoPran XL[®] (propranolol hydrochloride) Extended Release Capsules

DESCRIPTION

INNOPRAN XL (propranolol hydrochloride) is a nonselective, beta-adrenergic receptor-blocking agent for oral administration, available as an extended release product. INNOPRAN XL is available as 80-mg and 120-mg capsules which contain sustained-release beads. Each of the beads contains propranolol hydrochloride and is coated with dual membranes. These membranes are designed to retard release of propranolol hydrochloride for several hours after ingestion followed by the sustained release of propranolol.

The active ingredient in INNOPRAN XL is a synthetic beta-adrenergic receptor-blocking agent chemically described as 1-(Isopropylamino)-3-(1-naphthoxy)-2-propanol hydrochloride. Its structural formula is:



Propranolol hydrochloride is a stable, white, crystalline solid, which is readily soluble in water and ethanol. Its molecular weight is 295.81. Each capsule for oral administration contains sugar spheres, ethylcellulose, povidone, hypromellose phthalate, diethyl phthalate, hypromellose, polyethylene glycol, gelatin, titanium dioxide, and black iron oxide. In addition, INNOPRAN XL 120-mg capsules contain yellow iron oxide.

CLINICAL PHARMACOLOGY

General: Propranolol is a nonselective, beta-adrenergic receptor-blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor-stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by propranolol, chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately. At dosages greater than required for beta blockade, propranolol also exerts a quinidine-like or anesthetic-like membrane action, which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

30 **Mechanism of Action:** The mechanism of the antihypertensive effect of propranolol has not
31 been established. Among factors that contribute to the antihypertensive action are: (1) decreased
32 cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic
33 sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral
34 resistance may increase initially, it readjusts to or below the pretreatment level with chronic use
35 of propranolol. Effects of propranolol on plasma volume appear to be minor and somewhat
36 variable.

37 **Pharmacokinetics and Drug Metabolism: Absorption:** Propranolol is highly lipophilic
38 and is almost completely absorbed after oral administration. However, it undergoes high first-
39 pass metabolism by the liver and on average, only about 25% of propranolol reaches the
40 systemic circulation.

41 A single-dose, food-effect study in 36 healthy subjects showed that a high fat meal
42 administered with INNOPRAN XL at 10 p.m., increased the lag time from 3 to 5 hours and the
43 time to reach the maximum concentration from 11.5 to 15.4 hours, under fed conditions, with no
44 effect on the AUC (see DOSAGE AND ADMINISTRATION).

45 Following multiple-dose administration of INNOPRAN XL at 10 p.m. under fasting
46 conditions, the steady state lag time was between 4 and 5 hours and propranolol peak plasma
47 concentrations were reached approximately 12 to 14 hours after dosing. Propranolol trough
48 levels were achieved 24 to 27 hours after dosing, and persisted for 3 to 5 hours after the next
49 dose. The elimination half-life of propranolol was approximately 8 hours.

50 The plasma levels of propranolol showed dose-proportional increases after single and multiple
51 administration of 80-, 120-, and 160-mg of INNOPRAN XL.

52 At steady state, the bioavailability of a 160-mg dose of INNOPRAN XL and propranolol
53 hydrochloride long-acting capsules did not differ significantly.

54 **Distribution:** Approximately 90% of circulating propranolol is bound to plasma proteins
55 (albumin and alpha₁ acid glycoprotein). The binding is enantiomer-selective. The S-isomer is
56 preferentially bound to alpha₁ glycoprotein and the R-isomer preferentially bound to albumin.
57 The volume of distribution of propranolol is approximately 4 liters.

58 **Metabolism and Elimination:** Propranolol is extensively metabolized with most
59 metabolites appearing in the urine. Propranolol is metabolized through 3 primary routes:
60 Aromatic hydroxylation (mainly 4-hydroxylation), N-dealkylation followed by further side-chain
61 oxidation, and direct glucuronidation. It has been estimated that the percentage contributions of
62 these routes to total metabolism are 42%, 41%, and 17%, respectively, but with considerable
63 variability between individuals. The 4 major metabolites are propranolol glucuronide,
64 naphthyloxylactic acid, and glucuronic acid and sulfate conjugates of 4-hydroxy propranolol.

65 In vitro studies have indicated that the aromatic hydroxylation of propranolol is catalyzed
66 mainly by polymorphic CYP2D6. Side-chain oxidation is mediated mainly by CYP1A2 and to
67 some extent by CYP2D6. 4-hydroxy propranolol is a weak inhibitor of CYP2D6.

68 Propranolol is also a substrate for CYP2C19 and a substrate for the intestinal efflux
69 transporter, p-glycoprotein (p-gp). Studies suggest however that p-gp is not dose-limiting for
70 intestinal absorption of propranolol in the usual therapeutic dose range.

71 In healthy subjects, no difference was observed between CYP2D6 extensive metabolizers
72 (EMs) and poor metabolizers (PMs) with respect to oral clearance or elimination half-life. Partial
73 clearance to 4-hydroxy propranolol was significantly higher and to naphthyloxylactic acid was
74 significantly lower in EMs than PMs.

75 **Enantiomers:** Of the 2 enantiomers of propranolol, the S-enantiomer blocks beta-adrenergic
76 receptors. In normal subjects receiving oral doses of racemic propranolol, S-enantiomer
77 concentrations exceeded those of the R-enantiomer by 40 to 90% as a result of stereoselective
78 hepatic metabolism.

79 **Special Populations: Pediatric:** The pharmacokinetics of INNOPRAN XL have not been
80 investigated in patients younger than 18 years of age.

81 **Geriatric:** The pharmacokinetics of INNOPRAN XL have not been investigated in patients
82 older than 65 years. In a study of 12 elderly (62 to 79 years old) and 12 young (25 to 33 years
83 old) healthy subjects, the clearance of the S-enantiomer of propranolol was decreased in the
84 elderly. Additionally, the half-lives of both R- and S-propranolol were prolonged in the elderly
85 compared with the young (11 hours versus 5 hours).

86 **Gender:** In a dose-proportionality study, the pharmacokinetics of INNOPRAN XL were
87 evaluated in 22 male and 14 female healthy volunteers. Following single doses under fasting
88 conditions, the mean AUC and C_{max} were about 49% and 16% higher for females across the
89 dosage range. The mean elimination half-life was longer in females than in males (11 hours
90 versus 7.5 hours).

91 **Race:** A study conducted in 12 white and 13 African-American male subjects taking
92 propranolol showed, that at steady state, the clearance of R- and S-propranolol were about 76%
93 and 53% higher in African-Americans than in whites, respectively.

94 **Renal Insufficiency:** The pharmacokinetics of INNOPRAN XL have not been evaluated in
95 patients with renal insufficiency. In a study conducted in 5 patients with chronic renal failure, 6
96 patients on regular dialysis, and 5 healthy subjects, who received a single oral dose of 40 mg of
97 propranolol, the peak plasma concentrations (C_{max}) of propranolol in the chronic renal failure
98 group were 2- to 3-fold higher (161 ± 41 ng/mL) than those observed in the dialysis patients
99 (47 ± 9 ng/mL) and in the healthy subjects (26 ± 1 ng/mL). Propranolol plasma clearance was also
100 reduced in the patients with chronic renal failure.

101 Chronic renal failure has been associated with a decrease in drug metabolism via down
102 regulation of hepatic cytochrome P450 activity.

103 **Hepatic Insufficiency:** The pharmacokinetics of INNOPRAN XL have not been evaluated
104 in patients with hepatic impairment. However, propranolol is extensively metabolized by the
105 liver. In a study conducted in 7 patients with cirrhosis and 9 healthy subjects receiving 80-mg
106 oral propranolol every 8 hours for 7 doses, the steady-state unbound propranolol concentration in

107 patients with cirrhosis was increased 3-fold in comparison to controls. In cirrhosis, the half-life
108 increased to 11 hours compared to 4 hours (see PRECAUTIONS).

109 **Drug Interactions: Interactions with Substrates, Inhibitors or Inducers of**
110 **Cytochrome P450 Enzymes:** Because propranolol's metabolism involves multiple pathways
111 in the cytochrome P450 system (CYP2D6, 1A2, 2C19), administration of INNOPRAN XL with
112 drugs that are metabolized by, or affect the activity (induction or inhibition) of one or more of
113 these pathways may lead to clinically relevant drug interactions (see PRECAUTIONS, Drug
114 Interactions).

115 **Substrates or Inhibitors of CYP2D6:** Blood levels and/or toxicity of propranolol may
116 be increased by administration of INNOPRAN XL with substrates or inhibitors of CYP2D6,
117 such as amiodarone, cimetidine, delavudin, fluoxetine, paroxetine, quinidine, and ritonavir. No
118 interactions were observed with either ranitidine or lansoprazole.

119 **Substrates or Inhibitors of CYP1A2:** Blood levels and/or toxicity of propranolol may
120 be increased by administration of INNOPRAN XL with substrates or inhibitors of CYP1A2,
121 such as imipramine, cimetidine, ciprofloxacin, fluvoxamine, isoniazid, ritonavir, theophylline,
122 zileuton, zolmitriptan, and rizatriptan.

123 **Substrates or Inhibitors of CYP2C19:** Blood levels and/or toxicity of propranolol
124 may be increased by administration of INNOPRAN XL with substrates or inhibitors of
125 CYP2C19, such as fluconazole, cimetidine, fluoxetine, fluvoxamine, teniposide, and
126 tolbutamide. No interaction was observed with omeprazole.

127 **Inducers of Hepatic Drug Metabolism:** Blood levels of propranolol may be decreased
128 by administration of INNOPRAN XL with inducers such as rifampin and ethanol. Cigarette
129 smoking also induces hepatic metabolism and has been shown to increase up to 100% the
130 clearance of propranolol, resulting in decreased plasma concentrations.

131 **Cardiovascular Drugs: Antiarrhythmics:** The concomitant administration of
132 propranolol and propafenone increased propranolol average steady-state plasma concentrations
133 (213%), AUC (113%), C_{max} (83%), T_{max} (55%), and $T_{1/2}$ (30%), and significantly decreased
134 plasma levels of 4-hydroxy-propranolol. Co-administration of propranolol and propafenone did
135 not produce any significant change in propafenone pharmacokinetics. While the therapeutic
136 range for propranolol is wide, a reduction in dosage may be necessary during concomitant
137 administration with propafenone.

138 The metabolism of propranolol is reduced by co-administration of quinidine, leading to a 2- to
139 3-fold increase in blood concentrations and greater degrees of clinical beta-blockade.

140 Concomitant administration of propranolol with lidocaine, bupivacaine or mepivacaine has
141 been reported to decrease the clearance of these amide anesthetics significantly, resulting in
142 higher serum concentrations of the anesthetic.

143 **Calcium channel blockers:** The mean C_{max} and AUC of propranolol are increased
144 respectively, by 50% and 30% by co-administration of nisoldipine and by 80% and 47%, by co-
145 administration of nicardipine.

146 The mean C_{max} and AUC of nifedipine are increased by 64% and 79%, respectively, by co-
147 administration of propranolol.

148 Propranolol does not affect the pharmacokinetics of verapamil and norverapamil. Verapamil
149 does not affect the pharmacokinetics of propranolol.

150 **Non-Cardiovascular Drugs: Anti-Ulcer Drugs:** Co-administration of propranolol with
151 cimetidine, a non-specific CYP450 inhibitor, increased propranolol concentrations by about
152 40%. Co-administration with aluminum hydroxide gel (1,200 mg) resulted in a 50% decrease in
153 propranolol concentrations.

154 Co-administration of metoclopramide with propranolol did not have a significant effect on
155 propranolol's pharmacokinetics.

156 **Benzodiazepines:** Propranolol can inhibit the metabolism of diazepam, resulting in
157 increased concentrations of diazepam and its metabolites. Diazepam does not alter the
158 pharmacokinetics of propranolol.

159 The pharmacokinetics of oxazepam, triazolam, lorazepam, and alprazolam are not affected by
160 co-administration of propranolol.

161 **Lipid Lowering Drugs:** Co-administration of cholesteramine or colestipol with propranolol
162 resulted in up to a 50% decrease in propranolol concentrations.

163 Co-administration of propranolol with lovastatin or pravastatin decreased 20% to 25% the
164 AUC of both, but did not alter their pharmacodynamics. Propranolol did not have an effect on
165 the pharmacokinetics of fluvastatin.

166 **Migraine Drugs:** Administration of zolmitriptan or rizatriptan with propranolol resulted in
167 increased concentrations of zolmitriptan (AUC increased by 56% and C_{max} by 37%) or rizatriptan
168 (the AUC and C_{max} were increased by 67% and 75%, respectively).

169 **Neuroleptic Drugs:** Co-administration of propranolol at doses greater than or equal to 160
170 mg/day resulted in increased thioridazine plasma concentrations ranging from 50% to 370% and
171 increased thioridazine metabolites concentrations ranging from 33% to 210%.

172 Co-administration of chlorpromazine with propranolol resulted in increased plasma levels of
173 both drugs (70% increase in propranolol concentrations).

174 **Theophylline:** Co-administration of theophylline with propranolol decreases theophylline
175 oral clearance by 33% to 52%.

176 **Warfarin:** Concomitant administration of propranolol and warfarin has been shown to
177 increase warfarin bioavailability and increase prothrombin time.

178 **Pharmacodynamics and Clinical Effects: Hypertension:** In a double-blind, parallel
179 dose-response study in patients with mild-to-moderate hypertension (n=434), doses of
180 INNOPRAN XL from 80 to 640 mg were taken once daily at approximately 10 p.m.
181 INNOPRAN XL significantly lowered sitting systolic and diastolic blood pressure when
182 measurements were taken approximately 16 hours later. The placebo-subtracted diastolic blood
183 pressure effect for the 80- and 120-mg doses was -3.0 and -4.0 mm Hg, respectively. Higher
184 doses of INNOPRAN XL (160, 640 mg) had no additional blood-pressure lowering effect when
185 compared with 120 mg. The antihypertensive effects of INNOPRAN XL were seen in the elderly

186 (≥65 years old) and men and women. There were too few non-white patients to assess the
187 efficacy of INNOPRAN XL in these patients.

188 **INDICATIONS AND USAGE**

189 **Hypertension:** INNOPRAN XL is indicated in the management of hypertension; it may be
190 used alone or in combination with other antihypertensive agents.

191 **CONTRAINDICATIONS**

192 Propranolol is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia, sick sinus
193 syndrome, and greater than first-degree block unless a permanent pacemaker is in place;
194 3) bronchial asthma; and 4) in patients with known hypersensitivity to propranolol
195 hydrochloride.

196 **WARNINGS**

197 **Cardiac Failure:** Sympathetic stimulation may be a vital component supporting circulatory
198 function in patients with congestive heart failure, and its inhibition by beta-blockade may
199 precipitate more severe failure. Although beta-blockers should be avoided in overt congestive
200 heart failure, some have been shown to be highly beneficial when used with close follow-up in
201 patients with a history of failure who are well compensated and are receiving additional
202 therapies, including diuretics as needed. Beta-adrenergic blocking agents do not abolish the
203 inotropic action of digitalis on heart muscle.

204 **Angina Pectoris:** There have been reports of exacerbation of angina and, in some cases,
205 myocardial infarction, following abrupt discontinuance of propranolol therapy. Therefore, when
206 discontinuance of propranolol is planned, the dosage should be gradually reduced over at least a
207 few weeks, and the patient should be cautioned against interruption or cessation of therapy
208 without a physician's advice. If propranolol therapy is interrupted and exacerbation of angina
209 occurs, it is usually advisable to reinstitute propranolol therapy and take other measures
210 appropriate for the management of angina pectoris. Since coronary artery disease may be
211 unrecognized, it may be prudent to follow the above advice in patients considered at risk of
212 having occult atherosclerotic heart disease who are given propranolol for other indications.

213 **Nonallergic Bronchospasm (e.g., Chronic Bronchitis, Emphysema):** In general,
214 patients with bronchospastic lung disease should not receive beta-blockers. Propranolol should
215 be administered with caution in this setting since it may block bronchodilation produced by
216 endogenous and exogenous catecholamine stimulation of beta-receptors.

217 **Major Surgery:** The necessity or desirability of withdrawal of beta-blocking therapy prior to
218 major surgery is controversial. It should be noted, however, that the impaired ability of the heart
219 to respond to reflex adrenergic stimuli in propranolol-treated patients may augment the risks of
220 general anesthesia and surgical procedures.

221 Propranolol is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed
222 by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may
223 be subject to protracted severe hypotension.

224 **Diabetes and Hypoglycemia:** Beta-adrenergic blockade may prevent the appearance of
225 certain premonitory signs and symptoms (pulse rate and blood pressure changes) of acute
226 hypoglycemia, especially in labile insulin-dependent diabetics. In these patients, it may be more
227 difficult to adjust the dosage of insulin.

228 Propranolol therapy, particularly in infants and children, diabetic or not, has been associated
229 with hypoglycemia especially during fasting, as in preparation for surgery. Hypoglycemia has
230 been reported with propranolol use after prolonged physical exertion and in patients with renal
231 insufficiency.

232 **Thyrotoxicosis:** Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism.
233 Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms
234 of hyperthyroidism, including thyroid storm. Propranolol may change thyroid-function tests,
235 increasing T₄ and reversing T₃, and decreasing T₃.

236 **Wolff-Parkinson-White Syndrome:** Beta-adrenergic blockade in patients with Wolf-
237 Parkinson-White syndrome and tachycardia has been associated with severe bradycardia
238 requiring treatment with a pacemaker. In one case, this resulted after an initial dose of 5-mg
239 propranolol.

240 PRECAUTIONS

241 **General:** Propranolol should be used with caution in patients with impaired hepatic or renal
242 function. INNOPRAN XL is not indicated for the treatment of hypertensive emergencies.

243 Beta-adrenergic receptor blockade can cause reduction of intraocular pressure. Patients should
244 be told that INNOPRAN XL may interfere with the glaucoma screening test. Withdrawal may
245 lead to a return of intraocular pressure.

246 **Risk of Anaphylactic Reaction:** While taking beta-blockers, patients with a history of severe
247 anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either
248 accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of
249 epinephrine used to treat allergic reaction.

250 **Clinical Laboratory Tests:** In patients with hypertension, use of propranolol has been
251 associated with elevated levels of serum potassium, and serum transaminases and alkaline
252 phosphatase. In severe heart failure, the use of propranolol has been associated with increases in
253 blood urea nitrogen.

254 **Drug Interactions:** Caution should be exercised when INNOPRAN XL is administered with
255 drugs that have an effect on CYP2D6, 1A2, or 2C19 metabolic pathways. Co-administration of
256 such drugs with propranolol may lead to clinically relevant drug interactions and changes on its
257 efficacy and/or toxicity (see CLINICAL PHARMACOLOGY, Drug Interactions).

258 **Cardiovascular Drugs: ACE Inhibitors:** When combined with beta-blockers, ACE
259 inhibitors can cause hypotension, particularly in the setting of acute myocardial infraction.

260 Certain ACE inhibitors have been reported to increase bronchial hyperreactivity when
261 administered with propranolol.

262 The antihypertensive effects of clonidine may be antagonized by beta-blockers. INNOPRAN
263 XL should be administered cautiously to patients withdrawing from clonidine.

264 **Alpha Blockers:** Prazosin has been associated with prolongation of first dose hypotension
265 in the presence of beta-blockers.

266 Postural hypotension has been reported in patients taking both beta-blockers and terazosin or
267 doxazosin.

268 **Antiarrhythmics:** Propafenone has negative inotropic and beta-blocking properties that can
269 be additive to those of propranolol.

270 Quinidine increases the concentration of propranolol and produces greater degrees of clinical
271 beta-blockade and may cause postural hypotension.

272 Disopyramide is a Type I antiarrhythmic drug with potent negative inotropic and chronotropic
273 effects and has been associated with severe bradycardia, asystole, and heart failure when
274 administered with propranolol.

275 Amiodarone is an antiarrhythmic agent with negative chronotropic properties that may be
276 additive to those seen with propranolol.

277 The clearance of lidocaine and bupivacaine are significantly reduced with administration of
278 propranolol. Lidocaine and bupivacaine toxicity has been reported following coadministration
279 with propranolol. (see also PRECAUTIONS, Drug Interactions, Non-Cardiovascular Drugs,
280 Anesthetic Agents)

281 Caution should be exercised when administering INNOPRAN XL with drugs that slow A-V
282 nodal conduction, e.g. digitalis, lidocaine, and calcium channel blockers.

283 **Calcium Channel Blockers:** Caution should be exercised when patients receiving a beta-
284 blocker are administered a calcium-channel-blocking drug with negative inotropic and/or
285 chronotropic effects. Both agents may depress myocardial contractility or atrioventricular
286 conduction.

287 There have been reports of significant bradycardia, heart failure, and cardiovascular collapse
288 with concurrent use of verapamil and beta-blockers.

289 Co-administration of propranolol and diltiazem in patients with cardiac disease has been
290 associated with bradycardia, hypotension, high degree heart block, and heart failure.

291 **Digitalis Glycosides:** Both digitalis glycosides and beta-blockers slow atrioventricular
292 conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.

293 **Inotropic Agents:** Patients on long-term therapy with propranolol may experience
294 uncontrolled hypertension if administered epinephrine as a consequence of unopposed alpha-
295 receptor stimulation. Epinephrine is therefore not indicated in the treatment of propranolol
296 overdose (see OVERDOSAGE).

297 **Isoproterenol and Dobutamine:** Propranolol is a competitive inhibitor of beta-receptor
298 agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or

299 isoproterenol. Also, propranolol may reduce sensitivity to dobutamine stress echocardiography in
300 patients undergoing evaluation for myocardial ischemia.

301 **Reserpine:** Patients receiving catecholamine-depleting drugs, such as reserpine and
302 INNOPRAN XL, should be closely observed for excessive reduction of resting sympathetic
303 nervous activity, which may result in hypotension, marked bradycardia, vertigo, syncopal
304 attacks, or orthostatic hypotension. Administration of reserpine with propranolol may also
305 potentiate depression.

306 **Non-Cardiovascular Drugs: Anesthetic Agents:** Methoxyflurane and trichloroethylene
307 may depress myocardial contractility when administered with propranolol.

308 The clearance of local amide anesthetics (e.g., lidocaine, bupivacaine, mepivacaine) is
309 reduced with administration of propranolol. Lidocaine and bupivacaine toxicity has been
310 reported following coadministration with propranolol. Caution should be exercised when amide
311 anesthetic agents are administered concomitantly with propranolol.

312 **Antidepressants:** The hypotensive effects of MAO inhibitors or tricyclic antidepressants
313 may be exacerbated when administered with beta-blockers by interfering with the beta-blocking
314 activity of propranolol.

315 **Neuroleptic Drugs:** Hypotension and cardiac arrest have been reported with the
316 concomitant use of propranolol and haloperidol.

317 **Nonsteroidal Anti-Inflammatory Drugs:** Nonsteroidal anti-inflammatory drugs
318 (NSAIDs) have been reported to blunt the antihypertensive effect of beta-adrenoreceptor
319 blocking agents.

320 Administration of indomethacin with propranolol may reduce the efficacy of propranolol in
321 reducing blood pressure and heart rate.

322 **Thyroxine:** Thyroxine may result in a lower than expected T₃ concentration when used
323 concomitantly with propranolol.

324 **Warfarin:** Propranolol when administered with warfarin increases the concentration of
325 warfarin. Prothrombin time, therefore, should be monitored.

326 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** In dietary administration studies
327 in which mice and rats were treated with propranolol HCl for up to 18 months at doses of up to
328 150 mg/kg/day, there was no evidence of drug-related tumorigenesis. On a body surface area
329 basis, this dose in the mouse and rat is, respectively, about equal to and about twice the
330 maximum recommended human oral daily dose (MRHD) of 640 mg propranolol HCl. In a study
331 in which both male and female rats were exposed to propranolol HCl in their diets at
332 concentrations of up to 0.05% (about 50 mg/kg body weight and less than the MRHD), from
333 60 days prior to mating and throughout pregnancy and lactation for 2 generations, there were no
334 effects on fertility. Based on differing results from Ames tests performed by different
335 laboratories, there is equivocal evidence for a genotoxic effect of propranolol HCl in bacteria
336 (*S. typhimurium* strain TA 1538).

337 **Pregnancy: Pregnancy Category C:** In a series of reproductive and developmental
338 toxicology studies, propranolol was given to rats by gavage or in the diet throughout pregnancy

339 and lactation. At doses of 150 mg/kg/day, but not at doses of 80 mg/kg/day (equivalent to the
340 MRHD on a body surface area basis), treatment was associated with embryotoxicity (reduced
341 litter size and increased resorption rates) as well as neonatal toxicity (deaths). Propranolol HCl
342 also was administered (in the feed) to rabbits (throughout pregnancy and lactation) at doses as
343 high as 150 mg/kg/day (about 5 times the maximum recommended human oral daily dose). No
344 evidence of embryo or neonatal toxicity was noted.

345 There are no adequate and well controlled studies in pregnant women. Intrauterine growth
346 retardation has been reported for neonates whose mothers received propranolol HCl during
347 pregnancy. Neonates whose mothers received propranolol HCl at parturition have exhibited
348 bradycardia, hypoglycemia, and respiratory depression. Adequate facilities for monitoring such
349 infants at birth should be available. INNOPRAN XL should be used during pregnancy only if the
350 potential benefit justifies the potential risk to the fetus.

351 **Nursing Mothers:** Propranolol is excreted in human milk. Caution should be exercised when
352 INNOPRAN XL is administered to a nursing woman.

353 **Pediatric Use:** Safety and effectiveness of propranolol in pediatric patients have not been
354 established.

355 **Geriatric Use:** Clinical studies of INNOPRAN XL did not include sufficient numbers of
356 subjects aged 65 and over to determine whether they respond differently from younger subjects.
357 Other reported clinical experience has not identified differences in responses between the elderly
358 and younger patients. In general, dose selection for an elderly patient should be cautious, usually
359 starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic,
360 renal, or cardiac function, and of concomitant disease or other drug therapy.

361 **ADVERSE REACTIONS**

362 Adverse events occurring at a rate of $\geq 3\%$, excluding those reported more commonly in
363 placebo, encountered in the INNOPRAN XL placebo-controlled hypertension trials and
364 plausibly related to treatment are shown in Table 1.

365

366 **Table 1. Treatment Emergent Adverse Events Reported In $\geq 3\%$ of Subjects**

Body System	INNOPRAN XL		
	Placebo (N=88)	80 mg (N=89)	120 mg (N=85)
Fatigue	3 (3.0%)	4 (5.0%)	6 (7.0%)
Dizziness (except vertigo)	2 (2.0%)	6 (7.0%)	3 (4.0%)
Constipation	0	3 (3.0%)	1 (1.0%)

367

368 The following adverse events were observed and have been reported with use of formulations
369 of sustained- or immediate-release propranolol.

370 **Cardiovascular:** Bradycardia; congestive heart failure; intensification of AV block;
371 hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of
372 the Raynaud type.

373 **Central Nervous System:** Light-headedness, mental depression manifested by insomnia,
374 lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual
375 disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by
376 disorientation for time and place, short-term memory loss, emotional lability, slightly clouded
377 sensorium, and decreased performance on neuropsychometrics. For immediate-release
378 formulations, fatigue, lethargy, and vivid dreams appear dose-related.

379 **Gastrointestinal:** Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea,
380 constipation, mesenteric arterial thrombosis, ischemic colitis.

381 **Allergic:** Pharyngitis and agranulocytosis; erythematous rash, fever combined with aching and
382 sore throat, laryngospasm, and respiratory distress.

383 **Respiratory:** Bronchospasm.

384 **Hematologic:** Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

385 **Autoimmune:** In extremely rare instances, systemic lupus erythematosus has been reported.

386 **Miscellaneous:** Alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence,
387 and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the
388 skin, serous membranes, and conjunctivae reported for a beta-blocker (practolol) have not been
389 associated with propranolol.

390 **DOSAGE AND ADMINISTRATION**

391 INNOPRAN XL should be administered once daily at bedtime (approximately 10 p.m.) and
392 should be taken consistently either on an empty stomach or with food. The starting dose is 80 mg
393 but dosage should be individualized and titration may be needed to a dose of 120 mg. In the
394 clinical trial, doses of INNOPRAN XL above 120 mg had no additional effects on blood pressure
395 (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects). The time
396 needed for full antihypertensive response is variable, but is usually achieved within 2 to 3 weeks.

397 **OVERDOSAGE**

398 Most overdoses of propranolol are mild and respond to supportive care.

399 Propranolol is not significantly dialyzable. In the event of overdose or exaggerated response,
400 the following measures should be employed.

401 Hypotension and bradycardia have been reported following propranolol overdose and should
402 be treated appropriately. Glucagon can exert potent inotropic and chronotropic effects and may
403 be particularly useful for the treatment of hypotension or depressed myocardial function after a
404 propranolol overdose.

405 Glucagon should be administered as 50-150 mcg/kg intravenously followed by continuous
406 drip of 1-5 mg/hour for positive chronotropic effect. Isoproterenol, dopamine or
407 phosphodiesterase inhibitors may also be useful. Epinephrine, however, may provoke

408 uncontrolled hypertension. Bradycardia can be treated with atropine or isoproterenol. Serious
409 bradycardia may require temporary cardiac pacing.

410 The electrocardiogram, pulse, blood pressure, neurobehavioral status and intake and output
411 balance must be monitored. Isoproterenol and aminophylline may be used for bronchospasm.

412 **HOW SUPPLIED**

413 INNOPRAN XL (propranolol hydrochloride) Extended Release Capsules

414 Each gray/white capsule, imprinted with “80”, 2 segmented bands, “InnoPran XL”, and the
415 Reliant logo, contains 80 mg of propranolol hydrochloride in bottles of 30 (NDC 0173-0790-01),
416 bottles of 100 (0173-0790-02).

417 Each gray/off-white capsule, imprinted with “120”, 3 segmented bands, “InnoPran XL”, and
418 the Reliant logo, contains 120 mg of propranolol hydrochloride in bottles of 30 (NDC 0173-
419 0791-01), and bottles of 100 (NDC 0173-0791-02).

420 Store at 25°C (77°F); excursions permitted to 15 and 30°C (59 and 86°F) [see USP Controlled
421 Room Temperature] in a tightly closed container.

422

423

424 Manufactured for:



425

426 GlaxoSmithKline

427 Research Triangle Park, NC 27709

428 By: Eurand America, Inc.

429 Vandalia, OH 45377

430

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433 Month Year

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