



ACCUTANE®

(isotretinoin capsules)

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2

3

4

5 Rx only

6 CAUSES BIRTH

7 DEFECTS



8

9 DO NOT GET

10 PREGNANT

11

12 **CONTRAINDICATIONS AND WARNINGS**

13 Accutane must not be used by female patients who are or may become  
14 pregnant. There is an extremely high risk that severe birth defects will result  
15 if pregnancy occurs while taking Accutane in any amount, even for short  
16 periods of time. Potentially any fetus exposed during pregnancy can be  
17 affected. There are no accurate means of determining whether an exposed  
18 fetus has been affected.

19 Birth defects which have been documented following Accutane exposure  
20 include abnormalities of the face, eyes, ears, skull, central nervous system,  
21 cardiovascular system, and thymus and parathyroid glands. Cases of IQ  
22 scores less than 85 with or without other abnormalities have been reported.  
23 There is an increased risk of spontaneous abortion, and premature births  
24 have been reported.

25 Documented external abnormalities include: skull abnormality; ear  
26 abnormalities (including anotia, micropinna, small or absent external  
27 auditory canals); eye abnormalities (including microphthalmia); facial  
28 dysmorphism; cleft palate. Documented internal abnormalities include: CNS  
29 abnormalities (including cerebral abnormalities, cerebellar malformation,  
30 hydrocephalus, microcephaly, cranial nerve deficit); cardiovascular  
31 abnormalities; thymus gland abnormality; parathyroid hormone deficiency.  
32 In some cases death has occurred with certain of the abnormalities  
33 previously noted.

34 If pregnancy does occur during treatment of a female patient who is taking  
35 Accutane, Accutane must be discontinued immediately and she should be

36 referred to an Obstetrician-Gynecologist experienced in reproductive toxicity  
37 for further evaluation and counseling.

38 **Special Prescribing Requirements**

39 Because of Accutane's teratogenicity and to minimize fetal exposure,  
40 Accutane is approved for marketing only under a special restricted  
41 distribution program approved by the Food and Drug Administration. This  
42 program is called iPLEDGE™. Accutane must only be prescribed by prescribers  
43 who are registered and activated with the iPLEDGE program. Accutane must  
44 only be dispensed by a pharmacy registered and activated with iPLEDGE, and  
45 must only be dispensed to patients who are registered and meet all the  
46 requirements of iPLEDGE (see **PRECAUTIONS**).

47 **Table 1 Monthly Required iPLEDGE Interactions**

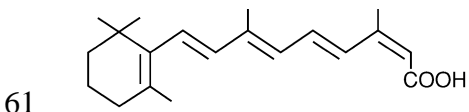
	Female Patients of Childbearing Potential	Male Patients, And Female Patients Not of Childbearing Potential
<b>PRESCRIBER</b>		
Confirms patient counseling	X	X
Enters the 2 contraception methods chosen by the patient	X	
Enters pregnancy test results	X	
<b>PATIENT</b>		
Answers educational questions before every prescription	X	
Enters 2 forms of contraception	X	
<b>PHARMACIST</b>		
Contacts system to get an authorization	X	X

48

49 **DESCRIPTION**

50 Isotretinoin, a retinoid, is available as Accutane in 10-mg, 20-mg and 40-mg soft  
51 gelatin capsules for oral administration. Each capsule contains beeswax, butylated  
52 hydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated  
53 vegetable oil, and soybean oil. Gelatin capsules contain glycerin and parabens  
54 (methyl and propyl), with the following dye systems: 10 mg — iron oxide (red)  
55 and titanium dioxide; 20 mg — FD&C Red No. 3, FD&C Blue No. 1, and  
56 titanium dioxide; 40 mg — FD&C Yellow No. 6, D&C Yellow No. 10, and  
57 titanium dioxide.

58 Chemically, isotretinoin is 13-*cis*-retinoic acid and is related to both retinoic acid  
59 and retinol (vitamin A). It is a yellow to orange crystalline powder with a  
60 molecular weight of 300.44. The structural formula is:



62 **CLINICAL PHARMACOLOGY**

63 Isotretinoin is a retinoid, which when administered in pharmacologic dosages of  
64 0.5 to 1.0 mg/kg/day (see **DOSAGE AND ADMINISTRATION**), inhibits  
65 sebaceous gland function and keratinization. The exact mechanism of action of  
66 isotretinoin is unknown.

67 **Nodular Acne**

68 Clinical improvement in nodular acne patients occurs in association with a  
69 reduction in sebum secretion. The decrease in sebum secretion is temporary and is  
70 related to the dose and duration of treatment with Accutane, and reflects a  
71 reduction in sebaceous gland size and an inhibition of sebaceous gland  
72 differentiation.<sup>1</sup>

73 **Pharmacokinetics**

74 **Absorption**

75 Due to its high lipophilicity, oral absorption of isotretinoin is enhanced when  
76 given with a high-fat meal. In a crossover study, 74 healthy adult subjects  
77 received a single 80 mg oral dose (2 x 40 mg capsules) of Accutane under fasted  
78 and fed conditions. Both peak plasma concentration ( $C_{max}$ ) and the total exposure  
79 (AUC) of isotretinoin were more than doubled following a standardized high-fat  
80 meal when compared with Accutane given under fasted conditions (see **Table 2**).  
81 The observed elimination half-life was unchanged. This lack of change in half-life  
82 suggests that food increases the bioavailability of isotretinoin without altering its  
83 disposition. The time to peak concentration ( $T_{max}$ ) was also increased with food  
84 and may be related to a longer absorption phase. Therefore, Accutane capsules  
85 should always be taken with food (see **DOSAGE AND ADMINISTRATION**).  
86 Clinical studies have shown that there is no difference in the pharmacokinetics of  
87 isotretinoin between patients with nodular acne and healthy subjects with normal  
88 skin.

89 **Table 2** **Pharmacokinetic Parameters of Isotretinoin Mean**  
90 **(%CV), N=74**

<b>Accutane 2 x 40 mg Capsules</b>	<b>AUC<sub>0-∞</sub> (ng·hr/mL)</b>	<b>C<sub>max</sub> (ng/mL)</b>	<b>T<sub>max</sub> (hr)</b>	<b>t<sub>1/2</sub> (hr)</b>
Fed*	10,004 (22%)	862 (22%)	5.3 (77%)	21 (39%)
Fasted	3,703 (46%)	301 (63%)	3.2 (56%)	21 (30%)

\*Eating a standardized high-fat meal

91 **Distribution**

92 Isotretinoin is more than 99.9% bound to plasma proteins, primarily albumin.

93 **Metabolism**

94 Following oral administration of isotretinoin, at least three metabolites have been  
95 identified in human plasma: 4-*oxo*-isotretinoin, retinoic acid (tretinoin), and

96 4-*oxo*-retinoic acid (4-*oxo*-tretinoin). Retinoic acid and 13-*cis*-retinoic acid are  
97 geometric isomers and show reversible interconversion. The administration of one  
98 isomer will give rise to the other. Isotretinoin is also irreversibly oxidized to  
99 4-*oxo*-isotretinoin, which forms its geometric isomer 4-*oxo*-tretinoin.

100 After a single 80 mg oral dose of Accutane to 74 healthy adult subjects,  
101 concurrent administration of food increased the extent of formation of all  
102 metabolites in plasma when compared to the extent of formation under fasted  
103 conditions.

104 All of these metabolites possess retinoid activity that is in some in vitro models  
105 more than that of the parent isotretinoin. However, the clinical significance of  
106 these models is unknown. After multiple oral dose administration of isotretinoin  
107 to adult cystic acne patients ( $\geq 18$  years), the exposure of patients to 4-*oxo*-  
108 isotretinoin at steady-state under fasted and fed conditions was approximately 3.4  
109 times higher than that of isotretinoin.

110 In vitro studies indicate that the primary P450 isoforms involved in isotretinoin  
111 metabolism are 2C8, 2C9, 3A4, and 2B6. Isotretinoin and its metabolites are  
112 further metabolized into conjugates, which are then excreted in urine and feces.

### 113 Elimination

114 Following oral administration of an 80 mg dose of  $^{14}\text{C}$ -isotretinoin as a liquid  
115 suspension,  $^{14}\text{C}$ -activity in blood declined with a half-life of 90 hours. The  
116 metabolites of isotretinoin and any conjugates are ultimately excreted in the feces  
117 and urine in relatively equal amounts (total of 65% to 83%). After a single 80 mg  
118 oral dose of Accutane to 74 healthy adult subjects under fed conditions, the  
119 mean  $\pm$  SD elimination half-lives ( $t_{1/2}$ ) of isotretinoin and 4-*oxo*-isotretinoin were  
120  $21.0 \pm 8.2$  hours and  $24.0 \pm 5.3$  hours, respectively. After both single and multiple  
121 doses, the observed accumulation ratios of isotretinoin ranged from 0.90 to 5.43  
122 in patients with cystic acne.

## 123 Special Patient Populations

### 124 Pediatric Patients

125 The pharmacokinetics of isotretinoin were evaluated after single and multiple  
126 doses in 38 pediatric patients (12 to 15 years) and 19 adult patients ( $\geq 18$  years)  
127 who received Accutane for the treatment of severe recalcitrant nodular acne. In  
128 both age groups, 4-*oxo*-isotretinoin was the major metabolite; tretinoin and 4-*oxo*-  
129 tretinoin were also observed. The dose-normalized pharmacokinetic parameters  
130 for isotretinoin following single and multiple doses are summarized in **Table 3** for  
131 pediatric patients. There were no statistically significant differences in the  
132 pharmacokinetics of isotretinoin between pediatric and adult patients.

133 **Table 3**      **Pharmacokinetic Parameters of Isotretinoin Following**  
 134 **Single and Multiple Dose Administration in Pediatric**  
 135 **Patients, 12 to 15 Years of Age**  
 136 **Mean ( $\pm$  SD), N=38\***

Parameter	Isotretinoin (Single Dose)	Isotretinoin (Steady-State)
C <sub>max</sub> (ng/mL)	573.25 (278.79)	731.98 (361.86)
AUC <sub>(0-12)</sub> (ng·hr/mL)	3033.37 (1394.17)	5082.00 (2184.23)
AUC <sub>(0-24)</sub> (ng·hr/mL)	6003.81 (2885.67)	–
T <sub>max</sub> (hr)†	6.00 (1.00-24.60)	4.00 (0-12.00)
C <sub>SSmin</sub> (ng/mL)	–	352.32 (184.44)
T <sub>1/2</sub> (hr)	–	15.69 (5.12)
CL/F (L/hr)	–	17.96 (6.27)

\*The single and multiple dose data in this table were obtained following a non-standardized meal that is not comparable to the high-fat meal that was used in the study in **Table 2**.

†Median (range)

137 In pediatric patients (12 to 15 years), the mean  $\pm$  SD elimination half-lives ( $t_{1/2}$ ) of  
 138 isotretinoin and 4-*oxo*-isotretinoin were 15.7  $\pm$  5.1 hours and 23.1  $\pm$  5.7 hours,  
 139 respectively. The accumulation ratios of isotretinoin ranged from 0.46 to 3.65 for  
 140 pediatric patients.

## 141 **INDICATIONS AND USAGE**

### 142 **Severe Recalcitrant Nodular Acne**

143 Accutane is indicated for the treatment of severe recalcitrant nodular acne.  
 144 Nodules are inflammatory lesions with a diameter of 5 mm or greater. The  
 145 nodules may become suppurative or hemorrhagic. “Severe,” by definition,<sup>2</sup> means  
 146 “many” as opposed to “few or several” nodules. Because of significant adverse  
 147 effects associated with its use, Accutane should be reserved for patients with  
 148 severe nodular acne who are unresponsive to conventional therapy, including  
 149 systemic antibiotics. In addition, Accutane is indicated only for those female  
 150 patients who are not pregnant, because Accutane can cause severe birth defects  
 151 (see **Boxed CONTRAINDICATIONS AND WARNINGS**).

152 A single course of therapy for 15 to 20 weeks has been shown to result in  
 153 complete and prolonged remission of disease in many patients.<sup>1,3,4</sup> If a second  
 154 course of therapy is needed, it should not be initiated until at least 8 weeks after  
 155 completion of the first course, because experience has shown that patients may  
 156 continue to improve while off Accutane. The optimal interval before retreatment  
 157 has not been defined for patients who have not completed skeletal growth (see  
 158 **WARNINGS: Skeletal: Bone Mineral Density, Hyperostosis, and Premature**  
 159 **Epiphyseal Closure**).

160 **CONTRAINDICATIONS**

161 **Pregnancy: Category X. See Boxed CONTRAINDICATIONS AND**  
162 **WARNINGS.**

163 **Allergic Reactions**

164 Accutane is contraindicated in patients who are hypersensitive to this medication  
165 or to any of its components. Accutane should not be given to patients who are  
166 sensitive to parabens, which are used as preservatives in the gelatin capsule (see  
167 **PRECAUTIONS: Hypersensitivity**).

168 **WARNINGS**

169 **Psychiatric Disorders**

170 Accutane may cause depression, psychosis and, rarely, suicidal ideation,  
171 suicide attempts, suicide, and aggressive and/or violent behaviors. No  
172 mechanism of action has been established for these events (see **ADVERSE**  
173 **REACTIONS: Psychiatric**). Prescribers should read the brochure,  
174 *Recognizing Psychiatric Disorders in Adolescents and Young Adults: A Guide*  
175 *for Prescribers of Isotretinoin*. Prescribers should be alert to the warning  
176 signs of psychiatric disorders to guide patients to receive the help they need.  
177 Therefore, prior to initiation of Accutane therapy, patients and family  
178 members should be asked about any history of psychiatric disorder, and at  
179 each visit during therapy patients should be assessed for symptoms of  
180 depression, mood disturbance, psychosis, or aggression to determine if  
181 further evaluation may be necessary. Signs and symptoms of depression, as  
182 described in the brochure (“Recognizing Psychiatric Disorders in  
183 Adolescents and Young Adults”), include sad mood, hopelessness, feelings of  
184 guilt, worthlessness or helplessness, loss of pleasure or interest in activities,  
185 fatigue, difficulty concentrating, change in sleep pattern, change in weight or  
186 appetite, suicidal thoughts or attempts, restlessness, irritability, acting on  
187 dangerous impulses, and persistent physical symptoms unresponsive to  
188 treatment. Patients should stop Accutane and the patient or a family member  
189 should promptly contact their prescriber if the patient develops depression,  
190 mood disturbance, psychosis, or aggression, without waiting until the next  
191 visit. Discontinuation of Accutane therapy may be insufficient; further  
192 evaluation may be necessary. While such monitoring may be helpful, it may  
193 not detect all patients at risk. Patients may report mental health problems or  
194 family history of psychiatric disorders. These reports should be discussed  
195 with the patient and/or the patient’s family. A referral to a mental health  
196 professional may be necessary. The physician should consider whether  
197 Accutane therapy is appropriate in this setting; for some patients the risks  
198 may outweigh the benefits of Accutane therapy.

199 **Pseudotumor Cerebri**

200 Accutane use has been associated with a number of cases of pseudotumor  
201 cerebri (benign intracranial hypertension), some of which involved  
202 concomitant use of tetracyclines. Concomitant treatment with tetracyclines

203 should therefore be avoided. Early signs and symptoms of pseudotumor  
204 cerebri include papilledema, headache, nausea and vomiting, and visual  
205 disturbances. Patients with these symptoms should be screened for  
206 papilledema and, if present, they should be told to discontinue Accutane  
207 immediately and be referred to a neurologist for further diagnosis and care  
208 (see ADVERSE REACTIONS: Neurological).

### 209 **Serious Skin Reactions**

210 There have been post-marketing reports of erythema multiforme and severe skin  
211 reactions [eg, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis  
212 (TEN)] associated with isotretinoin use. These events may be serious and result in  
213 death, life-threatening events, hospitalization, or disability. Patients should be  
214 monitored closely for severe skin reactions, and discontinuation of Accutane  
215 should be considered if warranted.

### 216 **Pancreatitis**

217 **Acute pancreatitis** has been reported in patients with either elevated or normal  
218 serum triglyceride levels. **In rare instances, fatal hemorrhagic pancreatitis has**  
219 **been reported.** Accutane should be stopped if hypertriglyceridemia cannot be  
220 controlled at an acceptable level or if symptoms of pancreatitis occur.

### 221 **Lipids**

222 Elevations of serum triglycerides in excess of 800 mg/dL have been reported in  
223 patients treated with Accutane. Marked elevations of serum triglycerides were  
224 reported in approximately 25% of patients receiving Accutane in clinical trials. In  
225 addition, approximately 15% developed a decrease in high-density lipoproteins  
226 and about 7% showed an increase in cholesterol levels. In clinical trials, the  
227 effects on triglycerides, HDL, and cholesterol were reversible upon cessation of  
228 Accutane therapy. Some patients have been able to reverse triglyceride elevation  
229 by reduction in weight, restriction of dietary fat and alcohol, and reduction in dose  
230 while continuing Accutane.<sup>5</sup>

231 Blood lipid determinations should be performed before Accutane is given and  
232 then at intervals until the lipid response to Accutane is established, which usually  
233 occurs within 4 weeks. Especially careful consideration must be given to  
234 risk/benefit for patients who may be at high risk during Accutane therapy  
235 (patients with diabetes, obesity, increased alcohol intake, lipid metabolism  
236 disorder or familial history of lipid metabolism disorder). If Accutane therapy is  
237 instituted, more frequent checks of serum values for lipids and/or blood sugar are  
238 recommended (see **PRECAUTIONS: Laboratory Tests**).

239 The cardiovascular consequences of hypertriglyceridemia associated with  
240 Accutane are unknown. *Animal Studies:* In rats given 8 or 32 mg/kg/day of  
241 isotretinoin (1.3 to 5.3 times the recommended clinical dose of 1.0 mg/kg/day  
242 after normalization for total body surface area) for 18 months or longer, the  
243 incidences of focal calcification, fibrosis and inflammation of the myocardium,  
244 calcification of coronary, pulmonary and mesenteric arteries, and metastatic

245 calcification of the gastric mucosa were greater than in control rats of similar age.  
246 Focal endocardial and myocardial calcifications associated with calcification of  
247 the coronary arteries were observed in two dogs after approximately 6 to 7  
248 months of treatment with isotretinoin at a dosage of 60 to 120 mg/kg/day (30 to  
249 60 times the recommended clinical dose of 1.0 mg/kg/day, respectively, after  
250 normalization for total body surface area).

### 251 **Hearing Impairment**

252 Impaired hearing has been reported in patients taking Accutane; in some cases,  
253 the hearing impairment has been reported to persist after therapy has been  
254 discontinued. Mechanism(s) and causality for this event have not been  
255 established. Patients who experience tinnitus or hearing impairment should  
256 discontinue Accutane treatment and be referred for specialized care for further  
257 evaluation (see **ADVERSE REACTIONS: Special Senses**).

### 258 **Hepatotoxicity**

259 Clinical hepatitis considered to be possibly or probably related to Accutane  
260 therapy has been reported. Additionally, mild to moderate elevations of liver  
261 enzymes have been observed in approximately 15% of individuals treated during  
262 clinical trials, some of which normalized with dosage reduction or continued  
263 administration of the drug. If normalization does not readily occur or if hepatitis is  
264 suspected during treatment with Accutane, the drug should be discontinued and  
265 the etiology further investigated.

### 266 **Inflammatory Bowel Disease**

267 Accutane has been associated with inflammatory bowel disease (including  
268 regional ileitis) in patients without a prior history of intestinal disorders. In some  
269 instances, symptoms have been reported to persist after Accutane treatment has  
270 been stopped. Patients experiencing abdominal pain, rectal bleeding or severe  
271 diarrhea should discontinue Accutane immediately (see **ADVERSE**  
272 **REACTIONS: Gastrointestinal**).

### 273 **Skeletal**

#### 274 **Bone Mineral Density**

275 Effects of multiple courses of Accutane on the developing musculoskeletal system  
276 are unknown. There is some evidence that long-term, high-dose, or multiple  
277 courses of therapy with isotretinoin have more of an effect than a single course of  
278 therapy on the musculoskeletal system. In an open-label clinical trial (N=217) of a  
279 single course of therapy with Accutane for severe recalcitrant nodular acne, bone  
280 density measurements at several skeletal sites were not significantly decreased  
281 (lumbar spine change >-4% and total hip change >-5%) or were increased in the  
282 majority of patients. One patient had a decrease in lumbar spine bone mineral  
283 density >4% based on unadjusted data. Sixteen (7.9%) patients had decreases in  
284 lumbar spine bone mineral density >4%, and all the other patients (92%) did not  
285 have significant decreases or had increases (adjusted for body mass index). Nine  
286 patients (4.5%) had a decrease in total hip bone mineral density >5% based on

287 unadjusted data. Twenty-one (10.6%) patients had decreases in total hip bone  
288 mineral density >5%, and all the other patients (89%) did not have significant  
289 decreases or had increases (adjusted for body mass index). Follow-up studies  
290 performed in 8 of the patients with decreased bone mineral density for up to 11  
291 months thereafter demonstrated increasing bone density in 5 patients at the  
292 lumbar spine, while the other 3 patients had lumbar spine bone density  
293 measurements below baseline values. Total hip bone mineral densities remained  
294 below baseline (range -1.6% to -7.6%) in 5 of 8 patients (62.5%).

295 In a separate open-label extension study of 10 patients, ages 13-18 years, who  
296 started a second course of Accutane 4 months after the first course, two patients  
297 showed a decrease in mean lumbar spine bone mineral density up to 3.25% (see  
298 **PRECAUTIONS: Pediatric Use**).

299 Spontaneous reports of osteoporosis, osteopenia, bone fractures, and delayed  
300 healing of bone fractures have been seen in the Accutane population. While  
301 causality to Accutane has not been established, an effect cannot be ruled out.  
302 Longer term effects have not been studied. It is important that Accutane be given  
303 at the recommended doses for no longer than the recommended duration.

#### 304 **Hyperostosis**

305 A high prevalence of skeletal hyperostosis was noted in clinical trials for  
306 disorders of keratinization with a mean dose of 2.24 mg/kg/day. Additionally,  
307 skeletal hyperostosis was noted in 6 of 8 patients in a prospective study of  
308 disorders of keratinization.<sup>6</sup> Minimal skeletal hyperostosis and calcification of  
309 ligaments and tendons have also been observed by x-ray in prospective studies of  
310 nodular acne patients treated with a single course of therapy at recommended  
311 doses. The skeletal effects of multiple Accutane treatment courses for acne are  
312 unknown.

313 In a clinical study of 217 pediatric patients (12 to 17 years) with severe  
314 recalcitrant nodular acne, hyperostosis was not observed after 16 to 20 weeks of  
315 treatment with approximately 1 mg/kg/day of Accutane given in two divided  
316 doses. Hyperostosis may require a longer time frame to appear. The clinical  
317 course and significance remain unknown.

#### 318 **Premature Epiphyseal Closure**

319 There are spontaneous reports of premature epiphyseal closure in acne patients  
320 receiving recommended doses of Accutane. The effect of multiple courses of  
321 Accutane on epiphyseal closure is unknown.

#### 322 **Vision Impairment**

323 Visual problems should be carefully monitored. All Accutane patients  
324 experiencing visual difficulties should discontinue Accutane treatment and have  
325 an ophthalmological examination (see **ADVERSE REACTIONS: Special**  
326 **Senses**).

327 **Corneal Opacities**

328 Corneal opacities have occurred in patients receiving Accutane for acne and more  
329 frequently when higher drug dosages were used in patients with disorders of  
330 keratinization. The corneal opacities that have been observed in clinical trial  
331 patients treated with Accutane have either completely resolved or were resolving  
332 at follow-up 6 to 7 weeks after discontinuation of the drug (see **ADVERSE**  
333 **REACTIONS: Special Senses**).

334 **Decreased Night Vision**

335 Decreased night vision has been reported during Accutane therapy and in some  
336 instances the event has persisted after therapy was discontinued. Because the  
337 onset in some patients was sudden, patients should be advised of this potential  
338 problem and warned to be cautious when driving or operating any vehicle at  
339 night.

340 **PRECAUTIONS**

341 Accutane must only be prescribed by prescribers who are registered and activated  
342 with the iPLEDGE program. Accutane must only be dispensed by a pharmacy  
343 registered and activated with iPLEDGE, and must only be dispensed to patients  
344 who are registered and meet all the requirements of iPLEDGE. Registered and  
345 activated pharmacies must receive Accutane only from wholesalers registered  
346 with iPLEDGE.

347 iPLEDGE program requirements for wholesalers, prescribers, and pharmacists are  
348 described below:

349 **Wholesalers:**

350 For the purpose of the iPLEDGE program, the term wholesaler refers to  
351 wholesaler, distributor, and/or chain pharmacy distributor. To distribute Accutane,  
352 wholesalers must be registered with iPLEDGE, and agree to meet all iPLEDGE  
353 requirements for wholesale distribution of isotretinoin products. Wholesalers must  
354 register with iPLEDGE by signing and returning the iPLEDGE wholesaler  
355 agreement that affirms they will comply with all iPLEDGE requirements for  
356 distribution of isotretinoin. These include:

- 357 • Registering prior to distributing isotretinoin and re-registering annually  
358 thereafter
- 359 • Distributing only FDA approved isotretinoin product
- 360 • Only shipping isotretinoin to
  - 361 – wholesalers registered in the iPLEDGE program with prior written  
362 consent from the manufacturer or
  - 363 – pharmacies licensed in the US and registered and activated in the  
364 iPLEDGE program
- 365 • Notifying the isotretinoin manufacturer (or delegate) of any non-registered  
366 and/or non-activated pharmacy or unregistered wholesaler that attempts to  
367 order isotretinoin

- 368 • Complying with inspection of wholesaler records for verification of  
369 compliance with the iPLEDGE program by the isotretinoin manufacturer (or  
370 delegate)
- 371 • Returning to the manufacturer (or delegate) any undistributed product if  
372 registration is revoked by the manufacturer or if the wholesaler chooses to not  
373 re-register annually

374 **Prescribers:**

375 To prescribe isotretinoin, the prescriber must be registered and activated with the  
376 pregnancy risk management program iPLEDGE. Prescribers can register by  
377 signing and returning the completed registration form. Prescribers can only  
378 activate their registration by affirming that they meet requirements and will  
379 comply with all iPLEDGE requirements by attesting to the following points:

- 380 • I know the risk and severity of fetal injury/birth defects from isotretinoin.
- 381 • I know the risk factors for unplanned pregnancy and the effective measures  
382 for avoidance of unplanned pregnancy.
- 383 • I have the expertise to provide the patient with detailed pregnancy prevention  
384 counseling or I will refer her to an expert for such counseling, reimbursed by  
385 the manufacturer.
- 386 • I will comply with the iPLEDGE program requirements described in the  
387 booklets entitled *The Guide to Best Practices for the iPLEDGE Program* and  
388 *The iPLEDGE Program Prescriber Contraception Counseling Guide*.
- 389 • Before beginning treatment of female patients of childbearing potential with  
390 isotretinoin and on a monthly basis, the patient will be counseled to avoid  
391 pregnancy by using two forms of contraception simultaneously and  
392 continuously one month before, during, and one month after isotretinoin  
393 therapy, unless the patient commits to continuous abstinence.
- 394 • I will not prescribe isotretinoin to any female patient of childbearing potential  
395 until verifying she has a negative screening pregnancy test and monthly  
396 negative CLIA-certified (Clinical Laboratory Improvement Amendment)  
397 pregnancy tests. Patients should have a pregnancy test at the completion of the  
398 entire course of isotretinoin and another pregnancy test 1 month later.
- 399 • I will report any pregnancy case that I become aware of while the female  
400 patient is on isotretinoin or 1 month after the last dose to the pregnancy  
401 registry.

402 To prescribe isotretinoin, the prescriber must access the iPLEDGE system via the  
403 internet ([www.ipledgeprogram.com](http://www.ipledgeprogram.com)) or telephone (1-866-495-0654) to:

- 404 1) Register each patient in the iPLEDGE program.
- 405 2) Confirm monthly that each patient has received counseling and education.

406 3) For *female patients of childbearing potential*:

- 407 • Enter patient's two chosen forms of contraception each month.
- 408 • Enter monthly result from CLIA-certified laboratory conducted pregnancy
- 409 test.

410 Isotretinoin must only be prescribed to female patients who are known not to be

411 pregnant as confirmed by a negative CLIA-certified laboratory conducted

412 pregnancy test.

413 Isotretinoin must only be dispensed by a pharmacy registered and activated with

414 the pregnancy risk management program iPLEDGE and only when the registered

415 patient meets all the requirements of the iPLEDGE program. Meeting the

416 requirements for a female patient of childbearing potential signifies that she:

417 • Has been counseled and has signed a Patient Information/Informed

418 Consent About Birth Defects (for female patients who can get pregnant)

419 form that contains warnings about the risk of potential birth defects if the

420 fetus is exposed to isotretinoin. The patient must sign the informed

421 consent form before starting treatment and patient counseling must also be

422 done at that time and on a monthly basis thereafter.

423 • Has had two negative urine or serum pregnancy tests with a sensitivity of

424 at least 25 mIU/mL before receiving the initial isotretinoin prescription.

425 The first test (a screening test) is obtained by the prescriber when the

426 decision is made to pursue qualification of the patient for isotretinoin. The

427 second pregnancy test (a confirmation test) must be done in a CLIA-

428 certified laboratory. The interval between the 2 tests should be at least 19

429 days.

430 – For patients with regular menstrual cycles, the second pregnancy test

431 should be done during the first 5 days of the menstrual period

432 immediately preceding the beginning of isotretinoin therapy and after

433 the patient has used 2 forms of contraception for 1 month.

434 – For patients with amenorrhea, irregular cycles, or using a

435 contraceptive method that precludes withdrawal bleeding, the second

436 pregnancy test must be done immediately preceding the beginning of

437 isotretinoin therapy and after the patient has used 2 forms of

438 contraception for 1 month.

439 • Has had a negative result from a urine or serum pregnancy test in a CLIA-

440 certified laboratory before receiving each subsequent course of

441 isotretinoin. A pregnancy test must be repeated every month, in a CLIA-

442 certified laboratory, prior to the female patient receiving each prescription.

443 • Has selected and has committed to use 2 forms of effective contraception

444 simultaneously, at least 1 of which must be a primary form, unless the

445 patient commits to continuous abstinence from heterosexual contact, or the

446 patient has undergone a hysterectomy or bilateral oophorectomy, or has  
 447 been medically confirmed to be post-menopausal. Patients must use 2  
 448 forms of effective contraception for at least 1 month prior to initiation of  
 449 isotretinoin therapy, during isotretinoin therapy, and for 1 month after  
 450 discontinuing isotretinoin therapy. Counseling about contraception and  
 451 behaviors associated with an increased risk of pregnancy must be repeated  
 452 on a monthly basis.

453 If the patient has unprotected heterosexual intercourse at any time 1 month  
 454 before, during, or 1 month after therapy, she must:

- 455 1. Stop taking Accutane immediately, if on therapy
- 456 2. Have a pregnancy test at least 19 days after the last act of  
 457 unprotected heterosexual intercourse
- 458 3. Start using 2 forms of effective contraception simultaneously again  
 459 for 1 month before resuming Accutane therapy
- 460 4. Have a second pregnancy test after using 2 forms of effective  
 461 contraception for 1 month as described above depending on  
 462 whether she has regular menses or not.

463 Effective forms of contraception include both primary and secondary  
 464 forms of contraception:

Primary forms	Secondary forms
<ul style="list-style-type: none"> <li>• tubal sterilization</li> <li>• partner's vasectomy</li> <li>• intrauterine device</li> <li>• hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring)</li> </ul>	<p><i>Barrier:</i></p> <ul style="list-style-type: none"> <li>• male latex condom with or without spermicide</li> <li>• diaphragm with spermicide</li> <li>• cervical cap with spermicide</li> </ul> <p><i>Other:</i></p> <ul style="list-style-type: none"> <li>• vaginal sponge (contains spermicide)</li> </ul>

465

466 Any birth control method can fail. There have been reports of pregnancy  
 467 from female patients who have used oral contraceptives, as well as  
 468 transdermal patch/injectable/implantable/vaginal ring hormonal birth  
 469 control products; these pregnancies occurred while these patients were  
 470 taking Accutane. These reports are more frequent for female patients who  
 471 use only a single method of contraception. Therefore, it is critically  
 472 important that female patients of childbearing potential use 2 effective  
 473 forms of contraception simultaneously. Patients must receive written  
 474 warnings about the rates of possible contraception failure (included in  
 475 patient education kits).

476 Using two forms of contraception simultaneously substantially reduces the  
 477 chances that a female will become pregnant over the risk of pregnancy  
 478 with either form alone. A drug interaction that decreases effectiveness of

479 hormonal contraceptives has not been entirely ruled out for Accutane (see  
480 **PRECAUTIONS: Drug Interactions**). Although hormonal  
481 contraceptives are highly effective, prescribers are advised to consult the  
482 package insert of any medication administered concomitantly with  
483 hormonal contraceptives, since some medications may decrease the  
484 effectiveness of these birth control products.

485 Patients should be prospectively cautioned not to self-medicate with the  
486 herbal supplement St. John's Wort because a possible interaction has been  
487 suggested with hormonal contraceptives based on reports of breakthrough  
488 bleeding on oral contraceptives shortly after starting St. John's Wort.  
489 Pregnancies have been reported by users of combined hormonal  
490 contraceptives who also used some form of St. John's Wort.

491 If a pregnancy does occur during isotretinoin treatment, isotretinoin must  
492 be discontinued immediately. The patient should be referred to an  
493 Obstetrician-Gynecologist experienced in reproductive toxicity for further  
494 evaluation and counseling. Any suspected fetal exposure during or 1  
495 month after isotretinoin therapy must be reported immediately to the FDA  
496 via the MedWatch number 1-800-FDA-1088 and also to the iPLEDGE  
497 pregnancy registry at 1-866-495-0654 or via the internet  
498 ([www.ipledgeprogram.com](http://www.ipledgeprogram.com)).

499 All Patients

500 Isotretinoin is contraindicated in female patients who are pregnant. To receive  
501 isotretinoin all patients must meet all of the following conditions:

- 502 • Must be registered with the iPLEDGE program by the prescriber
- 503 • Must understand that severe birth defects can occur with the use of  
504 isotretinoin by female patients
- 505 • Must be reliable in understanding and carrying out instructions
- 506 • Must sign a Patient Information/Informed Consent (for all patients) form that  
507 contains warnings about the potential risks associated with isotretinoin
- 508 • Must fill and pick up the prescription within 7 days of the date of specimen  
509 collection for the pregnancy test for female patients of childbearing potential
- 510 • Must fill and pick up the prescription within 30 days of the office visit for  
511 male patients and female patients not of childbearing potential
- 512 • Must not donate blood while on isotretinoin and for 1 month after treatment  
513 has ended
- 514 • Must not share isotretinoin with anyone, even someone who has similar  
515 symptoms

516 Female Patients of Childbearing Potential

517 Isotretinoin is contraindicated in female patients who are pregnant. In addition to  
518 the requirements for all patients described above, female patients of childbearing  
519 potential must meet the following conditions:

- 520 • Must NOT be pregnant or breast-feeding
- 521 • Must comply with the required pregnancy testing at a CLIA-certified  
522 laboratory
- 523 • Must fill and pick up the prescription within 7 days of the date of specimen  
524 collection for the pregnancy test
- 525 • Must be capable of complying with the mandatory contraceptive measures  
526 required for isotretinoin therapy, or commit to continuous abstinence from  
527 heterosexual intercourse, and understand behaviors associated with an  
528 increased risk of pregnancy
- 529 • Must understand that it is her responsibility to avoid pregnancy one month  
530 before, during and one month after isotretinoin therapy
- 531 • Must have signed an additional Patient Information/Informed Consent About  
532 Birth Defects (for female patients who can get pregnant) form, before starting  
533 isotretinoin, that contains warnings about the risk of potential birth defects if  
534 the fetus is exposed to isotretinoin

- 535 • Must access the iPLEDGE system via the internet  
536 (www.ipledgeprogram.com) or telephone (1-866-495-0654), before starting  
537 isotretinoin, on a monthly basis during therapy, and 1 month after the last dose  
538 to answer questions on the program requirements and to enter the patient's  
539 two chosen forms of contraception
- 540 • Must have been informed of the purpose and importance of providing  
541 information to the iPLEDGE program should she become pregnant while  
542 taking isotretinoin or within 1 month of the last dose

543 **Pharmacists:**

544 To dispense isotretinoin, pharmacies must be registered and activated with the  
545 pregnancy risk management program iPLEDGE.

546 The Responsible Site Pharmacist must register the pharmacy by signing and  
547 returning the completed registration form. After registration, the Responsible Site  
548 Pharmacist can only activate the pharmacy registration by affirming that they  
549 meet requirements and will comply with all iPLEDGE requirements by attesting  
550 to the following points:

- 551 • I know the risk and severity of fetal injury/birth defects from isotretinoin.  
552 • I will train all pharmacists, who participate in the filling and dispensing of  
553 isotretinoin prescriptions, on the iPLEDGE program requirements.  
554 • I will comply and seek to ensure all pharmacists who participate in the filling  
555 and dispensing of isotretinoin prescriptions comply with the iPLEDGE  
556 program requirements described in the booklet entitled *Pharmacist Guide for*  
557 *the iPLEDGE Program*.  
558 • I will obtain Accutane product only from iPLEDGE registered wholesalers.  
559 • I will not sell, buy, borrow, loan or otherwise transfer isotretinoin in any  
560 manner to or from another pharmacy.  
561 • I will return to the manufacturer (or delegate) any unused product if  
562 registration is revoked by the manufacturer or if the pharmacy chooses to not  
563 reactivate annually.  
564 • I will not fill isotretinoin for any party other than a qualified patient.

566 To dispense isotretinoin, the pharmacist must:

- 567 1) be trained by the Responsible Site Pharmacist concerning the iPLEDGE  
568 program requirements.
- 569 2) obtain authorization from the iPLEDGE program via the internet  
570 (www.ipledgeprogram.com) or telephone (1-866-495-0654) for every  
571 isotretinoin prescription. Authorization signifies that the patient has met all  
572 program requirements and is qualified to receive isotretinoin.
- 573 3) write the Risk Management Authorization (RMA) number on the prescription.

574 Accutane must only be dispensed:

- 575 • in no more than a 30-day supply
- 576 • with an Accutane Medication Guide
- 577 • after authorization from the iPLEDGE program
- 578 • prior to the “do not dispense to patient after” date provided by the iPLEDGE  
579 system (within 30 days of the office visit for male patients and female patients  
580 not of childbearing potential and within 7 days of the date of specimen  
581 collection for female patients of childbearing potential)
- 582 • with a new prescription for refills and another authorization from the  
583 iPLEDGE program (No automatic refills are allowed)
- 584 An Accutane Medication Guide must be given to the patient each time Accutane  
585 is dispensed, as required by law. This Accutane Medication Guide is an important  
586 part of the risk management program for the patients.
- 587 Accutane must not be prescribed, dispensed or otherwise obtained through the  
588 internet or any other means outside of the iPLEDGE program. Only FDA-  
589 approved Accutane products must be distributed, prescribed, dispensed, and used.  
590 Patients must fill Accutane prescriptions only at US licensed pharmacies.
- 591 A description of the iPLEDGE program educational materials available with  
592 iPLEDGE is provided below. The main goal of these educational materials is to  
593 explain the iPLEDGE program requirements and to reinforce the educational  
594 messages.
- 595 1) *The Guide to Best Practices for the iPLEDGE Program* includes: isotretinoin  
596 teratogenic potential, information on pregnancy testing, and the method to  
597 complete a qualified isotretinoin prescription.
- 598 2) *The iPLEDGE Program Prescriber Contraception Counseling Guide*  
599 includes: specific information about effective contraception, the limitations of  
600 contraceptive methods, behaviors associated with an increased risk of  
601 contraceptive failure and pregnancy and the methods to evaluate pregnancy  
602 risk.
- 603 3) *The Pharmacist Guide for the iPLEDGE Program* includes: isotretinoin  
604 teratogenic potential and the method to obtain authorization to dispense an  
605 isotretinoin prescription.
- 606 4) The iPLEDGE program is a systematic approach to comprehensive patient  
607 education about their responsibilities and includes education for contraception  
608 compliance and reinforcement of educational messages. The iPLEDGE  
609 program includes information on the risks and benefits of isotretinoin which is  
610 linked to the Medication Guide dispensed by pharmacists with each  
611 isotretinoin prescription.
- 612 5) Female patients not of childbearing potential and male patients, and female  
613 patients of childbearing potential are provided with separate booklets. Each

614 booklet contains information on isotretinoin therapy including precautions and  
615 warnings, a Patient Information/Informed Consent (for all patients) form, and  
616 a toll-free line which provides isotretinoin information in 2 languages.

617 6) The booklet for female patients not of childbearing potential and male  
618 patients, *The iPLEDGE Program Guide to Isotretinoin for Male Patients and*  
619 *Female Patients Who Cannot Get Pregnant*, also includes information about  
620 male reproduction and a warning not to share isotretinoin with others or to  
621 donate blood during isotretinoin therapy and for 1 month following  
622 discontinuation of isotretinoin.

623 7) The booklet for female patients of childbearing potential, *The iPLEDGE*  
624 *Program Guide to Isotretinoin for Female Patients Who Can Get Pregnant*,  
625 includes a referral program that offers female patients free contraception  
626 counseling, reimbursed by the manufacturer, by a reproductive specialist; and  
627 a second Patient Information/Informed Consent About Birth Defects (for  
628 female patients who can get pregnant) form concerning birth defects.

629 8) The booklet, *The iPLEDGE Program Birth Control Workbook* includes  
630 information on the types of contraceptive methods, the selection and use of  
631 appropriate, effective contraception, the rates of possible contraceptive failure  
632 and a toll-free contraception counseling line.

633 9) In addition, there is a patient educational DVD with the following videos —  
634 “Be Prepared, Be Protected” and “Be Aware: The Risk of Pregnancy While  
635 on Isotretinoin” (see **Information for Patients**).

### 636 **General**

637 Although an effect of Accutane on bone loss is not established, physicians should  
638 use caution when prescribing Accutane to patients with a genetic predisposition  
639 for age-related osteoporosis, a history of childhood osteoporosis conditions,  
640 osteomalacia, or other disorders of bone metabolism. This would include patients  
641 diagnosed with anorexia nervosa and those who are on chronic drug therapy that  
642 causes drug-induced osteoporosis/osteomalacia and/or affects vitamin D  
643 metabolism, such as systemic corticosteroids and any anticonvulsant.

644 Patients may be at increased risk when participating in sports with repetitive  
645 impact where the risks of spondylolisthesis with and without pars fractures and  
646 hip growth plate injuries in early and late adolescence are known. There are  
647 spontaneous reports of fractures and/or delayed healing in patients while on  
648 therapy with Accutane or following cessation of therapy with Accutane while  
649 involved in these activities. While causality to Accutane has not been established,  
650 an effect must not be ruled out.

### 651 **Information for Patients**

652 See **PRECAUTIONS** and **Boxed CONTRAINDICATIONS AND**  
653 **WARNINGS**.

- 654 • Patients must be instructed to read the Medication Guide supplied as required  
655 by law when Accutane is dispensed. The complete text of the Medication  
656 Guide is reprinted at the end of this document. For additional information,  
657 patients must also be instructed to read the iPLEDGE program patient  
658 educational materials. All patients must sign the Patient Information/Informed  
659 Consent (for all patients) form.
- 660 • Female patients of childbearing potential must be instructed that they must not  
661 be pregnant when Accutane therapy is initiated, and that they should use 2  
662 forms of effective contraception simultaneously for 1 month before starting  
663 Accutane, while taking Accutane, and for 1 month after Accutane has been  
664 stopped, unless they commit to continuous abstinence from heterosexual  
665 intercourse. They should also sign a second Patient Information/Informed  
666 Consent About Birth Defects (for female patients who can get pregnant) form  
667 prior to beginning Accutane therapy. They should be given an opportunity to  
668 view the patient DVD provided by the manufacturer to the prescriber. The  
669 DVD includes information about contraception, the most common reasons  
670 that contraception fails, and the importance of using 2 forms of effective  
671 contraception when taking teratogenic drugs and comprehensive information  
672 about types of potential birth defects which could occur if a female patient  
673 who is pregnant takes Accutane at any time during pregnancy. Female patients  
674 should be seen by their prescribers monthly and have a urine or serum  
675 pregnancy test, in a CLIA-certified laboratory, performed each month during  
676 treatment to confirm negative pregnancy status before another Accutane  
677 prescription is written (see **Boxed CONTRAINDICATIONS AND**  
678 **WARNINGS and PRECAUTIONS**).
- 679 • Accutane is found in the semen of male patients taking Accutane, but the  
680 amount delivered to a female partner would be about 1 million times lower  
681 than an oral dose of 40 mg. While the no-effect limit for isotretinoin induced  
682 embryopathy is unknown, 20 years of postmarketing reports include 4 with  
683 isolated defects compatible with features of retinoid exposed fetuses; however  
684 2 of these reports were incomplete, and 2 had other possible explanations for  
685 the defects observed.
- 686 • Prescribers should be alert to the warning signs of psychiatric disorders to  
687 guide patients to receive the help they need. Therefore, prior to initiation of  
688 Accutane treatment, patients and family members should be asked about any  
689 history of psychiatric disorder, and at each visit during treatment patients  
690 should be assessed for symptoms of depression, mood disturbance, psychosis,  
691 or aggression to determine if further evaluation may be necessary. **Signs and**  
692 **symptoms of depression include sad mood, hopelessness, feelings of guilt,**  
693 **worthlessness or helplessness, loss of pleasure or interest in activities,**  
694 **fatigue, difficulty concentrating, change in sleep pattern, change in weight**  
695 **or appetite, suicidal thoughts or attempts, restlessness, irritability, acting**  
696 **on dangerous impulses, and persistent physical symptoms unresponsive**  
697 **to treatment.** Patients should stop Accutane and the patient or a family

698 member should promptly contact their prescriber if the patient develops  
699 depression, mood disturbance, psychosis, or aggression, without waiting until  
700 the next visit. Discontinuation of Accutane treatment may be insufficient;  
701 further evaluation may be necessary. While such monitoring may be helpful,  
702 it may not detect all patients at risk. Patients may report mental health  
703 problems or family history of psychiatric disorders. These reports should be  
704 discussed with the patient and/or the patient's family. A referral to a mental  
705 health professional may be necessary. The physician should consider whether  
706 Accutane therapy is appropriate in this setting; for some patients the risks may  
707 outweigh the benefits of Accutane therapy.

- 708 • Patients must be informed that some patients, while taking Accutane or soon  
709 after stopping Accutane, have become depressed or developed other serious  
710 mental problems. Symptoms of depression include sad, "anxious" or empty  
711 mood, irritability, acting on dangerous impulses, anger, loss of pleasure or  
712 interest in social or sports activities, sleeping too much or too little, changes in  
713 weight or appetite, school or work performance going down, or trouble  
714 concentrating. Some patients taking Accutane have had thoughts about hurting  
715 themselves or putting an end to their own lives (suicidal thoughts). Some  
716 people tried to end their own lives. And some people have ended their own  
717 lives. There were reports that some of these people did not appear depressed.  
718 There have been reports of patients on Accutane becoming aggressive or  
719 violent. No one knows if Accutane caused these behaviors or if they would  
720 have happened even if the person did not take Accutane. Some people have  
721 had other signs of depression while taking Accutane.  
722
- 723 • Patients must be informed that they must not share Accutane with anyone else  
724 because of the risk of birth defects and other serious adverse events.
- 725 • Patients must be informed not to donate blood during therapy and for 1 month  
726 following discontinuation of the drug because the blood might be given to a  
727 pregnant female patient whose fetus must not be exposed to Accutane.
- 728 • Patients should be reminded to take Accutane with a meal (see **DOSAGE**  
729 **AND ADMINISTRATION**). To decrease the risk of esophageal irritation,  
730 patients should swallow the capsules with a full glass of liquid.
- 731 • Patients should be informed that transient exacerbation (flare) of acne has  
732 been seen, generally during the initial period of therapy.
- 733 • Wax epilation and skin resurfacing procedures (such as dermabrasion, laser)  
734 should be avoided during Accutane therapy and for at least 6 months  
735 thereafter due to the possibility of scarring (see **ADVERSE REACTIONS:**  
736 **Skin and Appendages**).
- 737 • Patients should be advised to avoid prolonged exposure to UV rays or  
738 sunlight.

- 739 • Patients should be informed that they may experience decreased tolerance to  
740 contact lenses during and after therapy.
- 741 • Patients should be informed that approximately 16% of patients treated with  
742 Accutane in a clinical trial developed musculoskeletal symptoms (including  
743 arthralgia) during treatment. In general, these symptoms were mild to  
744 moderate, but occasionally required discontinuation of the drug. Transient  
745 pain in the chest has been reported less frequently. In the clinical trial, these  
746 symptoms generally cleared rapidly after discontinuation of Accutane, but in  
747 some cases persisted (see **ADVERSE REACTIONS: Musculoskeletal**).  
748 There have been rare postmarketing reports of rhabdomyolysis, some  
749 associated with strenuous physical activity (see **Laboratory Tests: CPK**).
- 750 • Pediatric patients and their caregivers should be informed that approximately  
751 29% (104/358) of pediatric patients treated with Accutane developed back  
752 pain. Back pain was severe in 13.5% (14/104) of the cases and occurred at a  
753 higher frequency in female patients than male patients. Arthralgias were  
754 experienced in 22% (79/358) of pediatric patients. Arthralgias were severe in  
755 7.6% (6/79) of patients. Appropriate evaluation of the musculoskeletal system  
756 should be done in patients who present with these symptoms during or after a  
757 course of Accutane. Consideration should be given to discontinuation of  
758 Accutane if any significant abnormality is found.
- 759 • Neutropenia and rare cases of agranulocytosis have been reported. Accutane  
760 should be discontinued if clinically significant decreases in white cell counts  
761 occur.
- 762 • Patients should be advised that severe skin reactions (Stevens-Johnson  
763 syndrome and toxic epidermal necrolysis) have been reported in post-  
764 marketing data. Accutane should be discontinued if clinically significant skin  
765 reactions occur.

## 766 **Hypersensitivity**

767 Anaphylactic reactions and other allergic reactions have been reported. Cutaneous  
768 allergic reactions and serious cases of allergic vasculitis, often with purpura  
769 (bruises and red patches) of the extremities and extracutaneous involvement  
770 (including renal) have been reported. Severe allergic reaction necessitates  
771 discontinuation of therapy and appropriate medical management.

## 772 **Drug Interactions**

- 773 • *Vitamin A*: Because of the relationship of Accutane to vitamin A, patients  
774 should be advised against taking vitamin supplements containing vitamin A to  
775 avoid additive toxic effects.
- 776 • *Tetracyclines*: Concomitant treatment with Accutane and tetracyclines should  
777 be avoided because Accutane use has been associated with a number of cases  
778 of pseudotumor cerebri (benign intracranial hypertension), some of which  
779 involved concomitant use of tetracyclines.

- 780 • *Micro-dosed Progesterone Preparations:* Micro-dosed progesterone  
781 preparations (“minipills” that do not contain an estrogen) may be an  
782 inadequate method of contraception during Accutane therapy. Although other  
783 hormonal contraceptives are highly effective, there have been reports of  
784 pregnancy from female patients who have used combined oral contraceptives,  
785 as well as transdermal patch/injectable/implantable/vaginal ring hormonal  
786 birth control products. These reports are more frequent for female patients  
787 who use only a single method of contraception. It is not known if hormonal  
788 contraceptives differ in their effectiveness when used with Accutane.  
789 Therefore, it is critically important for female patients of childbearing  
790 potential to select and commit to use 2 forms of effective contraception  
791 simultaneously, at least 1 of which must be a primary form (see  
792 **PRECAUTIONS**).
- 793 • *Norethindrone/ethinyl estradiol:* In a study of 31 premenopausal female  
794 patients with severe recalcitrant nodular acne receiving OrthoNovum® 7/7/7  
795 Tablets as an oral contraceptive agent, Accutane at the recommended dose of  
796 1 mg/kg/day, did not induce clinically relevant changes in the  
797 pharmacokinetics of ethinyl estradiol and norethindrone and in the serum  
798 levels of progesterone, follicle-stimulating hormone (FSH) and luteinizing  
799 hormone (LH). Prescribers are advised to consult the package insert of  
800 medication administered concomitantly with hormonal contraceptives, since  
801 some medications may decrease the effectiveness of these birth control  
802 products.
- 803 • *St. John’s Wort:* **Accutane use is associated with depression in some**  
804 **patients (see WARNINGS: Psychiatric Disorders and ADVERSE**  
805 **REACTIONS: Psychiatric).** Patients should be prospectively cautioned not  
806 to self-medicate with the herbal supplement St. John’s Wort because a  
807 possible interaction has been suggested with hormonal contraceptives based  
808 on reports of breakthrough bleeding on oral contraceptives shortly after  
809 starting St. John's Wort. Pregnancies have been reported by users of combined  
810 hormonal contraceptives who also used some form of St. John's Wort.
- 811 • *Phenytoin:* Accutane has not been shown to alter the pharmacokinetics of  
812 phenytoin in a study in seven healthy volunteers. These results are consistent  
813 with the in vitro finding that neither isotretinoin nor its metabolites induce or  
814 inhibit the activity of the CYP 2C9 human hepatic P450 enzyme. Phenytoin is  
815 known to cause osteomalacia. No formal clinical studies have been conducted  
816 to assess if there is an interactive effect on bone loss between phenytoin and  
817 Accutane. Therefore, caution should be exercised when using these drugs  
818 together.
- 819 • *Systemic Corticosteroids:* Systemic corticosteroids are known to cause  
820 osteoporosis. No formal clinical studies have been conducted to assess if there  
821 is an interactive effect on bone loss between systemic corticosteroids and

822 Accutane. Therefore, caution should be exercised when using these drugs  
823 together.

## 824 **Laboratory Tests**

### 825 • *Pregnancy Test:*

826 – Female patients of childbearing potential must have had two negative urine or  
827 serum pregnancy tests with a sensitivity of at least 25 mIU/mL before  
828 receiving the initial Accutane prescription. The first test (a screening test) is  
829 obtained by the prescriber when the decision is made to pursue qualification  
830 of the patient for Accutane. The second pregnancy test (a confirmation test)  
831 must be done in a CLIA-certified laboratory. The interval between the two  
832 tests must be at least 19 days.

833 – For patients with regular menstrual cycles, the second pregnancy test must be  
834 done during the first 5 days of the menstrual period immediately preceding the  
835 beginning of Accutane therapy and after the patient has used 2 forms of  
836 contraception for 1 month.

837 – For patients with amenorrhea, irregular cycles, or using a contraceptive  
838 method that precludes withdrawal bleeding, the second pregnancy test must be  
839 done immediately preceding the beginning of Accutane therapy and after the  
840 patient has used 2 forms of contraception for 1 month.

841 – Each month of therapy, patients must have a negative result from a urine or  
842 serum pregnancy test. A pregnancy test must be repeated each month, in a  
843 CLIA-certified laboratory, prior to the female patient receiving each  
844 prescription.

845 • *Lipids:* Pretreatment and follow-up blood lipids should be obtained under  
846 fasting conditions. After consumption of alcohol, at least 36 hours should  
847 elapse before these determinations are made. It is recommended that these  
848 tests be performed at weekly or biweekly intervals until the lipid response to  
849 Accutane is established. The incidence of hypertriglyceridemia is 1 patient in  
850 4 on Accutane therapy (see **WARNINGS: Lipids**).

851 • *Liver Function Tests:* Since elevations of liver enzymes have been observed  
852 during clinical trials, and hepatitis has been reported, pretreatment and follow-  
853 up liver function tests should be performed at weekly or biweekly intervals  
854 until the response to Accutane has been established (see **WARNINGS:**  
855 **Hepatotoxicity**).

856 • *Glucose:* Some patients receiving Accutane have experienced problems in the  
857 control of their blood sugar. In addition, new cases of diabetes have been  
858 diagnosed during Accutane therapy, although no causal relationship has been  
859 established.

860 • *CPK:* Some patients undergoing vigorous physical activity while on Accutane  
861 therapy have experienced elevated CPK levels; however, the clinical  
862 significance is unknown. There have been rare postmarketing reports of

863 rhabdomyolysis, some associated with strenuous physical activity. In a  
864 clinical trial of 217 pediatric patients (12 to 17 years) with severe recalcitrant  
865 nodular acne, transient elevations in CPK were observed in 12% of patients,  
866 including those undergoing strenuous physical activity in association with  
867 reported musculoskeletal adverse events such as back pain, arthralgia, limb  
868 injury, or muscle sprain. In these patients, approximately half of the CPK  
869 elevations returned to normal within 2 weeks and half returned to normal  
870 within 4 weeks. No cases of rhabdomyolysis were reported in this trial.

### 871 **Carcinogenesis, Mutagenesis and Impairment of Fertility**

872 In male and female Fischer 344 rats given oral isotretinoin at dosages of 8 or  
873 32 mg/kg/day (1.3 to 5.3 times the recommended clinical dose of 1.0 mg/kg/day,  
874 respectively, after normalization for total body surface area) for greater than 18  
875 months, there was a dose-related increased incidence of pheochromocytoma  
876 relative to controls. The incidence of adrenal medullary hyperplasia was also  
877 increased at the higher dosage in both sexes. The relatively high level of  
878 spontaneous pheochromocytomas occurring in the male Fischer 344 rat makes it  
879 an equivocal model for study of this tumor; therefore, the relevance of this tumor  
880 to the human population is uncertain.

881 The Ames test was conducted with isotretinoin in two laboratories. The results of  
882 the tests in one laboratory were negative while in the second laboratory a weakly  
883 positive response (less than 1.6 x background) was noted in *S. typhimurium*  
884 TA100 when the assay was conducted with metabolic activation. No dose-  
885 response effect was seen and all other strains were negative. Additionally, other  
886 tests designed to assess genotoxicity (Chinese hamster cell assay, mouse  
887 micronucleus test, *S. cerevisiae* D7 assay, in vitro clastogenesis assay with  
888 human-derived lymphocytes, and unscheduled DNA synthesis assay) were all  
889 negative.

890 In rats, no adverse effects on gonadal function, fertility, conception rate, gestation  
891 or parturition were observed at oral dosages of isotretinoin of 2, 8, or 32  
892 mg/kg/day (0.3, 1.3, or 5.3 times the recommended clinical dose of 1.0  
893 mg/kg/day, respectively, after normalization for total body surface area).

894 In dogs, testicular atrophy was noted after treatment with oral isotretinoin for  
895 approximately 30 weeks at dosages of 20 or 60 mg/kg/day (10 or 30 times the  
896 recommended clinical dose of 1.0 mg/kg/day, respectively, after normalization for  
897 total body surface area). In general, there was microscopic evidence for  
898 appreciable depression of spermatogenesis but some sperm were observed in all  
899 testes examined and in no instance were completely atrophic tubules seen. In  
900 studies of 66 men, 30 of whom were patients with nodular acne under treatment  
901 with oral isotretinoin, no significant changes were noted in the count or motility  
902 of spermatozoa in the ejaculate. In a study of 50 men (ages 17 to 32 years)  
903 receiving Accutane (isotretinoin) therapy for nodular acne, no significant effects  
904 were seen on ejaculate volume, sperm count, total sperm motility, morphology or  
905 seminal plasma fructose.

906 **Pregnancy: Category X. See Boxed CONTRAINDICATIONS AND**  
907 **WARNINGS.**

908 **Nursing Mothers**

909 It is not known whether this drug is excreted in human milk. Because of the  
910 potential for adverse effects, nursing mothers should not receive Accutane.

911 **Pediatric Use**

912 The use of Accutane in pediatric patients less than 12 years of age has not been  
913 studied. The use of Accutane for the treatment of severe recalcitrant nodular acne  
914 in pediatric patients ages 12 to 17 years should be given careful consideration,  
915 especially for those patients where a known metabolic or structural bone disease  
916 exists (see **PRECAUTIONS: General**). Use of Accutane in this age group for  
917 severe recalcitrant nodular acne is supported by evidence from a clinical study  
918 comparing 103 pediatric patients (13 to 17 years) to 197 adult patients ( $\geq 18$   
919 years). Results from this study demonstrated that Accutane, at a dose of 1  
920 mg/kg/day given in two divided doses, was equally effective in treating severe  
921 recalcitrant nodular acne in both pediatric and adult patients.

922 In studies with Accutane, adverse reactions reported in pediatric patients were  
923 similar to those described in adults except for the increased incidence of back pain  
924 and arthralgia (both of which were sometimes severe) and myalgia in pediatric  
925 patients (see **ADVERSE REACTIONS**).

926 In an open-label clinical trial (N=217) of a single course of therapy with Accutane  
927 for severe recalcitrant nodular acne, bone density measurements at several  
928 skeletal sites were not significantly decreased (lumbar spine change  $> -4\%$  and  
929 total hip change  $> -5\%$ ) or were increased in the majority of patients. One patient  
930 had a decrease in lumbar spine bone mineral density  $> 4\%$  based on unadjusted  
931 data. Sixteen (7.9%) patients had decreases in lumbar spine bone mineral density  
932  $> 4\%$ , and all the other patients (92%) did not have significant decreases or had  
933 increases (adjusted for body mass index). Nine patients (4.5%) had a decrease in  
934 total hip bone mineral density  $> 5\%$  based on unadjusted data. Twenty-one  
935 (10.6%) patients had decreases in total hip bone mineral density  $> 5\%$ , and all the  
936 other patients (89%) did not have significant decreases or had increases (adjusted  
937 for body mass index). Follow-up studies performed in 8 of the patients with  
938 decreased bone mineral density for up to 11 months thereafter demonstrated  
939 increasing bone density in 5 patients at the lumbar spine, while the other 3  
940 patients had lumbar spine bone density measurements below baseline values.  
941 Total hip bone mineral densities remained below baseline (range  $-1.6\%$  to  
942  $-7.6\%$ ) in 5 of 8 patients (62.5%).

943 In a separate open-label extension study of 10 patients, ages 13 to 18 years, who  
944 started a second course of Accutane 4 months after the first course, two patients  
945 showed a decrease in mean lumbar spine bone mineral density up to 3.25% (see  
946 **WARNINGS: Skeletal: Bone Mineral Density**).

947 **Geriatric Use**

948 Clinical studies of isotretinoin did not include sufficient numbers of subjects aged  
949 65 years and over to determine whether they respond differently from younger  
950 subjects. Although reported clinical experience has not identified differences in  
951 responses between elderly and younger patients, effects of aging might be  
952 expected to increase some risks associated with isotretinoin therapy (see  
953 **WARNINGS** and **PRECAUTIONS**).

954 **ADVERSE REACTIONS**

955 **Clinical Trials and Postmarketing Surveillance**

956 The adverse reactions listed below reflect the experience from investigational  
957 studies of Accutane, and the postmarketing experience. The relationship of some  
958 of these events to Accutane therapy is unknown. Many of the side effects and  
959 adverse reactions seen in patients receiving Accutane are similar to those  
960 described in patients taking very high doses of vitamin A (dryness of the skin and  
961 mucous membranes, eg, of the lips, nasal passage, and eyes).

962 **Dose Relationship**

963 Cheilitis and hypertriglyceridemia are usually dose related. Most adverse  
964 reactions reported in clinical trials were reversible when therapy was  
965 discontinued; however, some persisted after cessation of therapy (see  
966 **WARNINGS** and **ADVERSE REACTIONS**).

967 **Body as a Whole**

968 allergic reactions, including vasculitis, systemic hypersensitivity (see  
969 **PRECAUTIONS: Hypersensitivity**), edema, fatigue, lymphadenopathy, weight  
970 loss

971 **Cardiovascular**

972 palpitation, tachycardia, vascular thrombotic disease, stroke

973 **Endocrine/Metabolic**

974 hypertriglyceridemia (see **WARNINGS: Lipids**), alterations in blood sugar levels  
975 (see **PRECAUTIONS: Laboratory Tests**)

976 **Gastrointestinal**

977 inflammatory bowel disease (see **WARNINGS: Inflammatory Bowel Disease**),  
978 hepatitis (see **WARNINGS: Hepatotoxicity**), pancreatitis (see **WARNINGS:**  
979 **Lipids**), bleeding and inflammation of the gums, colitis, esophagitis/esophageal  
980 ulceration, ileitis, nausea, other nonspecific gastrointestinal symptoms

981 **Hematologic**

982 allergic reactions (see **PRECAUTIONS: Hypersensitivity**), anemia,  
983 thrombocytopenia, neutropenia, rare reports of agranulocytosis (see  
984 **PRECAUTIONS: Information for Patients**). See **PRECAUTIONS:**  
985 **Laboratory Tests** for other hematological parameters.

- 986 Musculoskeletal
- 987 skeletal hyperostosis, calcification of tendons and ligaments, premature  
988 epiphyseal closure, decreases in bone mineral density (see **WARNINGS:**  
989 **Skeletal**), musculoskeletal symptoms (sometimes severe) including back pain,  
990 myalgia, and arthralgia (see **PRECAUTIONS: Information for Patients**),  
991 transient pain in the chest (see **PRECAUTIONS: Information for Patients**),  
992 arthritis, tendonitis, other types of bone abnormalities, elevations of CPK/rare  
993 reports of rhabdomyolysis (see **PRECAUTIONS: Laboratory Tests**).
- 994 Neurological
- 995 pseudotumor cerebri (see **WARNINGS: Pseudotumor Cerebri**), dizziness,  
996 drowsiness, headache, insomnia, lethargy, malaise, nervousness, paresthesias,  
997 seizures, stroke, syncope, weakness
- 998 Psychiatric
- 999 suicidal ideation, suicide attempts, suicide, depression, psychosis, aggression,  
1000 violent behaviors (see **WARNINGS: Psychiatric Disorders**), emotional  
1001 instability
- 1002 Of the patients reporting depression, some reported that the depression subsided  
1003 with discontinuation of therapy and recurred with reinstatement of therapy.
- 1004 Reproductive System
- 1005 abnormal menses
- 1006 Respiratory
- 1007 bronchospasms (with or without a history of asthma), respiratory infection, voice  
1008 alteration
- 1009 Skin and Appendages
- 1010 acne fulminans, alopecia (which in some cases persists), bruising, cheilitis (dry  
1011 lips), dry mouth, dry nose, dry skin, epistaxis, eruptive xanthomas,<sup>7</sup> erythema  
1012 multiforme, flushing, fragility of skin, hair abnormalities, hirsutism,  
1013 hyperpigmentation and hypopigmentation, infections (including disseminated  
1014 herpes simplex), nail dystrophy, paronychia, peeling of palms and soles,  
1015 photoallergic/photosensitizing reactions, pruritus, pyogenic granuloma, rash  
1016 (including facial erythema, seborrhea, and eczema), Stevens-Johnson syndrome,  
1017 sunburn susceptibility increased, sweating, toxic epidermal necrolysis, urticaria,  
1018 vasculitis (including Wegener's granulomatosis; see **PRECAUTIONS:**  
1019 **Hypersensitivity**), abnormal wound healing (delayed healing or exuberant  
1020 granulation tissue with crusting; see **PRECAUTIONS: Information for**  
1021 **Patients**)
- 1022 Special Senses
- 1023 *Hearing*
- 1024 hearing impairment (see **WARNINGS: Hearing Impairment**), tinnitus.

1025 *Vision*  
1026 corneal opacities (see **WARNINGS: Corneal Opacities**), decreased night vision  
1027 which may persist (see **WARNINGS: Decreased Night Vision**), cataracts, color  
1028 vision disorder, conjunctivitis, dry eyes, eyelid inflammation, keratitis, optic  
1029 neuritis, photophobia, visual disturbances

1030 **Urinary System**  
1031 glomerulonephritis (see **PRECAUTIONS: Hypersensitivity**), nonspecific  
1032 urogenital findings (see **PRECAUTIONS: Laboratory Tests** for other urological  
1033 parameters)

1034 **Laboratory**  
1035 Elevation of plasma triglycerides (see **WARNINGS: Lipids**), decrease in serum  
1036 high-density lipoprotein (HDL) levels, elevations of serum cholesterol during  
1037 treatment

1038 Increased alkaline phosphatase, SGOT (AST), SGPT (ALT), GGTP or LDH (see  
1039 **WARNINGS: Hepatotoxicity**)

1040 Elevation of fasting blood sugar, elevations of CPK (see **PRECAUTIONS:**  
1041 **Laboratory Tests**), hyperuricemia

1042 Decreases in red blood cell parameters, decreases in white blood cell counts  
1043 (including severe neutropenia and rare reports of agranulocytosis; see  
1044 **PRECAUTIONS: Information for Patients**), elevated sedimentation rates,  
1045 elevated platelet counts, thrombocytopenia

1046 White cells in the urine, proteinuria, microscopic or gross hematuria

1047 **OVERDOSAGE**  
1048 The oral LD<sub>50</sub> of isotretinoin is greater than 4000 mg/kg in rats and mice (>600  
1049 times the recommended clinical dose of 1.0 mg/kg/day after normalization of the  
1050 rat dose for total body surface area and >300 times the recommended clinical dose  
1051 of 1.0 mg/kg/day after normalization of the mouse dose for total body surface  
1052 area) and is approximately 1960 mg/kg in rabbits (653 times the recommended  
1053 clinical dose of 1.0 mg/kg/day after normalization for total body surface area). In  
1054 humans, overdosage has been associated with vomiting, facial flushing, cheilosis,  
1055 abdominal pain, headache, dizziness, and ataxia. These symptoms quickly resolve  
1056 without apparent residual effects.

1057 Accutane causes serious birth defects at any dosage (see **Boxed**  
1058 **CONTRAINDICATIONS AND WARNINGS**). Female patients of childbearing  
1059 potential who present with isotretinoin overdose must be evaluated for pregnancy.  
1060 Patients who are pregnant should receive counseling about the risks to the fetus,  
1061 as described in the **Boxed CONTRAINDICATIONS AND WARNINGS**. Non-  
1062 pregnant patients must be warned to avoid pregnancy for at least one month and  
1063 receive contraceptive counseling as described in **PRECAUTIONS**. Educational  
1064 materials for such patients can be obtained by calling the manufacturer. Because

1065 an overdose would be expected to result in higher levels of isotretinoin in semen  
1066 than found during a normal treatment course, male patients should use a condom,  
1067 or avoid reproductive sexual activity with a female patient who is or might  
1068 become pregnant, for 1 month after the overdose. All patients with isotretinoin  
1069 overdose should not donate blood for at least 1 month.

## 1070 **DOSAGE AND ADMINISTRATION**

1071 Accutane should be administered with a meal (see **PRECAUTIONS:**  
1072 **Information for Patients**).

1073 The recommended dosage range for Accutane is 0.5 to 1.0 mg/kg/day given in  
1074 two divided doses with food for 15 to 20 weeks. In studies comparing 0.1, 0.5,  
1075 and 1.0 mg/kg/day,<sup>8</sup> it was found that all dosages provided initial clearing of  
1076 disease, but there was a greater need for retreatment with the lower dosages.  
1077 During treatment, the dose may be adjusted according to response of the disease  
1078 and/or the appearance of clinical side effects — some of which may be dose  
1079 related. Adult patients whose disease is very severe with scarring or is primarily  
1080 manifested on the trunk may require dose adjustments up to 2.0 mg/kg/day, as  
1081 tolerated. Failure to take Accutane with food will significantly decrease  
1082 absorption. Before upward dose adjustments are made, the patients should be  
1083 questioned about their compliance with food instructions.

1084 The safety of once daily dosing with Accutane has not been established. Once  
1085 daily dosing is **not** recommended.

1086 If the total nodule count has been reduced by more than 70% prior to completing  
1087 15 to 20 weeks of treatment, the drug may be discontinued. After a period of 2  
1088 months or more off therapy, and if warranted by persistent or recurring severe  
1089 nodular acne, a second course of therapy may be initiated. The optimal interval  
1090 before retreatment has not been defined for patients who have not completed  
1091 skeletal growth. Long-term use of Accutane, even in low doses, has not been  
1092 studied, and is not recommended. It is important that Accutane be given at the  
1093 recommended doses for no longer than the recommended duration. The effect of  
1094 long-term use of Accutane on bone loss is unknown (see **WARNINGS: Skeletal:**  
1095 **Bone Mineral Density, Hyperostosis, and Premature Epiphyseal Closure**).

1096 Contraceptive measures must be followed for any subsequent course of therapy  
1097 (see **PRECAUTIONS**).

1098 **Table 4 Accutane Dosing by Body Weight (Based on**  
 1099 **Administration With Food)**

Body Weight		Total mg/day		
kilograms	pounds	0.5 mg/kg	1 mg/kg	2 mg/kg*
40	88	20	40	80
50	110	25	50	100
60	132	30	60	120
70	154	35	70	140
80	176	40	80	160
90	198	45	90	180
100	220	50	100	200

1100 \*See **DOSAGE AND ADMINISTRATION**: the recommended dosage range is  
 1101 0.5 to 1.0 mg/kg/day.

1102 **INFORMATION FOR PHARMACISTS**

1103 Access the iPLEDGE system via the internet ([www.ipledgeprogram.com](http://www.ipledgeprogram.com)) or  
 1104 telephone (1-866-495-0654) to obtain an authorization and the “**do not dispense**  
 1105 **to patient after**” date. Accutane must only be dispensed in no more than a 30-day  
 1106 supply.

1107 **REFILLS REQUIRE A NEW PRESCRIPTION AND A NEW**  
 1108 **AUTHORIZATION FROM THE iPLEDGE SYSTEM.**

1109 An Accutane Medication Guide must be given to the patient each time Accutane  
 1110 is dispensed, as required by law. This Accutane Medication Guide is an important  
 1111 part of the risk management program for the patient.

1112 **HOW SUPPLIED**

1113 Soft gelatin capsules, 10 mg (light pink), imprinted ACCUTANE 10 ROCHE.  
 1114 Boxes of 100 containing 10 Prescription Paks of 10 capsules (NDC 0004-0155-  
 1115 49).

1116 Soft gelatin capsules, 20 mg (maroon), imprinted ACCUTANE 20 ROCHE.  
 1117 Boxes of 100 containing 10 Prescription Paks of 10 capsules (NDC 0004-0169-  
 1118 49).

1119 Soft gelatin capsules, 40 mg (yellow), imprinted ACCUTANE 40 ROCHE. Boxes  
 1120 of 100 containing 10 Prescription Paks of 10 capsules (NDC 0004-0156-49).

1121 **Storage**

1122 Store at controlled room temperature (59° to 86°F, 15° to 30°C). Protect from  
 1123 light.

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1142 OrthoNovum 7/7/7 is a registered trademark of Ortho-McNeil Pharmaceutical, Inc.  
1143

1144

1145 **Patient Information/Informed Consent About Birth Defects (for**  
1146 **female patients who can get pregnant)**

1147 To be completed by the patient (and her parent or guardian\* if patient is under age  
1148 18) and signed by her doctor.

1149 Read each item below and initial in the space provided to show that you  
1150 understand each item and agree to follow your doctor's instructions. **Do not sign**  
1151 **this consent and do not take isotretinoin if there is anything that you do not**  
1152 **understand.**

1153 \*A parent or guardian of a minor patient (under age 18) must also read and initial  
1154 each item before signing the consent.

1155

1156

1157

\_\_\_\_\_  
(Patient's Name)

1158

1159

1160

1161

1. I understand that there is a very high chance that my unborn baby could have severe birth defects if I am pregnant or become pregnant while taking isotretinoin. This can happen with any amount and even if taken for short periods of time. This is why I must not be pregnant while taking isotretinoin.

1162

Initial: \_\_\_\_\_

1163

1164

1165

2. I understand that I must not get pregnant 1 month before, during the entire time of my treatment, and for 1 month after the end of my treatment with isotretinoin.

1166

Initial: \_\_\_\_\_

1167 3. I understand that I must avoid sexual intercourse completely, or I must use 2  
 1168 separate, effective forms of birth control (contraception) **at the same time**.  
 1169 The only exceptions are if I have had surgery to remove the uterus (a  
 1170 hysterectomy) or both of my ovaries (bilateral oophorectomy), or my doctor  
 1171 has medically confirmed that I am post-menopausal.

1172  
 1173 Initial: \_\_\_\_\_

1174  
 1175 4. I understand that hormonal birth control products are among the most  
 1176 effective forms of birth control. Combination birth control pills and other  
 1177 hormonal products include skin patches, shots, under-the-skin implants,  
 1178 vaginal rings, and intrauterine devices (IUDs). Any form of birth control can  
 1179 fail. That is why I must use 2 different birth control methods at the same time,  
 1180 starting 1 month before, during, and for 1 month after stopping therapy every  
 1181 time I have sexual intercourse, even if 1 of the methods I choose is hormonal  
 1182 birth control.

1183 Initial: \_\_\_\_\_

1184 5. I understand that the following are effective forms of birth control:

1185  
 1186

Primary forms	Secondary forms
<ul style="list-style-type: none"> <li>• tubal sterilization (tying my tubes)</li> <li>• partner's vasectomy</li> <li>• intrauterine device</li> <li>• hormonal (combination birth control pills, skin patches, shots, under-the-skin implants, or vaginal ring)</li> </ul>	<p><i>Barrier:</i></p> <ul style="list-style-type: none"> <li>• male latex condom with or without spermicide</li> <li>• diaphragm with spermicide</li> <li>• cervical cap with spermicide</li> </ul> <p><i>Other:</i></p> <ul style="list-style-type: none"> <li>• vaginal sponge (contains spermicide)</li> </ul>

1187  
 1188 A diaphragm and cervical cap must each be used with spermicide, a special  
 1189 cream that kills sperm

1190 I understand that at least 1 of my 2 forms of birth control must be a primary  
 1191 method.

1192 Initial: \_\_\_\_\_

1193 6. I will talk with my doctor about any medicines including herbal products I  
 1194 plan to take during my isotretinoin treatment because hormonal birth control  
 1195 methods may not work if I am taking certain medicines or herbal products.

1196 Initial: \_\_\_\_\_

1197 7. I may receive a free birth control counseling session from a doctor or other  
1198 family planning expert. My isotretinoin doctor can give me an isotretinoin  
1199 Patient Referral Form for this free consultation.

1200 Initial: \_\_\_\_\_

1201 8. I must begin using the birth control methods I have chosen as described above  
1202 at least 1 month before I start taking isotretinoin.

1203 Initial: \_\_\_\_\_

1204 9. I cannot get my first prescription for isotretinoin unless my doctor has told me  
1205 that I have 2 negative pregnancy test results. The first pregnancy test should  
1206 be done when my doctor decides to prescribe isotretinoin. The second  
1207 pregnancy test must be done in a lab during the first 5 days of my menstrual  
1208 period right before starting isotretinoin therapy treatment, or as instructed by  
1209 my doctor. I will then have 1 pregnancy test; in a lab.

1210

- 1211 • every month during treatment
- 1212 • at the end of treatment
- 1213 • and 1 month after stopping treatment

1214

1215 I must not start taking isotretinoin until I am sure that I am not pregnant, have  
1216 negative results from 2 pregnancy tests, and the second test has been done in a  
1217 lab.

1218 Initial: \_\_\_\_\_

1219 10. I have read and understand the materials my doctor has given to me, including  
1220 *The iPLEDGE Program Guide for Isotretinoin for Female Patients Who Can*  
1221 *Get Pregnant, The iPLEDGE Birth Control Workbook and The iPLEDGE*  
1222 *Program Patient Introductory Brochure.*

1223

1224 My doctor gave me and asked me to watch the DVD containing a video about  
1225 birth control and a video about birth defects and isotretinoin.

1226

1227 I was told about a private counseling line that I may call for more information  
1228 about birth control. I have received information on emergency birth control.

1229 Initial: \_\_\_\_\_

1230 11. I must stop taking isotretinoin right away and call my doctor if I get pregnant,  
1231 miss my expected menstrual period, stop using birth control, or have sexual  
1232 intercourse without using my 2 birth control methods at any time.

1233 Initial: \_\_\_\_\_

1234 12. My doctor gave me information about the purpose and importance of  
1235 providing information to the iPLEDGE program should I become pregnant  
1236 while taking isotretinoin or within 1 month of the last dose. I also understand  
1237 that if I become pregnant, information about my pregnancy, my health, and  
1238 my baby's health may be shared with the maker of isotretinoin and their  
1239 authorized parties who maintain the iPLEDGE program and government  
1240 health regulatory authorities.

1241 Initial: \_\_\_\_\_

1242 13. I understand that being qualified to receive isotretinoin in the iPLEDGE  
1243 program means that I:

- 1244
- 1245 • have had 2 negative urine or blood pregnancy tests before receiving the  
1246 first isotretinoin prescription. The second test must be done in a lab. I must  
1247 have a negative result from a urine or blood pregnancy test done in a lab  
1248 repeated each month before I receive another isotretinoin prescription.  
1249
- 1250 • have chosen and agreed to use 2 forms of effective birth control at the  
1251 same time. At least 1 method must be a primary form of birth control,  
1252 **unless I have chosen never to have sexual contact with a male**  
1253 **(abstinence)**, or I have undergone a hysterectomy. I must use 2 forms of  
1254 birth control for at least 1 month before I start isotretinoin therapy, during  
1255 therapy, and for 1 month after stopping therapy. I must receive counseling,  
1256 repeated on a monthly basis, about birth control and behaviors associated  
1257 with an increased risk of pregnancy.  
1258
- 1259 • have signed a Patient Information/Informed Consent About Birth Defects  
1260 (for female patients who can get pregnant) that contains warnings about  
1261 the chance of possible birth defects if I am pregnant or become pregnant  
1262 and my unborn baby is exposed to isotretinoin.  
1263
- 1264 • have been informed of and understand the purpose and importance of  
1265 providing information to the iPLEDGE program should I become pregnant  
1266 while taking isotretinoin or within 1 month of the last dose.  
1267
- 1268 • have interacted with the iPLEDGE program before starting isotretinoin  
1269 and on a monthly basis to answer questions on the program requirements  
1270 and to enter my two chosen forms of birth control.

1271 Initial: \_\_\_\_\_

1272 **My doctor has answered all my questions about isotretinoin and I**  
1273 **understand that it is my responsibility not to get pregnant 1 month before,**  
1274 **during isotretinoin treatment, or for 1 month after I stop taking isotretinoin.**

1275 Initial: \_\_\_\_\_

1276 I now authorize my doctor \_\_\_\_\_ to begin my treatment with  
1277 isotretinoin.

1278 Patient Signature: \_\_\_\_\_ Date: \_\_\_\_\_

1279 Parent/Guardian Signature (if under age 18): \_\_\_\_\_ Date: \_\_\_\_\_

1280 Please print: Patient Name and Address \_\_\_\_\_

1281 \_\_\_\_\_ Telephone \_\_\_\_\_

1282 I have fully explained to the patient, \_\_\_\_\_, the nature and  
1283 purpose of the treatment described above and the risks to female patients of  
1284 childbearing potential. I have asked the patient if she has any questions regarding  
1285 her treatment with isotretinoin and have answered those questions to the best of  
1286 my ability.

1287 Doctor Signature: \_\_\_\_\_ Date: \_\_\_\_\_

1288 **PLACE THE ORIGINAL SIGNED DOCUMENTS IN THE PATIENT'S**  
1289 **MEDICAL RECORD. PLEASE PROVIDE A COPY TO THE PATIENT.**

1290

1291 **Patient Information/Informed Consent (for all patients):**

1292 To be completed by patient (and parent or guardian if patient is under age 18) and  
1293 signed by the doctor.

1294 Read each item below and initial in the space provided if you understand each  
1295 item and agree to follow your doctor's instructions. A parent or guardian of a  
1296 patient under age 18 must also read and understand each item before signing the  
1297 agreement.

1298 **Do not sign this agreement and do not take isotretinoin if there is anything**  
1299 **that you do not understand about all the information you have received**  
1300 **about using isotretinoin.**

1301 1. I, \_\_\_\_\_,  
1302 (Patient's Name)

1303 understand that isotretinoin is a medicine used to treat severe nodular acne  
1304 that cannot be cleared up by any other acne treatments, including antibiotics.  
1305 In severe nodular acne, many red, swollen, tender lumps form in the skin. If  
1306 untreated, severe nodular acne can lead to permanent scars.

1307 Initials: \_\_\_\_\_

1308 2. My doctor has told me about my choices for treating my acne.

1309 Initials: \_\_\_\_\_

1310 3. I understand that there are serious side effects that may happen while I am  
1311 taking isotretinoin. These have been explained to me. These side effects  
1312 include serious birth defects in babies of pregnant patients. [Note: There is a  
1313 second Patient Information/Informed Consent About Birth Defects (for female  
1314 patients who can get pregnant)].

1315 Initials: \_\_\_\_\_

1316 4. I understand that some patients, while taking isotretinoin or soon after  
1317 stopping isotretinoin, have become depressed or developed other serious  
1318 mental problems. Symptoms of depression include sad, "anxious" or empty  
1319 mood, irritability, acting on dangerous impulses, anger, loss of pleasure or  
1320 interest in social or sports activities, sleeping too much or too little, changes in  
1321 weight or appetite, school or work performance going down, or trouble  
1322 concentrating. Some patients taking isotretinoin have had thoughts about  
1323 hurting themselves or putting an end to their own lives (suicidal thoughts).  
1324 Some people tried to end their own lives. And some people have ended their  
1325 own lives. There were reports that some of these people did not appear  
1326 depressed. There have been reports of patients on isotretinoin becoming  
1327 aggressive or violent. No one knows if isotretinoin caused these behaviors or  
1328 if they would have happened even if the person did not take isotretinoin. Some

1329 people have had other signs of depression while taking isotretinoin (see #7  
1330 below).

1331 Initials: \_\_\_\_\_

1332 5. Before I start taking isotretinoin, I agree to tell my doctor if I have **ever** had  
1333 symptoms of depression (see #7 below), been psychotic, attempted suicide,  
1334 had any other mental problems, or take medicine for any of these problems.  
1335 Being psychotic means having a loss of contact with reality, such as hearing  
1336 voices or seeing things that are not there.

1337 Initials: \_\_\_\_\_

1338 6. Before I start taking isotretinoin, I agree to tell my doctor if, to the best of my  
1339 knowledge, anyone in my family has ever had symptoms of depression, been  
1340 psychotic, attempted suicide, or had any other serious mental problems.

1341 Initials: \_\_\_\_\_

1342 7. Once I start taking isotretinoin, I agree to stop using isotretinoin and tell my  
1343 doctor right away if any of the following signs and symptoms of depression or  
1344 psychosis happen. I:

- 1345 • Start to feel sad or have crying spells
- 1346 • Lose interest in activities I once enjoyed
- 1347 • Sleep too much or have trouble sleeping
- 1348 • Become more irritable, angry, or aggressive than usual (for example,  
1349 temper outbursts, thoughts of violence)
- 1350 • Have a change in my appetite or body weight
- 1351 • Have trouble concentrating
- 1352 • Withdraw from my friends or family
- 1353 • Feel like I have no energy
- 1354 • Have feelings of worthlessness or guilt
- 1355 • Start having thoughts about hurting myself or taking my own life (suicidal  
1356 thoughts)
- 1357 • Start acting on dangerous impulses
- 1358 • Start seeing or hearing things that are not real

1359 Initials: \_\_\_\_\_

1360 **8. I agree to return to see my doctor every month I take isotretinoin to get a**  
1361 **new prescription for isotretinoin, to check my progress, and to check for**  
1362 **signs of side effects.**

1363 Initials: \_\_\_\_\_

1364 9. Isotretinoin will be prescribed just for me — I will not share isotretinoin with  
1365 other people because it may cause serious side effects, including birth defects.

1366 Initials: \_\_\_\_\_

1367 10. I will not give blood while taking isotretinoin or for 1 month after I stop  
1368 taking isotretinoin. I understand that if someone who is pregnant gets my  
1369 donated blood, her baby may be exposed to isotretinoin and may be born with  
1370 serious birth defects.

1371 Initials: \_\_\_\_\_

1372 11. I have read *The iPLEDGE Program Patient Introductory Brochure*, and other  
1373 materials my provider gave me containing important safety information about  
1374 isotretinoin. I understand all the information I received.

1375 Initials: \_\_\_\_\_

1376 12. My doctor and I have decided I should take isotretinoin. I understand that I  
1377 must be qualified in the iPLEDGE program to have my prescription filled  
1378 each month. I understand that I can stop taking isotretinoin at any time. I agree  
1379 to tell my doctor if I stop taking isotretinoin.

1380 Initials: \_\_\_\_\_

1381 I now allow my doctor \_\_\_\_\_ to begin my treatment  
1382 with isotretinoin.

1383 Patient Signature: \_\_\_\_\_ Date: \_\_\_\_\_

1384 Parent/Guardian Signature (if under age 18): \_\_\_\_\_ Date: \_\_\_\_\_

1385 Patient Name (print) \_\_\_\_\_

1386 Patient Address \_\_\_\_\_ Telephone (\_\_\_\_.\_\_\_\_.\_\_\_\_)

1387 \_\_\_\_\_

1388 I have:

- 1389 • fully explained to the patient, \_\_\_\_\_, the nature and purpose  
1390 of isotretinoin treatment, including its benefits and risks
- 1391 • given the patient the appropriate educational materials, *The iPLEDGE*  
1392 *Program Patient Introductory Brochure* and asked the patient if he/she has  
1393 any questions regarding his/her treatment with isotretinoin
- 1394 • answered those questions to the best of my ability

1395  
1396 Doctor Signature: \_\_\_\_\_ Date: \_\_\_\_\_

1397 **PLACE THE ORIGINAL SIGNED DOCUMENTS IN THE PATIENT'S**  
1398 **MEDICAL RECORD. PLEASE PROVIDE A COPY TO THE PATIENT.**

1399

1400

## **MEDICATION GUIDE**

1401

### **ACCUTANE (ACK-u-tane)**

1402

#### **(isotretinoin capsules)**

1403

1404 Read the Medication Guide that comes with Accutane before you start taking it  
1405 and each time you get a prescription. There may be new information. This  
1406 information does not take the place of talking with your doctor about your  
1406 medical condition or your treatment.

1407

#### **What is the most important information I should know about**

1408

##### **Accutane?**

1409

- Accutane is used to treat a type of severe acne (nodular acne) that has not  
1410 been helped by other treatments, including antibiotics.

1411

- Because Accutane can cause birth defects, Accutane is only for patients  
1412 who can understand and agree to carry out all of the instructions in the  
1413 iPLEDGE program.

1414

- Accutane may cause serious mental health problems.

1415

1416

- 1. Birth defects (deformed babies), loss of a baby before birth (miscarriage),  
1417 death of the baby, and early (premature) births.** Female patients who are  
1418 pregnant or who plan to become pregnant must not take Accutane. **Female  
1419 patients must not get pregnant:**

1420

1421

- for 1 month before starting Accutane

1422

- while taking Accutane

1423

- for 1 month after stopping Accutane.

1424

1425

**If you get pregnant while taking Accutane, stop taking it right away and  
1426 call your doctor.** Doctors and patients should report all cases of pregnancy  
1427 to:

1428

- FDA MedWatch at 1-800-FDA-1088, and

1429

- the iPLEDGE pregnancy registry at 1-866-495-0654

1430

1431

- 2. Serious mental health problems.** Accutane may cause:

1432

- **depression**

1433

- **psychosis** (seeing or hearing things that are not real)

1434

- **suicide.** Some patients taking Accutane have had thoughts about hurting  
1435 themselves or putting an end to their own lives (suicidal thoughts). Some  
1436 people tried to end their own lives. And some people have ended their own  
1437 lives.

1438

1439 **Stop Accutane and call your doctor right away if you or a family member**  
1440 **notices that you have any of the following signs and symptoms of**  
1441 **depression or psychosis:**

- 1442 • start to feel sad or have crying spells
- 1443 • lose interest in activities you once enjoyed
- 1444 • sleep too much or have trouble sleeping
- 1445 • become more irritable, angry, or aggressive than usual (for example,
- 1446 temper outbursts, thoughts of violence)
- 1447 • have a change in your appetite or body weight
- 1448 • have trouble concentrating
- 1449 • withdraw from your friends or family
- 1450 • feel like you have no energy
- 1451 • have feelings of worthlessness or guilt
- 1452 • start having thoughts about hurting yourself or taking your own life
- 1453 (suicidal thoughts)
- 1454 • start acting on dangerous impulses
- 1455 • start seeing or hearing things that are not real
- 1456

1457 After stopping Accutane, you may also need follow-up mental health care if you  
1458 had any of these symptoms.

#### 1459 **What is Accutane?**

1460 Accutane is a medicine taken by mouth to treat the most severe form of acne  
1461 (nodular acne) that cannot be cleared up by any other acne treatments, including  
1462 antibiotics. Accutane can cause serious side effects (see **“What is the most**  
1463 **important information I should know about Accutane?”**). Accutane can only  
1464 be:

- 1465 • prescribed by doctors that are registered in the iPLEDGE program
- 1466 • dispensed by a pharmacy that is registered with the iPLEDGE program
- 1467 • given to patients who are registered in the iPLEDGE program and agree to do
- 1468 everything required in the program

#### 1469 **What is severe nodular acne?**

1470 Severe nodular acne is when many red, swollen, tender lumps form in the skin.  
1471 These can be the size of pencil erasers or larger. If untreated, nodular acne can  
1472 lead to permanent scars.

#### 1473 **Who should not take Accutane?**

- 1474 • **Do not take Accutane if you are pregnant, plan to become pregnant, or**  
1475 **become pregnant during Accutane treatment.** Accutane causes severe birth  
1476 defects. See **“What is the most important information I should know**  
1477 **about Accutane?”**
- 1478

1479 • **Do not take Accutane if you are allergic to anything in it.** Accutane  
1480 contains **parabens** as the preservative. See the end of this Medication Guide  
1481 for a complete list of ingredients in Accutane.  
1482

### 1483 **What should I tell my doctor before taking Accutane?**

1484 **Tell your doctor if you or a family member has any of the following health**  
1485 **conditions:**

- 1486 • mental problems
- 1487 • asthma
- 1488 • liver disease
- 1489 • diabetes
- 1490 • heart disease
- 1491 • bone loss (osteoporosis) or weak bones
- 1492 • an eating problem called anorexia nervosa (where people eat too little)
- 1493 • food or medicine allergies

1494  
1495 **Tell your doctor if you are pregnant or breastfeeding. Accutane must not be**  
1496 **used by women who are pregnant or breastfeeding.**

1497 **Tell your doctor about all of the medicines you take including prescription**  
1498 **and non-prescription medicines, vitamins and herbal supplements.** Accutane  
1499 and certain other medicines can interact with each other, sometimes causing  
1500 serious side effects. Especially tell your doctor if you take:

- 1501 • **Vitamin A supplements.** Vitamin A in high doses has many of the same side  
1502 effects as Accutane. Taking both together may increase your chance of getting  
1503 side effects.
- 1504 • **Tetracycline antibiotics.** Tetracycline antibiotics taken with Accutane can  
1505 increase the chances of getting increased pressure in the brain.
- 1506 • **Progestin-only birth control pills (mini-pills).** They may not work while  
1507 you take Accutane. Ask your doctor or pharmacist if you are not sure what  
1508 type you are using.
- 1509 • **Dilantin (phenytoin).** This medicine taken with Accutane may weaken your  
1510 bones.
- 1511 • **Corticosteroid medicines.** These medicines taken with Accutane may  
1512 weaken your bones.
- 1513 • **St. John's Wort.** This herbal supplement may make birth control pills work  
1514 less effectively.

1515  
1516 **These medicines should not be used with Accutane unless your doctor tells**  
1517 **you it is okay.**

1518 Know the medicines you take. Keep a list of them to show to your doctor and  
1519 pharmacist. Do not take any new medicine without talking with your doctor.

1520 **How should I take Accutane?**

- 1521 • You must take Accutane exactly as prescribed. You must also follow all the  
1522 instructions of the iPLEDGE program. Before prescribing Accutane, your  
1523 doctor will:
- 1524 • explain the iPLEDGE program to you
  - 1525 • have you sign the Patient Information/Informed Consent (for all patients).  
1526 Female patients who can get pregnant must also sign another consent  
1527 form.
- 1528

1529 **You will not be prescribed Accutane if you cannot agree to or follow all**  
1530 **the instructions of the iPLEDGE program.**

- 1531 • You will get no more than a 30-day supply of Accutane at a time. This is to  
1532 make sure you are following the Accutane iPLEDGE program. You should  
1533 talk with your doctor each month about side effects.  
1534
- 1535 • The amount of Accutane you take has been specially chosen for you. It is  
1536 based on your body weight, and may change during treatment.  
1537
- 1538 • Take Accutane 2 times a day with a meal, unless your doctor tells you  
1539 otherwise. **Swallow your Accutane capsules whole with a full glass of**  
1540 **liquid. Do not chew or suck on the capsule.** Accutane can hurt the tube that  
1541 connects your mouth to your stomach (esophagus) if it is not swallowed  
1542 whole.  
1543
- 1544 • If you miss a dose, just skip that dose. Do **not** take 2 doses at the same time.  
1545
- 1546 • If you take too much Accutane or overdose, call your doctor or poison control  
1547 center right away.  
1548
- 1549 • Your acne may get worse when you first start taking Accutane. This should  
1550 last only a short while. Talk with your doctor if this is a problem for you.  
1551
- 1552 • You must return to your doctor as directed to make sure you don't have signs  
1553 of serious side effects. Your doctor may do blood tests to check for serious  
1554 side effects from Accutane. Female patients who can get pregnant will get a  
1555 pregnancy test each month.  
1556
- 1557 • Female patients who can get pregnant must agree to use 2 separate forms of  
1558 effective birth control at the same time 1 month before, while taking, and for 1  
1559 month after taking Accutane. **You must access the iPLEDGE system to**  
1560 **answer questions about the program requirements and to enter your 2**  
1561 **chosen forms of birth control.** To access the iPLEDGE system, go to  
1562 [www.ipledgeprogram.com](http://www.ipledgeprogram.com) or call 1-866-495-0654.  
1563

1564 You must talk about effective birth control methods with your doctor or go for  
1565 a free visit to talk about birth control with another doctor or family planning

1566 expert. Your doctor can arrange this free visit, which will be paid for by the  
1567 company that makes Accutane.

1568 **If you have sex at any time without using 2 forms of effective birth**  
1569 **control, get pregnant, or miss your expected period, stop using Accutane**  
1570 **and call your doctor right away.**

### 1571 **What should I avoid while taking Accutane?**

1572 • **Do not get pregnant** while taking Accutane and for 1 month after stopping  
1573 Accutane. See **“What is the most important information I should know**  
1574 **about Accutane?”**  
1575

1576 • **Do not breast feed** while taking Accutane and for 1 month after stopping  
1577 Accutane. We do not know if Accutane can pass through your milk and harm  
1578 the baby.  
1579

1580 • **Do not give blood** while you take Accutane and for 1 month after stopping  
1581 Accutane. If someone who is pregnant gets your donated blood, her baby may  
1582 be exposed to Accutane and may be born with birth defects.  
1583

1584 • **Do not take other medicines or herbal products** with Accutane unless you  
1585 talk to your doctor. See **“What should I tell my doctor before taking**  
1586 **Accutane?”**  
1587

1588 • **Do not drive at night until you know if Accutane has affected your vision.**  
1589 Accutane may decrease your ability to see in the dark.  
1590

1591 • **Do not have cosmetic procedures to smooth your skin, including waxing,**  
1592 **dermabrasion, or laser procedures, while you are using Accutane and for**  
1593 **at least 6 months after you stop.** Accutane can increase your chance of  
1594 scarring from these procedures. Check with your doctor for advice about when  
1595 you can have cosmetic procedures.  
1596

1597 • **Avoid sunlight and ultraviolet lights** as much as possible. Tanning machines  
1598 use ultraviolet lights. Accutane may make your skin more sensitive to light.  
1599

1600 • **Do not share Accutane with other people.** It can cause birth defects and  
1601 other serious health problems.  
1602

### 1603 **What are the possible side effects of Accutane?**

1604 • **Accutane can cause birth defects (deformed babies), loss of a baby before**  
1605 **birth (miscarriage), death of the baby, and early (premature) births.** See  
1606 **“What is the most important information I should know about**  
1607 **Accutane?”**  
1608

1609 • **Accutane may cause serious mental health problems.** See **“What is the**  
1610 **most important information I should know about Accutane?”**

- 1611 • **serious brain problems.** Accutane can increase the pressure in your brain.  
1612 This can lead to permanent loss of eyesight and, in rare cases, death. Stop  
1613 taking Accutane and call your doctor right away if you get any of these signs  
1614 of increased brain pressure:
- 1615 • bad headache
  - 1616 • blurred vision
  - 1617 • dizziness
  - 1618 • nausea or vomiting
  - 1619 • seizures (convulsions)
  - 1620 • stroke
  - 1621
- 1622 • **skin problems.** Skin rash can occur in patients taking Accutane. In some  
1623 patients a rash can be serious. Stop using Accutane and call your doctor right  
1624 away if you develop conjunctivitis (red or inflamed eyes, like “pink eye”), a  
1625 rash with a fever, blisters on legs, arms or face and/or sores in your mouth,  
1626 throat, nose, eyes, or if your skin begins to peel.
- 1627 • **stomach area (abdomen) problems.** Certain symptoms may mean that your  
1628 internal organs are being damaged. These organs include the liver, pancreas,  
1629 bowel (intestines), and esophagus (connection between mouth and stomach).  
1630 If your organs are damaged, they may not get better even after you stop taking  
1631 Accutane. Stop taking Accutane and call your doctor if you get:
- 1632 • severe stomach, chest or bowel pain
  - 1633 • trouble swallowing or painful swallowing
  - 1634 • new or worsening heartburn
  - 1635 • diarrhea
  - 1636 • rectal bleeding
  - 1637 • yellowing of your skin or eyes
  - 1638 • dark urine
  - 1639
- 1640 • **bone and muscle problems.** Accutane may affect bones, muscles, and  
1641 ligaments and cause pain in your joints or muscles. Tell your doctor if you  
1642 plan hard physical activity during treatment with Accutane. Tell your doctor if  
1643 you get:
- 1644 • back pain
  - 1645 • joint pain
  - 1646 • broken bone. Tell all healthcare providers that you take Accutane if you  
1647 break a bone.
  - 1648
- 1649 **Stop Accutane and call your doctor right away if you have muscle**  
1650 **weakness. Muscle weakness with or without pain can be a sign of**  
1651 **serious muscle damage.**
- 1652 Accutane may stop long bone growth in teenagers who are still growing.

1653 • **hearing problems.** Stop using Accutane and call your doctor if your hearing  
1654 gets worse or if you have ringing in your ears. Your hearing loss may be  
1655 permanent.

1656 • **vision problems.** Accutane may affect your ability to see in the dark. This  
1657 condition usually clears up after you stop taking Accutane, but it may be  
1658 permanent. Other serious eye effects can occur. Stop taking Accutane and call  
1659 your doctor right away if you have any problems with your vision or dryness  
1660 of the eyes that is painful or constant. If you wear contact lenses, you may  
1661 have trouble wearing them while taking Accutane and after treatment.

1662 • **lipid (fats and cholesterol in blood) problems.** Accutane can raise the level  
1663 of fats and cholesterol in your blood. This can be a serious problem. Return to  
1664 your doctor for blood tests to check your lipids and to get any needed  
1665 treatment. These problems usually go away when Accutane treatment is  
1666 finished.

1667 • **serious allergic reactions.** Stop taking Accutane and get emergency care  
1668 right away if you develop hives, a swollen face or mouth, or have trouble  
1669 breathing. Stop taking Accutane and call your doctor if you get a fever, rash,  
1670 or red patches or bruises on your legs.

1671 • **blood sugar problems.** Accutane may cause blood sugar problems including  
1672 diabetes. Tell your doctor if you are very thirsty or urinate a lot.

1673 • **decreased red and white blood cells.** Call your doctor if you have trouble  
1674 breathing, faint, or feel weak.

1675 • **The common, less serious side effects of Accutane** are dry skin, chapped  
1676 lips, dry eyes, and dry nose that may lead to nosebleeds. Call your doctor if  
1677 you get any side effect that bothers you or that does not go away.

1678 These are not all of the possible side effects with Accutane. Your doctor or  
1679 pharmacist can give you more detailed information. Call your doctor for medical  
1680 advice about side effects. You may report side effects to FDA at 1-800-FDA-1088  
1681 or Roche at 1-800-526-6367.

## 1682 **How should I store Accutane?**

1683 • Store Accutane at room temperature, between 59° and 86°F. Protect from  
1684 light.

1685 • **Keep Accutane and all medicines out of the reach of children.**

## 1687 **General Information about Accutane**

1688 Medicines are sometimes prescribed for conditions that are not mentioned in  
1689 Medication Guides. Do not use Accutane for a condition for which it was not  
1690 prescribed. Do not give Accutane to other people, even if they have the same  
1691 symptoms that you have. It may harm them.

1692 This Medication Guide summarizes the most important information about  
1693 Accutane. If you would like more information, talk with your doctor. You can ask  
1694 your doctor or pharmacist for information about Accutane that is written for  
1695 health care professionals. You can also call iPLEDGE program at 1-866-495-  
1696 0654 or visit [www.ipledgeprogram.com](http://www.ipledgeprogram.com).

1697 **What are the ingredients in Accutane?**

1698 **Active Ingredient: Isotretinoin**

1699 **Inactive Ingredients:** beeswax, butylated hydroxyanisole, edetate disodium,  
1700 hydrogenated soybean oil flakes, hydrogenated vegetable oil, and soybean oil.  
1701 Gelatin capsules contain glycerin and parabens (methyl and propyl), with the  
1702 following dye systems: 10 mg — iron oxide (red) and titanium dioxide; 20 mg —  
1703 FD&C Red No. 3, FD&C Blue No. 1, and titanium dioxide; 40 mg — FD&C  
1704 Yellow No. 6, D&C Yellow No. 10, and titanium dioxide.


1705

1706 This Medication Guide has been approved by the U.S. Food and Drug  
1707 Administration.

1708

1709 Dilantin is a registered trademark of Warner-Lambert Company LLC.

1710

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