

1 **Physician Information**

2 depo-subQ provera 104™
3 medroxyprogesterone acetate injectable suspension
4 104 mg/0.65 mL

6 **Women who use depo-subQ provera 104 may lose significant bone mineral density. Bone loss is greater with increasing duration of use and may not be completely reversible.**

10 **It is unknown if use of depo-subQ provera 104 during adolescence or early adulthood, a critical period of bone accretion, will reduce peak bone mass and increase the risk for osteoporotic fracture in later life.**

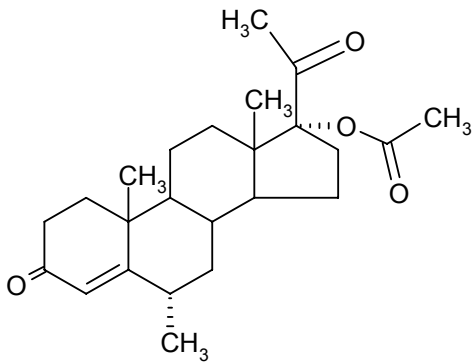
14 **depo-subQ provera 104 should be used long-term (e.g., longer than 2 years) only if other methods of birth control are inadequate (see WARNINGS, section 1).**

17 **Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.**

20 **DESCRIPTION**

22 depo-subQ provera 104 contains medroxyprogesterone acetate (MPA), a derivative of progesterone, as its active ingredient. Medroxyprogesterone acetate is active by the parenteral and oral routes of administration. It is a white to off-white, odorless crystalline powder that is stable in air and that melts between 205° and 209°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in alcohol and methanol, slightly soluble in ether, and insoluble in water.

29 The chemical name for medroxyprogesterone acetate is 17-hydroxy-6 α -methylpregn-4-ene-3,20-dione 17-acetate. The structural formula is as follows:



34 depo-subQ provera 104 for subcutaneous (SC) injection is available in pre-filled syringes
35 (160 mg/mL), each containing 0.65 mL (104 mg) of medroxyprogesterone acetate sterile
36 aqueous suspension.

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38 Each 0.65 mL contains:

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40	Medroxyprogesterone acetate	104 mg
41	Methylparaben	1.040 mg
42	Propylparaben	0.098 mg
43	Sodium Chloride	5.200 mg
44	Polyethylene Glycol	18.688 mg
45	Polysorbate 80	1.950 mg
46	Monobasic Sodium Phosphate · H ₂ O	0.451 mg
47	Dibasic Sodium Phosphate · 12H ₂ O	0.382 mg
48	Methionine	0.975 mg
49	Povidone	3.250 mg
50	Water for Injection	qs

51 When necessary, the pH is adjusted with sodium hydroxide or hydrochloric acid, or both.

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54 **CLINICAL PHARMACOLOGY**

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56 depo-subQ provera 104 (medroxyprogesterone acetate injectable suspension), when
57 administered at 104 mg/0.65 mL to women every 3 months (12 to 14 weeks), inhibits the
58 secretion of gonadotropins, which prevents follicular maturation and ovulation and
59 causes endometrial thinning. These actions produce its contraceptive effect.

60

61 Suppression of serum estradiol concentrations and a possible direct action of depo-subQ
62 provera 104 on the lesions of endometriosis are likely to be responsible for the
63 therapeutic effect on endometriosis-associated pain.

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65 **Pharmacokinetics**

66 The pharmacokinetic parameters of medroxyprogesterone acetate (MPA) following a
67 single SC injection of depo-subQ provera 104 are shown in Table 1 and Figure 1.

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Table 1. Pharmacokinetic Parameters of MPA after a Single SC Injection of depo-subQ provera 104 in Healthy Women (n = 42)

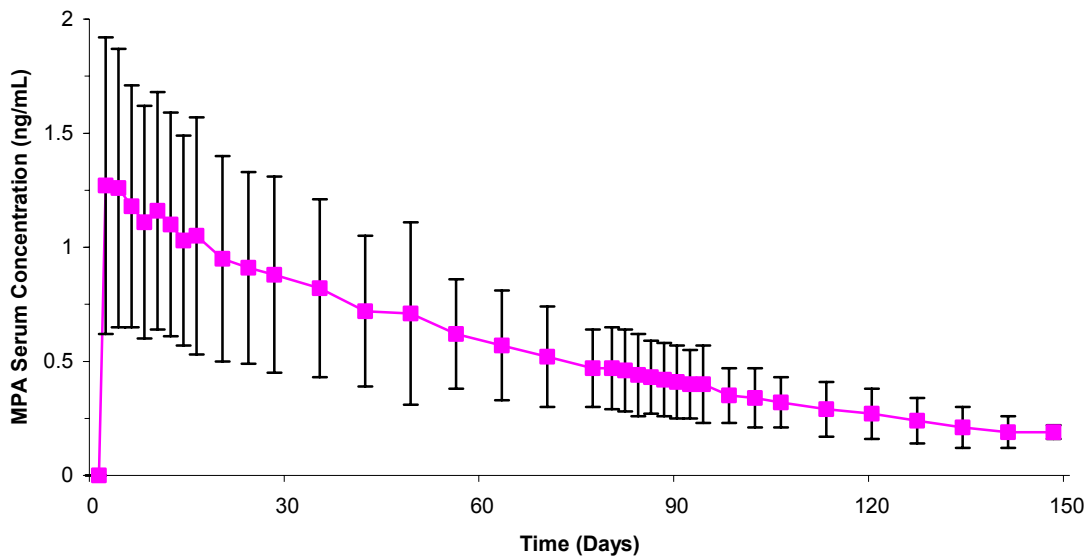
	C_{max} (ng/mL)	T_{max} (day)	C_{91} (ng/mL)	AUC_{0-91} (ng·day/mL)	$AUC_{0-\infty}$ (ng·day/mL)	$t_{1/2}$ (day)
Mean	1.56	8.8	0.402	66.98	92.84	43
Min	0.53	2.0	0.133	20.63	31.36	16
Max	3.08	80.0	0.733	139.79	162.29	114

C_{max} = peak serum concentration; T_{max} = time when C_{max} is observed; C_{91} = serum concentration at 91 days; AUC_{0-91} and $AUC_{0-\infty}$ = area under the concentration-time curve over 91 days or infinity, respectively; $t_{1/2}$ = terminal half-life

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Absorption: Following a single SC injection of depo-subQ provera 104, serum MPA concentrations reach ≥ 0.2 ng/mL within 24 hours. The mean T_{max} is attained approximately 1 week after injection.

Figure 1. Mean (SD) Serum Concentration-Time Profile of MPA after a Single Injection of depo-subQ provera 104 to Healthy Women



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In a study to assess accumulation and the achievement of steady state following multiple SC administrations, trough concentrations of MPA were determined after 6, 12, and 24 months, and in a subset of 8 subjects, bi-weekly concentrations were determined within one dosing interval in the second year of administration. The mean (SD) MPA trough

79 concentrations were 0.67 (0.36) ng/mL (n=157), 0.79 (0.36) ng/mL (n=144), and 0.87
80 (0.33) ng/mL (n=106) at 6, 12 and 24 months, respectively.

81
82 **Effect of Injection Site:** depo-subQ provera 104 was administered into the anterior thigh
83 or the abdomen to evaluate effects on the MPA concentration-time profile. MPA trough
84 concentrations (C_{\min} ; Day 91) were similar for the two injection locations.

85
86 **Distribution:** Plasma protein binding of MPA averages 86%. MPA binding occurs
87 primarily to serum albumin. No binding of MPA occurs with sex-hormone-binding
88 globulin (SHBG).

89
90 **Metabolism:** MPA is extensively metabolized in the liver by P450 enzymes. Its
91 metabolism primarily involves ring A and/or side-chain reduction, loss of the acetyl
92 group, hydroxylation in the 2-, 6-, and 21-positions or a combination of these positions,
93 resulting in more than 10 metabolites.

94
95 **Excretion:** Residual MPA concentrations at the end of the first dosing interval (12 to 14
96 weeks) of depo-subQ provera 104 are generally below 0.5 ng/mL, consistent with its
97 apparent terminal half-life of ~40 days after SC administration. Most MPA metabolites
98 are excreted in the urine as glucuronide conjugates with only small amounts excreted as
99 sulfates.

100
101 **Linearity/Non-Linearity:** Following a single SC administration of doses ranging from
102 50 to 150 mg, the AUC and C_{\min} (Day 91) increased with higher doses of depo-subQ
103 provera 104, but there was considerable overlap across dose levels. Serum MPA
104 concentrations at Day 91 increased in a dose proportional manner but C_{\max} did not appear
105 to increase proportionally with increasing dose. The AUC data were suggestive of dose
106 linearity.

107 108 **Special Populations**

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110 **Race:** There were no significant differences in the pharmacokinetics and/or
111 pharmacodynamics of MPA after SC administration of depo-subQ provera 104 in
112 African-American and Caucasian women. The pharmacokinetics/pharmacodynamics of
113 depo-subQ provera 104 were evaluated in Asian women in a separate study and also
114 found to be similar to African-American and Caucasian women.

115
116 **Effect of Body Weight:** Although total MPA exposure was lower in obese women, no
117 dosage adjustment of depo-subQ provera 104 is necessary based on body weight. The
118 effect of body weight on the pharmacokinetics of MPA following a single dose was
119 assessed in a subset of women (n = 42, body mass index [BMI] ranged from 18.2 to 46.7
120 kg/m²). The AUC₀₋₉₁ values for MPA were 71.6, 67.9, and 46.3 ng·day/mL in women
121 with BMI categories of ≤ 28 kg/m², >28-38 kg/m², and >38 kg/m², respectively. The
122 mean MPA C_{\max} was 1.74 ng/mL in women with BMI ≤ 28 kg/m², 1.53 ng/mL in women
123 with BMI >28-38 kg/m², and 1.02 ng/mL in women with BMI > 38 kg/m², respectively.

124 The MPA trough (C_{\min}) concentrations had a tendency to be lower in women with BMI
125 $>38 \text{ kg/m}^2$.

126

127 ***Hepatic Insufficiency:*** No clinical studies have evaluated the effect of hepatic disease
128 on the disposition of depo-subQ provera 104. However, steroid hormones may be poorly
129 metabolized in patients with severe liver dysfunction (see CONTRAINDICATIONS).

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131 ***Renal Insufficiency:*** No clinical studies have evaluated the effect of renal disease on the
132 pharmacokinetics of depo-subQ provera 104.

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134 **Drug-Drug Interactions**

135 See PRECAUTIONS, section 9

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138 **INDICATIONS AND USAGE**

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140 depo-subQ provera 104 is indicated for the prevention of pregnancy in women of child
141 bearing potential.

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143 depo-subQ provera 104 also is indicated for management of endometriosis-associated
144 pain.

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146 In considering use for either indication, the loss of bone mineral density (BMD) in
147 women of all ages and the impact on peak bone mass in adolescents should be
148 considered, along with the decrease in BMD that occurs during pregnancy and/or
149 lactation, in the risk/benefit assessment for women who use depo-subQ provera 104 long-
150 term (see WARNINGS, section 1).

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152 ***Contraception Studies***

153 In three clinical studies, no pregnancies were detected among 2,042 women using depo-
154 subQ provera 104 for up to 1 year. The Pearl Index pregnancy rate in women who were
155 less than 36 years old at baseline, based on cycles in which they used no other
156 contraceptive methods, was 0 pregnancies per 100 women-years of use (upper 95%
157 confidence interval = 0.25).

158

159 Pregnancy rates for various contraceptive methods are typically reported for only the first
160 year of use and are shown in Table 2.

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Table 2. Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Typical Use and the First Year of Perfect Use of Contraception and the Percentage Continuing Use at the End of the First Year: United States

Method	% of Women Experiencing an Unintended Pregnancy within the First Year of Use		% of Women Continuing Use at 1 Year ³
	Typical Use ¹	Perfect Use ²	
Chance ⁴	85	85	
Spermicides ⁵	26	6	40
Periodic Abstinence	25		63
Calendar		9	
Ovulation Method		3	
Symptothermal ⁶		2	
Post-ovulation		1	
Cap ⁷			
Parous Women	40	26	42
Nulliparous Women	20	9	56
Sponge			
Parous Women	40	20	42
Nulliparous Women	20	9	56
Diaphragm ⁷	20	6	56
Withdrawal	19	4	
Condom ⁸			
Female (Reality)	21	5	56
Male	14	3	61
Pill	5		71
Progestin only		0.5	
Combined		0.1	
IUD			
Progesterone T	2.0	1.5	81
Copper T 380A	0.8	0.6	78
LNg 20	0.1	0.1	81
Depo-Provera IM 150 mg	0.3	0.3	70
Norplant and Norplant-2	0.05	0.05	88
Female Sterilization	0.5	0.5	100
Male Sterilization	0.15	0.10	100

Emergency Contraceptive Pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.⁹

Lactational Amenorrhea Method: LAM is a highly effective, temporary method of contraception.¹⁰

Source: Hatcher et al., 1998.¹

162 ¹Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience
 163 an accidental pregnancy during the first year if they do not stop use for any other reason.
 164 ²Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both
 165 consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not
 166 stop use for any other reason.
 167 ³Among couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year.
 168 ⁴The percentages becoming pregnant in columns (2) and (3) are based on data from populations where contraception is
 169 not used and from women who cease using contraception in order to become pregnant. Among such populations, about
 170 89% become pregnant within 1 year. This estimate was lowered slightly (to 85%) to represent the percentages who

171 would become pregnant within 1 year among women now relying on reversible methods of contraception if they
172 abandoned contraception altogether.
173 ⁵Foams, creams, gels, vaginal suppositories, and vaginal film.
174 ⁶Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the
175 post-ovulatory phases.
176 ⁷With spermicidal cream or jelly.
177 ⁸Without spermicides.
178 ⁹The treatment schedule is one dose within 72 hours after unprotected intercourse, and a second dose 12 hours after the
179 first dose. The Food and Drug Administration has declared the following brands of oral contraceptives to be safe and
180 effective for emergency contraception: Ovral (1 dose is 2 white pills), Alesse (1 dose is 5 pink pills), Nordette or
181 Levlen (1 dose is 4 light-orange pills), Lo/Ovral (1 dose is 4 white pills), Triphasil or Tri-Levlen (1 dose is 4 yellow
182 pills).
183 ¹⁰However, to maintain effective protection against pregnancy, another method of contraception must be used as soon
184 as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby
185 reaches 6 months of age.

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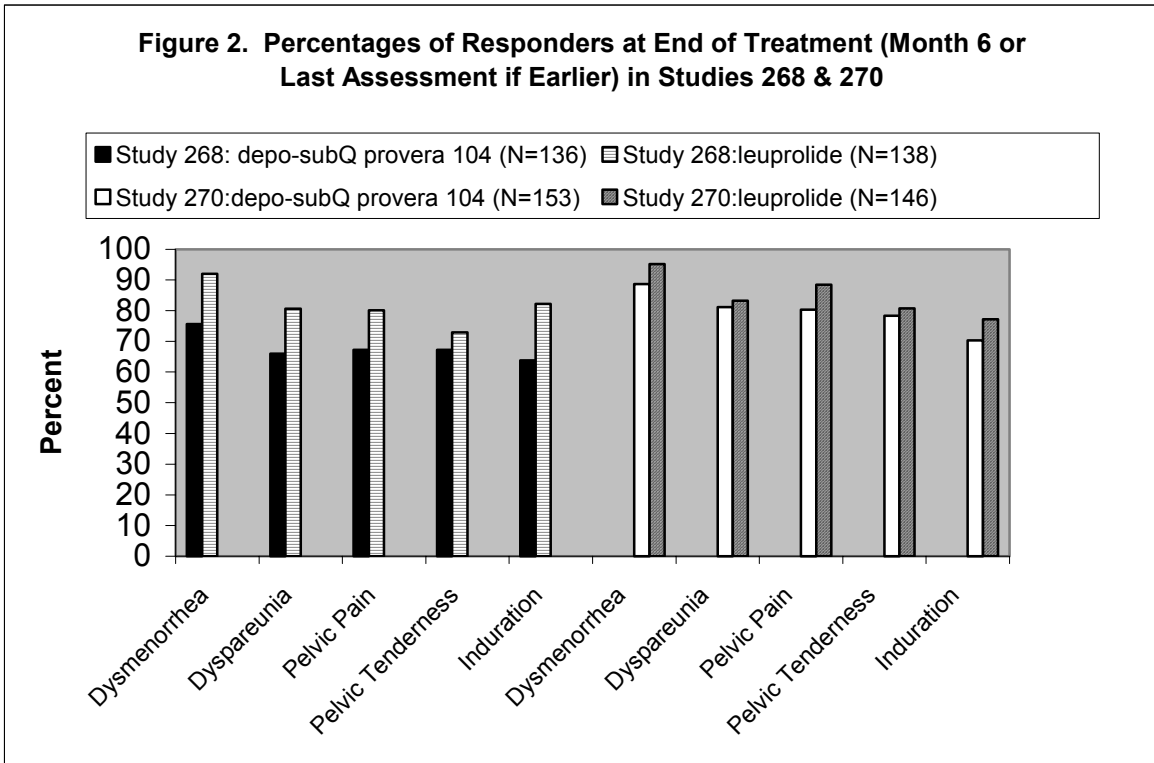
187 **Endometriosis Studies**

188 The efficacy of depo-subQ provera 104 in the reduction of endometriosis-associated pain
189 in women with the signs and symptoms of endometriosis was demonstrated in two active
190 comparator-controlled studies. Each study assessed reduction in endometriosis-associated
191 pain over 6 months of treatment and recurrence of symptoms for 12-months post
192 treatment. Subjects treated with depo-subQ provera 104 for 6 months received a 104 mg
193 dose every 3 months (2 injections), while women treated with leuprolide microspheres
194 for 6 months received a dose of 11.25 mg every 3 months (2 injections) or 3.75 mg every
195 month (6 injections). Study 268 was conducted in the U.S. and Canada and enrolled 274
196 subjects (136 on depo-subQ provera 104 and 138 on leuprolide). Study 270 was
197 conducted in South America, Europe and Asia, and enrolled 299 subjects (153 on depo-
198 subQ provera 104 and 146 on leuprolide).

199

200 Reduction in pain was evaluated using a modified Biberoglu and Behrman scale that
201 consisted of three patient-reported symptoms (dysmenorrhea, dyspareunia, and pelvic
202 pain not related to menses) and two signs assessed during pelvic examination (pelvic
203 tenderness and induration). For each category, a favorable response was defined as
204 improvement of at least 1 unit (severity was assessed on a scale of 0 to 3) relative to
205 baseline score (Figure 2).

206



207 Favorable Response = reduction in severity of symptom or sign of ≥ 1 point on a scale of 0 to 3, as
 208 compared to baseline
 209

210 Additionally, scores from each of the five categories were combined, with the total
 211 (composite score) considered a global measurement of overall disease improvement. For
 212 subjects with baseline scores for each of the 5 categories, a mean decrease of 4 points
 213 relative to baseline was considered a clinically meaningful improvement. Across both
 214 studies, for both treatment groups, the mean changes in the composite score met the
 215 protocol-defined criterion for improvement.
 216

217 In the clinical trials, treatment with depo-subQ provera 104 was limited to six months.
 218 Data on the persistence of benefit with longer treatment are not available.
 219

220 Subjects recorded daily the occurrence and severity of hot flushes. Of the depo-subQ
 221 provera 104 users, 28.6% reported experiencing moderate or severe hot flushes at
 222 baseline, 36.2% at month 3, and 26.7% at month 6. Of the leuprolide users, 32.8%
 223 reported experiencing moderate or severe hot flushes at baseline, 74.2% at month 3, and
 224 68.5% at month 6.
 225

226 **CONTRAINDICATIONS**

- 227
- 228 1. Known or suspected pregnancy.
 - 229 2. Undiagnosed vaginal bleeding.
 - 230 3. Known or suspected malignancy of breast.

- 231 4. Active thrombophlebitis, or current or past history of thromboembolic disorders, or
232 cerebral vascular disease.
233 5. Significant liver disease.
234 6. Known hypersensitivity to medroxyprogesterone acetate or any of its other
235 ingredients.

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238 WARNINGS

239

240 *1. Loss of Bone Mineral Density*

241 Use of depo-subQ provera 104 reduces serum estrogen levels and is associated with
242 significant loss of bone mineral density (BMD) as bone metabolism accommodates
243 to a lower estrogen level. This loss of BMD is of particular concern during
244 adolescence and early adulthood, a critical period of bone accretion. It is unknown
245 if use of depo-subQ provera 104 by younger women will reduce peak bone mass and
246 increase the risk for osteoporotic fracture in later life. In both adults and
247 adolescents, the decrease in BMD appears to be at least partially reversible after
248 depo-subQ provera 104 is discontinued and ovarian estrogen production increases.
249 A study to assess the reversibility of loss of BMD in adolescents is ongoing.

250

251 depo-subQ provera 104 should be used long-term (e.g., longer than 2 years) only if
252 other methods of birth control are inadequate. BMD should be evaluated when a
253 woman needs to use depo-subQ provera 104 long-term. In adolescents,
254 interpretation of BMD results should take into account patient age and skeletal
255 maturity.

256

257 Other treatments should be considered in the risk/benefit analysis for the use of
258 depo-subQ provera 104 in women with osteoporosis risk factors. depo-subQ
259 provera 104 can pose an additional risk in patients with risk factors for osteoporosis
260 (e.g., metabolic bone disease, chronic alcohol and/or tobacco use, anorexia nervosa,
261 strong family history of osteoporosis or chronic use of drugs that can reduce bone
262 mass such as anticonvulsants or corticosteroids).

263

264 Although there are no studies addressing whether calcium and Vitamin D lessen
265 BMD loss in women using depo-subQ provera 104, all patients should have
266 adequate calcium and Vitamin D intake.

267

268 **BMD Changes in Adult Women after Long-Term Treatment for Contraception**

269 A study comparing changes in BMD in women using depo-subQ provera 104 with
270 women using Depo-Provera Contraceptive Injection (Depo-Provera CI, 150 mg) showed
271 no significant differences in BMD loss between the two groups after two years of
272 treatment. Mean percent changes in BMD in the depo-subQ provera 104 group are listed
273 in Table 3.

274

275 **Table 3. Mean Percent Change from Baseline in BMD in Women Using depo-subQ**
 276 **provera 104**
 277

Time on Treatment	Lumbar Spine		Total Hip		Femoral Neck	
	N	Mean % Change (95% CI)	N	Mean % Change (95% CI)	N	Mean % Change (95% CI)
1 year	166	-2.7 (-3.1 to -2.3)	166	-1.7 (-2.1 to -1.3)	166	-1.9 (-2.5 to -1.4)
2 year	106	-4.1 (-4.6 to -3.5)	106	-3.5 (-4.2 to -2.7)	106	-3.5 (-4.3 to -2.6)

278
 279 In another controlled clinical study, adult women using Depo-Provera CI (150 mg) for up
 280 to 5 years showed spine and hip BMD mean decreases of 5-6%, compared to no
 281 significant change in BMD in the control group. The decline in BMD was more
 282 pronounced during the first two years of use, with smaller declines in subsequent years.
 283 Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38%
 284 after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the
 285 total hip and femoral neck were similar.

286
 287 After stopping use of Depo-Provera CI (150 mg) there was partial recovery of BMD
 288 toward baseline values during the 2-year post-therapy period. Longer duration of
 289 treatment was associated with less complete recovery during this 2-year period following
 290 the last injection. Table 4 shows the extent of recovery of BMD for women who
 291 completed 5 years of treatment.

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293 **Table 4. Mean Percent Change from Baseline in BMD in Women Using Depo-**
 294 **Provera CI (150 mg) or in Control Subjects**
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Time in Study	Lumbar Spine		Total Hip		Femoral Neck	
	Depo-Provera CI (150 mg)*	Control**	Depo-Provera CI (150 mg)*	Control**	Depo-Provera CI (150 mg)*	Control**
5 years	n=33 -5.38%	n=105 0.43%	n=21 -5.16%	n=65 0.19%	n=34 -6.12%	n=106 -0.27%
7 years	n=12 -3.13%	n=60 0.53%	n=7 -1.34%	n=39 0.94%	n=13 -5.38	n=63 -0.11%

296 *The treatment group consisted of women who received Depo-Provera CI (150 mg) for 5 years and were
 297 then followed for 2 years post-use.

298 **The control group consisted of women who did not use hormonal contraception and were followed for
 299 7 years.

300
 301 **BMD Changes in Adolescent Females (12-18 years) after Long-Term Treatment for**
 302 **Contraception**

303 Preliminary results from an ongoing, open-label, self-selected, non-randomized clinical
 304 study of adolescent females (12-18 years) also showed that Depo-Provera CI (150 mg)
 305 use was associated with a significant decline in BMD from baseline (Table 5). In
 306 general, adolescents increase bone density during the period of growth following
 307 menarche, as seen in the untreated cohort. However, the two cohorts were not matched
 308 at baseline for age, gynecologic age, race, BMD and other factors that influence the rate
 309 of acquisition of bone mineral density, with the result that they differed with respect to
 310 these demographic factors.

311
 312 Preliminary data from the small number of adolescents participating in the 2-year post-
 313 use observation period demonstrated partial recovery of BMD.

314
 315 **Table 5. Mean Percent Change from Baseline in BMD in Adolescents**
 316 **Using Depo-Provera CI (150 mg) and in Unmatched, Untreated Control Cohort**
 317 **Studies**

Duration of Treatment Or Observation Period	Lumbar Spine				Total Hip				Femoral Neck			
	Depo-Provera CI (150 mg)		Control (Unmatched/Untreated)		Depo-Provera CI (150 mg)		Control (Unmatched/Untreated)		Depo-Provera CI (150 mg)		Control (Unmatched/Untreated)	
	N	Mean % change	N	Mean % change	N	Mean % change	N	Mean % change	N	Mean % change	N	Mean % change
Week 60 (1.2 yrs)	104	-2.42	171	3.47	103	-2.82	171	1.32	103	-3.05	171	1.87
Week 144 (2.8 yrs)	46	-2.78	111	5.41	45	-6.16	111	1.74	45	-6.01	111	2.54
Week 240 (4.6 yrs)	9	-4.17	70	5.12	9	-6.92	69	1.12	9	-6.06	69	1.45

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BMD Changes in Adult Women after Six Months of Treatment for Endometriosis

In two clinical studies of 573 adult women with endometriosis, the BMD effects of 6 months of depo-subQ provera 104 treatment were compared to 6 months of leuprolide treatment. Subjects were then observed, off therapy, for an additional 12 months (Table 6).

Table 6. Mean Percent Change from Baseline in BMD after 6 Months on Therapy with depo-subQ provera 104 or Leuprolide and 6 and 12 Months after Stopping Therapy (Studies 268 and 270 Combined)

Time of Measurement	Lumbar Spine				Total Hip			
	depo-subQ provera 104		Leuprolide		depo-subQ provera 104		Leuprolide	
	N	Mean % change	N	Mean % change	N	Mean % change	N	Mean % change
Month 6 of treatment (EOT)	208	-1.20	229	-4.10	207	-0.03	227	-1.83
6 months off treatment	168	-1.06	180	-2.75	169	-0.05	181	-1.59
12 months off treatment	124	-0.54	133	-1.48	125	0.39	134	-1.15

329 EOT = End of Treatment

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2. Bleeding Irregularities

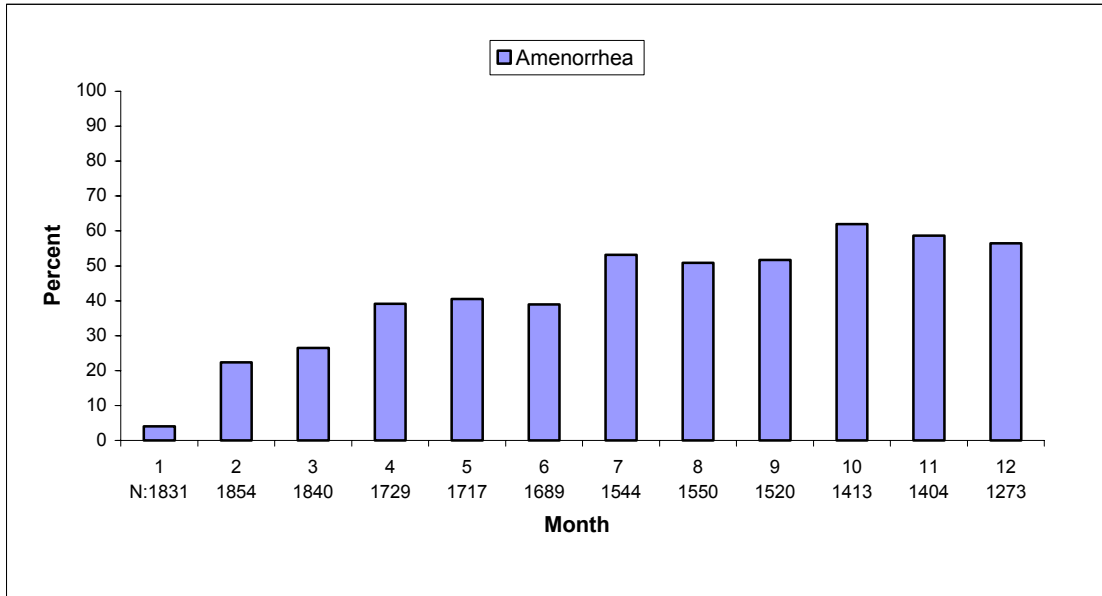
Most women using depo-subQ provera 104 experienced changes in menstrual bleeding patterns, such as amenorrhea, irregular spotting or bleeding, prolonged spotting or bleeding, and heavy bleeding. As women continued using depo-subQ provera 104, fewer experienced irregular bleeding and more experienced amenorrhea. If abnormal bleeding is persistent or severe, appropriate investigation and treatment should be instituted.

NDA 21-584, depo-subQ provera 104
(medroxyprogesterone acetate injectable suspension) 104 mg/0.65 mL
Proposed US Physician Package Insert, version updated as amendment no. 19 (superceding amendment no. 18), as per FDA labeling comments on March 22, 2005.

338 In three contraception trials, 39.0 % of women experienced amenorrhea during month
339 six, and 56.5% experienced amenorrhea during month 12. The changes in menstrual
340 bleeding patterns from the three contraception trials are presented in Figures 3 and 4.
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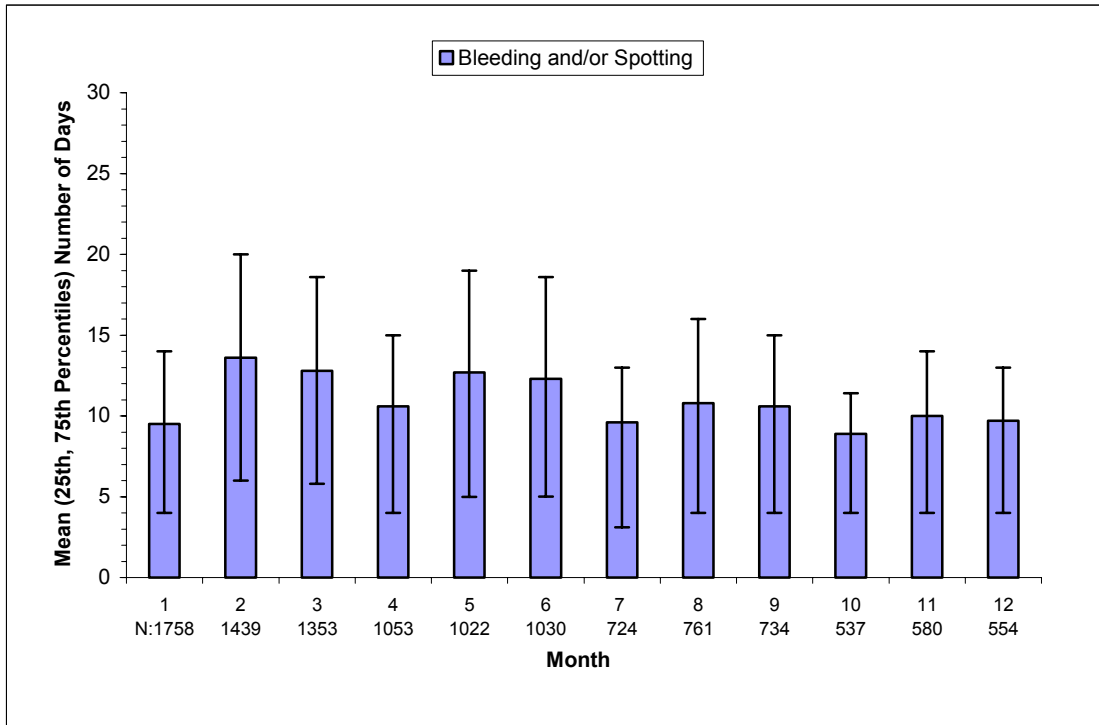
Figure 3. Percentages of depo-subQ provera 104 Treated Women with Amenorrhea per 30-Day Month in Contraception Studies (ITT Population, N=2053)



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N = Number of subjects in analysis for indicated month

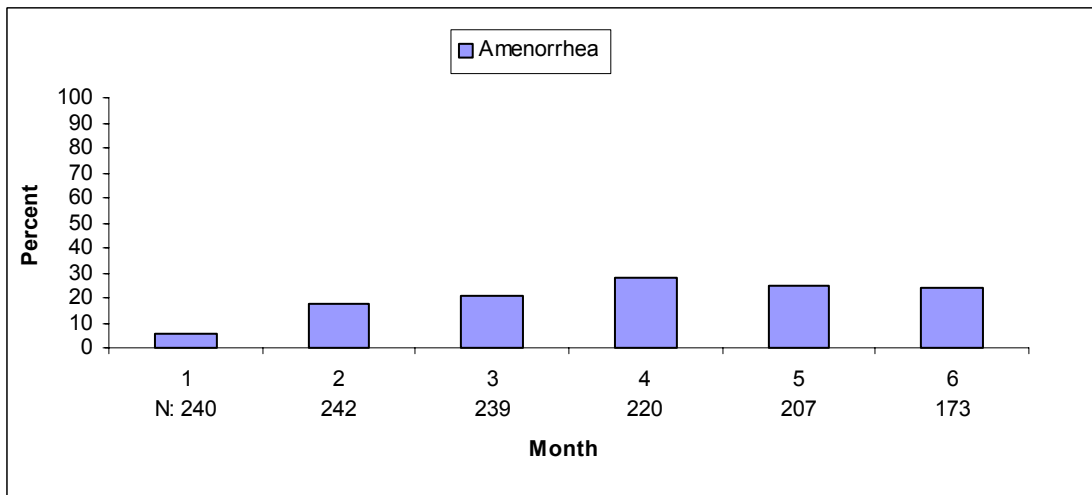
Figure 4. Mean (25th, 75th Percentiles) Number of Bleeding and/or Spotting Days in the Subgroup of Women with Bleeding and/or Spotting by Month for Women Treated with depo-subQ provera 104 in Contraception Studies



N = Number of subjects with bleeding and/or spotting during indicated month

The changes in menstrual patterns in the two endometriosis trials are presented in Figures 5 and 6.

Figure 5. Percentages of depo-subQ provera 104 Treated Women with Amenorrhea per 30-Day Month in Endometriosis Studies (Combined ITT Population, N=289)



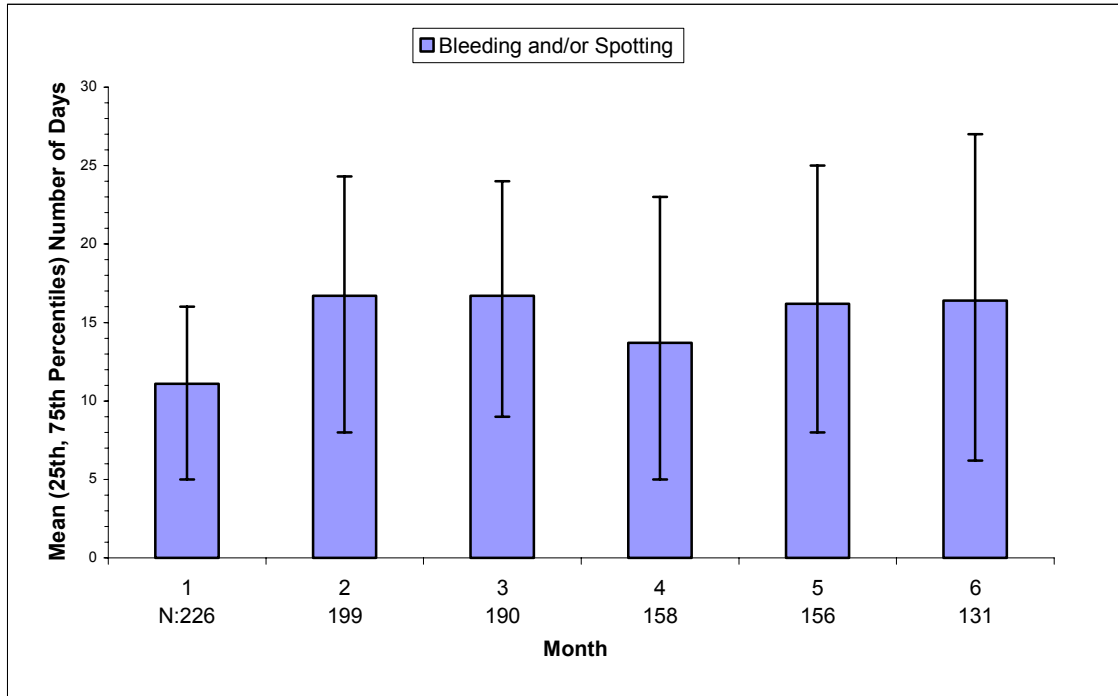
N = Number of subjects in analysis for indicated month

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Figure 6. Mean (25th, 75th Percentiles) Number of Bleeding and/or Spotting Days in the Subgroup of Women with Bleeding and/or Spotting by Month for Women Treated with depo-subQ provera 104 in Endometriosis Studies Combined



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N = Number of subjects with bleeding and/or spotting during indicated month

3. Cancer Risks

371 Long-term, case-controlled surveillance of users of depot medroxyprogesterone acetate
372 IM 150 mg (Depo-Provera CI, 150 mg) found slight or no increased overall risk of breast
373 cancer and no overall increased risk of ovarian, liver, or cervical cancer, and a prolonged,
374 protective effect of reducing the risk of endometrial cancer.

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376 A pooled analysisⁱⁱ from two case-control studies^{iii iv} reported the relative risk (RR) of
377 breast cancer for women who had ever used Depo-Provera CI (150 mg) as 1.1 (95%
378 confidence interval [CI] 0.97 to 1.4). Overall, there was no increase in risk with
379 increasing duration of use of Depo-Provera CI (150 mg). The RR of breast cancer for
380 women of all ages who had initiated use of Depo-Provera CI (150 mg) within the
381 previous 5 years was estimated to be 2.0 (95% CI 1.5 to 2.8). A component of the pooled
382 analysisⁱⁱⁱ described above, showed an increased RR of 2.19 (95% CI 1.23 to 3.89) of
383 breast cancer associated with use of Depo-Provera CI (150 mg) in women whose first
384 exposure to drug was within the previous 4 years and who were under 35 years of age.
385 However, the overall RR for ever-users of Depo-Provera CI (150 mg) was only 1.21
386 (95% CI 0.96 to 1.52).

387

388 [NOTE: The value of 2.19 means that women whose first exposure to drug was within
389 the previous 4 years and who were under 35 years of age had a 2.19-fold (95% CI 1.23 to
390 3.89-fold) increased risk of breast cancer relative to nonusers. The National Cancer
391 Institute^v reports an average annual incidence rate for breast cancer for US women, all
392 races, age 30 to 34 years of 26.7 per 100,000. A RR of 2.19, thus, increases the possible
393 risk from 26.7 to 58.5 cases per 100,000 women. The attributable risk, thus, is 31.8 per
394 100,000 women per year.]

395

396 The relative rate of invasive squamous-cell cervical cancer in women who ever used
397 Depo-Provera CI (150 mg) was estimated to be 1.11 (95% CI 0.96 to 1.29). No trends in
398 risk with duration of use or times since initial or most recent exposure were observed.

399

400 **4. Thromboembolic Disorders**

401 Although MPA has not been causally associated with the induction of thrombotic or
402 thromboembolic disorders, there have been rare reports of serious thrombotic events in
403 women using Depo-Provera CI (150 mg). Any patient who develops thrombosis while
404 undergoing therapy with depo-subQ provera 104 should discontinue treatment unless she
405 has no other acceptable options for birth control (see CONTRAINDICATIONS).

406

407 **5. Ocular Disorders**

408 Medication should not be re-administered pending examination if there is a sudden partial
409 or complete loss of vision or if there is a sudden onset of proptosis, diplopia or migraine.
410 If examination reveals papilledema or retinal vascular lesions, medication should not be
411 re-administered.

412

413 **6. Ectopic Pregnancy**

414 Healthcare providers should be alert to the possibility of an ectopic pregnancy among
415 women using depo-subQ provera 104 who become pregnant or complain of severe
416 abdominal pain.

417

418 **7. Anaphylaxis and Anaphylactoid Reaction**

419 Serious anaphylactic reactions have been infrequently reported in women using Depo-
420 Provera CI (150 mg). If an anaphylactic reaction occurs, appropriate emergency medical
421 treatment should be instituted.

422

423

424 **PRECAUTIONS**

425

426 **1. Physical Examination**

427 It is good medical practice for all women to have annual history and physical
428 examinations, including women using depo-subQ provera 104. The physical
429 examination, however, may be deferred until after initiation of depo-subQ provera 104 if
430 requested by the woman and judged appropriate by the clinician. The physical
431 examination should include special reference to blood pressure, breasts, abdomen and
432 pelvic organs, including cervical cytology and relevant laboratory tests. In case of

433 undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures
434 should be conducted to rule out malignancy. Women with a strong family history of
435 breast cancer or who have breast nodules should be monitored with particular care.
436

437 **2. Fluid Retention**

438 Because progestational drugs may cause some degree of fluid retention, conditions that
439 might be influenced by this condition, such as epilepsy, migraine, asthma, and cardiac or
440 renal dysfunction, require careful observation.
441

442 **3. Weight Gain**

443 Weight gain is a common occurrence in women using depo-subQ provera 104. In three
444 large clinical trials using depo-subQ provera 104, the mean weight gain was 3.5 lb in the
445 first year of use. In a small, two-year study comparing depo-subQ provera 104 to Depo-
446 Provera CI (150 mg), the mean weight gain observed for women using depo-subQ
447 provera 104 (7.5 lb) was similar to the mean weight gain for women using Depo-Provera
448 CI, 150 mg (7.6 lb).
449

450 Although there are no data related to weight gain beyond 2 years for depo-subQ provera
451 104, the data on Depo-Provera CI (150 mg) may be relevant. In a clinical study, after
452 five years, 41 women using Depo-Provera CI (150 mg) had a mean weight gain of 11.2
453 lb, while 114 women using non-hormonal contraception had a mean weight gain of 6.4
454 lb.
455

456 **4. Return to Ovulation and Fertility**

457 Return to ovulation is likely to be delayed after stopping therapy. Among 15 women who
458 received multiple doses of depo-subQ provera 104:

- 459 • Median time to ovulation was 10 months after the last injection
 - 460 • Earliest return to ovulation was 6 months after the last injection
 - 461 • 12 women (80%) ovulated within 1 year of the last injection
- 462

463 However, ovulation has occurred as early as 14 weeks after a single dose of depo-subQ
464 provera 104, and therefore it is important to follow the recommended dosing schedule.
465

466 Return to fertility also is likely to be delayed after stopping therapy. Among 28 women
467 using depo-subQ provera 104 for contraception who stopped treatment to become
468 pregnant, 1 became pregnant within 1 year of her last injection. A second woman
469 became pregnant 443 days after her last injection. Seven women were lost to follow-up.
470

471 **5. Depression**

472 Patients with a history of treatment for clinical depression should be carefully monitored
473 while receiving depo-subQ provera 104.
474

475 **6. Injection Site Reactions**

476 In 5 clinical studies of depo-subQ provera 104 involving 2,325 women (282 treated for
477 up to 6 months, 1,780 treated for up to 1 year and 263 women treated for up to 2 years),
478 5% of women reported injection site reactions, and 1% had persistent skin changes,
479 typically described as small areas of induration or atrophy.

480

481 **7. Carbohydrate/Metabolism**

482 Some patients receiving progestins may exhibit a decrease in glucose tolerance. Diabetic
483 patients should be carefully observed while receiving such therapy.

484

485 **8. Liver Function**

486 If jaundice or any other liver abnormality develops in any woman receiving depo-subQ
487 provera 104, treatment should be stopped while the cause is determined. Treatment may
488 be resumed when liver function is acceptable and when the healthcare provider has
489 determined that depo-subQ provera 104 did not cause the abnormality.

490

491 **9. Drug Interactions**

492 No drug-drug interaction studies have been conducted with depo-subQ provera 104.
493 Aminoglutethimide administered concomitantly with depo-subQ provera 104 may
494 significantly decrease the serum concentrations of MPA.

495

496 **10. Laboratory Tests**

497 The pathologist should be advised of progestin therapy when relevant specimens are
498 submitted. The physician should be informed that certain endocrine and liver function
499 tests, and blood components may be affected by progestin therapy:

- 500 (a) Plasma and urinary steroid levels are decreased (e.g., progesterone, estradiol,
501 pregnanediol, testosterone, cortisol).
- 502 (b) Plasma and urinary gonadotropin levels are decreased (e.g., LH, FSH).
- 503 (c) SHBG concentrations are decreased.
- 504 (d) T₃-uptake values may decrease.
- 505 (e) There may be small changes in coagulation factors.
- 506 (f) Sulfobromophthalein and other liver function test values may be increased slightly.
- 507 (g) There may be small changes in lipid profiles.

508

509 **11. Carcinogenesis, Mutagenesis, Impairment of Fertility**

510 See WARNINGS, section 3 and PRECAUTIONS, section 4

511

512 **12. Pregnancy**

513 Although depo-subQ provera 104 should not be used during pregnancy, there appears to
514 be little or no increased risk of birth defects in women who have inadvertently been
515 exposed to medroxyprogesterone acetate injections in early pregnancy. Neonates
516 exposed to medroxyprogesterone acetate in-utero and followed to adolescence showed no
517 evidence of any adverse effects on their health including their physical, intellectual,
518 sexual or social development.

519

520 **13. Nursing Mothers**

521 Although the drug is detectable in the milk of mothers receiving Depo-Provera CI (150
522 mg), milk composition, quality, and amount are not adversely affected. Neonates and
523 infants exposed to medroxyprogesterone acetate from breast milk have been studied for
524 developmental and behavioral effects through puberty, and no adverse effects have been
525 noted.

526

527 ***14. Pediatric Use***

528 depo-subQ provera 104 is not indicated before menarche. Use of depo-subQ provera 104
529 is associated with significant loss of bone mineral density (BMD). This loss of BMD is
530 of particular concern during adolescence and early adulthood, a critical period of bone
531 accretion. **In adolescents, interpretation of BMD results should take into account**
532 **patient age and skeletal maturity.** It is unknown if use of depo-subQ provera 104 by
533 younger women will reduce peak bone mass and increase the risk for osteoporotic
534 fractures in later life. Other than concerns about loss of BMD, the safety and
535 effectiveness are expected to be the same for postmenarchal adolescents and adult
536 women.

537

538 ***15. Geriatric Use***

539 depo-subQ provera 104 is intended for use in women with childbearing potential. Studies
540 with depo-subQ provera 104 in geriatric women have not been conducted.

541

542

543 **INFORMATION FOR THE PATIENT**

544 See PATIENT LABELING.

545

546

547 **ADVERSE REACTIONS**

548 In five clinical studies of depo-subQ provera 104 involving 2,325 women (282 treated for
549 up to 6 months, 1,780 treated for up to 1 year and 263 treated for up to 2 years), 9% of
550 women discontinued treatment for adverse reactions. Among these 212 women, the most
551 common reasons for discontinuation were:

552

- 553 • Uterine bleeding irregularities (35%, n=75)
- 554 • Increased weight (18%, n=39)
- 555 • Decreased libido (11%, n=23)
- 556 • Acne (10%, n=21)
- 557 • Injection site reactions (6%, n=12)

558

559 Adverse reactions reported by 5% or more of all women in these clinical trials included:

560

- 561 • Headache (9%)
- 562 • Intermenstrual bleeding (7%)
- 563 • Increased weight (6%)
- 564 • Amenorrhea (6%)

- 565 • Injection site reactions (5%)

566

567 Adverse reactions reported by 1% to <5% of all women in these clinical trials included:

568

569 **General disorders:** fatigue, injection site pain

570 **Gastrointestinal disorders:** abdominal distention, abdominal pain, diarrhea, nausea

571 **Infections:** bronchitis, influenza, nasopharyngitis, pharyngitis, sinusitis, upper respiratory
572 tract infection, urinary tract infection, vaginal candidiasis, vaginitis, vaginitis bacterial

573 **Investigations:** abnormal cervix smear

574 **Musculoskeletal, connective tissue, and bone disorders:** arthralgia, back pain, limb
575 pain

576 **Nervous system disorders:** dizziness, insomnia

577 **Psychiatric disorders:** anxiety, depression, irritability, decreased libido

578 **Reproductive system and breast disorders:** breast pain, breast tenderness,
579 menometrorrhagia, menorrhagia, menstruation irregular, uterine hemorrhage, vaginal
580 hemorrhage

581 **Skin disorders:** acne

582 **Vascular disorders:** hot flushes

583

584 **Postmarketing Experience**

585 There have been rare cases of osteoporosis including osteoporotic fractures reported
586 postmarketing in patients taking DEPO-PROVERA Contraceptive Injection. In addition,
587 infrequent voluntary reports of anaphylaxis and anaphylactoid reaction have been
588 received associated with use of Depo-Provera CI (150 mg).

589

590 The following additional reactions have been reported with Depo-Provera Contraceptive
591 Injection and may occur with use of depo-subQ provera 104:

592

593 **General disorders:** asthenia, axillary swelling, chills, chest pain, fever, excessive thirst

594 **Blood and lymphatic system disorders:** anemia, blood dyscrasia

595 **Cardiac disorders:** tachycardia

596 **Gastrointestinal disorders:** gastrointestinal disturbances, rectal bleeding

597 **Hepato-biliary disorders:** jaundice

598 **Immune system disorders:** allergic reaction

599 **Infections:** genitourinary infections

600 **Investigations:** decreased glucose tolerance

601 **Musculoskeletal, connective tissue, and bone disorders:** loss of bone mineral density,
602 scleroderma

603 **Neoplasms:** breast cancer, cervical cancer

604 **Nervous system disorders:** convulsions, facial palsy, fainting, paralysis, paresthesia,
605 somnolence

606 **Psychiatric disorders:** increased libido, nervousness

607 **Reproductive system and breast disorders:** breast lumps, galactorrhea, nipple
608 discharge or bleeding, oligomenorrhea, prevention of lactation, prolonged anovulation,
609 unexpected pregnancy, uterine hyperplasia, vaginal cyst

610 **Respiratory disorders:** asthma, dyspnea, hoarseness
611 **Skin disorders:** angioedema, dry skin, increased body odor, melasma, pruritus, urticaria
612 **Vascular disorders:** deep vein thrombosis, pulmonary embolus, thrombophlebitis

613
614

615 **DOSAGE AND ADMINISTRATION**

616

617 **CONTRACEPTION AND ENDOMETRIOSIS INDICATIONS**

618

619 **Route of Administration**

620 depo-subQ provera 104 must be given by subcutaneous injection into the anterior thigh or
621 abdomen, once every 3 months (12 to 14 weeks). depo-subQ provera 104 is not
622 formulated for intramuscular injection. Dosage does not need to be adjusted for body
623 weight. The pre-filled syringe of depo-subQ provera 104 must be vigorously shaken just
624 before use to create a uniform suspension.

625

626 **First Injection**

627 Ensure that the patient is not pregnant at the time of the first injection. For women who
628 are sexually active and having regular menses, the first injection should be given only
629 during the first 5 days of a normal menstrual period. Women who are breast-feeding may
630 have their first injection during or after their sixth postpartum week.

631

632 **Second and Subsequent Injections**

633 Dosing is every 12 to 14 weeks. If more than 14 weeks elapse between injections,
634 pregnancy should be ruled out before the next injection.

635

636 **IF USING FOR CONTRACEPTION AND SWITCHING FROM ANOTHER METHOD**

637 When switching from other contraceptive methods, depo-subQ provera 104 should be
638 given in a manner that ensures continuous contraceptive coverage. For example, patients
639 switching from combined (estrogen plus progestin) contraceptives should have their first
640 injection of depo-subQ provera 104 within 7 days after the last day of using that method
641 (7 days after taking the last active pill, removing the patch or ring). Similarly,
642 contraceptive coverage will be maintained in switching from Depo-Provera CI (150 mg)
643 to depo-subQ provera 104, provided the next injection is given within the prescribed
644 dosing period for Depo-Provera CI (150 mg).

645

646 **IF USING FOR TREATMENT OF ENDOMETRIOSIS**

647 Treatment for longer than two years is not recommended, due to the impact of long-term
648 depo-subQ provera 104 on bone mineral density. If symptoms return after
649 discontinuation of treatment, bone mineral density should be evaluated prior to
650 retreatment.

651

652

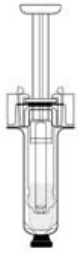
653

653 **Instructions for Administration of depo-subQ provera 104 for Subcutaneous Use**

654

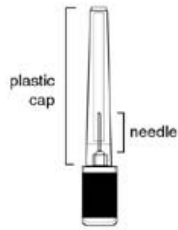
655 **Getting ready**

656 Ensure that the medication is at room temperature. Make sure the following components
657 (Diagrams 1, 2, and 3) are available.



Prefilled syringe
with needle guard

Diagram 1



Needle in
sterile package

Diagram 2



Alcohol pad

Diagram 3

658

659

660

661

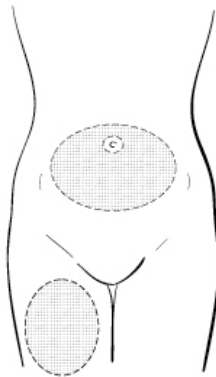
depo-subQ provera 104, as with other parenteral drug products, should be inspected visually for particulate matter and discoloration prior to administration.

662

663

664 **Step 1: Choosing and preparing the injection area.**

665 Choose the injection area. Avoid boney areas and the umbilicus. See shaded areas
666 (Diagram 4).



667

668 Upper thigh & Abdomen

669 **Diagram 4**

670

671 Use an alcohol pad to wipe the skin in the injection area you have chosen. Allow the skin
672 to dry.

673

674

674 **Step 2: Syringe preparation**

675 Gently twist off the protective end cap from the needle to break the seal (Diagram 5). Set
676 aside.

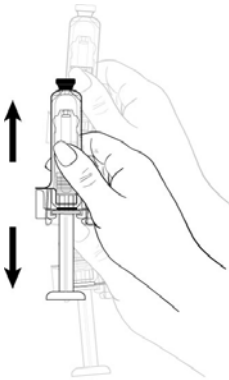


677
678

679 **Diagram 5**

680
681
682
683
684

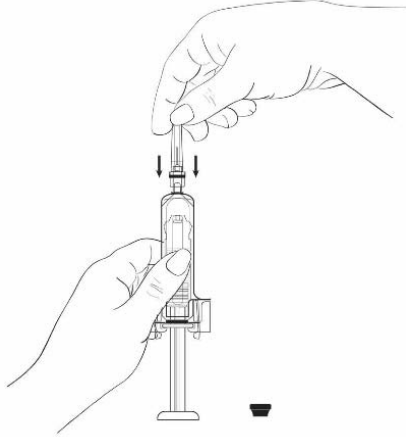
While holding the syringe firmly by the barrel pointing upward, shake it forcefully for at least 1 minute to thoroughly mix the medication (Diagram 6).



685
686
687
688

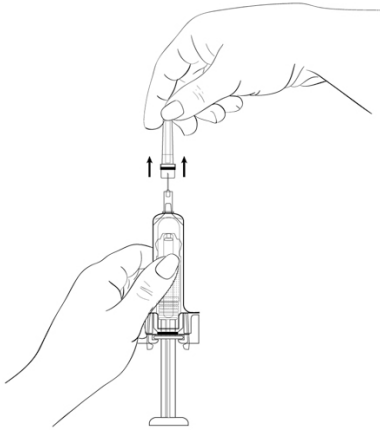
Diagram 6

688 Hold the syringe barrel firmly, remove the protective tip cap from the syringe and attach
689 the needle by pushing it onto the barrel tip (Diagram 7).



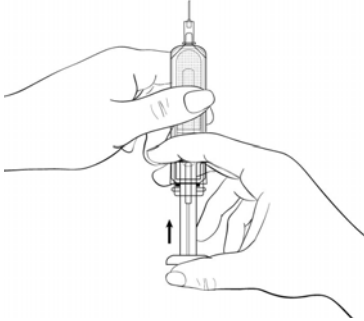
690
691 **Diagram 7**

692
693 While continuing to hold the syringe barrel firmly, remove the clear protective plastic
694 cover from the needle, making sure the needle is still firmly attached to the syringe
695 (Diagram 8).



696
697
698 **Diagram 8**
699

700 While holding the syringe with the needle pointing upward, gently push in the plunger
701 until the medicine is up to the top of the syringe (Diagram 9).



702
703 **Diagram 9**

704
705

706 **Step 3: Injecting the dose.**

707 Gently grasp and squeeze a large area of skin in the chosen injection area between the
708 thumb and fore-finger (Diagram 10) pulling it away from the body.

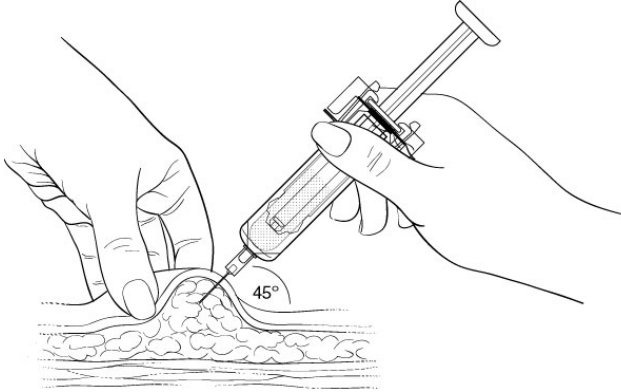
709



710
711 **Diagram 10**

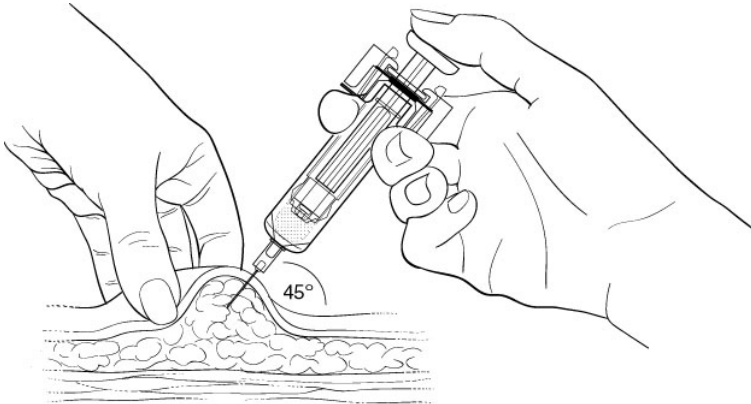
712
713

713 Insert the needle at a 45 degree angle so that most of the needle is in the fatty tissue. The
714 plastic hub of the needle should be nearly or almost touching the skin (Diagram 11).
715



716
717 **Diagram 11**

718
719
720 Inject the medication slowly until the syringe is empty (Diagram 12). This should take
721 about 5-7 seconds.
722



723
724 **Diagram 12**

725
726
727 **The entire dose must be given to activate the needle guard.** When the entire dose is
728 completely injected, gently pull the needle out of the skin. Remove your finger from the
729 plunger, allowing the syringe to move up inside the device until the needle guard
730 completely covers the exposed needle. **You will hear a ‘click’ when the needle guard**
731 **is fully activated.** It is very important that the entire dose of depo-subQ provera 104 is
732 given.

733
734 Use a clean cotton pad to press lightly on the injection area for a few seconds. **Do NOT**
735 **rub the area.**
736

737 Following the administration of each dose, the used syringe should be discarded in a safe
738 and proper manner.

739

740

741 **HOW SUPPLIED**

742 depo-subQ provera 104 for subcutaneous use (medroxyprogesterone acetate injectable
743 suspension 104 mg/0.65 mL) is available as a pre-filled syringe, pre-assembled with an
744 UltraSafe Passive™ Needle Guard* device, and packaged with a 26-gauge x 3/8 inch
745 needle in the following presentation:

746

747 NDC 0009-4709-01 0.65 mL single-use, disposable syringe

748

749 Store at controlled room temperature 20° to 25° C (68° to 77°F) [see USP].

750

751 **Rx only**

752

753 *UltraSafe Passive™ Needle Guard is a trademark of Safety Syringes, Inc.

754

755 Distributed by

756 Pharmacia and Upjohn Co

757 Division of Pfizer Inc, NY, NY 10017

758

759 Date (to be added)

760 Copy code (to be added)

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- v Surveillance, Epidemiology, and End Results: Incidence and Mortality Data, 1973-1977. National Cancer Institute Monograph, 57: June 1981. (NIH publication No. 81-2330).

Patient Information About

depo-subQ provera 104™
medroxyprogesterone acetate injectable suspension
104 mg/0.65 mL

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT depo-subQ provera 104?

Use of depo-subQ provera 104 may cause you to lose calcium stored in your bones. The longer you use depo-subQ provera 104 the more calcium you are likely to lose. The calcium may not return completely once you stop using depo-subQ provera 104.

Loss of calcium may cause weak, porous bones (osteoporosis) that could increase the risk that your bones might break, especially after menopause. It is not known whether your risk of developing osteoporosis may be greater if you are a teenager when you start to use depo-subQ provera 104.

You should use depo-subQ provera 104 long-term (for example, more than 2 years) only if other methods of birth control are not right for you.

depo-subQ provera 104 does not protect you from HIV (AIDS) and other diseases spread through sex (STDs).

WHAT IS depo-subQ provera 104?

depo-subQ provera 104 is a drug for birth control. It also helps relieve pain related to endometriosis (**en-do-ME-tree-OH-sis**). Symptoms of endometriosis arise when cells normally inside your uterus grow outside the uterus. The cells respond to menstrual cycle hormones, and may cause painful periods, pelvic pain, and painful sex.

depo-subQ provera 104 contains a hormone called medroxyprogesterone acetate (MPA). It is given as a shot (injection) every 3 months. Three months is the same as 12 to 14 weeks.

HOW WELL DOES depo-subQ provera 104 WORK FOR PREVENTING PREGNANCY?

When you use depo-subQ provera 104 correctly, the chance of getting pregnant is very low. In studies, no women became pregnant during the year they used depo-subQ provera 104 injection.

The list below estimates the chances of getting pregnant using different types of birth control. The numbers are based on typical use. Typical use includes people who use the method correctly and people who use the method incorrectly. The list shows the number of women out of 100 women who will likely get pregnant if they use the method for one year.

<i>Method</i>	<i>Typical chance of getting pregnant in 1 year (No. of pregnancies in 100 women)</i>
Shot Implant Female sterilization Male sterilization IUD (copper IUD and levonorgestrel IUD)	Less than 1
Pill	5
Condom alone (male)	14
Withdrawal	19
Diaphragm with spermicides	20
Condom alone (female)	21
Periodic abstinence	25
Spermicides alone	26
Vaginal sponge or Cervical cap with spermicide	20 to 40

HOW WILL I GET depo-subQ provera 104?

depo-subQ provera 104 is given as a shot just under the skin on your thigh or belly. You get it once every 3 months.

For Birth Control:

First Shot:

Your healthcare provider will want to be sure that you are not pregnant before you get your first shot. Normally, you get the shot by the 5th day from the START of your menstrual period. You get it whether or not you are still bleeding.

If you are breast-feeding, you may have your first shot as early as 6 weeks after you deliver your baby.

After the first shot:

It is very important to keep getting depo-subQ provera 104 every 3 months. If you wait more than 14 weeks between shots, you could become pregnant. Your healthcare provider must make sure you are not pregnant before you get your next shot.

When you get your shot, make an appointment for your next shot. Mark it on your calendar.

If you need a birth control method for more than two years, your healthcare provider may ask you to have a test of your bones or ask you to switch to another birth control method before continuing depo-subQ provera 104, especially if you have other risks for weak bones.

For Endometriosis:

If you have regular periods, you get depo-subQ provera 104 the same way as described above for birth control. If your periods have stopped or are not regular, your healthcare provider must test to make sure you are not pregnant before you get your first shot.

It is not recommended that you receive depo-subQ provera 104 for treatment of endometriosis for longer than two years. If your painful symptoms return after stopping treatment, your healthcare provider should ask you to have a test of your bones before restarting treatment.

WHAT IF I MISS A SHOT?

- If you miss a shot, or wait longer than 14 weeks between shots, you could get pregnant. The longer you wait, the greater the risk of getting pregnant.
- Talk with your healthcare provider to find out when to restart depo-subQ provera 104. You should be tested to be sure you are not pregnant.
- Use another kind of nonhormonal birth control, such as condoms, until you start depo-subQ provera 104 again.

DO NOT TAKE depo-subQ provera 104 IF YOU...

- Are pregnant or might be pregnant
- Have any unexplained vaginal bleeding
- Ever had breast cancer
- Ever had serious blood clots, such as blood clots in your legs (deep venous thrombophlebitis), lungs (pulmonary embolism), heart (heart attack), or head (stroke)
- Have liver disease
- Are allergic to anything in depo-subQ provera 104. (There is a list of what is in depo-subQ provera 104 at the end of this leaflet.)

BEFORE TAKING depo-subQ provera 104

Your healthcare provider may do a physical examination and check your blood and urine.

Tell your healthcare provider about all your medical conditions.

Most important, tell your healthcare provider if you:

- Are pregnant or might be pregnant. You should not get depo-subQ provera 104 if you are pregnant.
- Plan to become pregnant in the next year. After you stop getting depo-subQ provera 104, it takes time for your body to be able to get pregnant. It can be as early as 1 week after the last shot wears off. Most likely it will take up to 1 year or longer for you to get pregnant.
- Have breast cancer in your family
- Have an abnormal mammogram (breast X-ray), lumps in your breast, or bleeding from your nipples
- Have irregular, light, or heavy menstrual periods
- Have or had any of the following medical problems:
 - Kidney problems
 - High blood pressure
 - Migraine headaches
 - Asthma
 - Seizures
 - Diabetes, or if it runs in your family
 - Depression
 - Heart attack, stroke, or developed blood clots
 - Bone disease
 - Anorexia nervosa (an eating disorder)
 - A strong family history of osteoporosis
 - Drug use that can lower the amount of calcium in bones (drugs for epilepsy or steroids)
 - Drinking a lot of alcohol or smoking a lot

It is important to see your healthcare provider regularly if you have any of these conditions.

Tell your healthcare provider about all the medicines you take. This includes prescription and over-the-counter medicines, vitamins, and herbal products.

WHAT ELSE SHOULD I KNOW ABOUT TAKING depo-subQ provera 104?

Other Birth Control. If you can't take birth control pills or can't use a birth control patch or ring, you may be able to use depo-subQ provera 104. Ask your healthcare provider.

Pregnancy. When you take depo-subQ provera 104 every 3 months, your chance of getting pregnant is very low. You could miss a period or have a light period and not be pregnant. If you miss 1 or 2 periods and think you might be pregnant, see your healthcare provider as soon as possible.

You should not use depo-subQ provera 104 if you are pregnant. However, depo-subQ provera 104 taken by accident during pregnancy does not seem to cause birth defects.

Pregnancy in your tubes (Ectopic Pregnancy). If you have severe pain low in your belly, tell your healthcare provider right away. Infrequently, a baby may start to grow outside the uterus, most often in the tubes.

Nursing a baby. Wait at least 6 weeks after your baby is born to start depo-subQ provera 104. You can use depo-subQ provera 104 if you are nursing.

- It does not lower the amount of milk you can make.
- It can pass through breast milk into your baby, but it is not harmful.

Blood or urine tests. depo-subQ provera 104 may affect blood or urine test results. Tell your healthcare provider you are taking depo-subQ provera 104 if you are going to have blood or urine tests.

Other medicines. depo-subQ provera 104 may not work as well if you are also taking Cytadren (aminoglutethimide), a cancer medicine. You may need to use another kind of birth control.

WHAT ARE THE MOST SERIOUS RISKS OF depo-subQ provera 104?

- **Losing calcium from your bones.** depo-subQ provera 104 use may decrease the amount of calcium in your bones. The longer you use depo-subQ provera 104, the more calcium you are likely to lose. This increases the risk of your bones weakening if you use depo-subQ provera 104 continuously for a long time (for example, if you use depo-subQ provera 104 for more than two years). The loss of calcium may increase your risk of osteoporosis and broken bones, particularly after your menopause.

Calcium is generally added to the bones during teenage years. The decrease of calcium in your bones is of most concern if you are a teenager or have the following risk factors:

- Bone disease
- Anorexia nervosa (an eating disorder)
- A strong family history of osteoporosis
- Drug use that can lower the amount of calcium in bones (drugs for epilepsy or steroids), or
- Drinking a lot of alcohol or smoking a lot

If you need a birth control method for more than two years, your healthcare provider may ask you to have a test of your bones or ask you to switch to another birth control method before continuing depo-subQ provera 104, especially if you have other risks for weak bones. When depo-subQ provera 104 is stopped, the calcium in your bones begins to come back. The lost calcium may not return completely once you stop using depo-subQ provera 104. Your healthcare provider may tell you to take calcium and Vitamin D as this may lessen the loss of calcium from your bones.

- **Abnormal or very heavy bleeding.** If you start having very heavy or very long periods, tell your healthcare provider.
- **Liver problems.** Your healthcare provider may stop depo-subQ provera 104 if you have liver problems. Some signs of liver problems are yellow skin or eyes, feeling like you have the flu, feeling more tired than usual, and itching. Tell your healthcare provider if you have these symptoms.

- **Allergic reaction.** Allergic reactions to depo-subQ provera 104 are not common. If you have hives, problems breathing, or just do not feel right after your shot, call your healthcare provider or go to the Emergency Room right away.
- **Serious blood clots.** Call your healthcare provider immediately if you:
 - Have sharp chest pain, cough blood, or suddenly have trouble breathing
 - Have a sudden severe headache with vomiting, blindness or trouble talking, weakness, or numbness in an arm or leg, or get dizzy or faint
 - Have swelling or severe pain in your leg

WHAT ARE COMMON SIDE EFFECTS OF depo-subQ provera 104?

The most common side effects are:

- Changes in your monthly periods. You may not know when you will bleed, your periods may not be regular, you may have heavy bleeding, or you may have spotting. You may have more days of bleeding during the first 2 or 3 months after you start depo-subQ provera 104. Over time, you may have less and less bleeding. Many women stop having periods by the end of one year. Your periods will come back eventually after you stop using depo-subQ provera 104.
- Weight gain. In studies, women gained an average of 3 to 4 pounds during the first year they used depo-subQ provera 104. After 2 years of using depo-subQ provera 104, women gained an average of 7 to 8 pounds. Some women gained more, some gained less, some lost, and some stayed the same. Weight changes beyond 2 years of use with depo-subQ provera 104 have not been studied. Women who used a similar birth control product for 5 years gained on average 5 pounds more than women who did not use a hormone contraceptive product.
- Skin reaction where you got the shot. Lumps, skin dimpling, or pain are usually mild and usually don't last long. Scarring is unusual, but may happen. If there is swelling or your skin gets hot, has pus or looks bruised one or more days after your shot, call your healthcare provider.
- Headache.

Women using depo-subQ provera 104 for birth control or endometriosis had these less common side effects: abdominal pain, acne, breast tenderness, being irritable, depression, hot flushes, insomnia, joint pain, lack of energy, less sex drive, nausea and sleepiness.

If you feel you are having other side effects, talk with your healthcare provider.

DOES depo-subQ provera 104 CAUSE CANCER?

- Birth control like depo-subQ provera 104 was studied in women for many years. In general, the risk of breast cancer slightly increased or stayed about the same as in women not using birth control like depo-subQ provera 104.
- The risk of cancer of the ovary, liver, or cervix did not change.
- There is a decreased risk of cancer of the uterus (endometrial cancer).

WHAT IF I WANT TO BECOME PREGNANT?

Plan ahead. The effect of depo-subQ provera 104 can last for a long time after you stop getting shots. Although you may be able to get pregnant quickly, it is more likely to take a year or longer after your last shot before you get pregnant.

It's best to see your healthcare provider for a pre-pregnancy check-up. Your healthcare provider may also tell you to take a vitamin called folic acid every day if you are planning to become pregnant.

GENERAL ADVICE ABOUT depo-subQ provera 104

For more information about depo-subQ provera 104, ask your healthcare provider or pharmacist. You can also visit www.depo-subQprovera104.com or call 1-866-554 DEPO (3376). A nurse can answer questions in Spanish or English 24 hours-a-day, 7 days a week.

WHAT IS IN depo-subQ provera 104?

Active ingredient: medroxyprogesterone acetate

Inactive ingredients: methylparaben, propylparaben, sodium chloride, polyethylene glycol, polysorbate 80, monobasic sodium phosphate·H₂O, dibasic sodium phosphate·12H₂O, methionine, povidone, water for shot. When necessary, the pH is adjusted with sodium hydroxide or hydrochloric acid, or both.

Rx only

Distributed by
Pharmacia and Upjohn Co
Division of Pfizer Inc, NY, NY 10017

Date (to be added)
Copy code (to be added)

8P5712



NDC 0009-4709-99

Rx only



104mg/0.65mL

Single Use 0.65 mL prefilled syringe

Professional Sample —
Not For Sale

Distributed by



Rx only



104mg/0.65mL

Single Use 0.65 mL prefilled syringe

Distributed by
Pfizer
Pharmacia & Upjohn Company
Division of Pfizer Inc, NY, NY 10017



GLUE
AREA

Instructions for Use:

- Hold the syringe pointing upward and shake it forcefully for at least 1 minute to thoroughly mix the medication. **It is important that you give the injection within 1 minute of mixing the medication.**
 - Gently twist off the protective end cap from the needle to break the seal. Avoid touching the end that connects to the prefilled syringe; set aside.
 - Remove the protective tip cap from the syringe barrel and attach the needle by pushing it onto the barrel tip. The plastic end of the needle connects to the opening of the syringe where you remove the protective cap. Avoid touching the connecting ends.
 - Remove the clear protective plastic cover from the needle, making sure that it is still firmly attached to the syringe. Once the needle is uncovered, be careful to keep it clean by not letting it touch anything.
 - While holding the syringe with the needle pointing upward, gently push in the plunger until the medicine is up to the top of the syringe. This removes any air trapped in the syringe.
 - Administer dose subcutaneously.
- The entire dose must be given to activate the needle guard.**
- When entire dose has been injected and the needle has been withdrawn from the skin, remove your finger from the plunger. The syringe will move up inside the device until the needle guard completely covers the exposed needle. You will hear a 'click' when the needle guard is fully activated. Discard appropriately.



TSE-K678
SC140
ZWART
P266
BL541
R0675

NDC 0009-4709-99

Rx only



104mg/0.65mL

Single Use 0.65 mL prefilled syringe

Professional Sample —
Not For Sale

Distributed by



Store at controlled room temperature 20° to 25° C (68° to 77° F) [see USP].

DOSAGE AND USE

See accompanying prescription information.

Shake vigorously before use.

Each 0.65mL contains: Medroxyprogesterone acetate, 104 mg; methylparaben, 1.040 mg; propylparaben, 0.098 mg; sodium chloride, 5.200 mg; polyethylene glycol, 18.688 mg; polysorbate 80, 1.950 mg; monobasic sodium phosphate H₂O, 0.451 mg; dibasic sodium phosphate 12H₂O, 0.382 mg; methionine, 0.975 mg; povidone, 3.250 mg; water for injection, qs. When necessary, the pH is adjusted with sodium hydroxide or hydrochloric acid or both.

www.depo-provera.com
1 866 554 DEPO (3376)

MADE IN BELGIUM

820 119 000H

8P5712A

LOT
EXP



itemnr.: 8P5712A-SAMPLE

formatcode: K678

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sourcecode: 140

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P266C

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date:11-JAN-05 16:34:34



ITF-CODE = 5593

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previous itemnr.:

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date/initials: 6-JAN-05/GL

country: USA

sourcecode: 559

Process Black

P541C

PTrans.
WhiteC

OK for printing

Issue reason

Launch Depo-Provera Subcutaan.

