



VESANOID®

(tretinoin)

CAPSULES

Rx only

WARNINGS

1. Experienced Physician and Institution

Patients with acute promyelocytic leukemia (APL) are at high risk in general and can have severe adverse reactions to VESANOID (tretinoin). VESANOID should therefore be administered only to patients with APL under the strict supervision of a physician who is experienced in the management of patients with acute leukemia and in a facility with laboratory and supportive services sufficient to monitor drug tolerance and protect and maintain a patient compromised by drug toxicity, including respiratory compromise. Use of VESANOID requires that the physician concludes that the possible benefit to the patient outweighs the following known adverse effects of the therapy.

2. Retinoic Acid-APL Syndrome

About 25% of patients with APL treated with VESANOID have experienced a syndrome called the retinoic acid-APL (RA-APL) syndrome characterized by fever, dyspnea, acute respiratory distress, weight gain, radiographic pulmonary infiltrates, pleural and pericardial effusions, edema, and hepatic, renal, and multi-organ failure. This syndrome has occasionally been accompanied by impaired myocardial contractility and episodic hypotension. It has been observed with or without concomitant leukocytosis. Endotracheal intubation and mechanical ventilation have been required in some cases due to progressive hypoxemia, and several patients have expired with multi-organ failure. The syndrome generally occurs during the first month of treatment, with some cases reported following the first dose of VESANOID.

The management of the syndrome has not been defined rigorously, but high-dose steroids given at the first suspicion of the RA-APL syndrome appear to reduce morbidity and mortality. At the first signs suggestive of the syndrome (unexplained fever, dyspnea and/or weight gain, abnormal chest auscultatory findings or radiographic abnormalities), high-dose steroids (dexamethasone 10 mg intravenously administered every 12 hours for 3 days or until the resolution of symptoms) should be immediately initiated, irrespective of the leukocyte count. The majority of patients do not require termination of VESANOID therapy during treatment of the RA-APL syndrome. However, in cases of moderate and severe RA-APL syndrome, temporary interruption of VESANOID therapy should be considered.

37 **3. Leukocytosis at Presentation and Rapidly Evolving Leukocytosis During**
38 **VESANOID Treatment**

39 During VESANOID treatment about 40% of patients will develop rapidly evolving
40 leukocytosis. Patients who present with high WBC at diagnosis ($>5 \times 10^9/L$) have an
41 increased risk of a further rapid increase in WBC counts. Rapidly evolving leukocytosis
42 is associated with a higher risk of life-threatening complications.

43 If signs and symptoms of the RA-APL syndrome are present together with leukocytosis,
44 treatment with high-dose steroids should be initiated immediately. Some investigators
45 routinely add chemotherapy to VESANOID treatment in the case of patients presenting
46 with a WBC count of $>5 \times 10^9/L$ or in the case of a rapid increase in WBC count for
47 patients leukopenic at start of treatment, and have reported a lower incidence of the RA-
48 APL syndrome. Consideration could be given to adding full-dose chemotherapy
49 (including an anthracycline if not contraindicated) to the VESANOID therapy on day 1 or
50 2 for patients presenting with a WBC count of $>5 \times 10^9/L$, or immediately, for patients
51 presenting with a WBC count of $<5 \times 10^9/L$, if the WBC count reaches $\geq 6 \times 10^9/L$ by day 5,
52 or $\geq 10 \times 10^9/L$ by day 10, or $\geq 15 \times 10^9/L$ by day 28.

53 **4. Teratogenic Effects. Pregnancy Category D – see WARNINGS**

54 There is a high risk that a severely deformed infant will result if VESANOID is
55 administered during pregnancy. If, nonetheless, it is determined that VESANOID
56 represents the best available treatment for a pregnant woman or a woman of childbearing
57 potential, it must be assured that the patient has received full information and warnings of
58 the risk to the fetus if she were to be pregnant and of the risk of possible contraception
59 failure and has been instructed in the need to use two reliable forms of contraception
60 simultaneously during therapy and for 1 month following discontinuation of therapy, and
61 has acknowledged her understanding of the need for using dual contraception, unless
62 abstinence is the chosen method

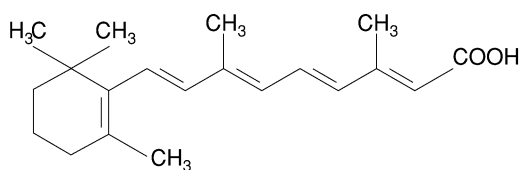
63 Within 1 week prior to the institution of VESANOID therapy, the patient should have
64 blood or urine collected for a serum or urine pregnancy test with a sensitivity of at least
65 50 mIU/mL. When possible, VESANOID therapy should be delayed until a negative
66 result from this test is obtained. When a delay is not possible, the patient should be placed
67 on two reliable forms of contraception. Pregnancy testing and contraception counseling
68 should be repeated monthly throughout the period of VESANOID treatment.

69 **DESCRIPTION**

70 VESANOID (tretinoin) is a retinoid that induces maturation of acute promyelocytic
71 leukemia (APL) cells in culture. It is available in a 10 mg soft gelatin capsule for oral
72 administration. Each capsule also contains beeswax, butylated hydroxyanisole, edetate
73 disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oils and soybean oil.
74 The gelatin capsule shell contains glycerin, yellow iron oxide, red iron oxide, titanium
75 dioxide, methylparaben and propylparaben.

76 Chemically, tretinoin is all-*trans* retinoic acid and is related to retinol (Vitamin A). It is a
77 yellow to light orange crystalline powder with a molecular weight of 300.44.

78 The structural formula is as follows:



79

80 **CLINICAL PHARMACOLOGY**

81 **Mechanism of Action**

82 Tretinoin is not a cytolytic agent but instead induces cytodifferentiation and decreased
83 proliferation of APL cells in culture and in vivo. In APL patients, tretinoin treatment
84 produces an initial maturation of the primitive promyelocytes derived from the leukemic
85 clone, followed by a repopulation of the bone marrow and peripheral blood by normal,
86 polyclonal hematopoietic cells in patients achieving complete remission (CR). The exact
87 mechanism of action of tretinoin in APL is unknown.

88 **Pharmacokinetics**

89 Tretinoin activity is primarily due to the parent drug. In human pharmacokinetics studies,
90 orally administered drug was well absorbed into the systemic circulation, with
91 approximately two-thirds of the administered radiolabel recovered in the urine. The
92 terminal elimination half-life of tretinoin following initial dosing is 0.5 to 2 hours in
93 patients with APL. There is evidence that tretinoin induces its own metabolism. Plasma
94 tretinoin concentrations decrease on average to one-third of their day 1 values during 1
95 week of continuous therapy. Mean \pm SD peak tretinoin concentrations decreased from
96 394 ± 89 to 138 ± 139 ng/mL, while area under the curve (AUC) values decreased from
97 537 ± 191 ng·h/mL to 249 ± 185 ng·h/mL during 45 mg/m^2 daily dosing in 7 APL
98 patients. Increasing the dose to “correct” for this change has not increased response.

99 **Absorption**

100 A single 45 mg/m^2 (~80 mg) oral dose to APL patients resulted in a mean \pm SD peak
101 tretinoin concentration of 347 ± 266 ng/mL. Time to reach peak concentration was
102 between 1 and 2 hours.

103 **Distribution**

104 The apparent volume of distribution of tretinoin has not been determined. Tretinoin is
105 greater than 95% bound in plasma, predominately to albumin. Plasma protein binding
106 remains constant over the concentration range of 10 to 500 ng/mL.

107 **Metabolism**

108 Tretinoin metabolites have been identified in plasma and urine. Cytochrome P450
109 enzymes have been implicated in the oxidative metabolism of tretinoin. Metabolites
110 include 13-*cis* retinoic acid, 4-oxo *trans* retinoic acid, 4-oxo *cis* retinoic acid, and 4-oxo
111 *trans* retinoic acid glucuronide. In APL patients, daily administration of a 45 mg/m^2 dose

112 of tretinoin resulted in an approximately tenfold increase in the urinary excretion of 4-
 113 oxo *trans* retinoic acid glucuronide after 2 to 6 weeks of continuous dosing, when
 114 compared to baseline values.

115 Excretion

116 Studies with radiolabeled drug have demonstrated that after the oral administration of
 117 2.75 and 50 mg doses of tretinoin, greater than 90% of the radioactivity was recovered in
 118 the urine and feces. Based upon data from 3 subjects, approximately 63% of radioactivity
 119 was recovered in the urine within 72 hours and 31% appeared in the feces within 6 days.

120 Special Populations

121 The pharmacokinetics of tretinoin have not been separately evaluated in women, in
 122 members of different ethnic groups, or in individuals with renal or hepatic insufficiency.

123 Drug-Drug Interactions

124 In 13 patients who had received daily doses of tretinoin for 4 consecutive weeks,
 125 administration of ketoconazole (400 to 1200 mg oral dose) 1 hour prior to the
 126 administration of the tretinoin dose on day 29 led to a 72% increase (218 ± 224 vs
 127 375 ± 285 ng·h/mL) in tretinoin mean plasma AUC. The precise cytochrome P450
 128 enzymes involved in these interactions have not been specified; *CYP* 3A4, 2C8 and 2E
 129 have been implicated in various preliminary reports.

130 Clinical Studies

131 VESANOID has been investigated in 114 previously treated APL patients and in 67
 132 previously untreated (“de novo”) patients in one open-label, uncontrolled single
 133 investigator clinical study (Memorial Sloan-Kettering Cancer Center [MSKCC]) and in
 134 two cohorts of compassionate cases treated by multiple investigators under the auspices
 135 of the National Cancer Institute (NCI). All patients received 45 mg/m²/day as a divided
 136 oral dose for up to 90 days or 30 days beyond the day that CR was reached. Results are
 137 shown in the following table:

	MSKCC		NCI Cohort 1		NCI Cohort 2	
	Relapsed N=20	De Novo n=15	Relapsed* n=48	De Novo n=14	Relapsed n=46	De Novo† n=38
Complete Remission	16 (80%)	11 (73%)	24 (50%)	5 (36%)	24 (52%)	26 (68%)
Median Survival (Mo)	10.8	NR	5.8	0.5	8.8	NR
Median Follow-up (Mo)	9.9	42.9	5.6	1.2	8.0	13.1
RA-APL Syndrome	4 (20%)	5 (33%)	10 (21%)	6 (43%)	NA	NA

138 NR = Not Reached

139 NA = Not Available

140 *Including 9 chemorefractory patients

141 †Including 8 patients who received chemotherapy but failed to enter remission

142

143 The median time to CR was between 40 and 50 days (range: 2 to 120 days). Most patients
 144 in these studies received cytotoxic chemotherapy during the remission phase. These

145 results compare to the 30% to 50% CR rate and ≤6 month median survival reported for
146 cytotoxic chemotherapy of APL in the treatment of relapse.

147 Ten of 15 pediatric cases achieved CR (8 of 10 males and 2 of 5 females). There were
148 insufficient patients of black, Hispanic or Asian derivation to estimate relative response
149 rates in these groups, but responses were seen in each category.

150 Responses were seen in 3 of 4 patients for whom cytogenetic analysis failed to detect the
151 t(15;17) translocation typically seen in APL. The t(15;17) translocation results in the
152 PML/RAR α gene, which appears necessary for this disease. Molecular genetic studies
153 were not conducted in these cases, but it is likely they represent cases with a masked
154 translocation giving rise to PML/RAR α . Responses to tretinoin have not been observed
155 in cases in which PML/RAR α fusion has been shown to be absent.

156 **INDICATIONS AND USAGE**

157 VESANOID (tretinoin) capsules are indicated for the induction of remission in patients
158 with acute promyelocytic leukemia (APL), French-American-British (FAB) classification
159 M3 (including the M3 variant), characterized by the presence of the t(15;17) translocation
160 and/or the presence of the PML/RAR α gene who are refractory to, or who have relapsed
161 from, anthracycline chemotherapy, or for whom anthracycline-based chemotherapy is
162 contraindicated. VESANOID is for the induction of remission only. The optimal
163 consolidation or maintenance regimens have not been defined, but all patients should
164 receive an accepted form of remission consolidation and/or maintenance therapy for APL
165 after completion of induction therapy with VESANOID.

166 **CONTRAINDICATIONS**

167 VESANOID is contraindicated in patients with a known hypersensitivity to VESANOID,
168 any of its components, or other retinoids. VESANOID should not be given to patients
169 who are sensitive to parabens, which are used as preservatives in the gelatin capsule.

170 **WARNINGS**

171 **Pregnancy Category D – See Boxed WARNINGS**

172 Tretinoin has teratogenic and embryotoxic effects in mice, rats, hamsters, rabbits and
173 pigtail monkeys, and may be expected to cause fetal harm when administered to a
174 pregnant woman. Tretinoin causes fetal resorptions and a decrease in live fetuses in all
175 animals studied. Gross external, soft tissue and skeletal alterations occurred at doses
176 higher than 0.7 mg/kg/day in mice, 2 mg/kg/day in rats, 7 mg/kg/day in hamsters, and at a
177 dose of 10 mg/kg/day, the only dose tested, in pigtail monkeys (about 1/20, 1/4, and 1/2
178 and 4 times the human dose, respectively, on a mg/m² basis).

179 There are no adequate and well-controlled studies in pregnant women. Although
180 experience with humans administered VESANOID is extremely limited, increased
181 spontaneous abortions and major human fetal abnormalities related to the use of other
182 retinoids have been documented in humans. Reported defects include abnormalities of the
183 CNS, musculoskeletal system, external ear, eye, thymus and great vessels; and facial

184 dysmorphism, cleft palate, and parathyroid hormone deficiency. Some of these
185 abnormalities were fatal. Cases of IQ scores less than 85, with or without obvious CNS
186 abnormalities, have also been reported. All fetuses exposed during pregnancy can be
187 affected and at the present time there is no antepartum means of determining which
188 fetuses are and are not affected.

189 Effective contraception must be used by all females during VESANOID therapy and for
190 1 month following discontinuation of therapy. Contraception must be used even when
191 there is a history of infertility or menopause, unless a hysterectomy has been performed.
192 Whenever contraception is required, it is recommended that two reliable forms of
193 contraception be used simultaneously, unless abstinence is the chosen method. If
194 pregnancy does occur during treatment, the physician and patient should discuss the
195 desirability of continuing or terminating the pregnancy.

196 **Patients Without the t(15;17) Translocation**

197 Initiation of therapy with VESANOID may be based on the morphological diagnosis of
198 acute promyelocytic leukemia. Confirmation of the diagnosis of APL should be sought
199 by detection of the t(15;17) genetic marker by cytogenetic studies. If these are negative,
200 PML/RAR α fusion should be sought using molecular diagnostic techniques. The
201 response rate of other AML subtypes to VESANOID has not been demonstrated;
202 therefore, patients who lack the genetic marker should be considered for alternative
203 treatment.

204 **Retinoic Acid-APL (RA-APL) Syndrome**

205 In up to 25% of patients with APL treated with VESANOID, a syndrome occurs which
206 can be fatal (see **boxed WARNINGS** and **ADVERSE REACTIONS**).

207 **Leukocytosis at Presentation and Rapidly Evolving Leukocytosis During 208 VESANOID Treatment**

209 See **boxed WARNINGS**.

210 **Pseudotumor Cerebri**

211 Retinoids, including VESANOID, have been associated with pseudotumor cerebri
212 (benign intracranial hypertension), especially in pediatric patients. The concomitant use
213 of other agents known to cause pseudotumor cerebri/intracranial hypertension, such as
214 tetracyclines, might increase the risk of this condition (see **PRECAUTIONS: Drug
215 Interactions**). Early signs and symptoms of pseudotumor cerebri include papilledema,
216 headache, nausea and vomiting, and visual disturbances. Patients with these symptoms
217 should be evaluated for pseudotumor cerebri, and, if present, appropriate care should be
218 instituted in concert with neurological assessment.

219 **Lipids**

220 Up to 60% of patients experienced hypercholesterolemia and/or hypertriglyceridemia,
221 which were reversible upon completion of treatment. The clinical consequences of
222 temporary elevation of triglycerides and cholesterol are unknown, but venous thrombosis

223 and myocardial infarction have been reported in patients who ordinarily are at low risk
224 for such complications.

225 **Elevated Liver Function Test Results**

226 Elevated liver function test results occur in 50% to 60% of patients during treatment.
227 Liver function test results should be carefully monitored during treatment and
228 consideration be given to a temporary withdrawal of VESANOID if test results reach >5
229 times the upper limit of normal values. However, the majority of these abnormalities
230 resolve without interruption of VESANOID or after completion of treatment.

231 **PRECAUTIONS**

232 **General**

233 VESANOID has potentially significant toxic side effects in APL patients. Patients
234 undergoing therapy should be closely observed for signs of respiratory compromise
235 and/or leukocytosis (see **boxed WARNINGS**). Supportive care appropriate for APL
236 patients, eg, prophylaxis for bleeding, prompt therapy for infection, should be maintained
237 during therapy with VESANOID.

238 There is a risk of thrombosis (both venous and arterial) which may involve any organ
239 system, during the first month of treatment (see **ADVERSE REACTIONS**). Therefore,
240 caution should be exercised when treating patients with the combination of VESANOID
241 and anti-fibrinolytic agents, such as tranexamic acid, aminocaproic acid or aprotinin (see
242 **Drug Interactions**).

243 The ability to drive or operate machinery might be impaired in patients treated with
244 VESANOID, particularly if they are experiencing dizziness or severe headache.

245 Microdosed progesterone preparations (“minipill”) may be an inadequate method of
246 contraception during treatment with VESANOID.

247 **Laboratory Tests**

248 The patient’s hematologic profile, coagulation profile, liver function test results, and
249 triglyceride and cholesterol levels should be monitored frequently.

250 **Drug Interactions**

251 Limited clinical data on potential drug interactions are available.

252 **Drugs Metabolized By the Hepatic P450 System**

253 As VESANOID is metabolized by the hepatic P450 system, there is a potential for
254 alteration of pharmacokinetics parameters in patients administered concomitant
255 medications that are also inducers or inhibitors of this system. Medications that generally
256 induce hepatic P450 enzymes include rifampicin, glucocorticoids, phenobarbital and
257 pentobarbital. Medications that generally inhibit hepatic P450 enzymes include
258 ketoconazole, cimetidine, erythromycin, verapamil, diltiazem and cyclosporine. To date
259 there are no data to suggest that co-use with these medications increases or decreases
260 either efficacy or toxicity of VESANOID.

261 Agents Known to Cause Pseudotumor Cerebri/Intracranial Hypertension (Such
262 as Tetracyclines)

263 VESANOID may cause pseudotumor cerebri/intracranial hypertension. Concomitant
264 administration of VESANOID and agents known to cause pseudotumor
265 cerebri/intracranial hypertension as well might increase the risk of this condition (see
266 **WARNINGS**).

267 Vitamin A

268 As with other retinoids, VESANOID must not be administered in combination with
269 vitamin A because symptoms of hypervitaminosis A could be aggravated.

270 Anti-fibrinolytic Agents (Such as Tranexamic Acid, Aminocaproic Acid, or
271 Aprotinin)

272 Cases of fatal thrombotic complications have been reported rarely in patients
273 concomitantly treated with VESANOID and anti-fibrinolytic agents. Therefore, caution
274 should be exercised when administering VESANOID concomitantly with these agents
275 (see **PRECAUTIONS: General**).

276 **Effect of Food**

277 No data on the effect of food on the absorption of VESANOID are available. The
278 absorption of retinoids as a class has been shown to be enhanced when taken together
279 with food.

280 **Carcinogenesis, Mutagenesis and Impairment of Fertility**

281 No long-term carcinogenicity studies with tretinoin have been conducted. In short-term
282 carcinogenicity studies, tretinoin at a dose of 30 mg/kg/day (about 2 times the human
283 dose on a mg/m² basis) was shown to increase the rate of diethylnitrosamine (DEN)-
284 induced mouse liver adenomas and carcinomas. Tretinoin was negative when tested in
285 the Ames and Chinese hamster V79 cell HGPRT assays for mutagenicity. A twofold
286 increase in the sister chromatid exchange (SCE) has been demonstrated in human diploid
287 fibroblasts, but other chromosome aberration assays, including an in vitro assay in human
288 peripheral lymphocytes and an in vivo mouse micronucleus assay, did not show a
289 clastogenic or aneuploidogenic effect. Adverse effects on fertility and reproductive
290 performance were not observed in studies conducted in rats at doses up to 5 mg/kg/day
291 (about 2/3 the human dose on a mg/m² basis). In a 6-week toxicology study in dogs,
292 minimal to marked testicular degeneration, with increased numbers of immature
293 spermatozoa, were observed at 10 mg/kg/day (about 4 times the equivalent human dose
294 in mg/m²).

295 **Nursing Mothers**

296 It is not known whether this drug is excreted in human milk. Because many drugs are
297 excreted in human milk, and because of the potential for serious adverse reactions from
298 VESANOID in nursing infants, mothers should discontinue nursing prior to taking this
299 drug.

300 **Pediatric Use**

301 There are limited clinical data on the pediatric use of VESANOID. Of 15 pediatric
302 patients (age range: 1 to 16 years) treated with VESANOID, the incidence of complete
303 remission was 67%. Safety and effectiveness in pediatric patients below the age of 1 year
304 have not been established. Some pediatric patients experience severe headache and
305 pseudotumor cerebri, requiring analgesic treatment and lumbar puncture for relief.
306 Increased caution is recommended in the treatment of pediatric patients. Dose reduction
307 may be considered for pediatric patients experiencing serious and/or intolerable toxicity;
308 however, the efficacy and safety of VESANOID at doses lower than 45 mg/m²/day have
309 not been evaluated in the pediatric population.

310 **Geriatric Use**

311 Of the total number of subjects in clinical studies of VESANOID, 21.4% were 60 and
312 over. No overall differences in safety or effectiveness were observed between these
313 subjects and younger subjects, and other reported clinical experience has not identified
314 differences in responses between the elderly and younger patients, but greater sensitivity
315 of some older individuals cannot be ruled out.

316 **ADVERSE REACTIONS**

317 Virtually all patients experience some drug-related toxicity, especially headache, fever,
318 weakness, and fatigue. These adverse effects are seldom permanent or irreversible nor do
319 they usually require interruption of therapy. Some of the adverse events are common in
320 patients with APL, including hemorrhage, infections, gastrointestinal hemorrhage,
321 disseminated intravascular coagulation, pneumonia, septicemia, and cerebral hemorrhage.
322 The following describes the adverse events, regardless of drug relationship, that were
323 observed in patients treated with VESANOID.

324 **Typical Retinoid Toxicity**

325 The most frequently reported adverse events were similar to those described in patients
326 taking high doses of vitamin A and included headache (86%), fever (83%), skin/mucous
327 membrane dryness (77%), bone pain (77%), nausea/vomiting (57%), rash (54%),
328 mucositis (26%), pruritus (20%), increased sweating (20%), visual disturbances (17%),
329 ocular disorders (17%), alopecia (14%), skin changes (14%), changed visual acuity (6%),
330 bone inflammation (3%), visual field defects (3%).

331 **RA-APL Syndrome**

332 APL patients treated with VESANOID have experienced a potentially fatal syndrome
333 characterized by fever, dyspnea, acute respiratory distress, weight gain, radiographic
334 pulmonary infiltrates, pleural and pericardial effusions, edema, and hepatic, renal, and
335 multi-organ failure. This syndrome has occasionally been accompanied by impaired
336 myocardial contractility and episodic hypotension and has been observed with or without
337 concomitant leukocytosis. Some patients have expired due to progressive hypoxemia and
338 multi-organ failure. The syndrome generally occurs during the first month of treatment,
339 with some cases reported following the first dose of VESANOID. The management of
340 the syndrome has not been defined rigorously, but high-dose steroids given at the first

341 signs of the syndrome appear to reduce morbidity and mortality. Treatment with
342 dexamethasone, 10 mg intravenously administered every 12 hours for 3 days or until
343 resolution of symptoms, should be initiated without delay at the first suspicion of
344 symptoms (one or more of the following: fever, dyspnea, weight gain, abnormal chest
345 auscultatory findings or radiographic abnormalities). Sixty percent or more of patients
346 treated with VESANOID may require high-dose steroids because of these symptoms. The
347 majority of patients do not require termination of VESANOID therapy during treatment
348 of the syndrome.

349 **Body as a Whole**

350 General disorders related to VESANOID administration and/or associated with APL
351 included malaise (66%), shivering (63%), hemorrhage (60%), infections (58%),
352 peripheral edema (52%), pain (37%), chest discomfort (32%), edema (29%),
353 disseminated intravascular coagulation (26%), weight increase (23%), injection site
354 reactions (17%), anorexia (17%), weight decrease (17%), myalgia (14%), flank pain
355 (9%), cellulitis (8%), face edema (6%), fluid imbalance (6%), pallor (6%), lymph
356 disorders (6%), acidosis (3%), hypothermia (3%), ascites (3%).

357 **Respiratory System Disorders**

358 Respiratory system disorders were commonly reported in APL patients administered
359 VESANOID. The majority of these events are symptoms of the RA-APL syndrome (see
360 **boxed WARNINGS**). Respiratory system adverse events included upper respiratory tract
361 disorders (63%), dyspnea (60%), respiratory insufficiency (26%), pleural effusion (20%),
362 pneumonia (14%), rales (14%), expiratory wheezing (14%), lower respiratory tract
363 disorders (9%), pulmonary infiltration (6%), bronchial asthma (3%), pulmonary edema
364 (3%), larynx edema (3%), unspecified pulmonary disease (3%).

365 **Ear Disorders**

366 Ear disorders were consistently reported, with earache or feeling of fullness in the ears
367 reported by 23% of the patients. Hearing loss and other unspecified auricular disorders
368 were observed in 6% of patients, with infrequent (<1%) reports of irreversible hearing
369 loss.

370 **Gastrointestinal Disorders**

371 GI disorders included GI hemorrhage (34%), abdominal pain (31%), other
372 gastrointestinal disorders (26%), diarrhea (23%), constipation (17%), dyspepsia (14%),
373 abdominal distention (11%), hepatosplenomegaly (9%), hepatitis (3%), ulcer (3%),
374 unspecified liver disorder (3%).

375 **Cardiovascular and Heart Rate and Rhythm Disorders**

376 Arrhythmias (23%), flushing (23%), hypotension (14%), hypertension (11%), phlebitis
377 (11%), cardiac failure (6%) and for 3% of patients: cardiac arrest, myocardial infarction,
378 enlarged heart, heart murmur, ischemia, stroke, myocarditis, pericarditis, pulmonary
379 hypertension, secondary cardiomyopathy.

380 **Central and Peripheral Nervous System Disorders and Psychiatric**

381 Dizziness (20%), paresthesias (17%), anxiety (17%), insomnia (14%), depression (14%),
382 confusion (11%), cerebral hemorrhage (9%), intracranial hypertension (9%), agitation
383 (9%), hallucination (6%) and for 3% of patients: abnormal gait, agnosia, aphasia,
384 asterixis, cerebellar edema, cerebellar disorders, convulsions, coma, CNS depression,
385 dysarthria, encephalopathy, facial paralysis, hemiplegia, hyporeflexia, hypotaxia, no light
386 reflex, neurologic reaction, spinal cord disorder, tremor, leg weakness, unconsciousness,
387 dementia, forgetfulness, somnolence, slow speech.

388 **Urinary System Disorders**

389 Renal insufficiency (11%), dysuria (9%), acute renal failure (3%), micturition frequency
390 (3%), renal tubular necrosis (3%), enlarged prostate (3%).

391 **Miscellaneous Adverse Events**

392 Isolated cases of erythema nodosum, basophilia and hyperhistaminemia, Sweet's
393 syndrome, organomegaly, hypercalcemia, pancreatitis and myositis have been reported.

394 **Additional Adverse Reactions Reported With VESANOID**

395 **Cardiovascular**

396 Cases of thrombosis (both venous and arterial) involving various sites (eg,
397 cerebrovascular accident, myocardial infarction, renal infarct) have been reported rarely
398 (see **PRECAUTIONS: General**).

399 **Hematologic**

400 Rare cases of thrombocytosis have been reported.

401 **Skin**

402 Genital ulceration

403 **Miscellaneous Adverse Events**

404 Rare cases of vasculitis, predominantly involving the skin, have been reported.

405 **OVERDOSAGE**

406 In case of overdose with VESANOID, reversible signs of hypervitaminosis A (headache,
407 nausea, vomiting, mucocutaneous symptoms) can appear. The maximal tolerated dose in
408 patients with myelodysplastic syndrome or solid tumors was 195 mg/m²/day. The
409 maximal tolerated dose in pediatric patients was lower at 60 mg/m²/day. Overdosage with
410 other retinoids has been associated with transient headache, facial flushing, cheilosis,
411 abdominal pain, dizziness and ataxia. These symptoms have quickly resolved without
412 apparent residual effects.

413 There is no specific treatment in the case of an overdose; however, it is important that the
414 patient be treated in a special hematological unit.

415 **DOSAGE AND ADMINISTRATION**

416 The recommended dose is 45 mg/m²/day administered as two evenly divided doses until
417 complete remission is documented. Therapy should be discontinued 30 days after
418 achievement of complete remission or after 90 days of treatment, whichever occurs first.

419 If after initiation of treatment of VESANOID the presence of the t(15;17) translocation is
420 not confirmed by cytogenetics and/or by polymerase chain reaction studies and the
421 patient has not responded to VESANOID, alternative therapy appropriate for acute
422 myelogenous leukemia should be considered.

423 **VESANOID is for the induction of remission only.** Optimal consolidation or
424 maintenance regimens have not been determined. All patients should, therefore, receive a
425 standard consolidation and/or maintenance chemotherapy regimen for APL after
426 induction therapy with VESANOID, unless otherwise contraindicated.

427 **HOW SUPPLIED**

428 VESANOID is supplied as 10 mg capsules, two-tone (lengthwise), orange-yellow and
429 reddish-brown and imprinted VESANOID 10 ROCHE. Supplied in high-density
430 polyethylene, opaque bottles of 100 capsules with child-resistant closure (NDC 0004-
431 0250-01).

432 Store at 15° to 30°C (59° to 86°F). Protect from light.

433

434 Distributed by:



Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

435

436

437 27899522

438 Revised: July 2008

439

440 Copyright © 1998-2008 by Roche Laboratories Inc. All rights reserved.