

Cephalon®

Initial REMS Approval: 7/2011

ACTIQ® (fentanyl citrate) oral transmucosal lozenge, CII

FENTORA® (fentanyl citrate) buccal tablet CII

NDA 20-747
ACTIQ® (fentanyl citrate) oral
transmucosal lozenge
[CII]
Opioid Analgesic

NDA 21-947
FENTORA® (fentanyl citrate) buccal
tablet
[CII]
Opioid Analgesic

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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

1 **I GOALS**

2 The goals of the ACTIQ® and FENTORA® REMS are to mitigate the risk of misuse,
3 abuse, addiction, overdose and serious complications due to medication errors by:

- 4 1. Prescribing and dispensing ACTIQ and FENTORA only to appropriate patients,
5 which includes use only in opioid-tolerant patients
- 6 2. Preventing inappropriate conversion between fentanyl products
- 7 3. Preventing accidental exposure to children and others for whom it was not
8 prescribed
- 9 4. Educating prescribers, pharmacists, and patients on the potential for misuse,
10 abuse, addiction, and overdose.

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12 **II REMS ELEMENTS**

13 **A. Medication Guide**

14 A Medication Guide will be dispensed with each ACTIQ and each FENTORA
15 prescription in accordance with 21 CFR 208.24.

16 The *Actiq Medication Guide* and *Fentora Medication Guide* are part of the REMS
17 and are appended.

18 **B. Elements to Assure Safe Use**

19 **1. Healthcare providers who prescribe ACTIQ and FENTORA for**
20 **outpatient use are specially certified.**

- 21 a. Cephalon will ensure that healthcare providers who prescribe ACTIQ and
22 FENTORA for **outpatient** use are specially certified.
- 23 b. To become certified to prescribe ACTIQ and FENTORA, prescribers will
24 be required to enroll in the ACTIQ and FENTORA REMS program.
25 Prescribers must complete the following requirements to be enrolled:
 - 26 i. Review the ACTIQ and FENTORA REMS prescriber educational
27 materials (*Education Program*), including the Full Prescribing
28 Information, and successfully complete the knowledge assessment
29 (*Knowledge Assessment*).
 - 30 ii. Complete and sign the *Prescriber Enrollment Form*. In signing the
31 *Prescriber Enrollment Form*, each prescriber is required to
32 acknowledge the following:
 - 33 a) I understand the responsible use conditions for ACTIQ and
34 FENTORA and the risks and benefits of chronic opioid therapy.
 - 35 b) I understand that ACTIQ and FENTORA can be abused and that
36 this risk should be considered when prescribing or dispensing

- 37 ACTIQ and FENTORA in situations where I am concerned about
38 an increased risk of misuse, abuse, or overdose, whether accidental
39 or intentional.
- 40 c) I understand that ACTIQ and FENTORA are indicated only for the
41 management of breakthrough pain in patients with cancer, who are
42 already receiving and who are tolerant to around-the-clock opioid
43 therapy for their underlying persistent cancer pain.
- 44 d) I understand that ACTIQ and FENTORA are contraindicated for
45 use in opioid non-tolerant patients, and know that fatal overdose
46 can occur at any dose.
- 47 e) I understand that ACTIQ and FENTORA must not be used to treat
48 any contraindicated conditions such as acute or postoperative pain,
49 including headache/migraine.
- 50 f) I understand that the initial starting dose for ACTIQ and
51 FENTORA for all patients is the lowest dose unless individual
52 labels provide product specific conversion recommendations, and
53 that patients must be titrated individually.
- 54 g) I understand that ACTIQ and FENTORA are not bioequivalent
55 with each other or any other fentanyl product (regardless of route
56 of administration), and that substitution may result in fatal
57 overdose. I understand that patients switching from another
58 fentanyl product to ACTIQ or FENTORA must not be converted
59 on a microgram-per-microgram basis, unless the patient is
60 converting from the branded product to its generic, or vice versa.
- 61 h) I will complete and sign an ACTIQ and FENTORA REMS
62 *Patient-Prescriber Agreement* with each new patient, before
63 writing the patient's first prescription, and renew the agreement
64 every two (2) years.
- 65 In signing the *Patient-Prescriber Agreement*, the prescriber
66 documents the following:
- 67 1) Patient is currently using around-the-clock opioid analgesia
68 and has been for at least one (1) week.
- 69 2) Patient is opioid tolerant. Patients considered opioid tolerant
70 are those who are regularly taking at least: 60 mg oral
71 morphine/day; 25 mcg transdermal fentanyl/hour; 30 mg oral
72 oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral
73 oxymorphone/day; or an equianalgesic dose of another opioid
74 for one week or longer.
- 75 3) A Medication Guide for ACTIQ or FENTORA has been
76 provided to and reviewed with the patient or their caregiver

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- 4) The patient or their caregiver has been counseled about the risks, benefits, and appropriate use of ACTIQ or FENTORA including communication of the following safety messages:
 - A. If patients stop taking their around-the-clock opioid medication, they must stop taking ACTIQ or FENTORA.
 - B. NEVER share ACTIQ or FENTORA
 - C. Giving ACTIQ or FENTORA to someone for whom it has not been prescribed can result in a fatal overdose.
 - D. ACTIQ and FENTORA can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home.
- In signing the *Patient-Prescriber Agreement*, the patient and/or their caregiver document the following:
- 1) My prescriber has given me a copy of the Medication Guide and has reviewed it with me.
 - 2) I understand that before I can take this medication, I must be regularly using another opioid pain medication, around-the-clock, for my constant pain.
 - 3) I understand that if I stop taking my around-the-clock opioid pain medication for my constant pain, I must stop taking this medication.
 - 4) I understand how I should take this medication, including how much I can take, and how often I can take it.
 - 5) I understand that this medication can cause serious side effects, including life threatening breathing problems which can lead to death, especially if I do not take this medicine exactly as my prescriber has directed me to take it.
 - 6) I agree to contact my prescriber if this medication does not relieve my pain. I will not change my dose of this medication myself or take it more often than my prescriber has directed.
 - 7) I agree that I will never give this medication to anyone else, even if they have the same symptoms, since it may harm them or even cause death.
 - 8) I will store this medication in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.

- 115 9) I have been instructed on how to properly dispose of unused
116 and remaining medication and will dispose of this medication
117 as soon as I no longer need it.
- 118 10) I understand that selling or giving away this medication is
119 against the law.
- 120 11) I have asked my prescriber all the questions I have about this
121 medication. If I have any additional questions or concerns in
122 the future about my treatment with this medication, I will
123 contact my prescriber.
- 124 12) I have reviewed the Patient Authorization for Disclosure and
125 Use of Health Information Statement and I agree to its terms
126 and conditions which authorize my healthcare providers and
127 health plans to disclose my personal and medical information
128 to Cephalon, Inc. (the maker of this medication) and their
129 agents and contractors to administer the REMS program.
- 130 i) I will provide a completed, signed copy of the *Patient-Prescriber*
131 *Agreement* to the patient and retain a copy for my records. I will
132 also provide a completed, signed copy to the ACTIQ and
133 FENTORA REMS program (by fax, or through the ACTIQ and
134 FENTORA REMS website) within ten (10) working days.
- 135 j) At all follow-up visits, I agree to assess the patient for
136 appropriateness of the dose, and for signs of misuse and abuse.
- 137 k) I understand that ACTIQ and FENTORA are only available
138 through the ACTIQ and FENTORA REMS program. I understand
139 and agree to comply with the ACTIQ and FENTORA REMS
140 program requirements for prescribers.
- 141 c. Prescribers are required to re-enroll every two (2) years. Additionally,
142 prescribers must re-counsel their patients and complete a new *Patient-*
143 *Prescriber Agreement* at least every two (2) years.
- 144 d. Cephalon will:
- 145 i. Ensure that prescriber enrollment can successfully be completed via
146 the ACTIQ and FENTORA REMS website, mail, fax, or by scanning
147 and e-mailing the forms.
- 148 ii. Ensure that, as part of the enrollment process, prescribers receive the
149 following materials that are part of the ACTIQ and FENTORA REMS
150 program and are appended:
- 151 • *Prescriber Overview*
- 152 • *Education Program*
- 153 • *Knowledge Assessment*
- 154 • *Prescriber Enrollment Form*

- 155 • *Patient-Prescriber Agreement*
- 156 • *ACTIQ and FENTORA REMS Website*
- 157 iii. Ensure that prescribers have successfully completed the knowledge
158 assessment, and ensure that enrollment forms are complete before
159 activating a prescriber's enrollment in the ACTIQ and FENTORA
160 REMS program.
- 161 iv. Ensure that prescribers are notified when they are successfully
162 enrolled in the ACTIQ and FENTORA REMS program, and therefore,
163 are certified to prescribe ACTIQ and FENTORA.
- 164 v. Monitor education and enrollment requirements for prescribers and
165 may inactivate noncompliant prescribers. Upon initial activation,
166 prescribers remain active until inactivation occurs or expiration of the
167 enrollment period.
- 168 vi. Ensure that within sixty (60) days after the ACTIQ and FENTORA
169 REMS program approval, a Dear Healthcare Provider Letter will be
170 sent. The target audience for the letter will include pain management
171 specialists (comprised of anesthesiologists, physical medicine and
172 rehabilitation physicians and primary care physicians), oncologists,
173 oncology nurse practitioners who treat breakthrough pain in patients
174 with cancer, and other appropriately licensed healthcare professionals
175 who prescribe oral transmucosal fentanyl products. The letter will
176 include information on the risks associated with the use of ACTIQ and
177 FENTORA and will explain to healthcare providers that if they wish to
178 treat patients using ACTIQ or FENTORA, they must enroll in the
179 ACTIQ and FENTORA REMS program. The letter will be
180 accompanied by a copy of the Full Prescribing Information (which will
181 include the Medication Guide), and will be available on the ACTIQ
182 and FENTORA REMS website for 1 year from the date of the mailing.

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184 The *Dear Healthcare Provider Letter* is part of the ACTIQ and FENTORA
185 REMS Program and is appended.

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187 **2. ACTIQ and FENTORA will only be dispensed by pharmacies that are**
188 **specially certified.**

- 189 a. Cephalon will ensure that ACTIQ and FENTORA will only be dispensed
190 by certified pharmacies. To become certified to dispense ACTIQ and
191 FENTORA, each pharmacy must be enrolled in the ACTIQ and
192 FENTORA REMS program.
- 193 b. Each pharmacy will be required to designate an authorized pharmacist to
194 complete enrollment on behalf of the pharmacy.
- 195 c. There is a different set of enrollment requirements for **outpatient**
196 **pharmacies** (e.g., retail, mail order, institutional outpatient pharmacies)

197 that dispense for outpatient use) and **inpatient pharmacies** (e.g.,
198 hospitals, hospices, and long-term care facilities that dispense for inpatient
199 use).

200 d. **Outpatient Pharmacies:**

201 The authorized pharmacist must complete the following requirements to
202 enroll their **outpatient pharmacy**:

- 203 i. Review the ACTIQ and FENTORA REMS education program
204 (*Education Program*) and successfully complete the *Knowledge*
205 *Assessment*).
- 206 ii. Ensure the pharmacy enables their pharmacy management system to
207 support communication with the ACTIQ and FENTORA REMS
208 system, using established telecommunication standards, and runs the
209 standardized validation test transaction to validate the system
210 enhancements.
- 211 iii. Complete and sign the *Outpatient Pharmacy Enrollment Form*. In
212 signing the *Pharmacy Enrollment Form*, the authorized pharmacist is
213 required to acknowledge the following:
- 214 a) I understand the risks and benefits associated with ACTIQ and
215 FENTORA and the requirements of the ACTIQ and FENTORA
216 REMS program for pharmacies.
- 217 b) I will ensure that all pharmacy staff who participate in dispensing
218 ACTIQ and FENTORA have been educated on the risks associated
219 with ACTIQ and FENTORA and the requirements of the ACTIQ
220 and FENTORA REMS program, as described in the *Pharmacy*
221 *Education Program*. This training should be documented and is
222 subject to audit.
- 223 c) I understand that ACTIQ and FENTORA are not bioequivalent
224 with each other or any other fentanyl product on a microgram-per-
225 microgram basis and therefore must not be substituted for any
226 other fentanyl products, unless the patient is converting from the
227 branded product to its generic, or vice versa.
- 228 d) I understand that ACTIQ and FENTORA are contraindicated for
229 use in opioid non-tolerant patients.
- 230 e) I understand that the initial starting dose for ACTIQ and
231 FENTORA for all patients is the lowest dose, unless individual
232 labels provide product specific conversion recommendations.
- 233 f) I understand the importance of discussing the risks and benefits of
234 ACTIQ and FENTORA with patients and their caregivers, and in
235 particular the importance of taking the drug as prescribed, not
236 sharing with others, and proper disposal.

- 238 g) I understand that the product-specific Medication Guide must be
239 given to the patient or their caregiver each time ACTIQ and
240 FENTORA is dispensed.
- 241 h) I understand that ACTIQ and FENTORA will not be dispensed
242 without verifying through our pharmacy management system that
243 the prescriber and pharmacy are enrolled and active, and that the
244 patient has not been inactivated in the program.
- 245 i) I understand that ALL ACTIQ and FENTORA prescriptions,
246 regardless of the method of payment, must be processed through
247 our pharmacy management system.
- 248 j) I understand that all dispensing locations must be enrolled in the
249 ACTIQ and FENTORA REMS program to dispense ACTIQ and
250 FENTORA.
- 251 k) I understand that ACTIQ and FENTORA can only be obtained
252 from wholesalers/distributors that are enrolled in the ACTIQ and
253 FENTORA REMS program.
- 254 l) I understand that our pharmacy will not sell, loan or transfer
255 ACTIQ and FENTORA inventory to any other pharmacy,
256 institution, distributor, or prescriber.
- 257 m) I understand that our pharmacy must re-enroll in the ACTIQ and
258 FENTORA REMS program and successfully complete the
259 enrollment requirements every two (2) years.
- 260 n) I understand that ACTIQ and FENTORA are only available
261 through the REMS program. I understand that the pharmacy must
262 comply with the ACTIQ and FENTORA REMS program
263 requirements for outpatient pharmacies.
- 264 e. ***Inpatient Pharmacies:***
- 265 The authorized pharmacist must complete the following requirements to
266 successfully enroll their **inpatient pharmacy**:
- 267 i. Review the ACTIQ and FENTORA REMS education program
268 (*Education Program*) and successfully complete the *Knowledge*
269 *Assessment*
- 270 ii. Complete and sign the *Inpatient Pharmacy Enrollment Form* In
271 signing the Inpatient Pharmacy Enrollment Form the authorized
272 pharmacist is required to acknowledge the following:
- 273 a) I understand the benefits and risks associated with ACTIQ and
274 FENTORA and the requirements of the ACTIQ and FENTORA
275 REMS program.
- 276 b) I will ensure that our inpatient pharmacists are educated on the
277 risks associated with ACTIQ and FENTORA and the requirements

- 278 of the ACTIQ and FENTORA REMS program, as described in the
279 *Education Program*.
- 280 c) I understand that ACTIQ and FENTORA are not bioequivalent to
281 each other or to any other fentanyl product on a microgram-per-
282 microgram basis and therefore must not be substituted for other
283 fentanyl products, unless the patient is converting from the branded
284 product to its generic, or vice versa.
- 285 d) I understand that ACTIQ and FENTORA are contraindicated for
286 use in opioid non-tolerant patients.
- 287 e) I understand that the initial starting dose for ACTIQ and
288 FENTORA for all patients is the lowest dose, unless individual
289 labels provide product specific conversion recommendations.
- 290 f) I understand that pharmacies within or associated with the
291 healthcare facility that dispense to outpatients must also be
292 enrolled in and comply with the ACTIQ and FENTORA REMS
293 program to dispense ACTIQ and FENTORA to outpatients, as
294 described in section B.2.d, above.
- 295 g) I understand that our inpatient pharmacy is not to dispense ACTIQ
296 or FENTORA for outpatient use.
- 297 h) I understand that a prescriber who wants to discharge a patient
298 with an ACTIQ or FENTORA prescription, intended to be
299 dispensed by an outpatient pharmacy, will be required to enroll in
300 the ACTIQ and FENTORA REMS program, as described in
301 section B.1 of this REMS.
- 302 i) I will establish or oversee the establishment of a system, order sets,
303 protocols and/or other measures to help ensure appropriate patient
304 selection and compliance with the requirements of the ACTIQ and
305 FENTORA REMS.
- 306 j) I understand that our pharmacy will not sell, loan, or transfer
307 ACTIQ or FENTORA inventory to any other pharmacy,
308 institution, distributor, or prescriber.
- 309 k) I understand that ACTIQ and FENTORA can only be obtained
310 from wholesalers/distributors that are enrolled in the ACTIQ and
311 FENTORA REMS program.
- 312 l) I understand that our pharmacy must re-enroll in the ACTIQ and
313 FENTORA REMS program every two (2) years.
- 314 m) I understand that ACTIQ and FENTORA are available only
315 through the REMS program. I understand and agree to comply
316 with the ACTIQ and FENTORA REMS program requirements for
317 inpatient pharmacies.

- 318 f. Pharmacies (authorized pharmacist) are required to re-enroll every two (2)
319 years.
- 320 g. Cephalon will:
- 321 i. Ensure that pharmacy enrollment can successfully be completed via
322 the ACTIQ and FENTORA REMS website, mail, fax, or by scanning
323 and e-mailing the forms.
- 324 ii. Ensure that, as part of the enrollment process, pharmacies receive the
325 following materials that are part of the ACTIQ and FENTORA REMS
326 program and are appended:
- 327 • *Pharmacy Overviews (Outpatient Pharmacy Overview or Inpatient*
328 *Pharmacy Overview, as applicable)*
 - 329 • *Education Program*
 - 330 • *Knowledge Assessment*
 - 331 • *Pharmacy Enrollment Form (Outpatient, Chain, or Inpatient, as*
332 *applicable)*
 - 333 • *ACTIQ and FENTORA REMS Website*
- 334 iii. Ensure that all enrollment forms are complete, and that the authorized
335 pharmacist has successfully completed the knowledge assessment
336 before activating a pharmacy's enrollment in the ACTIQ and
337 FENTORA REMS program. For outpatient pharmacies only,
338 Cephalon will also ensure that the upgrades to the pharmacy
339 management system have been validated before enrolling a pharmacy
340 in the ACTIQ and FENTORA REMS program.
- 341 iv. Ensure that pharmacies are notified when they are successfully
342 enrolled in the ACTIQ and FENTORA REMS program, and therefore,
343 certified to dispense ACTIQ and FENTORA.
- 344 v. Monitor education and enrollment requirements for pharmacies and
345 inactivate non-compliant pharmacies. Upon initial activation of
346 enrollment, pharmacies remain active until a corrective action of
347 inactivation occurs or expiration of the enrollment period.
- 348 vi. Ensure that within sixty (60) days after the ACTIQ and FENTORA
349 REMS program approval, Dear Pharmacy Letters will be sent (one for
350 inpatient pharmacies and one for outpatient pharmacies). The target
351 audience for the letter will include outpatient and inpatient pharmacies
352 that dispense Schedule II drugs and may be involved in dispensing
353 ACTIQ or FENTORA. The letter will include information on the risks
354 associated with the use of ACTIQ and FENTORA and the
355 requirements of the ACTIQ and FENTORA REMS program. The
356 letter will be accompanied by a copy of the Full Prescribing
357 Information (which will include the Medication Guide), and will be

358 available on the ACTIQ and FENTORA REMS website for 1 year
359 from the date of the mailing.

360 The Dear Pharmacy Letters (*Outpatient* and *Inpatient*) are part of the
361 ACTIQ and FENTORA REMS Program and are appended.

362 **3. ACTIQ and FENTORA will only be dispensed for outpatient use with**
363 **evidence or other documentation of safe-use conditions.**

- 364 a. Cephalon will ensure that ACTIQ and FENTORA will only be dispensed
365 for outpatient use if there is documentation in the ACTIQ and FENTORA
366 REMS system that the dispensing pharmacy, prescriber, and patient are all
367 enrolled and active in the ACTIQ and FENTORA REMS program.
- 368 b. Patients are passively enrolled in the ACTIQ and FENTORA REMS
369 program when their first ACTIQ or FENTORA prescription is processed
370 at the pharmacy. This enrollment will be part of the normal prescription
371 processing at the pharmacy and will be captured in the ACTIQ and
372 FENTORA REMS system. Prescribers and outpatient pharmacies are
373 enrolled, as previously described in sections B.1 and B.2.a-d, respectively.
- 374 c. Prior to dispensing ACTIQ or FENTORA, enrolled outpatient pharmacies
375 will electronically verify documentation of the required enrollments by
376 processing the ACTIQ or FENTORA prescription through their pharmacy
377 management system.
- 378 i. If the required enrollments are verified, a unique authorization code
379 will be issued to allow processing and dispensing of the prescription
380 to the patient
- 381 ii. If one or more of the required enrollments cannot be verified, the
382 ACTIQ and FENTORA REMS system will reject the prescription
383 (prior to a claim being forwarded to the payer) and the pharmacy will
384 receive a rejection notice.
- 385 d. Following initial activation, patients remain active until a trigger for
386 inactivation occurs. Triggers for patient inactivation include:
- 387 i. The patient has not filled a prescription for more than six (6) months
- 388 ii. The patient receives prescriptions for ACTIQ or FENTORA from
389 multiple prescribers within an overlapping time frame that is
390 suggestive of misuse, abuse, or addiction.
- 391 e. If an active patient transfers from an enrolled prescriber to a non-enrolled
392 or inactive prescriber, the ACTIQ and FENTORA REMS program cannot
393 fill the prescription for ACTIQ and FENTORA until the new prescriber is
394 active in the ACTIQ and FENTORA REMS program.
- 395 f. A patient may have more than one current prescriber (e.g., pain
396 management specialist, primary care physician) provided that
397 prescriptions for ACTIQ or FENTORA are not for the same or

398 overlapping period of treatment.

399 g. Documentation and verification of safe-use conditions are not required for
400 prescriptions ordered within an inpatient healthcare setting and given to an
401 inpatient.

402 C. Implementation System

403 1) Cephalon will ensure that wholesalers/distributors who distribute ACTIQ
404 and FENTORA are enrolled in the ACTIQ and FENTORA REMS program.
405 The wholesaler/distributor enrollment process is comprised of the following
406 steps that must be completed by the distributor's authorized representative,
407 prior to receiving ACTIQ and FENTORA inventory for distribution:

408 a. Review the distributor ACTIQ and FENTORA REMS program
409 materials

410 b. Complete and sign the *Distributor Enrollment Form* and send it to
411 Cephalon (by fax, scan and e-mail, mail or through the ACTIQ and
412 FENTORA REMS website). In signing the *Distributor Enrollment*
413 *Form*, each distributor is required to indicate they understand that
414 ACTIQ and FENTORA are available only through the ACTIQ and
415 FENTORA REMS program and that they must comply with program
416 requirements, and acknowledge that:

417 i. I will ensure that relevant staff are trained on the ACTIQ and
418 FENTORA REMS program procedures and will follow the
419 requirements of the ACTIQ and FENTORA REMS program.

420 ii. I will ensure that ACTIQ and FENTORA are only distributed to
421 pharmacies whose enrollment has been validated in the ACTIQ and
422 FENTORA REMS program.

423 iii. I will provide data to the ACTIQ and FENTORA REMS program
424 including information on shipment to enrolled pharmacies.

425 iv. I will cooperate with periodic audits or noncompliance investigations
426 to ensure that ACTIQ and FENTORA are distributed in accordance
427 with the program requirements.

428 c. Cephalon will ensure that all forms are complete, prior to enrolling a
429 distributor in the ACTIQ and FENTORA REMS program.

430 d. Cephalon will notify distributors when they are enrolled in the ACTIQ
431 and FENTORA REMS program, and therefore, able to distribute
432 ACTIQ and FENTORA.

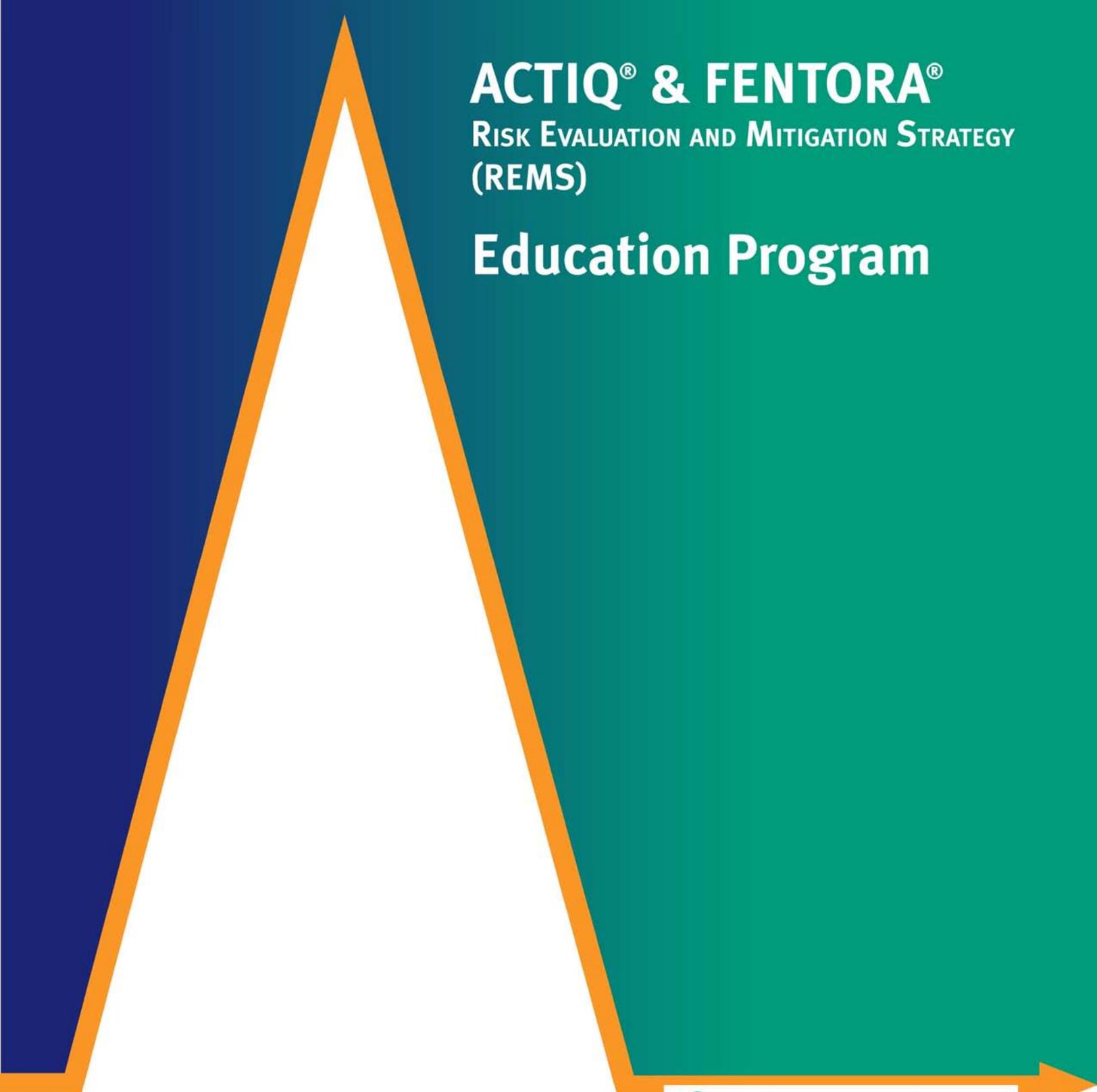
433 e. Upon initial activation, distributors remain active until an action of
434 inactivation occurs, expiration of the enrollment period, or failure to
435 comply with the pharmacy enrollment verification obligations. If a
436 previously active distributor becomes inactive, the distributor may
437 become active again by completing the distributor enrollment process in

- 438 its entirety.
- 439 f. Distributors will be re-educated and re-enrolled in the ACTIQ and
440 FENTORA REMS program every two (2) years.
- 441 g. The following distributor materials are part of the ACTIQ and
442 FENTORA REMS program and are appended:
- 443 • Dear Distributor Letter
- 444 • *Distributor Enrollment Form*
- 445 2) Cephalon will maintain a database of all enrolled entities (prescribers,
446 pharmacies, patients, and distributors) and their status (i.e., active or
447 inactive), and will monitor and evaluate implementation of the ACTIQ and
448 FENTORA REMS requirements.
- 449 3) Cephalon will develop a REMS system that uses existing pharmacy
450 management systems that allow for the transmission of REMS information
451 using established telecommunication standards. The REMS system should
452 incorporate an open framework that allows a variety of distributors, systems
453 vendors, pharmacies, and prescribers to participate, and that is flexible
454 enough to support the expansion or modification of the REMS requirements,
455 if deemed necessary in the future.
- 456 4) Cephalon will monitor distribution data and prescription data to ensure that
457 only actively enrolled distributors are distributing, actively enrolled
458 pharmacies are dispensing, and actively enrolled prescribers for outpatient
459 use are prescribing ACTIQ and FENTORA. Additionally, Cephalon will
460 monitor to ensure that ACTIQ and FENTORA are only being dispensed for
461 outpatient use to actively enrolled patients of actively enrolled prescribers.
462 Corrective action or inactivation will be instituted by Cephalon if
463 noncompliance is found.
- 464 5) Cephalon will monitor prescribers' compliance with the requirement to
465 complete a *Patient-Prescriber Agreement* with each ACTIQ or FENTORA
466 patient, and to submit it to the REMS program within ten (10) business days.
467 This will be accomplished through patient surveys and by reconciling the
468 *Patient-Prescriber Agreements* submitted to the REMS program with
469 patient enrollment data captured through the pharmacy management system.
- 470 6) Cephalon will monitor and evaluate all enrolled outpatient pharmacies,
471 distributors, and the ACTIQ and FENTORA REMS program vendors to
472 validate the necessary system upgrades and ensure the program is
473 implemented as directed.
- 474 7) Cephalon will evaluate enrolled inpatient pharmacies' compliance with
475 REMS requirements through surveys.
- 476 8) Cephalon will maintain a call center to support patients, prescribers,
477 pharmacies, and distributors in interfacing with the ACTIQ and FENTORA
478 REMS program.

- 479 9) Cephalon will ensure that all materials listed in or appended to the ACTIQ
480 and FENTORA REMS will be available through the ACTIQ and
481 FENTORA REMS website (www.actiqandfentorarems.com) or by calling
482 the program Coordinating Center toll-free support line at 888-688-6885.
- 483 10) Cephalon will notify pharmacies, prescribers, and distributors of
484 forthcoming enrollment expiration and the need to re-enroll in the REMS
485 program. Notifications for patients will be sent to the patient’s prescriber.
- 486 11) If there are substantive changes to the ACTIQ and FENTORA REMS
487 program, Cephalon will update all affected materials and notify pharmacies,
488 prescribers, and distributors of the changes, as applicable. Notifications for
489 patients will be sent to the patient’s prescriber. Substantive changes to the
490 ACTIQ and FENTORA REMS program are defined as:
- 491 a. Significant changes to the operation of the ACTIQ and FENTORA
492 REMS program.
- 493 b. Changes to the Prescribing Information and Medication Guide that affect
494 the risk benefit profile of ACTIQ and FENTORA.
- 495 12) Based on monitoring and evaluation of the REMS Elements to Assure
496 Safe Use, Cephalon will take reasonable steps to improve implementation
497 of these elements and to maintain compliance with the ACTIQ and
498 FENTORA REMS program requirements, as applicable.
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500 **III TIMETABLE FOR SUBMISSION OF ASSESSMENTS**

501 Cephalon will submit REMS Assessments to the FDA every six (6) months for the first
502 year following the approval of the ACTIQ and FENTORA REMS, and annually
503 thereafter. To facilitate inclusion of as much information as possible while allowing
504 reasonable time to prepare the submission, the reporting interval covered by each
505 assessment should conclude no earlier than sixty (60) days before the submission date of
506 the assessment. Cephalon will submit each assessment so that it will be received by the
507 FDA on or before the due date.



ACTIQ® & FENTORA®
RISK EVALUATION AND MITIGATION STRATEGY
(REMS)

Education Program

 **FENTORA.**
fentanyl buccal tablet @

Actiq®
(oral transmucosal
fentanyl citrate)

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Welcome and Introduction

Welcome to the ACTIQ and FENTORA mandatory education program. The Risk Evaluation and Mitigation Strategy (REMS) program requires distributors, outpatient prescribers, outpatient and inpatient pharmacies, and patients to be enrolled in order to ship, prescribe, dispense, or use ACTIQ and FENTORA. Prescribers writing orders for inpatient use only do not need to enroll.

Before you can enroll in the ACTIQ and FENTORA REMS program, you must:

- review the education program
- successfully complete the knowledge assessment
- sign the acknowledgment statements

Renewal of enrollment is required every 2 years or in cases of major safety updates to the label for ACTIQ and FENTORA. You will receive a reminder to renew your enrollment at the appropriate time.

Although, this educational program discusses both ACTIQ and FENTORA, these products are NOT equivalent to each other or to any other fentanyl product on a microgram-per-microgram basis.

For information about the REMS program requirements and operations, please review the ACTIQ and FENTORA REMS Program Overview, which can be found at www.actiqandfentorarems.com.

Please review the Full Prescribing Information. This educational program is NOT a substitute for the Prescribing Information

Goals of ACTIQ and FENTORA REMS

The goals of the ACTIQ and FENTORA REMS program are to mitigate the risks of misuse, abuse, addiction, overdose, and serious complications due to medication errors, by:

1. Prescribing and dispensing only to appropriate patients, which includes use only in opioid tolerant patients
2. Preventing inappropriate conversions between fentanyl products
3. Preventing accidental exposure to children and others for whom they were not prescribed

4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose

Appropriate Patient Selection

Indication and Usage

ACTIQ and FENTORA are indicated only for the management of breakthrough cancer pain in patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

- ACTIQ is indicated in patients who are 16 and older.

ACTIQ and FENTORA must not be used in opioid non-tolerant patients, because life-threatening respiratory depression could occur in patients not taking chronic opiates.

Opioid tolerant means that the patient has had the requisite exposure to, and is still taking around-the-clock opioids for, persistent pain. In this context, opioid tolerant does not refer to analgesic tolerance or a loss of treatment efficacy over time.

Patients must also continue to take their around-the-clock opioids for as long as they are taking ACTIQ or FENTORA. It is important that healthcare professionals communicate this to their patients/caregivers.

Definition of Opioid Tolerance

Patients considered opioid tolerant, are those who are taking around-the-clock opioids consisting of at least 60 mg of oral morphine daily, or an equivalent dose of another opioid daily for one week or longer.

Patients considered opioid tolerant are those who are regularly taking at least 60 mg oral morphine/day; 25 mcg transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for 1 week or longer. Equivalent doses for the other commonly used opioids are based on the published literature.

Generic name	Dose for opioid tolerance
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ACTIQ AND FENTORA REMS PROGRAM

RISK EVALUATION AND MITIGATION STRATEGY

Morphine	60 (oral) mg/day
Transdermal fentanyl	25 mcg/hour
Oxycodone	30 (oral) mg/day
Hydromorphone	8 (oral) mg/day
Oxymorphone	25 (oral) mg/day

Contraindications

ACTIQ and FENTORA are contraindicated in opioid non-tolerant patients.

- Serious adverse events in patients treated with ACTIQ or FENTORA have been reported.
- Deaths have occurred as a result of improper patient selection and/or improper dosing.

Life-threatening respiratory depression and death could result at any dose in patients not on a chronic regimen of opioids. For this reason, ACTIQ and FENTORA are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain.

ACTIQ and FENTORA are contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl.

Understanding Patient-specific Risk Factors

Risk of Misuse, and Abuse, and Overdose

ACTIQ and FENTORA contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. This should be considered when prescribing or dispensing ACTIQ or FENTORA in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Patient risk factors for opioid abuse include:

- A history of past or current alcohol use
- A history of psychiatric illness
- A history of illicit drug use

However, concerns about abuse and addiction should not prevent the proper management of pain. All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Measures to take to help limit abuse of opioid products:

- Proper assessment of patients
- Safe prescribing practices
- Periodic prescribing practices
- Proper dispensing and storage
- Keep detailed records of prescribing information
- Keep a signed ACTIQ and FENTORA Patient-Prescriber Agreement
- Inform patients/caregivers to protect against theft and misuse of ACTIQ and FENTORA

Risk of Accidental Exposure

Patients and their caregivers must be instructed that ACTIQ and FENTORA contain medicine in an amount that can be fatal to a child.

- Death has been reported in children who have accidentally ingested ACTIQ.
- Accidental exposure can occur in children of all ages, including toddlers through teens.
- Inform patients that these formulations have a rapid onset.

Inform patients/caregivers to safely store ACTIQ and FENTORA to protect against accidental exposure to children and others for whom they were not prescribed.

Risk of Drug Interaction

Fentanyl is metabolized mainly via the human cytochrome P450 3A4 isoenzyme system (CYP3A4); therefore, potential interactions may occur when ACTIQ or FENTORA is given concurrently with agents that affect CYP3A4 activity.

The concomitant use of ACTIQ or FENTORA with CYP3A4 inhibitors* may result in increased fentanyl plasma concentrations, potentially causing serious adverse drug effects including fatal respiratory depression.

Patients receiving ACTIQ or FENTORA, who begin therapy with or increase the dose of CYP3A4 inhibitors, should be carefully monitored for signs of opioid toxicity over an extended period of time. Dosage increase of ACTIQ or FENTORA should be done conservatively.

*CYP3A4 inhibitors may include:

Ritonavir,	clarithromycin
ketoconazole	nelfinavir,
itraconazole	nefazodone
troleandomycin	erythromycin
amprenavir	fluconazole
aprepitant	fosamprenavir
diltiazem	verapamil

Dosage and Administration

Initial Dose: Follow dosing instructions for ACTIQ and FENTORA carefully:

- The initial dose for ACTIQ is always 200 mcg
- The initial dose for FENTORA is always 100 mcg (unless the patient is being converted from ≥ 600 mcg ACTIQ - please see full prescribing information)

In cases where the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose of ACTIQ or FENTORA at the same strength for that episode.

- Patients should not take more than 2 doses of ACTIQ or FENTORA per breakthrough pain episode.

After an episode of breakthrough pain has been treated, patients must wait at least 4 hours before treating another episode with ACTIQ or FENTORA. Once a successful dose has been found, an average breakthrough pain episode can be treated with a single unit.

The patient should be educated on appropriate administration of ACTIQ and FENTORA, according to the prescribing information. For example, ACTIQ and FENTORA should not be chewed or swallowed, as this will result in lower plasma concentrations than when taken as directed.

Limit the number of ACTIQ or FENTORA dosage strengths provided to the patient, to prevent confusion and possible overdose. The initial supply of ACTIQ should be limited to **six** 200-mcg ACTIQ units. Patients should have only one strength of ACTIQ and FENTORA available at any one time to reduce the risk of overdose.

If patients stop taking their around-the-clock medication, they must stop taking ACTIQ or FENTORA.

Appropriate Conversion

ACTIQ and FENTORA are NOT equivalent to each other or to any other fentanyl product on a microgram-per-microgram basis.

Substantial differences exist in the pharmacokinetic profile of ACTIQ and FENTORA compared with each other and to other fentanyl products. As a result of these differences, the substitution of ACTIQ and FENTORA for each other or any other fentanyl product may result in fatal overdose.

Do not convert patients from another immediate-release fentanyl product to ACTIQ or FENTORA without re-titrating according to the prescribing information.

When dispensing any transmucosal immediate-release fentanyl product, do not substitute ACTIQ and FENTORA for any other fentanyl product, unless converting from the branded product to its generic, or vice versa.

Do not prescribe more than one transmucosal immediate-release fentanyl product at one time for the treatment of breakthrough pain.

Dose Titration

If adequate analgesia was not obtained with the initial dose, continue dose escalation in a stepwise manner over consecutive breakthrough pain episodes until adequate analgesia with tolerable side effects is achieved.

Maintenance Dosing

Once titrated to an effective dose, each breakthrough pain episode should be treated with a single unit of ACTIQ or FENTORA.

If the prescribed dose no longer adequately manages the cancer breakthrough pain for several consecutive episodes, increase the dose as described in the titration section of the prescribing information.

Re-evaluate the dose of the around-the-clock opioid if the patient experiences more than 4 breakthrough pain episodes per day.

For additional detail surrounding titration and maintenance dosing for ACTIQ and FENTORA, please see full prescribing information.

Patient Counseling

- Review the Medication Guide with patients, and counsel them on the risks and safe use of these medicines.
- Explain that ACTIQ and FENTORA contain medicine in an amount that could be fatal to children of all ages, in individuals for whom they were not prescribed, and in those who are not opioid tolerant.
- Explain what it means to be opioid tolerant. Tell patients that they must not take ACTIQ or FENTORA unless they are opioid tolerant.
- Inform patients that ACTIQ and FENTORA must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.
- Instruct patients that, if they stop taking their around-the-clock opioid medication, they must stop taking ACTIQ or FENTORA.
- Instruct patients to never share ACTIQ or FENTORA with anyone else even if that person has the same symptoms
- Instruct patients to take ACTIQ and FENTORA strictly as prescribed, with special regard to dosage, dose titration, and administration.
- Patients must be instructed not to switch from ACTIQ or FENTORA to another fentanyl product, without discussing it with their physician.
- Instruct patients to safely store both used and unused dosage units out of the reach of children living in or likely to visit the home. Partially consumed units represent a special risk to children.
- Inform patients and their caregivers of the need to take precautions to protect against theft, accidental access, overdose, misuse, or abuse of ACTIQ and FENTORA in the work or home environment.
- Instruct patients on proper disposal of unused and remaining ACTIQ and FENTORA.

Storage and Disposal of ACTIQ and FENTORA

When counseling patients, instruct them on the need to properly dispose of ACTIQ and FENTORA units and to keep ACTIQ and FENTORA out of the reach of children at all times.

If an ACTIQ or FENTORA unit is not completely consumed, it must be disposed of as soon as possible.

- Partially consumed ACTIQ units are a particular risk to children.

- An ACTIQ Child Safety Kit is available to patients and their caregivers to store ACTIQ out of the reach of children (additional details provided in the ACTIQ Medication Guide).
- Partially used ACTIQ should be dissolved under hot running water, and the handle should be thrown away out of the reach of children.

To dispose of unused FENTORA, FENTORA tablets must be removed from blister packages and flushed down the toilet.

To dispose of unused or partially used ACTIQ units, patients should follow instructions in the Medication Guide to flush units down the toilet.

- Blister packages or cartons should not be flushed down the toilet.

Patients should also be instructed to promptly dispose of any remaining ACTIQ or FENTORA units when they are no longer needed. For assistance with disposal of ACTIQ or FENTORA units or to obtain an ACTIQ Child Safety Kit, patients should contact Cephalon at 1-800-896-5855.

Effective Patient Management and Follow-up

On an ongoing basis, monitor patients' treatment, including assessing the appropriateness of the dosage and the need for continued opioid therapy. Monitor patients for efficacy and frequency of use of ACTIQ and FENTORA, and adjust the around-the-clock opioid dosage as needed to optimize pain management.

Monitor for signs of abuse and addiction:

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

- Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, is strongly advised.
- Encourage patients to record how much/how often ACTIQ or FENTORA is being used so that appropriate and necessary dose adjustment of ACTIQ or FENTORA or of their around-the-clock opioid medication occurs.
- Be aware that abuse and addiction are separate and distinct from physical dependence and tolerance.
- Abuse of opioids can occur in the absence of addiction, and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances.

- The possibility of psychological dependence should be considered when a pattern of inappropriate behavior is observed.

Promptly report suspected adverse events including misuse, abuse, and overdose directly to Cephalon by calling 1-800-896-5855. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse of these products.

Conclusion

You have reached the end of this program. You will need to complete the assessment to enroll in the ACTIQ and FENTORA REMS program. Go to the following page to complete the assessment.

Knowledge Assessment

You are now going to answer 12 questions, which will test your knowledge of appropriate use and prescribing of ACTIQ and FENTORA.

If you do not have access to www.actiqandfentorarems.com, you must send this to the ACTIQ and FENTORA REMS program via fax (888-688-1050).

<p>Prescriber/Authorized Pharmacist*</p> <p>First Name: _____ MI: _____ Last Name: _____</p> <p>DEA #s: _____ NPI #: _____</p> <p>Chain ID #: _____ NCPDP #: _____</p> <p>E-mail: _____</p> <p>Phone: (____) _____ Fax: (____) _____</p> <p><small>*or Authorized Corporate Representative</small></p>

1. All of the patients described are experiencing breakthrough pain, but ONE of them is not an appropriate patient for ACTIQ or FENTORA. Which one should not receive ACTIQ or FENTORA? Select one option.
 - A. A 28-year-old female patient on 60 mg of oral morphine daily for persistent pain for 6 weeks
 - B. A 60-year-old male patient managed with a 50-mcg/hour transdermal fentanyl patch for persistent pain for the last month
 - C. A 43-year-old female patient managed with 8 mg of oral hydromorphone per day for persistent pain for the last 2 weeks
 - D. A 31-year-old male patient managed with 20 mg of oral oxycodone per day for persistent pain for the last 3 weeks
2. All of the patients described are experiencing breakthrough pain, but ONE of them is not an appropriate patient for ACTIQ or FENTORA. Which one should not receive ACTIQ or FENTORA? Select one option.
 - A. A 68-year-old female patient on her third day of 30 mg of oral oxycodone for persistent pain
 - B. A 55-year-old male patient currently managed with a 25-mcg/hour transdermal fentanyl patch for persistent pain for the last month
 - C. A 52-year-old female patient on 60 mg of oral morphine daily for persistent pain for the last 2 months
 - D. A 38-year-old female patient on two 8-mg tablets of hydromorphone per day for persistent pain for the last 3 weeks

3. All of the patients described are experiencing breakthrough pain, but ONE of them is not an appropriate patient for ACTIQ. Which one should not receive ACTIQ? Select one option.
 - A. A 16-year-old female patient on 60 mg of oral morphine daily for persistent pain for 6 weeks
 - B. A 31-year-old male patient managed with 30 mg of oral oxycodone daily for persistent pain for 3 months
 - C. A 50-year-old male patient currently on a 25-mcg/hour transdermal fentanyl patch for persistent pain for the last month
 - D. A 12-year-old female patient on 8 mg of oral hydromorphone daily for persistent pain for the last 5 weeks

4. Certain factors may increase the risk of misuse, abuse, addiction, and overdose of opiate medications. Which of the following would be a consideration when prescribing ACTIQ or FENTORA? Select one option.
 - A. Patient has a history of prescription drug abuse.
 - B. Patient's mother has a history of alcohol abuse.
 - C. Patient has a history of psychiatric illness.
 - D. All of the above

5. There is a risk of fatal overdose with inappropriate use of ACTIQ and FENTORA. Which of the following answers is most accurate? Select one option.
 - A. ACTIQ and FENTORA can be fatal if taken by children.
 - B. ACTIQ and FENTORA can be fatal if taken by anyone for whom they are not prescribed.
 - C. ACTIQ and FENTORA can be fatal if taken by anyone who is not opioid tolerant.
 - D. All of the above

6. A patient is taking another transmucosal fentanyl product (e.g., Abstral[®]) and wants to change his/her medication. His/her doctor decides to prescribe ACTIQ. How should the doctor proceed? Select one option.
 - A. The doctor can switch from the other transmucosal product to ACTIQ at half the dose.
 - B. The doctor can safely substitute the equivalent dosage of ACTIQ, as it has the same effect as other transmucosal fentanyl products.
 - C. The doctor should start the patient on 200 mcg of ACTIQ.
 - D. The doctor should base the starting dose of ACTIQ on the dose of the opioid medication used for the underlying persistent pain.

7. A prescriber has started titrating a patient with 100 mcg of FENTORA. However, after 20 minutes, the breakthrough pain has not been sufficiently relieved. What could the prescriber advise the patient to do? Select one option.
- A. Wait 2 hours, then, if the pain is still present, take another 100 mcg.
 - B. Take another dose of 100 mcg immediately.
 - C. Wait an additional 10 minutes (i.e., for a total of 30 minutes since the initial FENTORA dose), then, if the pain is still present, take another 100 mcg dose.
 - D. Double the dose to 200 mcg and take immediately.
8. A patient currently taking 600 mcg of ACTIQ for breakthrough pain wishes to change his/her medication. His/her doctor decides to prescribe FENTORA. How should the doctor proceed? Select one option.
- A. The doctor can safely substitute the equivalent dosage of FENTORA, as it has the same effect as ACTIQ.
 - B. Based on the initial dosing guidelines in the prescribing information, a patient converting from 600 mcg of ACTIQ to FENTORA should be started at a dose of 200 mcg.
 - C. The doctor should base the starting dose of FENTORA on the dose of the opioid medication used for the underlying persistent pain.
 - D. Based on the initial dosing guidelines in the prescribing information, a patient converting from 600 mcg of ACTIQ to FENTORA should be started at a dose of 800 mcg.
9. The FENTORA package insert and Medication Guide contain important information on the proper storage and disposal of FENTORA. Which of the following statements is correct? Select one option.
- A. The amount of fentanyl contained in FENTORA can be fatal to a child.
 - B. Patients and their caregivers should be instructed to keep FENTORA in a safe and secure place, out of the reach of children, and protected against theft.
 - C. Patients and their household members must be advised to dispose of any tablets remaining from a prescription as soon as they are no longer needed.
 - D. All of the above

10. An opioid tolerant patient taking 600 mcg of ACTIQ is increased in his/her dose to 800 mcg of ACTIQ and still has 2 boxes of 600 mcg of ACTIQ in the home. What should the patient do? Select the best option.
- A. Keep the 600 mcg ACTIQ units in a safe place in his/her home.
 - B. Dispose of the remaining units according to the instructions for disposal listed in the ACTIQ Medication Guide.
 - C. Return the remaining 600 mcg ACTIQ units to his/her doctor.
 - D. Return the ACTIQ units to his/her pharmacy.
11. Before initiating treatment with ACTIQ or FENTORA, prescribers must review the Medication Guide with the patient. Which of the following counseling statements is not correct? Select one option.
- A. ACTIQ and FENTORA contain medicine in an amount that could be fatal to children of all ages, in individuals for whom they were not prescribed, and in those who are not opioid tolerant.
 - B. Inform patients that ACTIQ and FENTORA must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.
 - C. Instruct patients that, if they stop taking their around-the-clock opioid medication, they can continue to take ACTIQ or FENTORA.
 - D. Instruct patients to never share ACTIQ or FENTORA with anyone else, even if that person has the same symptoms.
12. A patient taking FENTORA is prescribed ketoconazole, a CYP3A4 inhibitor, by his/her doctor. Which of the following statements is correct? Select one option.
- A. There is no potential drug-drug interaction between FENTORA and ketoconazole.
 - B. The dosage strength of FENTORA may need to be increased.
 - C. Concomitant use of a CYP3A4 inhibitor may increase the plasma concentration of fentanyl and increase the risk of fatal respiratory depression. The patient should be carefully monitored for an extended period of time, and the dosage strength of FENTORA may need to be decreased.
 - D. The dose of FENTORA must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.

**ACTIQ and FENTORA Risk Evaluation and Mitigation Strategy (REMS) Program
PRESCRIBER ENROLLMENT FORM**

The Prescriber must complete and submit this form.

Prescribers must be enrolled in the ACTIQ and FENTORA REMS program to prescribe ACTIQ and FENTORA.

I understand that ACTIQ and FENTORA are available only through the ACTIQ and FENTORA REMS program and that I must comply with the program requirements, and I acknowledge that:

1. I have reviewed the ACTIQ and FENTORA Full Prescribing Information, *Prescriber Education Program*, and I have completed the *Prescriber Knowledge Assessment*. I understand the responsible use conditions for ACTIQ and FENTORA and the risks and benefits of chronic opioid therapy.
2. I understand that ACTIQ and FENTORA can be abused and that this risk should be considered when prescribing or dispensing ACTIQ and FENTORA in situations where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.
3. I understand that ACTIQ and FENTORA are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.
4. I understand that ACTIQ and FENTORA are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.
5. I understand that ACTIQ and FENTORA must not be used to treat any contraindicated conditions such as acute or postoperative pain, including headache/migraine.
6. I understand that the initial starting dose for ACTIQ and FENTORA for all patients is the lowest dose, unless individual labels provide product specific conversion recommendations, and that patients must be titrated individually.
7. I understand that ACTIQ and FENTORA are not bioequivalent with each other or any other fentanyl product (regardless of route of administration), and that substitution may result in fatal overdose. I understand that patients switching from another fentanyl product to ACTIQ or FENTORA must not be converted on a microgram-per-microgram basis, unless the patient is converting from branded product to its generic, or vice versa.
8. I will complete and sign an ACTIQ and FENTORA REMS *Patient-Prescriber Agreement* form with each new patient, before writing the patient's first prescription, and re-new the agreement every two (2) years.
9. I will provide a completed, signed copy of the *Patient-Prescriber Agreement* to the patient and retain a copy for my records, I will send a completed, signed copy to the ACTIQ and FENTORA REMS program (by fax or through the ACTIQ and FENTORA REMS website) within ten (10) working days
10. At all follow-up visits, I agree to assess the patient for appropriateness of the dose, and for signs of misuse and abuse.
11. I understand that ACTIQ and FENTORA are only available through the ACTIQ and FENTORA REMS program. I understand and agree to comply with the ACTIQ and FENTORA REMS program requirements for prescribers.

Prescriber First Name: _____ **MI:** _____ **Last Name:** _____

Signature _____ **Date:** _____

Degree: MD DO NP Nurse with prescriptive authority Other (specify) _____

State License #: _____ **State of Issue:** _____

DEA #: _____ **NPI #:** _____

E-mail: _____

Address: _____

City: _____ **State:** _____ **ZIP:** _____

Phone: () _____ **Alternate Phone:** () _____ **Fax:** () _____

Preferred Method of Contact: E-mail FAX

Office Contact First Name: _____ **MI:** _____ **Last Name:** _____

Phone: () _____ **Fax:** () _____ **E-Mail:** _____
(if different from above) (if different from above) (if different from above)

If you do not have access to www.actiqandfentorarems.com, you must send a copy of this agreement to the ACTIQ and FENTORA REMS program via fax (888-688-1050).

If you have additional sites, state license or DEA numbers that you may use when prescribing ACTIQ or FENTORA please complete next page

Please retain a copy of the completed form for your records.

You must re-enroll every two (2) years or in case of major safety updates to the ACTIQ or FENTORA label and/or major program changes.

For more information about the ACTIQ and FENTORA program please visit www.actiqandfentorarems.com or call 1-888-688-6885.

For more information about ACTIQ or FENTORA, please see accompanying full prescribing information, including boxed warning.

This form is part of an FDA-approved REMS.

Additional Prescriber Information

Prescriber Last Name: _____

Site Name _____

Address _____

City _____ **State** _____ **Zip Code** _____

Phone _____ **Fax** _____

Site Name _____

Address _____

City _____ **State** _____ **Zip Code** _____

Phone _____ **Fax** _____

Site Name _____

Address _____

City _____ **State** _____ **Zip Code** _____

Phone _____ **Fax** _____

DEA Number _____

DEA Number _____

DEA Number _____

State License Number _____ **State Issued** _____

State License Number _____ **State Issued** _____

State License Number _____ **State Issued** _____

Please retain a copy of the completed form for your records.

You must re-enroll every two (2) years or in case of major safety updates to the ACTIQ or FENTORA label and/or major program changes.

For more information about the ACTIQ and FENTORA program please visit www.actiqandfentorarems.com or call 1-888-688-6885.

For more information about ACTIQ or FENTORA, please see accompanying full prescribing information, including boxed warning.

This form is part of an FDA-approved REMS.

PATIENT-PRESCRIBER AGREEMENT

Prescriber: If you do not have access to the program website (www.actiqandfentorarems.com) for completion of this form, you must fax this form (888-688-1050) to the ACTIQ and FENTORA REMS program as soon as possible. Your patient will not be able to receive a second prescription if this form is not received by the REMS Program.

Prescriber and patient must sign this form to complete.

Prescriber will provide a completed, signed copy of this form to the patient and retain signed original.

As the prescriber of ACTIQ® or FENTORA®, I acknowledge that:

1. Patient is currently using around-the-clock opioid analgesia and has been for at least one (1) week.
2. Patient is opioid tolerant. Patients considered opioid tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 mcg transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.
3. A Medication Guide for ACTIQ or FENTORA has been provided to and reviewed with the patient or their caregiver
4. The patient or their caregiver has been counseled about the risks, benefits, and appropriate use of ACTIQ and FENTORA including communication of the following safety messages:
 - A. If patients stop taking their around-the-clock opioid medication, they must stop taking their ACTIQ or FENTORA.
 - B. NEVER share ACTIQ or FENTORA
 - C. Giving ACTIQ or FENTORA to someone for whom it has not been prescribed can result in a fatal overdose.
 - D. ACTIQ and FENTORA can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home.

Prescriber Signature

Date

Please print: Prescriber Name, Credentials

Prescriber NPI#

Fax Number

Email

Prescriber DEA#

As the patient being prescribed ACTIQ® or FENTORA®, or a legally authorized representative, I acknowledge that:

1. My prescriber has given me a copy of the Medication Guide and has reviewed it with me.
2. I understand that before I can take this medication, I must be regularly using another opioid pain medication, around-the-clock, for my constant pain.
3. I understand that if I stop taking my around-the-clock opioid pain medication for my constant pain, I must stop taking this medication.
4. I understand how I should take this medication, including how much I can take, and how often I can take it.
5. I understand that this medication can cause serious side effects, including life threatening breathing problems which can lead to death, especially if I do not take this medicine exactly as my prescriber has directed me to take it.
6. I agree to contact my prescriber if this medication does not relieve my pain. I will not change my dose of this medication myself or take it more often than my prescriber has directed.
7. I agree that I will never give this medication to anyone else, even if they have the same symptoms, since it may harm them or even cause death.
8. I will store this medication in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.
9. I have been instructed on how to properly dispose of unused and remaining medication and will dispose of this medication as soon as I no longer need it.
10. I understand that selling or giving away this medication is against the law.
11. I have asked my prescriber all the questions I have about this medication. If I have any additional questions or concerns in the future about my treatment with this medication, I will contact my prescriber.
12. Patient Authorization for Disclosure and Use of Health Information Statement: I have reviewed the Patient Authorization for Disclosure and Use of Health Information Statement and I agree to its terms and conditions to authorize my healthcare providers and health plans to disclose my personal and medical information to Cephalon, Inc. (the maker of this medication) and their agents and contractors, to administer the REMS program.

Patient Signature/Date

Legally Authorized Representative Signature/Date

- Spouse Legal Guardian
 Designated Representative per Power of Attorney

Please print: Patient Full Legal Name (Last)

(First)

Please print: Legally Authorized Representative Name

If prescriber does not have access to www.actiqandfentorarems.com, prescriber must send a copy of this agreement to the ACTIQ and FENTORA REMS program via fax (888-688-1050) within ten (10) working days of patient's first prescription.

Patient Authorization for Disclosure and Use of Health Information for ACTIQ and FENTORA REMS Program

I hereby authorize each of my physicians, pharmacists, and other healthcare providers (together, my "Providers") and each of my health insurers (together, my "Insurers") to disclose my personally identifiable health information, including information related to my medical diagnosis, condition, and treatment (including lab and prescription information), and my name, address, and telephone number (together, my "Health Information") to Cephalon, Inc., its agents and representatives, including third parties authorized by Cephalon, Inc. to administer the ACTIQ and FENTORA REMS program (together, "Cephalon") for the purposes described below.

Specifically, I authorize Cephalon to receive, use, and disclose my Health Information in order to:

- I. Enroll me in the ACTIQ and FENTORA REMS program and administer my participation (including contacting me) in the ACTIQ and FENTORA REMS program.
- II. Evaluate the appropriate use of ACTIQ and FENTORA and the effectiveness of the ACTIQ and FENTORA REMS program.
- III. Provide me with educational information with respect to the ACTIQ and FENTORA REMS program.
- IV. Contact my Providers to collect, enter and maintain my Health Information in a secure ACTIQ and FENTORA REMS database.
- V. Make submissions to the FDA regarding matters such as adverse events and ACTIQ and FENTORA REMS program effectiveness.

I understand that I am not required to sign this Authorization. However, if I do not sign, I will not be able to enroll in the ACTIQ and FENTORA REMS program and will not be able to receive ACTIQ or FENTORA.

I understand that I may revoke (withdraw) this Authorization at any time by faxing a signed, written request to the ACTIQ and FENTORA REMS program at 1-888-688-1050. Cephalon shall notify my Providers and Insurers of my revocation, who may no longer disclose my Health Information to Cephalon once they have received and processed that notice. However, revoking this Authorization will not affect Cephalon's ability to use and disclose my Health Information that it has already received to the extent permitted under applicable law. If I revoke this Authorization, I will no longer be able to participate in the ACTIQ and FENTORA REMS program to receive ACTIQ or FENTORA.

Cephalon agrees to protect my information by using and disclosing it only for the purposes described.

This form is part of an FDA approved REMS.

ACTIQ and FENTORA REMS Program

An Overview for Prescribers

The ACTIQ and FENTORA REMS Program

The ACTIQ[®] (oral transmucosal fentanyl citrate) and FENTORA[®] (fentanyl buccal tablet) REMS is a restricted distribution program designed to help ensure appropriate patient selection and the safe use of ACTIQ and FENTORA. Because of the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors, only prescribers, pharmacies, distributors and patients enrolled in the program are able to prescribe, dispense, distribute, and receive ACTIQ and FENTORA in an outpatient setting.

In order to reduce the risks of inappropriate patient selection and ensure appropriate dosing and administration of ACTIQ and FENTORA, you will be enrolled only after successful completion of the knowledge assessment. Educational opportunities and knowledge assessment questions are available online at the ACTIQ and FENTORA REMS program website (www.actiqandfentorarems.com) or by contacting the ACTIQ and FENTORA REMS call center at 1-888-688-6885 to request materials. You will be required to attest to your understanding of the appropriate use of ACTIQ and FENTORA and adherence to the ACTIQ and FENTORA REMS program.

Without this enrollment, you will not be eligible to prescribe ACTIQ and FENTORA for outpatient use. In addition, only enrolled pharmacies are eligible to dispense ACTIQ and FENTORA prescriptions. Outpatient prescriptions written by non-enrolled prescribers will not be authorized by the ACTIQ and FENTORA REMS program and will not be dispensed to the patient.

Inpatient Prescribers

Prescribers and patients are not required to be enrolled in the ACTIQ and FENTORA REMS program for inpatient use. However, if a prescriber would like to prescribe ACTIQ or FENTORA upon a patient's discharge, prescribers will need to be enrolled in the REMS program and patients will need to receive counseling and sign a Patient-Prescriber Agreement.

Steps for Outpatient Prescribing for ACTIQ and FENTORA REMS program.

Step 1 Prescriber Education and Enrollment (Outpatient Use)

- Create an account and register on www.actiqandfentorarems.com Review the ACTIQ and FENTORA REMS prescriber educational materials including the Full Prescribing Information, and Successfully complete the Knowledge Assessment. The Education Program and Knowledge Assessment are available on line at www.actiqandfentorarems.com or by contacting the ACTIQ and FENTORA REMS program at 1-888-688-6885
- Complete and sign the Prescriber Enrollment Form and re-new the agreement every two years.

Step 2 Patient Education

- Identify appropriate patients.

- Counsel the patient about the benefits and risks of ACTIQ or FENTORA and together review the Medication Guide.
- Encourage the patient to ask questions.
- Complete the Patient-Prescriber Agreement, which must be signed by both you and your patient (not required for inpatients).
- Submit the signed Patient-Prescriber Agreement to the ACTIQ and FENTORA REMS program via fax or through the ACTIQ and FENTORA REMS website at www.actiqandfentorarems.com
- This agreement needs to be submitted within 10 business day of completing the agreement. If this form is not received by the ACTIQ and FENTORA REMS program, the patients' next prescription for ACTIQ or FENTORA will not be authorized.

Step 3 Prescribing

- Write prescription for ACTIQ or FENTORA.
- Help each patient to find pharmacies which are enrolled in the ACTIQ and FENTORA REMS program.
 - A list of ACTIQ and FENTORA REMS pharmacies can be located on www.actiqandfentorarems.com or by calling 1-888-688-6885.

Step 4 Monitoring

- Promptly report suspected adverse events including misuse, abuse, and overdose directly to Cephalon by calling 1-800-896-5855.
- Respond to requests for additional information form the ACTIQ and FENTORA REMS program.

For more information you can call the ACTIQ and FENTORA REMS program at 1-888-688-6885 or visit www.actiqandfentorarems.com

Important Safety Information

WARNING: IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

Reports of serious adverse events, including deaths in patients treated with ACTIQ have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of ACTIQ for any other fentanyl product may result in fatal overdose.

ACTIQ is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of

transdermal fentanyl/hour, at least 30 mg of oral oxycodone daily, at least 8 mg oral hydromorphone daily, at least 25 mg oral oxymorphone daily, or an equianalgesic dose of another opioid for a week or longer.

ACTIQ is not indicated for use in opioid non-tolerant patients including those with only as needed (PRN) prior exposure.

Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients.

ACTIQ is contraindicated in the management of acute or postoperative pain including headache/migraine.

When prescribing, do not convert patients on a mcg per mcg basis to ACTIQ from other fentanyl products.

When dispensing, do not substitute an ACTIQ prescription for other fentanyl products. Substantial differences exist in the pharmacokinetic profile of ACTIQ compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl. As a result of these differences, the substitution of ACTIQ for any other fentanyl product may result in fatal overdose.

Special care must be used when dosing ACTIQ. If the breakthrough pain episode is not relieved 15 minutes after completion of the ACTIQ unit, patients may take **ONLY ONE** additional dose using the same strength and then must wait at least 4 hours before taking another dose [see *Dosage And Administration (2.2)*].

ACTIQ contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. ACTIQ can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing ACTIQ in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Patients and their caregivers must be instructed that ACTIQ contains a medicine in an amount which can be fatal to a child. Death has been reported in children who have accidentally ingested ACTIQ. All units must be kept out of the reach of children and opened units properly discarded [see *Warnings And Precautions (5.3)*, *Patient Counseling Information (17.5, 17.6)*, and *How Supplied/Storage And Handling (16.2)*].

ACTIQ is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

The concomitant use of ACTIQ with strong and moderate cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression [see *Drug Interactions (7)*].

Because of the risk for misuse, abuse, addiction, and overdose, ACTIQ is available only through a restricted program, required by the Food and Drug Administration, called the Actiq and Fentora REMS (Risk Evaluation and Mitigation Strategy) Program. Under the Actiq and Fentora REMS program, healthcare professionals (who prescribe to outpatients), as well as outpatients, pharmacies and distributors must enroll in the program to prescribe, receive, dispense, and distribute ACTIQ, respectively. [see Warnings and Precautions (5.11)]. Further information is available at www.actiqandfentorarems.com or by calling [-1-888-688-6885]

WARNINGS: IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

Reports of serious adverse events, including deaths in patients treated with FENTORA have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of FENTORA for any other fentanyl product may result in fatal overdose.

FENTORA is indicated only for the management of breakthrough pain in adult patients with cancer who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg/hour of transdermal fentanyl, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, at least 25 mg oxymorphone daily, or an equianalgesic dose of another opioid daily for a week or longer.

FENTORA is contraindicated in the management of acute or postoperative pain including headache/migraine. FENTORA is not indicated for use in opioid non-tolerant patients including those with only as needed (PRN) prior exposure to opioids.

Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients.

When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl products to FENTORA. Carefully consult the Initial Dosing Recommendations table. [See Dosage and Administration (2.1)]

When dispensing, do not substitute a FENTORA prescription for other fentanyl products. Substantial differences exist in the pharmacokinetic profile of FENTORA compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl. As a result of these differences, the substitution of FENTORA for any other fentanyl product may result in fatal overdose.

Special care must be used when dosing FENTORA. If the breakthrough pain episode is not relieved after 30 minutes, patients may take ONLY one

additional dose using the same strength and must wait at least 4 hours before taking another dose. [See *Dosage and Administration (2.1)*.]

FENTORA contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. FENTORA can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing FENTORA in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Patients and their caregivers must be instructed that FENTORA contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all tablets out of the reach of children. [See *Patient Counseling Information (17.1)* and *How Supplied/Storage and Handling (16.1)*]

FENTORA is intended to be used only in the care of opioid tolerant cancer patients and only by healthcare professionals who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

The concomitant use of FENTORA with CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression [see *Drug Interactions (7)*].

Because of the risk for misuse, abuse, addiction, and overdose, FENTORA is available only through a restricted program, required by the Food and Drug Administration, called the Actiq and Fentora REMS Program REMS (Risk Evaluation and Mitigation Strategy). Under the REMS, healthcare professionals (who prescribe to outpatients), as well as outpatients, pharmacies and distributors must enroll in the program to prescribe, receive, dispense, and distribute FENTORA, respectively. [see *Warnings and Precautions (5.11)*]. Further information is available at www.actiqandfentorarems.com or by calling [1-888-688-6885]

Contraindications:

- ACTIQ and *FENTORA* **must not** be used in opioid non-tolerant patients because life-threatening respiratory depression and death can occur at any dose in opioid non-tolerant patients
- ACTIQ and *FENTORA* are contraindicated in the management of acute or postoperative pain including headache/migraine and dental pain
- ACTIQ and *FENTORA* are contraindicated in patients with known hypersensitivity to any of the components or the drug fentanyl

Warnings and Precautions:

- Clinically significant respiratory and CNS depression can occur. Monitor patients accordingly

- Use with other CNS depressants and cytochrome P450 3A4 inhibitors may increase depressant effects including hypoventilation, hypotension, and profound sedation. Consider dosage adjustments if warranted
- Titrate ACTIQ and *FENTORA* cautiously in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to respiratory depression
- Administer ACTIQ and *FENTORA* with extreme caution in patients susceptible to intracranial effects of CO₂ retention
- Application site reactions occurred in 10% of patients in *FENTORA* clinical trials and ranged from paresthesia to ulceration and bleeding
- Full and partially consumed ACTIQ units contain medicine that can be fatal to a child. Ensure proper storage and disposal. Interim safe storage container available (ACTIQ Child Safety Kit)

Adverse Reactions:

- For ACTIQ, most common adverse reactions during titration phase (frequency ≥5%): nausea, dizziness, somnolence, vomiting, asthenia, and headache. Most common adverse reactions during longer-term treatment (frequency ≥5%): dyspnea, constipation, anxiety, confusion, depression, rash, and insomnia.
- For *FENTORA*, most common adverse reactions during titration phase (frequency ≥10%): nausea and dizziness. Most common adverse reactions during longer-term treatment (frequency ≥10%): nausea, vomiting, fatigue, anemia, dizziness, peripheral edema, constipation, asthenia, dehydration, and headache

Drug Interactions:

- Monitor patients who begin therapy with, or increase dose of, inhibitors of CYP 3A4 for signs of opioid toxicity
- Monitor patients who stop therapy with, or decrease dose of, inducers of CYP 3A4 for signs of opioid toxicity

Use in Specific Populations:

- Administer *FENTORA* with caution to patients with severe hepatic or renal disease. Please see accompanying full prescribing information.

Please see accompanying full prescribing information, including boxed warning.

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This Overview is part of an FDA-approved REMS.

Patient Overview for ACTIQ

ACTIQ® (oral transmucosal fentanyl citrate) is a prescription medicine that contains the drug fentanyl. ACTIQ is used to manage breakthrough pain in adults with cancer (16 years of age or older) who are routinely taking other opioid pain medicines around the clock for their cancer pain. ACTIQ is started only after you have been taking other opioid pain medicines for at least one week and your body has become used to them. Your doctor has determined that ACTIQ may help you control your breakthrough pain.

The ACTIQ REMS Program

Before you can receive ACTIQ you must become part of the ACTIQ REMS program and agree to all program requirements. The ACTIQ REMS program is required by the Food and Drug Administration (FDA) and is designed to help you understand ACTIQ and how to use it correctly and safely. ACTIQ can cause life threatening breathing problems which can lead to death, especially if you take more than your healthcare provider tells you to take or it is taken by anyone other than you.

Overview of Steps for the ACTIQ REMS Program for Patients

Step 1 Joining the Program

- Your doctor will discuss the ACTIQ Medication Guide with you. This will include important information about proper use, storage and disposal of Actiq
- You will read and sign the Patient-Prescriber Agreement along with your doctor.
- You will need to complete a new Patient-Prescriber Agreement every 2 years
- Your doctor will submit a copy to the ACTIQ REMS program
- Your doctor will also give you a copy and keep a copy in your medical records

Step 2 Getting a Prescription

- Once you have signed the Patient-Prescriber Agreement your doctor will write you a prescription for ACTIQ
- Your doctor can help you find a participating pharmacy to have your ACTIQ prescription filled, because only pharmacies that are in the ACTIQ REMS program can dispense ACTIQ. You can also find a participating pharmacy by calling the ACTIQ REMS program at 1-888-688-6885.

Step 3 Taking your Prescription to the Pharmacy

- The pharmacy will check to make sure that your doctor is enrolled in the ACTIQ REMS program so that they are allowed to dispense ACTIQ to you.
- You will be enrolled in the ACTIQ REMS program when your first ACTIQ prescription is processed at the pharmacy
- The pharmacy will also provide you with a Medication Guide. Read and keep the Medication Guide

For more Information

- Call the Actiq REMS program at 1-888-688-6885 or
- Visit www.actiqandfentorarems.com.

This Overview is approved by the U.S. Food and Drug Administration.

Note: The Medication Guide for Actiq will be included with this overview.

Patient Overview for FENTORA

FENTORA® (fentanyl buccal tablet) is a prescription medicine that contains the drug fentanyl. FENTORA is used to manage breakthrough pain in adults with cancer (18 years of age or older) who are routinely taking other opioid pain medicines around the clock for their cancer pain. FENTORA is started only after you have been taking other opioid pain medicines for at least one week and your body has become used to them. Your doctor has determined that FENTORA may help you control your breakthrough pain.

The FENTORA REMS Program

Before you can receive FENTORA you must become part of the FENTORA REMS program and agree to all program requirements. The FENTORA REMS program is required by the Food and Drug Administration (FDA) and is designed to help you understand FENTORA and how to use it correctly and safely. FENTORA can cause life threatening breathing problems which can lead to death, especially if you take more than your healthcare provider tells you to take or it is taken by anyone other than you.

Overview of Steps for the FENTORA REMS Program for Patients

Step 1 Joining the Program

- Your doctor will discuss the FENTORA Medication Guide with you. This will include important information about proper use, storage and disposal of FENTORA
- You will read and sign the Patient-Prescriber Agreement along with your doctor.
- You will need to complete a new Patient-Prescriber Agreement every 2 years
- Your doctor will submit a copy to the FENTORA REMS program
- Your doctor will also give you a copy and keep a copy in your medical records

Step 2 Getting a Prescription

- Once you have signed the Patient-Prescriber Agreement your doctor will write you a prescription for FENTORA
- Your doctor can help you find a participating pharmacy to have your FENTORA prescription filled, because only pharmacies that are in the FENTORA REMS program can dispense FENTORA. You can also find a participating pharmacy by calling the FENTORA REMS program at 1-888-688-6885.

Step 3 Taking your Prescription to the Pharmacy

- The pharmacy will check to make sure that your doctor is enrolled in the FENTORA REMS program so that they are allowed to dispense FENTORA to you.
- You will be enrolled in the FENTORA REMS program when your first FENTORA prescription is processed at the pharmacy
- The pharmacy will also provide you with a Medication Guide. Read and keep the Medication Guide

For more Information

- Call the FENTORA REMS program at 1-888-688-6885 or
- Visit www.actiqandfentorarems.com.

This Overview is approved by the U.S. Food and Drug Administration.

Note: The Medication Guide for Fentora will be included with this overview.

ACTIQ® and FENTORA® REMS Program Home

Welcome to the ACTIQ and FENTORA REMS Program

The ACTIQ and FENTORA REMS Program is the Risk Evaluation and Mitigation Strategy (REMS) for ACTIQ (oral transmucosal fentanyl citrate) and FENTORA (fentanyl buccal tablet).

The goals of the ACTIQ and FENTORA REMS are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

- Prescribing and dispensing ACTIQ and FENTORA only to appropriate patients, which includes use only in opioid-tolerant patients
- Preventing inappropriate conversion between fentanyl products
- Preventing accidental exposure to children and others for whom it was not prescribed
- Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose

How to use the ACTIQ and FENTORA REMS site:

On this site you can enroll in the REMS program in order to manage patients, find participating pharmacies, or access helpful reference materials relating to the products and programs. To begin the enrollment process in the ACTIQ and FENTORA REMS program online, click [Create My Account](#).

After you create an account, you must do the following to complete your enrollment:

1. Register
2. Review the educational materials and complete the online Knowledge Assessment
3. Submit completed enrollment form

You can then [Log In](#) and use the Dashboard to navigate to commonly used program functions.

For assistance or to enroll over the phone call the ACTIQ and FENTORA REMS Program at 1-888-688-6885.

Log In	Create New Account
User ID: <input type="text"/> Password: <input type="password"/> Forgot Password?	Enter here if you are a first time user to the ACTIQ and FENTORA REMS website. <input type="button" value="Log In"/> <input type="button" value="Create My Account"/>

WARNING: IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

Reports of serious adverse events, including deaths in patients treated with ACTIQ have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of ACTIQ for any other fentanyl product may result in fatal overdose.

ACTIQ is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, at least 25 mg oxymorphone daily, or an equianalgesic dose of another opioid for a week or longer.

ACTIQ is not indicated for use in opioid non-tolerant patients including those with only as needed (PRN) prior exposure.

Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients.

ACTIQ is contraindicated in the management of acute or postoperative pain including headache/migraine.

When prescribing, do not convert patients on a mcg per mcg basis to ACTIQ from other fentanyl products.

When dispensing, do not substitute an ACTIQ prescription for other fentanyl products. Substantial differences exist in the pharmacokinetic profile of ACTIQ compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl. As a result of these differences, the substitution of ACTIQ for any other fentanyl product may result in fatal overdose.

Special care must be used when dosing ACTIQ. If the breakthrough pain episode is not relieved 15 minutes after completion of the ACTIQ unit, patients may take **ONLY ONE** additional dose using the same strength and then must wait at least 4 hours before taking another dose [see Dosage and Administration (2.2)].

ACTIQ contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. ACTIQ can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing ACTIQ in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Patients and their caregivers must be instructed that ACTIQ contains a medicine in an amount which can be fatal to a child. Death has been reported in children who have accidentally ingested ACTIQ. All units must be kept out of the reach of children and opened units properly discarded [see Warnings And Precautions (5.3), Patient Counseling Information (17.5, 17.6), and How Supplied/Storage And Handling (16.2)].

ACTIQ is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

The concomitant use of ACTIQ with strong and moderate cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression [see Drug Interactions (7)].

Because of the risk for misuse, abuse, addiction, and overdose, ACTIQ is available only through a restricted program, required by the Food and Drug Administration, called the Actiq and Fentora REMS (Risk Evaluation and Mitigation Strategy) Program. Under the Actiq and Fentora REMS program, healthcare professionals (who prescribe to outpatients), as well as outpatients, pharmacies and distributors must enroll in the program to prescribe, receive, dispense, and distribute ACTIQ, respectively. [see Warnings and Precautions (5.11)]. Further information is available at www.actiqandfentorarems.com or by calling [1-888-688-6885]

WARNINGS: IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

Reports of serious adverse events, including deaths in patients treated with FENTORA have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of FENTORA for any other fentanyl product may result in fatal overdose.

FENTORA is indicated only for the management of breakthrough pain in adult patients with cancer who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain. Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg/hour of transdermal fentanyl, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, at least 25 mg oxymorphone daily, or an equianalgesic dose of another opioid daily for a week or longer.

FENTORA is contraindicated in the management of acute or postoperative pain including headache/migraine. FENTORA is not indicated for use in opioid non-tolerant patients including those with only as needed (PRN) prior exposure to opioids.

Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients.

When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl products to FENTORA. Carefully consult the Initial Dosing Recommendations table. [See Dosage and Administration (2.1)]

When dispensing, do not substitute a FENTORA prescription for other fentanyl products. Substantial differences exist in the pharmacokinetic profile of FENTORA compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl. As a result of these differences, the substitution of FENTORA for any other fentanyl product may result in fatal overdose.

Special care must be used when dosing FENTORA. If the breakthrough pain episode is not relieved after 30 minutes, patients may take **ONLY one** additional dose using the same strength and must wait at least 4 hours before taking another dose. [See Dosage and Administration (2.1).]

FENTORA contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. FENTORA can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing FENTORA in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Patients and their caregivers must be instructed that FENTORA contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all tablets out of the reach of children. [See Patient Counseling Information (17.1) and How Supplied/Storage and Handling (16.1)]

FENTORA is intended to be used only in the care of opioid tolerant cancer patients and only by healthcare professionals who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

The concomitant use of FENTORA with CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression [see Drug Interactions (7)].

Because of the risk for misuse, abuse, addiction, and overdose, FENTORA is available only through a restricted program, required by the Food and Drug Administration, called the Actiq and Fentora REMS Program (Risk Evaluation and Mitigation Strategy). Under the REMS, healthcare professionals (who prescribe to outpatients), as well as outpatients, pharmacies and distributors must enroll in the program to prescribe, receive, dispense, and distribute FENTORA, respectively. [see Warnings and Precautions (5.11)]. Further information is available at www.actiqandfentorarems.com or by calling [1-888-688-6885]

[Month day, year]

Important Drug Warning

Subject: Risk of misuse, abuse, addiction and overdose for ACTIQ and FENTORA;
FDA required restricted distribution program

Dear Healthcare Professional,

Cephalon would like to inform you of the implementation of a restricted distribution program designed to help ensure appropriate patient selection and the safe use of ACTIQ (oral transmucosal fentanyl citrate) C-II and FENTORA (fentanyl buccal tablet) C-II. Because of the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors, ACTIQ and FENTORA are only available through the FDA mandated ACTIQ and FENTORA Risk Evaluation and Mitigation Strategy (REMS). **Beginning [Date], only prescribers, pharmacies, distributors, and patients enrolled in the program are able to prescribe, dispense, distribute, and receive ACTIQ or FENTORA in an outpatient setting.**

For inpatient administration of ACTIQ and FENTORA, patient and prescriber enrollment in the ACTIQ and FENTORA REMS program is not required.

ACTIQ is indicated only for the management of breakthrough cancer pain in patients 16 and older with malignancies who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

FENTORA is indicated only for the management of breakthrough pain in adult patients with cancer who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl an hour, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, at least 25 mg of oral oxymorphone daily, or an equianalgesic dose of another opioid daily for a week or longer.

In order for you to take part in the ACTIQ and FENTORA REMS program, and prescribe these medications in an outpatient setting, you must:

- Review the Prescriber Education Program
- Successfully complete the Prescriber Knowledge Assessment
- Complete the Prescriber Enrollment Form
- Complete and sign a Patient-Prescriber Agreement with each new patient
- Re-enroll every two (2) years

To begin the enrollment process, please visit www.actiqandfentorarems.com or call 1-888-688-6885.

The goals of the ACTIQ and FENTORA REMS are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

1. Prescribing and dispensing ACTIQ and FENTORA only to appropriate patients, which includes use only in opioid tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed

4. Education prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

Important Safety Information

WARNING: IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

Reports of serious adverse events, including deaths in patients treated with ACTIQ have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of ACTIQ for any other fentanyl product may result in fatal overdose.

ACTIQ is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oral oxycodone daily, at least 8 mg oral hydromorphone daily, at least 25 mg oxymorphone daily, or an equianalgesic dose of another opioid for a week or longer.

ACTIQ is not indicated for use in opioid non-tolerant patients including those with only as needed (PRN) prior exposure.

Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients.

ACTIQ is contraindicated in the management of acute or postoperative pain including headache/migraine.

When prescribing, do not convert patients on a mcg per mcg basis to ACTIQ from other fentanyl products.

When dispensing, do not substitute an ACTIQ prescription for other fentanyl products. Substantial differences exist in the pharmacokinetic profile of ACTIQ compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl. As a result of these differences, the substitution of ACTIQ for any other fentanyl product may result in fatal overdose.

Special care must be used when dosing ACTIQ. If the breakthrough pain episode is not relieved 15 minutes after completion of the ACTIQ unit, patients may take **ONLY ONE** additional dose using the same strength and then must wait at least 4 hours before taking another dose [*see Dosage And Administration (2.2)*].

ACTIQ contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. ACTIQ can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing ACTIQ in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Patients and their caregivers must be instructed that ACTIQ contains a medicine in an amount which can be fatal to a child. Death has been reported in children who have accidentally ingested ACTIQ. All units must be kept out of the reach of children and opened units properly discarded [*see Warnings And Precautions (5.3), Patient Counseling Information (17.5, 17.6), and How Supplied/Storage And Handling (16.2)*].

ACTIQ is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

The concomitant use of ACTIQ with strong and moderate cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression [see *Drug Interactions (7)*].

Because of the risk for misuse, abuse, addiction, and overdose, ACTIQ is available only through a restricted program, required by the Food and Drug Administration, called the Actiq and Fentora REMS (Risk Evaluation and Mitigation Strategy) Program. Under the Actiq and Fentora REMS program, healthcare professionals (who prescribe to outpatients), as well as outpatients, pharmacies and distributors must enroll in the program to prescribe, receive, dispense, and distribute ACTIQ, respectively. [see Warnings and Precautions (5.11)]. Further information is available at www.actiqandfentorarems.com or by calling [-1-888-688-6885]

WARNINGS: IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

Reports of serious adverse events, including deaths in patients treated with FENTORA have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of FENTORA for any other fentanyl product may result in fatal overdose.

FENTORA is indicated only for the management of breakthrough pain in adult patients with cancer who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg/hour of transdermal fentanyl, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, at least 25 mg oxymorphone daily, or an equianalgesic dose of another opioid daily for a week or longer.

FENTORA is contraindicated in the management of acute or postoperative pain including headache/migraine. FENTORA is not indicated for use in opioid non-tolerant patients including those with only as needed (PRN) prior exposure to opioids.

Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients.

When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl products to FENTORA. Carefully consult the Initial Dosing Recommendations table. [See *Dosage and Administration (2.1)*]

When dispensing, do not substitute a FENTORA prescription for other fentanyl products. Substantial differences exist in the pharmacokinetic profile of FENTORA compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl. As a result of these differences, the substitution of FENTORA for any other fentanyl product may result in fatal overdose.

Special care must be used when dosing FENTORA. If the breakthrough pain episode is not relieved after 30 minutes, patients may take ONLY one additional dose using the same strength and must wait at least 4 hours before taking another dose. [See *Dosage and Administration (2.1)*.]

FENTORA contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. FENTORA can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing FENTORA in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Patients and their caregivers must be instructed that FENTORA contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all tablets out of the reach of children. [See Patient Counseling Information (17.1) and How Supplied/Storage and Handling (16.1)]

FENTORA is intended to be used only in the care of opioid tolerant cancer patients and only by healthcare professionals who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

The concomitant use of FENTORA with CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression [see Drug Interactions (7)].

Because of the risk for misuse, abuse, addiction, and overdose, FENTORA is available only through a restricted program, required by the Food and Drug Administration, called the Actiq and Fentora REMS Program REMS (Risk Evaluation and Mitigation Strategy). Under the REMS, healthcare professionals (who prescribe to outpatients), as well as outpatients, pharmacies and distributors must enroll in the program to prescribe, receive, dispense, and distribute FENTORA, respectively. [see Warnings and Precautions (5.11)]. Further information is available at www.actiqandfentorarems.com or by calling [1-888-688-6885]

Contraindications:

- ACTIQ and *FENTORA* **must not** be used in opioid non-tolerant patients because life-threatening respiratory depression and death can occur at any dose in opioid non-tolerant patients
- ACTIQ and *FENTORA* are contraindicated in the management of acute or postoperative pain including headache/migraine and dental pain
- ACTIQ and *FENTORA* are contraindicated in patients with known hypersensitivity to any of the components or the drug fentanyl

Warnings and Precautions:

- Clinically significant respiratory and CNS depression can occur. Monitor patients accordingly
- Use with other CNS depressants and cytochrome P450 3A4 inhibitors may increase depressant effects including hypoventilation, hypotension, and profound sedation. Consider dosage adjustments if warranted
- Titrate ACTIQ and *FENTORA* cautiously in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to respiratory depression
- Administer ACTIQ and *FENTORA* with extreme caution in patients susceptible to intracranial effects of CO₂ retention
- Application site reactions occurred in 10% of patients in *FENTORA* clinical trials and ranged from paresthesia to ulceration and bleeding
- Full and partially consumed ACTIQ units contain medicine that can be fatal to a child. Ensure proper storage and disposal. Interim safe storage container available (ACTIQ Child Safety Kit)

Adverse Reactions:

- For ACTIQ, most common adverse reactions during titration phase (frequency $\geq 5\%$): nausea, dizziness, somnolence, vomiting, asthenia, and headache. Most common adverse reactions during longer-term treatment (frequency $\geq 5\%$): dyspnea, constipation, anxiety, confusion, depression, rash, and insomnia.
- For FENTORA, most common adverse reactions during titration phase (frequency $\geq 10\%$): nausea and dizziness. Most common adverse reactions during longer-term treatment (frequency $\geq 10\%$): nausea, vomiting, fatigue, anemia, dizziness, peripheral edema, constipation, asthenia, dehydration, and headache

Drug Interactions:

- Monitor patients who begin therapy with, or increase dose of, inhibitors of CYP 3A4 for signs of opioid toxicity
- Monitor patients who stop therapy with, or decrease dose of, inducers of CYP 3A4 for signs of opioid toxicity

Use in Specific Populations:

- Administer FENTORA with caution to patients with severe hepatic or renal disease

Please see accompanying full prescribing information.

Adverse Event Reporting

Prescribers should report all adverse events associated with the use of ACTIQ and FENTORA to Cephalon at 1-800-896-5855 and/or FDA MedWatch program at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm.

Medication Guide

The FDA requires that you provide a copy of the enclosed Medication Guide to each patient with each prescription for ACTIQ and FENTORA. Additional copies of the Medication Guide are available at www.actiqandfentorarems.com or by calling 1-888-688-6885.

Please see the attached Full Prescribing Information, including boxed warnings, and Medication Guide for important safety information for ACTIQ and FENTORA.

Sincerely,

Medical Affairs
Cephalon, Inc.

 www.cephalon.com

Cephalon, Inc. / 41 Moores Road / P.O. Box 4011 / Frazer, PA 19355
Phone 610.344.0200 / Fax 610.344.0065

This letter is part of an FDA-approved REMS.

ACTIQ and FENTORA Risk Evaluation and Mitigation Strategy (REMS) Program Outpatient Pharmacy Program Overview

The ACTIQ and FENTORA REMS Program

The ACTIQ[®] (oral transmucosal fentanyl citrate) and FENTORA[®] (fentanyl buccal tablet) REMS is a restricted distribution program designed to help ensure appropriate patient selection and the safe use of ACTIQ and FENTORA. Because of the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors, only prescribers, pharmacies, distributors and patients enrolled in the program are able to prescribe, dispense, distribute, and receive ACTIQ and FENTORA in an outpatient setting. Inpatient prescribing of ACTIQ and FENTORA is detailed in the Inpatient Pharmacy Program Overview.

In order to reduce the risks of inappropriate patient selection and ensure appropriate dosing and administration of ACTIQ and FENTORA, your pharmacy will need to be enrolled in the ACTIQ and FENTORA REMS program. Enrollment requires the authorized pharmacist at the pharmacy to complete the ACTIQ and FENTORA REMS education program and knowledge assessment on behalf of the pharmacy. The authorized pharmacist must acknowledge that they will train all other pharmacy staff involved in the dispensing of ACTIQ and FENTORA.

The Education Program is available online at the ACTIQ and FENTORA REMS program website (www.actiqandfentorarems.com) or by contacting the ACTIQ and FENTORA REMS call center at 1-888-688-6885. Once the education program and knowledge assessment are completed, the authorized pharmacist, on behalf of the pharmacy, will be required to attest to their understanding of the appropriate use of ACTIQ and FENTORA and adherence to the ACTIQ and FENTORA REMS program requirements. Supply of ACTIQ and FENTORA to pharmacies is controlled by enrolled distributors, who will verify current enrollment of the pharmacy in the ACTIQ and FENTORA REMS program before shipping ACTIQ and FENTORA. Pharmacies will be required to re-enroll in the ACTIQ and FENTORA REMS program every two years.

Only enrolled pharmacies will be eligible to purchase or dispense ACTIQ and FENTORA. In addition, pharmacies can only dispense prescriptions if the patient and the prescriber are enrolled in the ACTIQ and FENTORA REMS program. Patients will be automatically enrolled in ACTIQ and FENTORA REMS upon processing of their first ACTIQ or FENTORA prescription. If the patient and/or the prescriber are not enrolled in the REMS program, the ACTIQ or FENTORA prescription will not be authorized by the ACTIQ and FENTORA REMS program and should not be dispensed to the patient.

Overview of Steps for the ACTIQ and FENTORA REMS

Program for Outpatient Pharmacies

The Authorized Pharmacist is responsible for completing the following steps on the behalf of the pharmacy.

Step 1 Pharmacy Education, Enrollment & Pharmacy Management Systems

- Create an account and register on www.actiqandfentorarems.com Review the ACTIQ and FENTORA REMS Pharmacy Education Program and successfully complete the Knowledge Assessment. The Education Program and Knowledge Assessment are available on line at www.actiqandfentorarems.com or by contacting

the ACTIQ and FENTORA REMS program at 1-888-688-6885

- Complete and sign the Pharmacy Enrollment Form. Re-enroll every two (2) years
- Ensure the pharmacy enables their pharmacy management system to support communication with the ACTIQ and FENTORA REMS system, using established telecommunication standards, and runs the three (3) standardized validation test transactions to validate the system configuration.

Step 2 Training Other Pharmacy Staff

- Ensure that all pharmacy staff involved in the processing and dispensing of ACTIQ and FENTORA have been trained to only dispense ACTIQ and FENTORA in accordance with the ACTIQ and FENTORA REMS program requirements.
- Ensure that this training is documented and retained by the pharmacy. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training as a minimum. This training document is subject to audit.

Step 3 Enrollment Confirmation

- Confirm the prescriber and patient are enrolled in the ACTIQ and FENTORA REMS program with each prescription by submitting a transaction from your pharmacy practice management system. Submitting a claim for a patient's first ACTIQ and FENTORA prescription through the pharmacy management system will automatically enroll that patient in ACTIQ and FENTORA REMS program.
- If the prescriber or patient enrollment is not validated, contact the ACTIQ and FENTORA REMS call center at 1-888-688-6885.

Step 4 Dispensing

- Receive approval and an authorization ID number from the ACTIQ and FENTORA REMS program and then prepare label and dispense medication.

Step 5 Counseling patients and provision of Medication Guide

- Advise the patient on how to take, store and dispose of ACTIQ and FENTORA appropriately.
- Provide a copy of the Medication Guide to the patient with each prescription.

Step 6 Monitoring

- Promptly report suspected adverse events including misuse, abuse, addiction and overdose directly to Cephalon by calling 1- 800-896-5855.
- Respond to requests for additional information from the ACTIQ and FENTORA REMS program

For more information you can call the ACTIQ and FENTORA REMS program at 1-888-688-6885 or visit www.actiqandfentorarems.com.

Important Safety Information

WARNING: IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

Reports of serious adverse events, including deaths in patients treated with ACTIQ have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of ACTIQ for any other fentanyl product may result in fatal overdose.

ACTIQ is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oral oxycodone daily, at least 8 mg oral hydromorphone daily, at least 25 mg oxymorphone daily, or an equianalgesic dose of another opioid for a week or longer.

ACTIQ is not indicated for use in opioid non-tolerant patients including those with only as needed (PRN) prior exposure.

Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients.

ACTIQ is contraindicated in the management of acute or postoperative pain including headache/migraine.

When prescribing, do not convert patients on a mcg per mcg basis to ACTIQ from other fentanyl products.

When dispensing, do not substitute an ACTIQ prescription for other fentanyl products. Substantial differences exist in the pharmacokinetic profile of ACTIQ compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl. As a result of these differences, the substitution of ACTIQ for any other fentanyl product may result in fatal overdose.

Special care must be used when dosing ACTIQ. If the breakthrough pain episode is not relieved 15 minutes after completion of the ACTIQ unit, patients may take **ONLY ONE** additional dose using the same strength and then must wait at least 4 hours before taking another dose [see *Dosage And Administration (2.2)*].

ACTIQ contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. ACTIQ can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing ACTIQ in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Patients and their caregivers must be instructed that ACTIQ contains a medicine in an amount which can be fatal to a child. Death has been reported in children who have accidentally ingested ACTIQ. All units must be kept out of the reach of children

and opened units properly discarded [see Warnings And Precautions (5.3), Patient Counseling Information (17.5, 17.6), and How Supplied/Storage And Handling (16.2)].

ACTIQ is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

The concomitant use of ACTIQ with strong and moderate cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression [see *Drug Interactions (7)*].

Because of the risk for misuse, abuse, addiction, and overdose, ACTIQ is available only through a restricted program, required by the Food and Drug Administration, called the Actiq and Fentora REMS (Risk Evaluation and Mitigation Strategy) Program. Under the Actiq and Fentora REMS program, healthcare professionals (who prescribe to outpatients), as well as outpatients, pharmacies and distributors must enroll in the program to prescribe, receive, dispense, and distribute ACTIQ, respectively. [see Warnings and Precautions (5.11)]. Further information is available at www.actiqandfentorarems.com or by calling [-1-888-688-6885]

WARNINGS: IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

Reports of serious adverse events, including deaths in patients treated with FENTORA have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of FENTORA for any other fentanyl product may result in fatal overdose.

FENTORA is indicated only for the management of breakthrough pain in adult patients with cancer who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg/hour of transdermal fentanyl, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, at least 25 mg oxymorphone daily, or an equianalgesic dose of another opioid daily for a week or longer.

FENTORA is contraindicated in the management of acute or postoperative pain including headache/migraine. FENTORA is not indicated for use in opioid non-tolerant patients including those with only as needed (PRN) prior exposure to opioids.

Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients.

When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl products to FENTORA. Carefully consult the Initial Dosing Recommendations table. [See Dosage and Administration (2.1)]

When dispensing, do not substitute a FENTORA prescription for other fentanyl products. Substantial differences exist in the pharmacokinetic profile of FENTORA compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl. As a result of these differences, the substitution of FENTORA for any other fentanyl product may result in fatal overdose.

Special care must be used when dosing FENTORA. If the breakthrough pain episode is not relieved after 30 minutes, patients may take ONLY one additional dose using the same strength and must wait at least 4 hours before taking another dose. [See Dosage and Administration (2.1).]

FENTORA contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. FENTORA can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing FENTORA in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Patients and their caregivers must be instructed that FENTORA contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all tablets out of the reach of children. [See Patient Counseling Information (17.1) and How Supplied/Storage and Handling (16.1)]

FENTORA is intended to be used only in the care of opioid tolerant cancer patients and only by healthcare professionals who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

The concomitant use of FENTORA with CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression [see Drug Interactions (7)].

Because of the risk for misuse, abuse, addiction, and overdose, FENTORA is available only through a restricted program, required by the Food and Drug Administration, called the Actiq and Fentora REMS Program REMS (Risk Evaluation and Mitigation Strategy). Under the REMS, healthcare professionals (who prescribe to outpatients), as well as outpatients, pharmacies and distributors must enroll in the program to prescribe, receive, dispense, and distribute FENTORA, respectively. [see Warnings and Precautions (5.1.1)]. Further information is available at www.actiqandfentorarems.com or by calling [1-888-688-6885]

Contraindications:

- **ACTIQ and FENTORA must not be used in opioid non-tolerant patients because life-threatening respiratory depression and death can occur at any dose in opioid non-tolerant patients**
- **ACTIQ and FENTORA are contraindicated in the management of acute or postoperative pain including headache/migraine and dental pain**
- **ACTIQ and FENTORA are contraindicated in patients with known hypersensitivity to any of the components or the drug fentanyl**

Warnings and Precautions:

- **Clinically significant respiratory and CNS depression can occur. Monitor patients accordingly**
- **Use with other CNS depressants and cytochrome P450 3A4 inhibitors may increase depressant effects including hypoventilation, hypotension, and profound sedation. Consider dosage adjustments if warranted**
- **Titrate ACTIQ and FENTORA cautiously in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to respiratory depression**

- Administer ACTIQ and *FENTORA* with extreme caution in patients susceptible to intracranial effects of CO₂ retention
- Application site reactions occurred in 10% of patients in *FENTORA* clinical trials and ranged from paresthesia to ulceration and bleeding
- Full and partially consumed ACTIQ units contain medicine that can be fatal to a child. Ensure proper storage and disposal. Interim safe storage container available (ACTIQ Child Safety Kit)

Adverse Reactions:

- For ACTIQ, most common adverse reactions during titration phase (frequency ≥5%): nausea, dizziness, somnolence, vomiting, asthenia, and headache. Most common adverse reactions during longer-term treatment (frequency ≥5%): dyspnea, constipation, anxiety, confusion, depression, rash, and insomnia.
- For *FENTORA*, most common adverse reactions during titration phase (frequency ≥10%): nausea and dizziness. Most common adverse reactions during longer-term treatment (frequency ≥10%): nausea, vomiting, fatigue, anemia, dizziness, peripheral edema, constipation, asthenia, dehydration, and headache

Drug Interactions:

- Monitor patients who begin therapy with, or increase dose of, inhibitors of CYP 3A4 for signs of opioid toxicity
- Monitor patients who stop therapy with, or decrease dose of, inducers of CYP 3A4 for signs of opioid toxicity

Use in Specific Populations:

- Administer *FENTORA* with caution to patients with severe hepatic or renal disease
- Please see accompanying full prescribing information.

Please see accompanying full prescribing information, including boxed warning.
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This Overview is part of an FDA-approved REMS.

ACTIQ and FENTORA Risk Evaluation and Mitigation Strategy (REMS) Program Inpatient Pharmacy Program Overview*

The ACTIQ and FENTORA REMS Program

The ACTIQ® (oral transmucosal fentanyl citrate) and FENTORA® (fentanyl buccal tablet) REMS is a restricted distribution program designed to help ensure appropriate patient selection and the safe use of ACTIQ and FENTORA. Because of the risk for misuse, abuse, addiction, overdose and serious complications due to medication errors, ACTIQ and FENTORA can only be dispensed by a pharmacy enrolled in the ACTIQ and FENTORA REMS program.

Inpatient Pharmacy Enrollment

An authorized pharmacist representing an inpatient pharmacy in a healthcare facility will need to review the ACTIQ and FENTORA REMS education program (Pharmacy Education Program) and successfully complete the Pharmacy Knowledge Assessment and enroll the inpatient pharmacy in the ACTIQ and FENTORA REMS program. The Pharmacy Education Program is available online at the ACTIQ and FENTORA REMS program website (www.actiqandfentorarems.com) or by contacting the ACTIQ and FENTORA REMS call center at 1-888-688-6885. Once the education program and knowledge assessment are completed, the authorized pharmacist will attest to their understanding of the appropriate use of ACTIQ and FENTORA and adherence to the ACTIQ and FENTORA REMS program requirements, on behalf of their inpatient pharmacy.

Product supply of ACTIQ and FENTORA to the inpatient pharmacy will be controlled by enrolled distributors. Enrolled distributors will verify current enrollment of the inpatient pharmacy in the ACTIQ and FENTORA REMS program, before shipping ACTIQ and FENTORA. Unless enrolled in the ACTIQ and FENTORA REMS program, the inpatient pharmacy will not be eligible to purchase or dispense ACTIQ and FENTORA. Inpatient pharmacies (authorized pharmacist) will be required to re-enroll in the ACTIQ and FENTORA REMS program every two years.

Inpatient Prescribers

Prescribers and patients are not required to be enrolled in the ACTIQ and FENTORA REMS program for inpatient use. However, if a prescriber would like to prescribe ACTIQ or FENTORA upon a patient's discharge, prescribers will need to be enrolled in the REMS program and patients will need to receive counseling and sign a Patient-Prescriber Agreement.

Outpatient Pharmacies

Outpatient pharmacies, within or associated with the healthcare facility, that provide dispensing services to outpatients must also be separately enrolled in the ACTIQ and FENTORA REMS program to dispense ACTIQ and FENTORA REMS to outpatients. See the ACTIQ and FENTORA REMS program – Outpatient Pharmacy Program Overview.

Overview of Steps for the ACTIQ and FENTORA REMS Program for Inpatient Pharmacies

Step 1. Select an Authorized Inpatient Pharmacist

- The representative is authorized by the inpatient pharmacy to establish and oversee the ACTIQ and FENTORA REMS program requirements within the inpatient healthcare facility.

Step 2. Complete ACTIQ and FENTORA REMS Education Program

- The authorized pharmacist must successfully complete the ACTIQ and FENTORA REMS Pharmacy Education Program and Knowledge Assessment. The Education Program is available on line at www.actiqandfentorarems.com or by contacting the ACTIQ and FENTORA REMS program at 1-888-688-6885.

Step 3. Enroll

- The inpatient authorized pharmacist must enroll in the ACTIQ and FENTORA REMS program by completing the ACTIQ and FENTORA REMS program Inpatient Pharmacy Enrollment Form and re-enroll every two (2) years or when there have been major safety updates to the ACTIQ or FENTORA label or substantial changes to the program.
- To enroll, access the ACTIQ and FENTORA REMS program website at www.actiqandfentorarems.com or by contacting the ACTIQ and FENTORA REMS program at 1-888-688-6885.

Step 4. Implement

- The inpatient authorized pharmacist must establish or oversee the system, order sets, protocols, and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the ACTIQ and FENTORA REMS program.
- The inpatient authorized pharmacist must ensure and document that inpatient pharmacists are educated on the risks associated with ACTIQ and FENTORA and the requirements of the ACTIQ and FENTORA REMS program, as described in the Pharmacy Education Program. This training document is subject to audit.
- The inpatient authorized pharmacist must ensure that the inpatient pharmacy does not sell, loan or transfer ACTIQ and FENTORA inventory to any other pharmacy, institution, distributor, or prescriber.
- Inpatient pharmacies may not dispense ACTIQ and FENTORA for outpatient use.

Step 5. Monitoring

- Ensure that suspected adverse events including misuse, abuse, addiction and overdose are promptly reported directly to Cephalon by calling 1-800-896-5855.
- Respond to requests for additional information from the ACTIQ and FENTORA REMS program.

For more information you can call the ACTIQ and FENTORA REMS program at 1-888-688-6885 or visit www.actiqandfentorarems.com

Important Safety Information

WARNING: IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

Reports of serious adverse events, including deaths in patients treated with ACTIQ have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of ACTIQ for any other fentanyl product may result in fatal overdose.

ACTIQ is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oral oxycodone daily, at least 8 mg oral hydromorphone daily, at least 25 mg oral oxymorphone daily, or an equianalgesic dose of another opioid for a week or longer.

ACTIQ is not indicated for use in opioid non-tolerant patients including those with only as needed (PRN) prior exposure.

Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients.

ACTIQ is contraindicated in the management of acute or postoperative pain including headache/migraine.

When prescribing, do not convert patients on a mcg per mcg basis to ACTIQ from other fentanyl products.

When dispensing, do not substitute an ACTIQ prescription for other fentanyl products. Substantial differences exist in the pharmacokinetic profile of ACTIQ compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl. As a result of these differences, the substitution of ACTIQ for any other fentanyl product may result in fatal overdose.

Special care must be used when dosing ACTIQ. If the breakthrough pain episode is not relieved 15 minutes after completion of the ACTIQ unit, patients may take **ONLY ONE** additional dose using the same strength and then must wait at least 4 hours before taking another dose [see *Dosage And Administration (2.2)*].

ACTIQ contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. ACTIQ can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing ACTIQ in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Patients and their caregivers must be instructed that ACTIQ contains a medicine in an amount which can be fatal to a child. Death has been reported in children who

have accidentally ingested ACTIQ. All units must be kept out of the reach of children and opened units properly discarded [see Warnings And Precautions (5.3), Patient Counseling Information (17.5, 17.6), and How Supplied/Storage And Handling (16.2)].

ACTIQ is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

The concomitant use of ACTIQ with strong and moderate cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression [see *Drug Interactions (7)*].

Because of the risk for misuse, abuse, addiction, and overdose, ACTIQ is available only through a restricted program, required by the Food and Drug Administration, called the Actiq and Fentora REMS (Risk Evaluation and Mitigation Strategy) Program. Under the Actiq and Fentora REMS program, healthcare professionals (who prescribe to outpatients), as well as outpatients, pharmacies and distributors must enroll in the program to prescribe, receive, dispense, and distribute ACTIQ, respectively. [see Warnings and Precautions (5.11)]. Further information is available at www.actiqandfentorarems.com or by calling [-1-888-688-6885]

WARNINGS: IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

Reports of serious adverse events, including deaths in patients treated with FENTORA have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of FENTORA for any other fentanyl product may result in fatal overdose.

FENTORA is indicated only for the management of breakthrough pain in adult patients with cancer who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg/hour of transdermal fentanyl, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, at least 25 mg oxymorphone daily, or an equianalgesic dose of another opioid daily for a week or longer.

FENTORA is contraindicated in the management of acute or postoperative pain including headache/migraine. FENTORA is not indicated for use in opioid non-tolerant patients including those with only as needed (PRN) prior exposure to opioids.

Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients.

When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl products to FENTORA. Carefully consult the Initial Dosing Recommendations table. [See Dosage and Administration (2.1)]

When dispensing, do not substitute a FENTORA prescription for other fentanyl products. Substantial differences exist in the pharmacokinetic profile of FENTORA compared to other fentanyl products that result in clinically important differences in

the extent of absorption of fentanyl. As a result of these differences, the substitution of FENTORA for any other fentanyl product may result in fatal overdose.

Special care must be used when dosing FENTORA. If the breakthrough pain episode is not relieved after 30 minutes, patients may take ONLY one additional dose using the same strength and must wait at least 4 hours before taking another dose. [See *Dosage and Administration (2.1)*.]

FENTORA contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. FENTORA can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing FENTORA in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Patients and their caregivers must be instructed that FENTORA contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all tablets out of the reach of children. [See *Patient Counseling Information (17.1)* and *How Supplied/Storage and Handling (16.1)*]

FENTORA is intended to be used only in the care of opioid tolerant cancer patients and only by healthcare professionals who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

The concomitant use of FENTORA with CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression [see *Drug Interactions (7)*].

Because of the risk for misuse, abuse, addiction, and overdose, FENTORA is available only through a restricted program, required by the Food and Drug Administration, called the Actiq and Fentora REMS Program REMS (Risk Evaluation and Mitigation Strategy). Under the REMS, healthcare professionals (who prescribe to outpatients), as well as outpatients, pharmacies and distributors must enroll in the program to prescribe, receive, dispense, and distribute FENTORA, respectively. [see Warnings and Precautions (5.11)]. Further information is available at www.actiqandfentorarems.com or by calling [1-888-688-6885]

Contraindications:

- ACTIQ and FENTORA **must not** be used in opioid non-tolerant patients because life-threatening respiratory depression and death can occur at any dose in opioid non-tolerant patients
- ACTIQ and FENTORA are contraindicated in the management of acute or postoperative pain including headache/migraine and dental pain
- ACTIQ and FENTORA are contraindicated in patients with known hypersensitivity to any of the components or the drug fentanyl

Warnings and Precautions:

- Clinically significant respiratory and CNS depression can occur. Monitor patients accordingly

- Use with other CNS depressants and cytochrome P450 3A4 inhibitors may increase depressant effects including hypoventilation, hypotension, and profound sedation. Consider dosage adjustments if warranted
- Titrate ACTIQ and *FENTORA* cautiously in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to respiratory depression
- Administer ACTIQ and *FENTORA* with extreme caution in patients susceptible to intracranial effects of CO₂ retention
- Application site reactions occurred in 10% of patients in *FENTORA* clinical trials and ranged from paresthesia to ulceration and bleeding
- Full and partially consumed ACTIQ units contain medicine that can be fatal to a child. Ensure proper storage and disposal. Interim safe storage container available (ACTIQ Child Safety Kit)

Adverse Reactions:

- For ACTIQ, most common adverse reactions during titration phase (frequency ≥5%): nausea, dizziness, somnolence, vomiting, asthenia, and headache. Most common adverse reactions during longer-term treatment (frequency ≥5%): dyspnea, constipation, anxiety, confusion, depression, rash, and insomnia.
- For *FENTORA*, most common adverse reactions during titration phase (frequency ≥10%): nausea and dizziness. Most common adverse reactions during longer-term treatment (frequency ≥10%): nausea, vomiting, fatigue, anemia, dizziness, peripheral edema, constipation, asthenia, dehydration, and headache

Drug Interactions:

- Monitor patients who begin therapy with, or increase dose of, inhibitors of CYP 3A4 for signs of opioid toxicity
- Monitor patients who stop therapy with, or decrease dose of, inducers of CYP 3A4 for signs of opioid toxicity

Use in Specific Populations:

- Administer *FENTORA* with caution to patients with severe hepatic or renal disease. Please see accompanying full prescribing information.

Please see accompanying full prescribing information, including boxed warning.

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This Overview is part of an FDA-approved REMS.

This Guide is part of an FDA-approved REMS.

Please see accompanying full prescribing information, including boxed warning.

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**ACTIQ and FENTORA Risk Evaluation and Mitigation Strategy (REMS) Program
PHARMACY ENROLLMENT FORM – OUTPATIENT PHARMACY**

The Authorized Pharmacist must complete and submit this form.

Pharmacies are required to enroll in order to purchase and dispense ACTIQ® and FENTORA.® For corporate pharmacy enrollment, please complete the Chain Pharmacy Enrollment form.

I understand that ACTIQ and FENTORA are available only through the ACTIQ and FENTORA REMS program and that I must comply with the program requirements for outpatient pharmacies, and I acknowledge that:

1. I have reviewed the ACTIQ and FENTORA Full Prescribing Information, and *Pharmacy Education Program* and I have completed the *Pharmacy Knowledge Assessment*. I understand the risks and benefits associated with ACTIQ and FENTORA and the requirements of the ACTIQ and FENTORA REMS program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing ACTIQ and FENTORA have been educated on the risks associated with ACTIQ and FENTORA and the requirements of the ACTIQ and FENTORA REMS program, as described in the *Pharmacy Education Program*. This training should be documented and is subject to audit.
3. I understand that ACTIQ and FENTORA are not bioequivalent with each other or any other fentanyl product on a microgram-per-microgram basis and therefore must not be substituted for any other fentanyl products, unless the patient is converting from the branded product to its generic, or vice versa.
4. I understand that ACTIQ and FENTORA are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for ACTIQ and FENTORA for all patients is the lowest dose, unless individual labels provide product specific conversion recommendations.
6. I understand the importance of discussing the risks and benefits of ACTIQ and FENTORA with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time ACTIQ and FENTORA is dispensed.
8. I understand that ACTIQ and FENTORA will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that ALL ACTIQ and FENTORA prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.
10. I understand that all dispensing locations must be enrolled in the ACTIQ and FENTORA REMS program to dispense ACTIQ and FENTORA.
11. I understand that ACTIQ and FENTORA can only be obtained from wholesalers/distributors that are enrolled in the ACTIQ and FENTORA REMS program.
12. I understand that our pharmacy will not sell, loan or transfer ACTIQ and FENTORA inventory to any other pharmacy, institution, distributor, or prescriber.
13. I understand that our pharmacy must re-enroll in the ACTIQ and FENTORA REMS program and successfully complete the enrollment requirements every two (2) years.
14. I understand that ACTIQ and FENTORA are available only through the ACTIQ and FENTORA REMS program. I understand and agree to comply with the ACTIQ and FENTORA REMS program requirements for outpatient pharmacies.

Authorized Pharmacist (Please print) _____

Signature _____

Date: _____

Pharmacy Name: _____	DEA#: _____	NCPDP#: _____	NPI #: _____
Address 1: _____	Address 2: _____		
City: _____	State: _____	ZIP: _____	
Phone: () _____	Alternate Phone: () _____	Fax: () _____	
Medicaid ID: _____	State Issued: _____		
Authorized Pharmacist: First Name: _____	MI: _____	Last Name: _____	
Phone: () _____	Fax: () _____	E-Mail: _____	
(if different from above)		(if different from above)	
Preferred Method of Contact: <input type="checkbox"/> E-mail <input type="checkbox"/> FAX			

If you do not have access to www.actiqandfentorarems.com, you must send a copy of this agreement to the ACTIQ and FENTORA REMS program via fax (888-688-1050).

Please retain a copy of the completed form for your records.

You must re-enroll every two (2) years or in case of major safety updates to the ACTIQ or FENTORA label and/or major program changes.

For more information about the ACTIQ and FENTORA program, please visit www.actiqandfentorarems.com or call 888-688-6885

For more information about ACTIQ or FENTORA, please see full prescribing information, including boxed warning.

This form is part of an FDA-approved REMS.

ACTIQ and FENTORA REMS Program Additional Terms and Conditions

Pharmacy ("Pharmacy") agrees to the following requirements, with respect to the ACTIQ and FENTORA REMS Program (the "Program"), sponsored by ___Cephalon Inc_____, ("Program Sponsor") and supported, under the direction of __Cephalon_Inc___, by McKesson Specialty Inc. and its affiliates including NDCHealth Corporation d/b/a RelayHealth ("RelayHealth") or another pharmacy transaction switch system (collectively, "Switch Systems").

Pharmacy represents that (i) it shall perform its obligations under these terms and conditions in compliance with all applicable laws and regulations, (ii) Pharmacy's participation in the Program does not conflict with its obligations under any contracts or other arrangements with any third party, and (iii) Pharmacy is authorized to submit patient information to the Switch Systems for purposes of verifying and tracking each patient's eligibility to participate in the Program and Pharmacy authorizes Program Sponsor and Switch Systems to use the submitted information for such purposes.

Pharmacy agrees to the following Program Requirements: (a) If applicable, enable Pharmacy's pharmacy practice management system to support the Program, including submission of required data fields and display of Program messages; (b) Respond appropriately to Program messages and alerts in order to comply with Program requirements, including contacting the call center when an exception process occurs; (c) Report all Program Drug dispensing activity for the Program Drug NDC #'s listed below to Switch Systems via submission of all billing and reversal requests or via the program web portal or call center; and (d) purchase the Program Drug(s) from a distributor enrolled in the Program.

Program Drug(s):	Carton	Lozenge Unit
ACTIQ 200mcg	NDC#63459-0502-30	NDC#63459-0502-01
ACTIQ 400mcg	NDC#63459-0504-30	NDC#63459-0504-01
ACTIQ 600mcg	NDC#63459-0506-30	NDC#63459-0506-01
ACTIQ 800mcg	NDC#63459-0508-30	NDC#63459-0508-01
ACTIQ 1200mcg	NDC#63459-0512-30	NDC#63459-0512-01
ACTIQ 1600mcg	NDC#63459-0516-30	NDC#63459-0516-01
	Carton	Blister Card
FENTORA 100mcg	NDC#63459-0541-28	NDC#63459-0541-04
FENTORA 200mcg	NDC#63459-0542-28	NDC#63459-0542-04
FENTORA 300mcg	NDC#63459-0543-28	NDC#63459-0543-04
FENTORA 400mcg	NDC#63459-0544-28	NDC#63459-0544-04
FENTORA 600mcg	NDC#63459-0546-28	NDC#63459-0546-04
FENTORA 800mcg	NDC#63459-0548-28	NDC#63459-0548-04

Includes all current and future generic NDCs associated with the brand NDCs listed above deemed by the FDA to be included in the Program.

Subscriber acknowledges that when processing a claim utilizing the switch system under the Program, a billing request for the Program Drug will not pass to the payer, or cash prescription processor, if the prescriber or pharmacy is not verified. Submitting a claim for a patient's first prescription through the pharmacy management system will automatically enroll that patient in the Program and the same patient's subsequent claims for the Program Drug will not be processed until a completed patient-prescriber agreement is properly received by Switch Systems

Pharmacy authorizes the Switch Systems to de-identify, in accordance with the Health Insurance Portability and Accountability Act of 1996, as amended, its historical and prospective prescriptions claims data submitted to the Switch Systems and/or its affiliates in connection with the Program on behalf of Pharmacy, and to use that de-identified data for purposes of (i) analyzing, identifying, designing and/or enabling a REMS service; (ii) developing communication documentation for such services for both Program Sponsors and Pharmacy; and (iii) providing the Program Sponsors with reports and information (including any fees paid, which will be aggregated), for purposes of implementing, maintaining, supporting, monitoring or improving a Program. These reports may contain information aggregated by NCPDP or NABP number. In addition, Pharmacy authorizes Program Sponsor and its contractors Switch Systems, to receive from wholesaler(s) of the Program Drug(s) distribution and purchasing data, including 867 data, with respect to the Program Drug(s).

Pharmacy acknowledges that the FDA or Program Sponsor may mandate modification, suspension or termination of a Program. The Switch Systems reserves the right to modify, suspend or terminate any REMS service for any reason, without liability to Switch Systems.

EXCEPT FOR SWITCH SYSTEMS'S FRAUD OR INTENTIONAL MISCONDUCT ARISING OUT OF THE SERVICES OR THE PROGRAM, IN NO EVENT WILL THE PROGRAM SPONSOR OR SWITCH SYSTEMS BE LIABLE TO PHARMACY UNDER, IN CONNECTION WITH, OR RELATED TO THE PROGRAM OR THE SERVICES FOR ANY DIRECT, SPECIAL, INCIDENTAL, INDIRECT, OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, LOST PROFITS OR LOSS OF GOODWILL, WHETHER BASED ON BREACH OF CONTRACT, WARRANTY, TORT, PRODUCT LIABILITY, OR OTHERWISE, AND WHETHER OR NOT SWITCH SYSTEMS OR PROGRAM SPONSOR HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGE.

To the extent any of these terms and conditions conflict with any other written agreement between the parties with respect to the Program, the terms and conditions of such other written agreement shall prevail.

ACTIQ and FENTORA Risk Evaluation and Mitigation Strategy (REMS) Program PHARMACY ENROLLMENT FORM – INPATIENT PHARMACY

The Authorized Pharmacist must complete and submit this form.

Pharmacies are required to enroll in order to purchase and dispense ACTIQ® and FENTORA.®

I understand that ACTIQ and FENTORA are available only through the ACTIQ and FENTORA REMS program and that I must comply with the program requirements for inpatient pharmacies, and I acknowledge that:

1. I have reviewed the ACTIQ and FENTORA Full Prescribing Information and the *Pharmacy Education Program*, and I have completed the *Pharmacy Knowledge Assessment*. I understand the benefits and risks associated with ACTIQ and FENTORA and the requirements of the ACTIQ/FENTORA REMS program.
2. I will ensure that our inpatient pharmacists are educated on the risks associated with ACTIQ and FENTORA and the requirements of the ACTIQ and FENTORA REMS program, as described in the *Pharmacy Education Program*.
3. I understand that ACTIQ and FENTORA are not bioequivalent to each other or to any other fentanyl product on a microgram-per-microgram basis and therefore must not be substituted for other fentanyl products, unless the patient is converting from the branded product to its generic, or vice versa..
4. I understand that ACTIQ and FENTORA are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for ACTIQ and FENTORA for all patients is the lowest dose, unless the individual labels provide product specific conversion recommendations.
6. I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must also be enrolled in and comply with the ACTIQ and FENTORA REMS program to dispense ACTIQ and FENTORA to outpatients.
7. I understand that our inpatient pharmacy is not to dispense ACTIQ and FENTORA for outpatient use.
8. I understand that a prescriber who wants to discharge a patient with an ACTIQ and FENTORA prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the ACTIQ and FENTORA REMS program.
9. I will establish or oversee the establishment of a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the ACTIQ and FENTORA REMS.
10. I understand that our pharmacy will not sell, loan or transfer ACTIQ and FENTORA inventory to any other pharmacy, institution, distributor, or prescriber.
11. I understand that ACTIQ and FENTORA can only be obtained from wholesalers/distributors that are enrolled in the ACTIQ and FENTORA REMS program.
12. I understand that our pharmacy must re-enroll in the ACTIQ and FENTORA REMS program every two (2) years.
13. I understand that ACTIQ and FENTORA are available only through the ACTIQ and FENTORA REMS program. I understand and agree to comply with the ACTIQ and FENTORA REMS program requirements for inpatient pharmacies.

Authorized Pharmacist (Please Print) _____

Signature _____

Date: _____

Pharmacy Name: _____	DEA #: _____	State Pharmacy License# _____
_____	State of Issuance _____	
Address 1: _____	Address 2: _____	
City: _____	State: _____	ZIP: _____
Phone: () _____	Alternate Phone: () _____	Fax: () _____
Authorized Pharmacist: First Name: _____	MI: _____	Last Name: _____
Phone: () _____	Fax: () _____	E-mail: _____
(if different from above)	(if different from above)	
Preferred Method of Contact: <input type="checkbox"/> E-mail <input type="checkbox"/> FAX		

If you do not have access to www.actiqandfentorarems.com, you must send a copy of this agreement to the ACTIQ and FENTORA REMS program via fax (888-688-1050).

Please retain a copy of the completed form for your records.

You must re-enroll every two (2) years or in case of major safety updates to the ACTIQ or FENTORA label and/or major program changes.

For more information about the ACTIQ and FENTORA REMS program, please visit www.actiqandfentorarems.com or call 888-688-6885

For more information about ACTIQ and FENTORA, please see full prescribing information, including boxed warning.

This form is part of an FDA-approved REMS.

**ACTIQ and FENTORA Risk Evaluation and Mitigation Strategy (REMS) Program
CHAIN PHARMACY ENROLLMENT FORM**

The Authorized Chain Pharmacy Representative must complete the form below.
Pharmacies are required to enroll in order to purchase and dispense ACTIQ® and FENTORA.®

I understand that ACTIQ and FENTORA are available only through the ACTIQ and FENTORA REMS program and that I must comply with the program requirements for outpatient pharmacies, and I acknowledge that:

1. I have reviewed the ACTIQ and FENTORA Full Prescribing Information, and *Pharmacy Education Program* and I have completed the *Pharmacy Knowledge Assessment*. I understand the risks and benefits associated with ACTIQ and FENTORA and the requirements of the ACTIQ and FENTORA REMS program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing ACTIQ and FENTORA have been educated on the risks associated with ACTIQ and FENTORA and the requirements of the ACTIQ and FENTORA REMS program, as described in the *Pharmacy Education Program*. This training should be documented and is subject to audit.
3. I understand that ACTIQ and FENTORA are not bioequivalent with each other or any other fentanyl product on a microgram-per-microgram basis and therefore must not be substituted for any other fentanyl products, unless the patient is converting from the branded product to its generic, or vice versa.
4. I understand that ACTIQ and FENTORA are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for ACTIQ and FENTORA for all patients is the lowest dose, unless individual labels provide product specific conversion recommendations.
6. I understand the importance of discussing the risks and benefits of ACTIQ and FENTORA with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time ACTIQ and FENTORA is dispensed.
8. I understand that ACTIQ and FENTORA will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that ALL ACTIQ and FENTORA prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.
10. I understand that all dispensing locations must be enrolled in the ACTIQ and FENTORA REMS program to dispense ACTIQ and FENTORA.
11. I understand that ACTIQ and FENTORA can only be obtained from wholesalers/distributors that are enrolled in the ACTIQ and FENTORA REMS program.
12. I understand that our pharmacy will not sell, loan or transfer ACTIQ and FENTORA inventory to any other pharmacy, institution, distributor, or prescriber.
13. I understand that our pharmacy must re-enroll in the ACTIQ and FENTORA REMS program and successfully complete the enrollment requirements every two (2) years.
14. I understand that ACTIQ and FENTORA are available only through the ACTIQ and FENTORA REMS program. I understand and agree to comply with the ACTIQ and FENTORA REMS program requirements for outpatient pharmacies.

Authorized Chain Representative Signature _____

Date: _____

Chain Pharmacy Name: _____	Chain ID: _____
Address 1: _____	Address 2: _____
City: _____	State: _____ ZIP: _____
Primary Phone: () _____	Secondary Phone: () _____ Fax: () _____
Authorized Chain Representative: First Name: _____	MI: _____ Last Name: _____
Phone: () _____ (if different from above)	Fax: () _____ (if different from above) E-Mail: _____
Preferred Method of Contact: <input type="checkbox"/> E-mail <input type="checkbox"/> FAX	

If you do not have access to www.actiqandfentorarems.com, you must send a copy of this agreement to the ACTIQ and FENTORA REMS program via fax (888-688-1050).

Please retain a copy of the completed form for your records.

You must re-enroll every two (2) years or in case of major safety updates to the ACTIQ or FENTORA label and/or major program changes.

For more information about the ACTIQ and FENTORA program, please visit www.actiqandfentorarems.com or call 888-688-6885

For more information about ACTIQ or FENTORA, please see full prescribing information, including boxed warning.

A list of pharmacy sites that have been trained can be updated using the on-line dashboard at www.actiqandfentorarems.com or faxed to 888-688-1050.

This form is part of an FDA-approved REMS.

ACTIQ and FENTORA REMS Program Additional Terms and Conditions

Pharmacy ("Pharmacy") agrees to the following requirements, with respect to the ACTIQ and FENTORA REMS Program (the "Program"), sponsored by ___Cephalon Inc_____, ("Program Sponsor") and supported, under the direction of ___Cephalon Inc_____, by McKesson Specialty Inc. and its affiliates including NDCHealth Corporation d/b/a RelayHealth ("RelayHealth") or another pharmacy transaction switch system (collectively, "Switch Systems").

Pharmacy represents that (i) it shall perform its obligations under these terms and conditions in compliance with all applicable laws and regulations, (ii) Pharmacy's participation in the Program does not conflict with its obligations under any contracts or other arrangements with any third party, and (iii) Pharmacy is authorized to submit patient information to the Switch Systems for purposes of verifying and tracking each patient's eligibility to participate in the Program and Pharmacy authorizes Program Sponsor and Switch Systems to use the submitted information for such purposes.

Pharmacy agrees to the following Program Requirements: (a) If applicable, enable Pharmacy's pharmacy practice management system to support the Program, including submission of required data fields and display of Program messages; (b) Respond appropriately to Program messages and alerts in order to comply with Program requirements, including contacting the call center when an exception process occurs; (c) Report all Program Drug dispensing activity for the Program Drug NDC #'s listed below to Switch Systems via submission of all billing and reversal requests or via the program web portal or call center; and (d) purchase the Program Drug(s) from a distributor enrolled in the Program.

Program Drug(s):	Carton	Lozenge Unit
ACTIQ 200mcg	NDC#63459-0502-30	NDC#63459-0502-01
ACTIQ 400mcg	NDC#63459-0504-30	NDC#63459-0504-01
ACTIQ 600mcg	NDC#63459-0506-30	NDC#63459-0506-01
ACTIQ 800mcg	NDC#63459-0508-30	NDC#63459-0508-01
ACTIQ 1200mcg	NDC#63459-0512-30	NDC#63459-0512-01
ACTIQ 1600mcg	NDC#63459-0516-30	NDC#63459-0516-01
	Carton	Blister Card
FENTORA 100mcg	NDC#63459-0541-28	NDC#63459-0541-04
FENTORA 200mcg	NDC#63459-0542-28	NDC#63459-0542-04
FENTORA 300mcg	NDC#63459-0543-28	NDC#63459-0543-04
FENTORA 400mcg	NDC#63459-0544-28	NDC#63459-0544-04
FENTORA 600mcg	NDC#63459-0546-28	NDC#63459-0546-04
FENTORA 800mcg	NDC#63459-0548-28	NDC#63459-0548-04

Includes all current and future generic NDCs associated with the brand NDCs listed above deemed by the FDA to be included in the Program.

Subscriber acknowledges that when processing a claim utilizing the switch system under the Program, a billing request for the Program Drug will not pass to the payer, or cash prescription processor, if the prescriber or pharmacy is not verified. Submitting a claim for a patient's first prescription through the pharmacy management system will automatically enroll that patient in the Program and the same patient's subsequent claims for the Program Drug will not be processed until a completed patient-prescriber agreement is properly received by Switch Systems

Pharmacy authorizes the Switch Systems to de-identify, in accordance with the Health Insurance Portability and Accountability Act of 1996, as amended, its historical and prospective prescriptions claims data submitted to the Switch Systems and/or its affiliates in connection with the Program on behalf of Pharmacy, and to use that de-identified data for purposes of (i) analyzing, identifying, designing and/or enabling a REMS service; (ii) developing communication documentation for such services for both Program Sponsors and Pharmacy; and (iii) providing the Program Sponsors with reports and information (including any fees paid, which will be aggregated), for purposes of implementing, maintaining, supporting, monitoring or improving a Program. These reports may contain information aggregated by NCPDP or NABP number. In addition, Pharmacy authorizes Program Sponsor and its contractors Switch Systems, to receive from wholesaler(s) of the Program Drug(s) distribution and purchasing data, including 867 data, with respect to the Program Drug(s).

Pharmacy acknowledges that the FDA or Program Sponsor may mandate modification, suspension or termination of a Program. The Switch Systems reserves the right to modify, suspend or terminate any REMS service for any reason, without liability to Switch Systems.

EXCEPT FOR SWITCH SYSTEMS'S FRAUD OR INTENTIONAL MISCONDUCT ARISING OUT OF THE SERVICES OR THE PROGRAM, IN NO EVENT WILL THE PROGRAM SPONSOR OR SWITCH SYSTEMS BE LIABLE TO PHARMACY UNDER, IN CONNECTION WITH, OR RELATED TO THE PROGRAM OR THE SERVICES FOR ANY DIRECT, SPECIAL, INCIDENTAL, INDIRECT, OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, LOST PROFITS OR LOSS OF GOODWILL, WHETHER BASED ON BREACH OF CONTRACT, WARRANTY, TORT, PRODUCT LIABILITY, OR OTHERWISE, AND WHETHER OR NOT SWITCH SYSTEMS OR PROGRAM SPONSOR HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGE.

To the extent any of these terms and conditions conflict with any other written agreement between the parties with respect to the Program, the terms and conditions of such other written agreement shall prevail.

[Month day, year]

Important Drug Warning

Subject: Risk of misuse, abuse, addiction and overdose for ACTIQ and FENTORA;
FDA required restricted distribution program

Dear Outpatient Pharmacy,

Cephalon would like to inform you of the implementation of a restricted distribution program designed to help ensure appropriate patient selection and the safe use of ACTIQ (oral transmucosal fentanyl citrate) C-II and FENTORA (fentanyl buccal tablet) C-II. Because of the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors, ACTIQ and FENTORA are only available through the FDA mandated ACTIQ and FENTORA Risk Evaluation and Mitigation Strategy (REMS).

Beginning [Date], only prescribers, pharmacies, distributors and patients enrolled in the program are able to prescribe, dispense, distribute, and receive ACTIQ and FENTORA in an outpatient setting.

ACTIQ is indicated only for the management of breakthrough cancer pain in patients 16 and older with malignancies who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

FENTORA is indicated only for the management of breakthrough pain in adult patients with cancer who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl an hour, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, at least 25 mg of oral oxymorphone daily, or an equianalgesic dose of another opioid daily for a week or longer.

In order for an outpatient pharmacy to take part in the ACTIQ and FENTORA REMS program, and dispense ACTIQ and FENTORA, an authorized Pharmacist must:

- Review the Pharmacy Education Program
- Successfully complete the Pharmacy Knowledge Assessment
- Complete the Pharmacy Enrollment Form
- Ensure the pharmacy enables their pharmacy management system to support communication with the ACTIQ and FENTORA REMS system.
- Re-enroll every two years

To begin the enrollment process, visit www.actiqandfentorarems.com or call 1-888-688-6885.

The goals of the ACTIQ and FENTORA REMS are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

1. Prescribing and dispensing ACTIQ and FENTORA only to appropriate patients, which includes use only in opioid tolerant patients.

2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed
4. Education prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

Important Safety Information

WARNING: IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

Reports of serious adverse events, including deaths in patients treated with ACTIQ have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of ACTIQ for any other fentanyl product may result in fatal overdose.

ACTIQ is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oral oxycodone daily, at least 8 mg oral hydromorphone daily, at least 25 mg oxymorphone daily, or an equianalgesic dose of another opioid for a week or longer.

ACTIQ is not indicated for use in opioid non-tolerant patients including those with only as needed (PRN) prior exposure.

Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients.

ACTIQ is contraindicated in the management of acute or postoperative pain including headache/migraine.

When prescribing, do not convert patients on a mcg per mcg basis to ACTIQ from other fentanyl products.

When dispensing, do not substitute an ACTIQ prescription for other fentanyl products. Substantial differences exist in the pharmacokinetic profile of ACTIQ compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl. As a result of these differences, the substitution of ACTIQ for any other fentanyl product may result in fatal overdose.

Special care must be used when dosing ACTIQ. If the breakthrough pain episode is not relieved 15 minutes after completion of the ACTIQ unit, patients may take **ONLY ONE** additional dose using the same strength and then must wait at least 4 hours before taking another dose [*see Dosage And Administration (2.2)*].

ACTIQ contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. ACTIQ can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing ACTIQ in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone,

oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Patients and their caregivers must be instructed that ACTIQ contains a medicine in an amount which can be fatal to a child. Death has been reported in children who have accidentally ingested ACTIQ. All units must be kept out of the reach of children and opened units properly discarded [see Warnings And Precautions (5.3), Patient Counseling Information (17.5, 17.6), and How Supplied/Storage And Handling (16.2)].

ACTIQ is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

The concomitant use of ACTIQ with strong and moderate cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression [see Drug Interactions (7)].

Because of the risk for misuse, abuse, addiction, and overdose, ACTIQ is available only through a restricted program, required by the Food and Drug Administration, called the Actiq and Fentora REMS (Risk Evaluation and Mitigation Strategy) Program. Under the Actiq and Fentora REMS program, healthcare professionals (who prescribe to outpatients), as well as outpatients, pharmacies and distributors must enroll in the program to prescribe, receive, dispense, and distribute ACTIQ, respectively. [see Warnings and Precautions (5.11)]. Further information is available at www.actiqandfentorarems.com or by calling [-1-888-688-6885]

WARNINGS: IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

Reports of serious adverse events, including deaths in patients treated with FENTORA have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of FENTORA for any other fentanyl product may result in fatal overdose.

FENTORA is indicated only for the management of breakthrough pain in adult patients with cancer who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg/hour of transdermal fentanyl, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, at least 25 mg oxymorphone daily, or an equianalgesic dose of another opioid daily for a week or longer.

FENTORA is contraindicated in the management of acute or postoperative pain including headache/migraine. FENTORA is not indicated for use in opioid non-tolerant patients including those with only as needed (PRN) prior exposure to opioids.

Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients.

When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl products to FENTORA. Carefully consult the Initial Dosing Recommendations table. [See Dosage and Administration (2.1)]

When dispensing, do not substitute a FENTORA prescription for other fentanyl products. Substantial differences exist in the pharmacokinetic profile of FENTORA compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl. As a result of these differences, the substitution of FENTORA for any other fentanyl product may result in fatal overdose.

Special care must be used when dosing FENTORA. If the breakthrough pain episode is not relieved after 30 minutes, patients may take ONLY one additional dose using the same strength and must wait at least 4 hours before taking another dose. [See Dosage and Administration (2.1).]

FENTORA contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. FENTORA can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing FENTORA in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Patients and their caregivers must be instructed that FENTORA contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all tablets out of the reach of children. [See Patient Counseling Information (17.1) and How Supplied/Storage and Handling (16.1)]

FENTORA is intended to be used only in the care of opioid tolerant cancer patients and only by healthcare professionals who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

The concomitant use of FENTORA with CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression [see Drug Interactions (7)].

Because of the risk for misuse, abuse, addiction, and overdose, FENTORA is available only through a restricted program, required by the Food and Drug Administration, called the Actiq and Fentora REMS Program REMS (Risk Evaluation and Mitigation Strategy). Under the REMS, healthcare professionals (who prescribe to outpatients), as well as outpatients, pharmacies and distributors must enroll in the program to prescribe, receive, dispense, and distribute FENTORA, respectively. [see Warnings and Precautions (5.11)]. Further information is available at www.actiqandfentorarems.com or by calling [1-888-688-6885]

Contraindications:

- ACTIQ and FENTORA must not be used in opioid non-tolerant patients because life-threatening respiratory depression and death can occur at any dose in opioid non-tolerant patients

- ACTIQ and *FENTORA* are contraindicated in the management of acute or postoperative pain including headache/migraine and dental pain
- ACTIQ and *FENTORA* are contraindicated in patients with known hypersensitivity to any of the components or the drug fentanyl

Warnings and Precautions:

- Clinically significant respiratory and CNS depression can occur. Monitor patients accordingly
- Use with other CNS depressants and cytochrome P450 3A4 inhibitors may increase depressant effects including hypoventilation, hypotension, and profound sedation. Consider dosage adjustments if warranted
- Titrate ACTIQ and *FENTORA* cautiously in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to respiratory depression
- Administer ACTIQ and *FENTORA* with extreme caution in patients susceptible to intracranial effects of CO₂ retention
- Application site reactions occurred in 10% of patients in *FENTORA* clinical trials and ranged from paresthesia to ulceration and bleeding
- Full and partially consumed ACTIQ units contain medicine that can be fatal to a child. Ensure proper storage and disposal. Interim safe storage container available (ACTIQ Child Safety Kit)

Adverse Reactions:

- For ACTIQ, most common adverse reactions during titration phase (frequency ≥5%): nausea, dizziness, somnolence, vomiting, asthenia, and headache. Most common adverse reactions during longer-term treatment (frequency ≥5%): dyspnea, constipation, anxiety, confusion, depression, rash, and insomnia.
- For *FENTORA*, most common adverse reactions during titration phase (frequency ≥10%): nausea and dizziness. Most common adverse reactions during longer-term treatment (frequency ≥10%): nausea, vomiting, fatigue, anemia, dizziness, peripheral edema, constipation, asthenia, dehydration, and headache

Drug Interactions:

- Monitor patients who begin therapy with, or increase dose of, inhibitors of CYP 3A4 for signs of opioid toxicity
- Monitor patients who stop therapy with, or decrease dose of, inducers of CYP 3A4 for signs of opioid toxicity

Use in Specific Populations:

- Administer *FENTORA* with caution to patients with severe hepatic or renal disease

Please see accompanying full prescribing information.

Adverse Event Reporting

Healthcare professionals should report all adverse events associated with the use of ACTIQ and *FENTORA* to Cephalon at 1-800-896-5855 and/or FDA MedWatch program at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm.

Medication Guide

The FDA requires that you distribute a copy of the enclosed Medication Guide to each patient with each prescription filled for ACTIQ and *FENTORA*. Additional copies of the

Medication Guide are available at www.actigandfentorarems.com or by calling 1-888-688-6885.

Please see the attached Full Prescribing Information, including boxed warnings, and Medication Guide for important safety information for ACTIQ and FENTORA.

Sincerely,

Pharmacy Relations
Cephalon, Inc.

 **Cephalon** www.cephalon.com

Cephalon, Inc. / 41 Moores Road / P.O. Box 4011 / Frazer, PA 19355
Phone 610.344.0200 / Fax 610.344.0065

This letter is part of an FDA-approved REMS.

[Month day, year]

Important Drug Warning

Subject: Risk of misuse, abuse, addiction and overdose for ACTIQ and FENTORA; FDA required restricted distribution program

Dear Inpatient Pharmacy,

Cephalon would like to inform you of the implementation of a restricted distribution program designed to help ensure appropriate patient selection and the safe use of ACTIQ (oral transmucosal fentanyl citrate) C-II and FENTORA (fentanyl buccal tablet) C-II. Because of the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors, ACTIQ and FENTORA are only available through the FDA mandated ACTIQ and FENTORA Risk Evaluation and Mitigation Strategy (REMS). **If ACTIQ and/or FENTORA are prescribed and dispensed to patients in your Healthcare Facility, you must enroll your inpatient pharmacy in the ACTIQ and FENTORA REMS program.**

ACTIQ is indicated only for the management of breakthrough cancer pain in patients 16 and older with malignancies who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

FENTORA is indicated only for the management of breakthrough pain in adult patients with cancer who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl an hour, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, at least 25 mg of oral oxymorphone daily, or an equianalgesic dose of another opioid daily for a week or longer.

Beginning [DATE], only ACTIQ and FENTORA REMS program participants will be able to prescribe, dispense, or use ACTIQ and FENTORA.

In order for an inpatient pharmacy to take part in the ACTIQ/FENTORA REMS program, and dispense ACTIQ and FENTORA, an authorized Pharmacist must:

- Review the Pharmacy Education Program
- Successfully complete the Pharmacy Knowledge Assessment
- Complete the Pharmacy Enrollment Form
- Re-enroll every two years

To enroll in the ACTIQ and FENTORA REMS program, visit www.actiqandfentorarems.com or call 1-888-688-6885.

The goals of the ACTIQ and FENTORA REMS are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

1. Prescribing and dispensing ACTIQ and FENTORA only to appropriate patients, which includes use only in opioid tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed
4. Education prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

Important Safety Information

WARNING: IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

Reports of serious adverse events, including deaths in patients treated with ACTIQ have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of ACTIQ for any other fentanyl product may result in fatal overdose.

ACTIQ is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oral oxycodone daily, at least 8 mg oral hydromorphone daily, at least 25 mg oxymorphone daily, or an equianalgesic dose of another opioid for a week or longer.

ACTIQ is not indicated for use in opioid non-tolerant patients including those with only as needed (PRN) prior exposure.

Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients.

ACTIQ is contraindicated in the management of acute or postoperative pain including headache/migraine.

When prescribing, do not convert patients on a mcg per mcg basis to ACTIQ from other fentanyl products.

When dispensing, do not substitute an ACTIQ prescription for other fentanyl products. Substantial differences exist in the pharmacokinetic profile of ACTIQ compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl. As a result of these differences, the substitution of ACTIQ for any other fentanyl product may result in fatal overdose.

Special care must be used when dosing ACTIQ. If the breakthrough pain episode is not relieved 15 minutes after completion of the ACTIQ unit, patients may take **ONLY ONE** additional dose using the same strength and then must wait at least 4 hours before taking another dose [*see Dosage And Administration (2.2)*].

ACTIQ contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. ACTIQ can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing ACTIQ in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone,

oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Patients and their caregivers must be instructed that ACTIQ contains a medicine in an amount which can be fatal to a child. Death has been reported in children who have accidentally ingested ACTIQ. All units must be kept out of the reach of children and opened units properly discarded [see Warnings And Precautions (5.3), Patient Counseling Information (17.5, 17.6), and How Supplied/Storage And Handling (16.2)].

ACTIQ is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

The concomitant use of ACTIQ with strong and moderate cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression [see Drug Interactions (7)].

Because of the risk for misuse, abuse, addiction, and overdose, ACTIQ is available only through a restricted program, required by the Food and Drug Administration, called the Actiq and Fentora REMS (Risk Evaluation and Mitigation Strategy) Program. Under the Actiq and Fentora REMS program, healthcare professionals (who prescribe to outpatients), as well as outpatients, pharmacies and distributors must enroll in the program to prescribe, receive, dispense, and distribute ACTIQ, respectively. [see Warnings and Precautions (5.11)]. Further information is available at www.actiqandfentorarems.com or by calling [-1-888-688-6885]

WARNINGS: IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

Reports of serious adverse events, including deaths in patients treated with FENTORA have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of FENTORA for any other fentanyl product may result in fatal overdose.

FENTORA is indicated only for the management of breakthrough pain in adult patients with cancer who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg/hour of transdermal fentanyl, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, at least 25 mg oxymorphone daily, or an equianalgesic dose of another opioid daily for a week or longer.

FENTORA is contraindicated in the management of acute or postoperative pain including headache/migraine. FENTORA is not indicated for use in opioid non-tolerant patients including those with only as needed (PRN) prior exposure to opioids.

Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients.

When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl products to FENTORA. Carefully consult the Initial Dosing Recommendations table. [See Dosage and Administration (2.1)]

When dispensing, do not substitute a FENTORA prescription for other fentanyl products. Substantial differences exist in the pharmacokinetic profile of FENTORA compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl. As a result of these differences, the substitution of FENTORA for any other fentanyl product may result in fatal overdose.

Special care must be used when dosing FENTORA. If the breakthrough pain episode is not relieved after 30 minutes, patients may take ONLY one additional dose using the same strength and must wait at least 4 hours before taking another dose. [See Dosage and Administration (2.1).]

FENTORA contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. FENTORA can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing FENTORA in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Patients and their caregivers must be instructed that FENTORA contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all tablets out of the reach of children. [See Patient Counseling Information (17.1) and How Supplied/Storage and Handling (16.1)]

FENTORA is intended to be used only in the care of opioid tolerant cancer patients and only by healthcare professionals who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

The concomitant use of FENTORA with CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression [see Drug Interactions (7)].

Because of the risk for misuse, abuse, addiction, and overdose, FENTORA is available only through a restricted program, required by the Food and Drug Administration, called the Actiq and Fentora REMS Program REMS (Risk Evaluation and Mitigation Strategy). Under the REMS, healthcare professionals (who prescribe to outpatients), as well as outpatients, pharmacies and distributors must enroll in the program to prescribe, receive, dispense, and distribute FENTORA, respectively. [see Warnings and Precautions (5.11)]. Further information is available at www.actiqandfentorarems.com or by calling [1-888-688-6885]

Contraindications:

- ACTIQ and FENTORA must not be used in opioid non-tolerant patients because life-threatening respiratory depression and death can occur at any dose in opioid non-tolerant patients

- ACTIQ and *FENTORA* are contraindicated in the management of acute or postoperative pain including headache/migraine and dental pain
- ACTIQ and *FENTORA* are contraindicated in patients with known hypersensitivity to any of the components or the drug fentanyl

Warnings and Precautions:

- Clinically significant respiratory and CNS depression can occur. Monitor patients accordingly
- Use with other CNS depressants and cytochrome P450 3A4 inhibitors may increase depressant effects including hypoventilation, hypotension, and profound sedation. Consider dosage adjustments if warranted
- Titrate ACTIQ and *FENTORA* cautiously in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to respiratory depression
- Administer ACTIQ and *FENTORA* with extreme caution in patients susceptible to intracranial effects of CO₂ retention
- Application site reactions occurred in 10% of patients in *FENTORA* clinical trials and ranged from paresthesia to ulceration and bleeding
- Full and partially consumed ACTIQ units contain medicine that can be fatal to a child. Ensure proper storage and disposal. Interim safe storage container available (ACTIQ Child Safety Kit)

Adverse Reactions:

- For ACTIQ, most common adverse reactions during titration phase (frequency ≥5%): nausea, dizziness, somnolence, vomiting, asthenia, and headache. Most common adverse reactions during longer-term treatment (frequency ≥5%): dyspnea, constipation, anxiety, confusion, depression, rash, and insomnia.
- For *FENTORA*, most common adverse reactions during titration phase (frequency ≥10%): nausea and dizziness. Most common adverse reactions during longer-term treatment (frequency ≥10%): nausea, vomiting, fatigue, anemia, dizziness, peripheral edema, constipation, asthenia, dehydration, and headache

Drug Interactions:

- Monitor patients who begin therapy with, or increase dose of, inhibitors of CYP 3A4 for signs of opioid toxicity
- Monitor patients who stop therapy with, or decrease dose of, inducers of CYP 3A4 for signs of opioid toxicity

Use in Specific Populations:

- Administer *FENTORA* with caution to patients with severe hepatic or renal disease

Please see accompanying full prescribing information.

Adverse Event Reporting

Prescribers should report all adverse events associated with the use of ACTIQ and *FENTORA* directly to Cephalon at 1-800-896-5855 and/or FDA MedWatch program at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm.

Please see the attached Full Prescribing Information, including boxed warnings, and Medication Guide for important safety information for ACTIQ and *FENTORA*.

Sincerely,

Pharmacy Relations
Cephalon, Inc.

 **Cephalon** www.cephalon.com

Cephalon, Inc. / 41 Moores Road / P.O. Box 4011 / Frazer, PA 19355
Phone 610.344.0200 / Fax 610.344.0065

This letter is part of an FDA-approved REMS.

**ACTIQ and FENTORA Risk Evaluation and Mitigation Strategy (REMS) Program
DISTRIBUTOR ENROLLMENT FORM**

Distributor must complete and submit this form.

The ACTIQ and FENTORA REMS program is an FDA-mandated program that restricts distribution of ACTIQ and FENTORA. Under the ACTIQ and FENTORA REMS program, only prescribers, pharmacies, distributors and patients enrolled in the program are able to prescribe, dispense, distribute, and receive ACTIQ and FENTORA.

The goals of the ACTIQ and FENTORA REMS are to mitigate the risk of misuse, abuse addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing ACTIQ and FENTORA only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

Distributor Name: _____
Corporate Address: _____
City: _____ State: _____ ZIP: _____
Phone: (____) _____ Alternate Phone: (____) _____ Fax: (____) _____
Contact Name: _____
Contact Phone: (____) _____ Fax: (____) _____ E-Mail: _____ (if different from above) (if different from above)
Preferred Method of Contact: <input type="checkbox"/> E-mail <input type="checkbox"/> FAX

I understand that ACTIQ and FENTORA are available only through the ACTIQ and FENTORA REMS program and that I must comply with the program requirements and acknowledge that:

1. I will ensure that relevant staff are trained on the ACTIQ and FENTORA REMS program procedures and will follow the requirements of the ACTIQ and FENTORA REMS program.
2. I will ensure that ACTIQ and FENTORA are only distributed to pharmacies whose enrollment has been validated in the ACTIQ and FENTORA REMS program.
3. I will provide data to the ACTIQ and FENTORA REMS program including information on shipment to enrolled pharmacies.
4. I will cooperate with periodic audits or noncompliance investigations to ensure that ACTIQ and FENTORA are distributed in accordance with the program requirements.

Contact Name: (please print) _____

Signature: _____ Date: _____

Fax this completed form to the ACTIQ and FENTORA REMS program at 1-888-688-1050

Please retain a copy of the completed form for your records.

You must re-enroll every two (2) years or in case of major safety updates to the ACTIQ or FENTORA label and/or major program changes.

For more information about the ACTIQ and FENTORA REMS program, please visit www.actiqandfentorarems.com or call 888-688-6885

This form is part of an FDA-approved REMS.

[Month day, year]

Dear Distributor,

Cephalon would like to inform you of the implementation of a restricted distribution program designed to help ensure appropriate patient selection and the safe use of ACTIQ (oral transmucosal fentanyl citrate) C-II and FENTORA (fentanyl buccal tablet) C-II. Because of the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors, Actiq and Fentora are only available through the FDA mandated ACTIQ and FENTORA Risk Evaluation and Mitigation Strategy (REMS). Only prescribers, pharmacies, distributors, and patients enrolled in the program are able to prescribe, dispense, distribute, and receive ACTIQ and FENTORA. Each distributor that purchases and sells ACTIQ and/or FENTORA is required to complete an ACTIQ and FENTORA REMS program Distributor Enrollment Form and agree to comply with all of the requirements outlined on the form.

Beginning [DATE], only ACTIQ and FENTORA REMS participants will be able to purchase and distribute ACTIQ and FENTORA.

Distributor Overview of the ACTIQ and FENTORA REMS Program

Step 1 Distributor Enrollment into the ACTIQ and FENTORA REMS Program

- Review and understand the requirements of the ACTIQ and FENTORA REMS program
- Verify ability to comply with program requirements.
- Verify that relevant staff are trained on the ACTIQ and FENTORA REMS program procedures.
- Complete the Distributor Enrollment Form (Distributors will be required to re-enroll every two years).
- Fax Distributor Enrollment Form to the ACTIQ and FENTORA REMS call center at 1-888-688-1050.
- Receive enrollment ID information to access the ACTIQ and FENTORA REMS program website to create an on-line account (secure username and password).

Step 2 Verification of ACTIQ and FENTORA REMS Program Pharmacy Enrollment Prior to Distributing ACTIQ and FENTORA

- Obtain the current list of enrolled pharmacies after enrollment by either:
 - A secure FTP site, accessing the electronic file listing currently enrolled Pharmacies
 - Accessing a secure web-based portal with fully functional search capabilities
 - Calling the ACTIQ and FENTORA REMS call center at 1-888-688-6885
- Ensure that pharmacies are enrolled in the ACTIQ and FENTORA REMS program before distributing ACTIQ or FENTORA.
- If a pharmacy wants to place an order for ACTIQ or FENTORA, but is not listed on the enrolled list for the ACTIQ and FENTORA REMS program, do not distribute ACTIQ or FENTORA. Instruct the pharmacy that they will need to become enrolled in the ACTIQ and FENTORA REMS program in order to purchase ACTIQ and FENTORA.

Step 3 Provide periodic distribution data

- Provide data to the ACTIQ and FENTORA REMS program including information on shipments to verify shipments to only enrolled pharmacies

The goals of the ACTIQ and FENTORA REMS are to mitigate the risk of misuse, abuse addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing ACTIQ and FENTORA only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

Cephalon will contact you in the near future to review additional details regarding the ACTIQ and FENTORA REMS program distributor requirements.

Adverse Event Reporting

Distributors should report any adverse events associated with the use of ACTIQ and/or FENTORA to Cephalon by calling 1-800-896-5855 and/or FDA MedWatch program at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm.

Please see enclosed Full Prescribing Information for more information about ACTIQ and FENTORA.

Sincerely,

Trade Relations
Cephalon, Inc.

 **Cephalon** www.cephalon.com

Cephalon, Inc. / 41 Moores Road / P.O. Box 4011 / Frazer, PA 19355
Phone 610.344.0200 / Fax 610.344.0065

This letter is part of an FDA-approved REMS.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BOB A RAPPAPORT
07/20/2011