NDA 206323

LABELING ORDER

MainPointe Pharmaceuticals, LLC
Attention: John G. Lay
VP, Regulatory Affairs and Quality Assurance
2604 River Green Circle
Louisville, KY 40206

Dear John G. Lay:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tuxarin ER (codeine phosphate and chlorpheniramine maleate) extended release tablet.

On July 31, 2025, we sent you a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related label changes to the labeling of Tuxarin ER to address the risk of long-term opioid therapy, toxic leukoencephalopathy, opioid-induced esophageal dysfunction, drug-drug interaction with gabapentinoids, and to update labeling on opioid overdose reversal agents. The decision to require safety labeling changes was based on new safety information about this risk identified since this product was approved. You were directed to submit, within 30 days of the date of that letter, a supplement proposing changes to the approved labeling, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

The 30 days have passed and we have not received any submission from you addressing our letter dated July 31, 2025.

You failed to respond to our July 31, 2025, letter within 30 days. Under the authority of Section 505(o)(4)(E), we are ordering you to make all of the changes in the labeling listed in the July 31, 2025, letter (attached).

Pursuant to Section 505(o)(4)(E), a changes being effected (CBE) supplement containing all of the changes to the labeling that are listed in the July 31, 2025, letter, as modified in accordance with this letter, must be received by FDA by March 17, 2026, for Tuxarin ER.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

SAFETY LABELING CHANGES UNDER 505(o)(4) – CHANGES BEING EFFECTED

Alternatively, by March 7, 2026, you may appeal this Order using the Agency's established formal dispute resolution process as described in 21 CFR 10.75 and the guidance for industry *Formal Dispute Resolution: Appeals Above the Division Level*.[1] The appeal should be submitted as a correspondence to your NDA referenced above. Identify the submission as "**Formal Dispute Resolution Request**" both on the cover letter and on the outside envelope. A copy of the submission should be sent to:

Melissa Sage
CDER Formal Dispute Resolution Project Manager
Food and Drug Administration
Office of New Drugs
Building 51, Room 6158
10903 New Hampshire Avenue
Silver Spring, MD 20993

In addition, to expedite coordination of any such appeal, a copy of the submission should also be sent to:

Elaine Sit, PharmD
Safety Regulatory Project Manager
Food and Drug Administration
Division of Pulmonology, Allergy, and Critical Care
Building 22, Room 3319
10903 New Hampshire Avenue
Silver Spring, MD 20993

Refer to the guidance for industry *Formal Dispute Resolution: Sponsor Appeals Above the Division Level* for further instruction regarding the content and format of your request. Questions regarding the formal dispute resolution process may be directed to Melissa Sage, CDER Formal Dispute Resolution Project Manager, at (301) 796-6449 or melissa.sage@fda.hhs.gov. Appeals received by the Agency later than March 7, 2026, will not be entertained.

Failure to respond to this Order within the specified timeframes is a violation of section 505(o)(4) of the FDCA and could subject you to civil monetary penalties under section 303(f)(4) of the FDCA, 21 U.S.C. 333(f)(4), in the amount of up to $250,000 per violation, with additional penalties if the violation continues uncorrected. Further, such a violation would cause your product to be misbranded under section 502(z) of the Act, 21 U.S.C. 352(z), which could subject you to additional enforcement actions, included but not limited to seizure of your product and injunction.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, call Elaine Sit, Regulatory Project Manager, at (301) 796-5073 or e-mail at elaine.sit@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Nikolay Nikolov, MD
Director
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Safety Labeling Change Notification Letter
- Emails/faxes/letters
- Redlined Prescribing Information Text
- Redlined Medication Guide Text

NDA 206323

SAFETY LABELING CHANGE NOTIFICATION

MainPointe Pharmaceuticals, LLC
Attention: John G. Lay
VP, Regulatory Affairs and Quality Assurance
2604 River Green Circle
Louisville, KY 40206

Dear John G. Lay:

Please refer to your new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tuxarin ER (codeine phosphate and chlorpheniramine maleate) extended release tablet.

Section 505(o)(4) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to make safety labeling changes based upon new safety information that FDA becomes aware of after approval of the drug or biological product.

Risks Related to Long-Term Opioid Therapy

Since Tuxarin ER was approved on June 22, 2015, we have become aware of postapproval observational study results that include quantitative estimates of the risks of misuse, abuse, addiction, and opioid-involved fatal and non-fatal overdose associated with transitioning to long-term use of opioid analgesics for management of chronic pain.[1] Some patients using long-term opioid analgesics experienced one or more of these serious adverse outcomes, and these risks persisted throughout opioid therapy. These findings, confirmed by the postapproval observational study results for opioid-involved fatal and non-fatal overdose, are consistent with information found in medical literature.[2,3,4] Notably, some of these risks have been described previously

[1] Food and Drug Administration (FDA), 2025, May 5, 2025, Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee - FDA Briefing Document, accessed June 12, 2025, https://www.fda.gov/media/186254/download.
[2] Bialas, P, C Maier, P Klose, W Häuser, 2020, Efficacy and harms of long-term opioid therapy in chronic non-cancer pain: Systematic review and meta-analysis of open-label extension trials with a study duration >/=26 weeks, Eur J Pain, 24(2):265-278.
[3] Hoffman, EM, JC Watson, J St Sauver, NP Staff, CJ Klein, 2017, Association of Long-term Opioid Therapy With Functional Status, Adverse Outcomes, and Mortality Among Patients With Polyneuropathy, JAMA Neurol, 74(7):773-779.
[4] Chou, R, R Deyo, B Devine, R Hansen, S Sullivan, JG Jarvik, I Blazina, T Dana, C Bougatsos, J Turner, 2014, The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain, Evid Rep Technol Assess (Full Rep), 2014 Sep:(218):1-219.

across all opioid analgesic labeling.[5] However, these new quantitative estimates further characterize risks for patients using opioid analgesics long-term and can contribute to the benefit-risk assessment of these products when providers are considering treatment options to manage chronic pain. We consider this to be "new safety information" as defined in section 505-1(b)(3) of the FDCA. In making the determination to require changes to the labeling language, we also considered the discussions held at the May 5, 2025, Joint Meeting of the Drug Safety and Risk Management and Anesthetic and Analgesic Drug Products Advisory Committees, regarding the findings of the postapproval epidemiological studies referenced above.[6]

We have determined that opioid analgesic products and opioid-containing cough/cold products represent a class of products that have the potential for serious risks of misuse, abuse, addiction (moderate-to-severe opioid use disorder), and overdose, as related to long-term opioid treatment.

Opioid Overdose Reversal Agents

Since Tuxarin ER was approved on June 22, 2015, we have become aware that patients and providers may not be familiar with strategies to reduce opioid-related harm, and may lack knowledge regarding opioid overdose reversal agents and their availability.[7,8,9,10] Furthermore, unintentional opioid-related pediatric poisonings remain a concern. Providers should discuss the availability of opioid overdose reversal agents with patients receiving opioid prescriptions, especially when there are children in the household.[11,12] In 2020, FDA required safety labeling changes, recommending that health professionals discuss naloxone with all patients when

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[5] FDA, 2013, FDA News Release - FDA announces safety labeling changes and postmarket study requirements for extended-release and long-acting opioid analgesics, accessed June 12, 2025, https://wayback.archive-it.org/7993/20170112130229/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm367726.htm

[6] FDA, 2025, May 5, 2025, Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee Meeting Announcement, accessed June 12, 2025, https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-meeting-date-and-public-participation-information-may-5-2025-joint-meeting-drug-safety-and.

[7] Bredenberg E, H Olsen, M Ladka, K Beekman, JC Black, MS Ellis, AA Monte, 2025, People entering opioid substance use treatment have low rates of naloxone knowledge and possession, Drug Alcohol Depend, 271:112645.

[8] Dahan A, TS Franko, JW Carroll, DS Craig, C Crow, JL Galinkin, DB Rausch, 2024, Fact vs. fiction: naloxone in the treatment of opioid-induced respiratory depression in the current era of synthetic opioids, Front Public Health, 12:1346109.

[9] Ramdin C, M Zembrzuska, K Zembrzuski, L Nelson, 2025, Layperson knowledge on naloxone and medications for opioid use disorder in an urban population: a cross sectional survey study, J Addict Dis, 43(2):153-161.

[10] Xuan Z, AY Walley, S Yan, A Chatterjee, TG Green, RA Pollini, 2024, Pharmacy Naloxone Standing Order and Community Opioid Fatality Rates Over Time, JAMA Netw Open, 7(8):e2427236.

[11] Gaither JR, S McCollum, K Bechtel, JM Leventhal, S Mintz, 2024, The Circumstances Surrounding Fatal Pediatric Opioid Poisonings, 2004-2020, Pediatrics, 154(Suppl 3):e2024067043N.

[12] Rosen PE, HA Greller, C Ramdin, B Ruck, LS Nelson, DP Calello, 2024, Preventing Pediatric Opioid Poisoning: Unusual Sources and Scenarios, J Pediatr, 275:114236.

prescribing opioid analgesics or medicines to treat opioid use disorder.[13] Since that regulatory action, additional products used to reverse opioid overdose have been approved (i.e., nalmefene), additional strengths of naloxone have been approved, and availability of some products has changed (e.g., the approval of over-the-counter product).[14,15,16] These changes have expanded the list of options from which a health care professional may select, prescribe, or recommend. We have determined that opioid-containing products used in the outpatient setting (e.g., analgesics and cough/cold) and all products used to treat opioid use disorder (OUD) represent a class of products that have the potential for the serious risk of opioid overdose, and increased awareness of the availability of opioid overdose reversal agents may help reduce the risk of fatal opioid overdose. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

Toxic Leukoencephalopathy

Since Tuxarin ER was approved on June 22, 2015, we have become aware of reports in the medical literature of toxic leukoencephalopathy associated with opioid overdose, with multiple case reports describing this adverse event among a variety of opioid moieties.[17,18,19,20,21,22] The causal relationship in these cases was based on the temporal relationship to opioid intake before event onset and absence of reported factors with confounding roles. Toxic leukoencephalopathy has previously

[13] U.S. Food and Drug Administration (FDA), 2020, FDA recommends health care professionals discuss naloxone with all patients when prescribing opioid pain relievers or medicines to treat opioid use disorder, accessed June 4, 2025, https://www.fda.gov/drugs/drug-safety-and-availability/fda-recommends-health-care-professionals-discuss-naloxone-all-patients-when-prescribing-opioid-pain.
[14] Dahan A, TS Franko, JW Carroll, DS Craig, C Crow, JL Galinkin, DB Rausch, 2024, Fact vs. fiction: naloxone in the treatment of opioid-induced respiratory depression in the current era of synthetic opioids, Front Public Health, 12:1346109.
[15] Loera LJ, JE Lines, SR Mayberry, SA Hilzendager, AP Ferguson, LG Hill, 2025, Over-the-Counter Naloxone and Nonprescription Syringe Availability in Community Pharmacies, JAMA Netw Open, 8(2):e2458095.
[16] Nallani SC, Z Li, J Florian, Y Xu, S Sabarinath, T Brescia-Oddo, MU Mehta, 2025, FDA Approval Summary: Nalmefene Nasal Spray for the Emergency Treatment of Known or Suspected Opioid Overdose, Clin Pharmacol Ther, 117(3):620-626.
[17] Bellot B, F Michel, L Thomachot, K Chaumoitre, F Battaglia, P Lagier, 2011, Acute leukoencephalopathy after buprenorphine intoxication in a 2-year-old child, Eur J Paediatr Neurol, 15(4):368-371.
[18] Chan IYM, R Syed, MT Jurkiewicz, 2022, Natural history of pediatric morphine leukoencephalopathy on CT and MRI, Emerg Radiol, 29(6):1055-1058.
[19] Chen CH, AJ Mullen, D Hofstede, T Rizvi, 2019, Malignant cerebellar edema in three-year-old girl following accidental opioid ingestion and fentanyl administration, Neuroradiol J, 32(5):386-391.
[20] Haut LN, R Radhakrishnan, R Lutfi, LW Kao, LL Ackerman, 2021, Acute Cytotoxic Cerebellar Edema Subsequent to Fentanyl Patch Intoxication in an Infant, Case Rep Crit Care, 2021:9449565.
[21] Jones E, U Umasankar, H Mallu, T Hampton, A Kulendran, M Patel, 2020, Lesson of the month: Oxycodone-induced leukoencephalopathy: a rare diagnosis, Clin Med (Lond), 20(6):600-602.
[22] Morales Odia Y, M Jinka, WC Ziai, 2010, Severe leukoencephalopathy following acute oxycodone intoxication, Neurocrit Care, 13(1):93-97.

been associated with heroin use,[23,24] but recent publications have called for a heightened awareness of this condition with non-heroin opioids.[25,26] We have determined that opioid-containing products represent a class of products that have the potential for the same serious risk of toxic leukoencephalopathy in the setting of overdose. We consider this to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

Opioid-Induced Esophageal Dysfunction

Since Tuxarin ER was approved on June 22, 2015, we have become aware of cases and studies in the medical literature describing opioid-induced esophageal dysfunction, otherwise known as OIED.[27,28,29] OIED is more often associated with patients using opioids longer term.[30,31] Evidence of OIED in short-term opioid use is less clear but cannot be ruled out.[32] Additionally, at least one study suggests that OIED is more prevalent with some opioids compared to others,[33] but none of the evidence reviewed suggests that this risk was absent from any specific opioid moiety. Therefore, we have determined that opioid-containing products represent a class of products that have the potential for the serious or otherwise clinically significant risk of OIED. We consider this to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

Drug-Drug Interaction: Gabapentinoids and Opioids

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[23] Filley CM, BK Kleinschmidt-DeMasters, 2001, Toxic leukoencephalopathy, N Engl J Med, 345(6):425-432.
[24] Kashyap S, G Majeed, I Bowen, Y Beamer, D Miulli, 2020, Toxic Leukoencephalopathy Due to Inhalational Heroin Abuse, Ann Indian Acad Neurol, 23(4):542-544.
[25] Agarwal A, M Evans, R Mogallapu, N Kothe, M Ang-Rabanes, 2023, Toxic Leukoencephalopathy After "Chasing the Dragon" With a Non-Heroin Opioid, Cureus, 15(9):e45774.
[26] Chan IYM, R Syed, MT Jurkiewicz, 2022, Natural history of pediatric morphine leukoencephalopathy on CT and MRI, Emerg Radiol, 29(6):1055-1058.
[27] Alcalá-González, L. G., Jiménez-Masip, A., Relea Pérez, L., Barber-Caselles, C., & Barba-Orozco, E. (2022). Opioid-induced esophageal dysfunction - Prevalence and manometric findings. *Rev Esp Enferm Dig, 114*(1), 16-21.
[28] Halasz V, L Knittel, MR Fox, 2023, Opioid-Induced Esophageal Dysmotility (OIED) - A Case Report, Z Gastroenterol, 61(9):1221-1224.
[29] Niu C, J Zhang, J Bapaye, H Liu, K Zhu, U Farooq, PI Okolo, 2023, Systematic Review with Meta-Analysis: Chronic Opioid Use Is Associated With Esophageal Dysmotility in Symptomatic Patients, Am J Gastroenterol, 118(12):2123-2132.
[30] Ladrón Abia P, V Ortiz, M García-Campos, E Saéz-González, A Mínguez Sabater, R Izquierdo, V Garrigues, 2023, Incidence of opioid-induced esophageal dysfunction, Gastroenterol Hepatol, 46(4):249-254.
[31] Ratuapli SK, MD Crowell, JK DiBaise, MF Vela, FC Ramirez, GE Burdick, JA Murray, 2015, Opioid-Induced Esophageal Dysfunction (OIED) in Patients on Chronic Opioids, Am J Gastroenterol, 110(7):979-984.
[32] Balko RA, DA Katzka, JA Murray, JA Alexander, KC Mara, K Ravi, 2021, Same-day opioid administration in opiate naïve patients is not associated with opioid-induced esophageal dysfunction (OIED), Neurogastroenterol Motil, 33(5):e14059.
[33] Snyder DL, MD Crowell, J Horsley-Silva, K Ravi, BE Lacy, MF Vela, 2019, Opioid-Induced Esophageal Dysfunction: Differential Effects of Type and Dose, Am J Gastroenterol, 114(9):1464-1469.

Since Tuxarin ER was approved on June 22, 2015, we have become aware of a growing body of evidence demonstrating that gabapentinoids can potentiate the respiratory depressant effects of opioids.[34] Multiple studies have shown that the combination of opioids and gabapentinoids can lead to significant increases in respiratory depression.[35,36] Furthermore, there is agreement in the literature that clinicians should exercise caution in prescribing these two products together.[37,38] We have determined that opioid-containing products represent a class of products that have the potential for this serious risk. We consider this to be "new safety information" as defined in section 505-1(b)(3) of the FDCA. Furthermore, these changes to opioid labeling align with corresponding safety labeling changes that have already been incorporated into labeling for gabapentinoid products.[39]

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above, we have determined that the new safety information should be included in the labeling for Tuxarin ER as follows:

> *Instructions included as italics. Unless otherwise noted, additions are indicated by **bold underline**, and deletions by ~~strikethrough~~.*

HIGHLIGHTS OF PRESCRIBING INFORMATION

(The Recent Major Changes section should be updated to include changes to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS based on changes in Full Prescribing Information listed in this letter. Additionally, make the following changes as indicated.)

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[34] Bykov K, BT Bateman, JM Franklin, SM Vine, E Patorno, 2020, Association of Gabapentinoids with the Risk of Opioid-Related Adverse Events in Surgical Patients in the United States, JAMA Netw Open, 3(12):e2031647.
[35] Gold LS, PJ Heagerty, RN Hansen, JL Friedly, RA Deyo, M Curatolo, P Suri, 2024, Adverse respiratory events during treatment with gabapentin and opioids among older adults with spine-related conditions: a propensity-matched cohort study in the US Medicare population, medRxiv [Preprint], 2024 Sep 30:2024.09.30.24314627.
[36] Lakkad M, B Martin, C Li, S Harrington, L Dayer, JT Painter, 2024, The use of gabapentinoids and opioids and risk of developing opioid-induced respiratory depression among older breast cancer survivors with neuropathic pain, J Cancer Surviv, 18(3):917-927.
[37] Gold LS, PJ Heagerty, RN Hansen, JL Friedly, RA Deyo, M Curatolo, P Suri, 2024, Adverse respiratory events during treatment with gabapentin and opioids among older adults with spine-related conditions: a propensity-matched cohort study in the US Medicare population, medRxiv [Preprint], 2024 Sep 30:2024.09.30.24314627.
[38] Tambon M, B Montarnal, M Lepetit, M Lapeyre-Mestre, 2023, Non-opioid antinociceptive drugs: risk of respiratory depression and death related to concomitant use of gabapentinoids in addition to opioids, Expert Opin Drug Saf, 22(3):183-194.
[39] U.S. Food and Drug Administration (FDA), 2019, FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR), accessed June 4, 2025, https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-serious-breathing-problems-seizure-and-nerve-pain-medicines-gabapentin-neurontin.

BOXED WARNING

- TUXARIN ER is not recommended for use in pregnant women. **Advise pregnant women using opioids for an extended period of time of the risk of Neonatal Opioid Withdrawal Syndrome, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery.** ~~Prolonged use of TUXARIN ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If TUXARIN ER is used for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.~~ (5.15, 8.1)

----------INDICATIONS AND USAGE----------

Important Limitations of Use (1)

- Because of the risks of addiction, abuse, ~~and~~ misuse**, overdose, and death** ~~with opioids~~ **which can occur at any dosage or duration and persist over the course of therapy** ~~even at recommended doses~~, reserve TUXARIN ER for use in adult patients for whom ~~the benefits of cough suppression are expected to outweigh the risks, and in whom an adequate assessment of the etiology of the cough has been made.~~ **alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of cough.**

FULL PRESCRIBING INFORMATION: CONTENTS*

(Update this section based on other changes in Full Prescribing Information listed in this letter.)

BOXED WARNING

Neonatal Opioid Withdrawal Syndrome

TUXARIN ER is not recommended for use in pregnant women *[see Use in Specific Populations (8.1)*]. **Advise pregnant women using opioids for an extended period of time of the risk of Neonatal Opioid Withdrawal Syndrome, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery.**~~Prolonged use of TUXARIN ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If TUXARIN ER is used for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal~~

~~syndrome and ensure that appropriate treatment will be available~~ *[see Warnings and Precautions (5.15)]*.

1 INDICATIONS AND USAGE

Important Limitations of Use

- Because of the risks of addiction, abuse, ~~and~~ misuse with opioids, **overdose, and death, which can occur at any dosage or duration, and persist over the course of therapy,** ~~with opioids, even at recommended doses~~ *[see Warnings and Precautions (5.1)],* reserve TUXARIN ER for use in adult patients for whom ~~the benefits of cough suppression are expected to outweigh the risks, and in whom an adequate assessment of the etiology of the cough has been made.~~ **alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of cough**.

2 DOSAGE AND ADMINISTRATION

2.3 Monitoring, Maintenance, and Discontinuation of Therapy

Do not **rapidly reduce or** abruptly discontinue TUXARIN ER in a physically-dependent patient *[see Drug Abuse and Dependence (9.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed TUXARIN ER. Addiction can occur at recommended dosages and if the drug is misused or abused. **The risk of opioid-related overdose or overdose-related death is increased with higher opioid doses, and this risk persists over the course of therapy. In postmarketing studies, addiction, abuse, misuse, and fatal and non-fatal opioid overdose were observed in patients with long-term opioid use.** Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression).

5.2 Life-Threatening Respiratory Depression

Management of respiratory depression includes discontinuation of TUXARIN ER, close observation, supportive measures, and use of opioid ~~antagonists~~ **overdose**

reversal agents (e.g., naloxone **or nalmefene**), depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

5.9 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Concomitant use of opioids, including TUXARIN ER, with benzodiazepines, **gabapentinoids,** or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Because of these risks, avoid use of opioid cough medications in patients taking benzodiazepines, other CNS depressants, or alcohol *[see Drug Interactions (7.5)]*.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of similar pharmacologic properties, it is reasonable to expect similar risk with concomitant use of opioid cough medications and benzodiazepines, **gabapentinoids,** other CNS depressants, or alcohol.

Advise both patients and caregivers about the risks of respiratory depression and sedation if OBREDON is used with benzodiazepines, **gabapentinoids,** alcohol, or other CNS depressants *[see Patient Counseling Information (17)]*.

5.10 Risks of ~~Use in Patients with~~ Gastrointestinal ~~Conditions~~ Complications

(Add the following to the end of the information currently in this subsection.)

Cases of opioid-induced esophageal dysfunction (OIED) have been reported in patients taking opioids. The risk of OIED may increase as the dose and/or duration of opioids increases. Regularly evaluate patients for signs and symptoms of OIED (e.g., dysphagia, regurgitation, non-cardiac chest pain), and if necessary, adjust opioid therapy as clinically appropriate.

6 ADVERSE REACTIONS

(Add the following to the end of the information currently in this subsection. Note that the information regarding OIED should cross-reference 5.11 Risks of Gastrointestinal Complications and that the subheading for "Adverse Reactions from Observational Studies" should be underlined.)

Opioid-induced esophageal dysfunction (OIED): Cases of OIED have been reported in patients taking opioids, and may occur more frequently in patients

taking higher doses of opioid, and/or in patients taking opioids longer term *[see Warnings and Precautions (5.10)]*.

7 DRUG INTERACTIONS

7.5 Benzodiazepines, and Other CNS Depressants

Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, **gabapentinoids,** and other opioids, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death. Avoid the use of TUXARIN ER in patients who are taking benzodiazepines, **gabapentinoids,** or other CNS depressants *[see Warnings and Precautions (5.9)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Clinical Considerations

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid ~~antagonist~~ **overdose reversal agent**, such as naloxone **or nalmefene**, must be available for reversal of opioid-induced respiratory depression in the neonate.

10 OVERDOSAGE

Clinical Presentation

Codeine

Acute overdose with codeine is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, partial or complete airway obstruction, atypical snoring, hypotension, hypoglycemia, circulatory collapse, cardiac arrest, and death. **Toxic leukoencephalopathy has been reported after opioid overdose and can present hours, days, or weeks after apparent recovery from the initial intoxication.**

Treatment of Overdose

~~The opioid antagonists, naloxone and nalmefene, are specific antidotes for respiratory depression resulting from opioid overdose.~~ For clinically significant respiratory or circulatory depression secondary to codeine overdose, administer an opioid ~~antagonist~~ **overdose reversal agent such as naloxone or nalmefene**. An ~~antagonist~~ **opioid overdose reversal agent** should not be administered in the absence of clinically significant respiratory depression. Because the duration of opioid reversal is expected to be less than the duration of action of codeine in TUXARIN ER, carefully monitor the patient until spontaneous respiration is reliably reestablished. If the response to an opioid ~~antagonist~~ **overdose reversal agent** is suboptimal or only brief in nature, administer additional ~~antagonist~~ **opioid overdose reversal agent** as directed by the product's prescribing information.

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

Effects on the Gastrointestinal Tract and Other Smooth Muscle

(Add the following as the last sentence in this subsection.)

Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, ~~and~~ transient elevations in serum amylase**, and opioid-induced esophageal dysfunction (OIED)**.

MEDICATION GUIDE

What is the most important information I should know about TUXARIN ER?

- **Severe drowsiness, breathing problems (respiratory depression), coma, and death** can happen in people who take TUXARIN ER with benzodiazepines, **gabapentinoids (gabapentin or pregabalin),** or other central nervous system depressants, including alcohol.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a prior approval supplement (PAS) proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a rebuttal statement detailing the reasons why such a change is not warranted.

The Agency will strive to act on all the labeling supplements for the class on the same day. In accordance with this policy, we have determined that an extension of the discussion period will be warranted to allow us to complete our review and reach agreement on the content of the labeling. Therefore, the discussion period for your supplement or rebuttal statement will begin when the submission is received, and will end by April 1, 2026, unless additional discussion extensions are warranted.

Requirements under section 505(o)(4) apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug approved under an NDA, including discontinued products, unless approval of an application has been withdrawn in the Federal Register. Therefore, the requirements described in this letter apply to you, unless approval of your application has been withdrawn in the Federal Register.

Under section 502(z), failure to submit a response in 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – REBUTTAL (CHANGE NOT WARRANTED).

Prominently identify subsequent submissions related to the safety labeling changes supplement with the following wording in bold capital letters at the top of the first page of the submission:

SUPPLEMENT <<insert assigned #>>
SAFETY LABELING CHANGES UNDER 505(o)(4) - AMENDMENT

We remind you that requirements under section 505(o)(4) also apply to any authorized generic products marketed under this NDA.

If you have any questions, email Elaine Sit, PharmD, Safety Regulatory Project Manager, at Elaine.Sit@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Banu Karimi-Shah, MD
Acting Director
Division of Pulmonology, Allergy, and Critical Care
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TUXARIN ER™ safely and effectively. See full prescribing information for TUXARIN ER.

TUXARIN ER (codeine phosphate and chlorpheniramine maleate) extended-release tablets, for oral use, CIII

Initial U.S. Approval: 1985

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTIAL INGESTION; ULTRA-RAPID METABOLISM OF CODEINE AND OTHER RISK FACTORS FOR LIFE-THREATENING RESPIRATORY DEPRESSION IN CHILDREN; MEDICATION ERRORS; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; NEONATAL OPOID WITHDRAWAL SYNDROME

See full prescribing information for complete boxed warning.

- **TUXARIN ER exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor closely for these behaviors and conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or when used in patients at higher risk. (5.2)**
- **Accidental ingestion of TUXARIN ER, especially by children, can result in a fatal overdose of codeine. (5.2)**
- **Life-threatening respiratory depression and death have occurred in children who received codeine; most cases followed tonsillectomy and/or adenoidectomy, and many of the children had evidence of being an ultra-rapid metabolizer of codeine due to a CYP2D6 polymorphism. (5.3) TUXARIN ER is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy. (4) Avoid the use of TUXARIN ER in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine.**
- **Ensure accuracy when prescribing, dispensing, and administering TUXARIN ER. Dosing errors can result in accidental overdose and death. (2.1, 5.6)**
- **The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with codeine are complex, requiring careful consideration of the effects on the parent drug, codeine, and the active metabolite, morphine. Avoid the use of TUXARIN ER in these patients. (5.4, 7.1, 7.2, 7.4)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Avoid the use of TUXARIN ER in patients taking benzodiazepines, other CNS depressants, or alcohol. (5.9, 7.5)**
- **TUXARIN ER is not recommended for use in pregnant women. Advise pregnant women using opioids for an extended period of time of the risk of Neonatal Opioid Withdrawal Syndrome, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery. ~~Prolonged use of TUXARIN ER during pregnancy can result in neonatal opioid withdrawal syndrome,~~**

----------INDICATIONS AND USAGE----------

TUXARIN ER is a combination of codeine, an opioid agonist; and chlorpheniramine, a histamine-1 (H_1) receptor antagonist, indicated for the temporary relief of cough and upper respiratory symptoms associated with allergy or the common cold in patients 18 years of age and older. (1)

Important Limitations of Use (1)

- Not indicated for pediatric patients under 18 years of age.
- Because of the risks of addiction, abuse, ~~and~~ misuse, overdose, and death, which can occur at any dosage or duration and persist over the course of therapy, ~~with opioids, even at recommended doses,~~ reserve TUXARIN ER for use in adult patients for whom alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of cough~~the benefits of cough suppression are expected to outweigh the risks, and in whom an adequate assessment of the etiology of the cough has been made~~.

----------DOSAGE AND ADMINISTRATION----------

- Adults 18 years of age and older: 1 tablet every 12 hours as needed, not to exceed 2 tablets in 24 hours. (2.2)
- Do not increase the dose or dosing frequency. (2.1)
- Prescribe for the shortest duration consistent with treatment goals. (2.3)
- Reevaluate patients with unresponsive cough in 5 days or sooner for possible underlying pathology. (2.3)
- Reevaluate patient prior to refilling. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Extended-release (ER) tablet: contains 54.3 mg of codeine phosphate; and 8 mg of chlorpheniramine maleate. (3)

----------CONTRAINDICATIONS----------

- Children younger than 12 years of age (4)
- Significant respiratory depression. (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment. (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus. (4)
- Concurrent use of monoamine oxidase inhibitor (MAOI) therapy or within the last 14 days. (4)
- Hypersensitivity to codeine or other opiates, chlorpheniramine, or any of the inactive ingredients in TUXARIN ER. (4)

----------WARNINGS AND PRECAUTIONS----------

See Boxed WARNINGS

- Life-threatening respiratory depression in patients with chronic pulmonary disease or in elderly, cachectic, or debilitated patients: Monitor closely, particularly during initiation of therapy. (5.5)
- Activities requiring mental alertness: Avoid engaging in hazardous tasks requiring mental alertness such as driving or operating machinery. (5.7)
- Risks of use in patients with head injury, impaired consciousness, increased intracranial pressure, or brain tumors: Avoid use. May increase intracranial pressure and obscure the clinical course of head injuries. (5.11)
- Seizures in patients with seizure disorders: Monitor during therapy. (5.12)
- Severe hypotension: Monitor during initiation of therapy. Avoid use in patients with circulatory shock. (5.14)
- Adrenal insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.16)

----------ADVERSE REACTIONS----------

Common adverse reactions of TUXARIN ER include: Sedation (somnolence, mental clouding, lethargy), impaired mental and physical performance, lightheadedness, dizziness, headache, dry mouth, nausea, vomiting, constipation, shortness of breath, and sweating. (6)

To report SUSPECTED ADVERSE REACTIONS, contact MainPointe Pharmaceuticals, LLC at 502-709-7544 or go to mainpointepharmaceuticals.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Phenytoin: Avoid concomitant use; may increase phenytoin levels. (7.4)
- Serotonergic drugs: Concomitant use may result in serotonin syndrome. Discontinue if serotonin syndrome is suspected. (7.6)
- Muscle relaxants: Avoid concomitant use. (7.8)
- Diuretics: Codeine may reduce the efficacy of diuretics. Monitor for reduced effect. (7.9)
- Anticholinergic drugs: Concurrent use may cause paralytic ileus. (5.10, 7.10)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Avoid use in pregnant women. May cause fetal harm. (8.1)
- Lactation: Breastfeeding not recommended. (8.2)
- Renal Impairment: Use with caution in patients with severe renal impairment. (8.6)
- Hepatic Impairment: Use with caution in patients with severe hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 12/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTIAL INGESTION; ULTRA-RAPID METABOLISM OF CODEINE AND OTHER RISK FACTORS FOR LIFE-THREATENING RESPIRATORY DEPRESSION IN CHILDREN; MEDICATION ERRORS; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; NEONATAL OPOID WITHDRAWAL SYNDROME

Addiction, Abuse, and Misuse

TUXARIN ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Reserve TUXARIN ER for use in adult patients for whom the benefits of cough suppression are expected to outweigh the risks, and in whom an adequate assessment of the etiology of the cough has been made. Assess each patient's risk prior to prescribing TUXARIN ER, prescribe TUXARIN ER for the shortest duration that is consistent with individual patient treatment goals, monitor all patients regularly for the development of addition or abuse, and refill only after reevaluation of the need for continued treatment. [*see Warnings and Precautions (5.1)*]

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of TUXARIN ER. Monitor for respiratory depression, especially during initiation of TUXARIN ER therapy or when used in patients at higher risk [*see Warnings and Precautions (5.2)*].

Accidental Ingestion

Accidental ingestion of even one dose of TUXARIN ER, especially by children, can result in a fatal overdose of codeine [*see Warnings and Precautions (5.2)*].

Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children

Life threatening respiratory depression and death have occurred in children who received codeine. Most of the reported cases occurred following tonsillectomy and/or adenoidectomy, and many of the children had evidence of being an ultra-rapid metabolizer of codeine due to a CYP2D6 polymorphism. [*See Warnings and Precautions (5.3)*]. TUXARIN ER is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy [*See Contraindications (4)*]. Avoid the use of TUXARIN ER in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine. [*See Warnings and Precautions (5.1)*].

Risk of Medication Errors

Ensure accuracy when prescribing, dispensing, and administering TUXARIN ER. Dosing errors can result in accidental overdose and death. [*see Dosage and Administration (2.1), Warnings and Precautions (5.6)*].

Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with codeine are complex, requiring careful consideration of the effects on the parent drug, codeine, and the active metabolite, morphine. Avoid the use of TUXARIN ER in patients who are taking a CYP3A4 inhibitor, CYP3A4 inducer, or 2D6 inhibitor [*see Warnings and Precautions (5.8), Drug Interactions (7.1, 7.2, 7.4)*].

Risks from Concomitant Use with Benzodiazepines, CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Avoid use of TUXARIN ER in patients taking benzodiazepines, other CNS depressants, or alcohol. [*see Warning and Precautions (5.9) Drug Interactions (7.5)*].

Neonatal Opioid Withdrawal Syndrome

TUXARIN ER is not recommended for use in pregnant women [*see Use in Specific Populations (8.1)*].
Advise pregnant women using opioids for an extended period of time of the risk of Neonatal Opioid Withdrawal Syndrome, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery ~~**Prolonged use of TUXARIN ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If TUXARIN ER is used for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available**~~ **[*see Warnings and Precautions (5.15)*].**

1 INDICATIONS AND USAGE

TUXARIN ER is indicated for the temporary relief of cough and upper respiratory symptoms associated with allergy or the common cold in patients 18 years of age and older.

Important Limitations of Use

- Not indicated for pediatric patients under 18 years of age *[see Use in Specific Population (8.4)]*.
- Contraindicated in pediatric patients under 12 years of age [*see Contraindications (4), Use in Specific Populations (8.4)*].
- Contraindicated in pediatric patients 12 to 18 years of age after tonsillectomy or adenoidectomy *[see Contraindications (4), Use in Specific Populations (8.4)*].
- Because of the risks of addiction, abuse, ~~and~~ misuse, overdose, and death, which can occur at any dosage or duration and persist over the course of therapy ~~with opioids, even at recommended doses~~ [*see Warnings and Precautions (5.1)*], reserve TUXARIN ER for use in adult patients for whom alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of cough~~the benefits of cough suppression are expected to outweigh the risks, and in whom an adequate assessment of the etiology of the cough has been made~~.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

Administer TUXARIN ER by the oral route only.

Advise patients not to increase the dose or dosing frequency of TUXARIN ER because serious adverse events such as respiratory depression may occur with overdosage [*see Warnings and Precautions (5.2), Overdosage (10)*]. The dosage of TUXARIN ER should not be increased if cough fails to respond; an unresponsive cough should be reevaluated for possible underlying pathology [*see Dosage and Administration (2.3), Warnings and Precautions (5.5)*].

2.2 Recommended Dosage

Adults 18 years of age and older: one tablet every 12 hours as needed, not to exceed 2 tablets in 24 hours.

2.3 Monitoring, Maintenance, and Discontinuation of Therapy

Prescribe TUXARIN ER for the shortest duration that is consistent with individual patient treatment goals [*see Warnings and Precautions (5.1)*]

Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy [*see Warnings and Precautions (5.2)*].

Reevaluate patients with unresponsive cough in 5 days or sooner for possible underlying pathology, such as foreign body or lower respiratory tract disease [*see Warnings and Precautions (5.5)*]. If a patient requires a refill, reevaluate the cause of the cough and assess the need for continued treatment with TUXARIN ER, the relative incidence of adverse reactions, and the development of addiction, abuse, or misuse [*see Warnings and Precautions (5.1)*].

Do not rapidly reduce or abruptly discontinue TUXARIN ER in a physically-dependent patient [*see Drug Abuse and Dependence (9.3)*]. When a patient who has been taking TUXARIN ER regularly and may be physically dependent no longer requires therapy with TUXARIN ER, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both.

3 DOSAGE FORMS AND STRENGTHS

Extended-release tablets: Each tablet contains 54.3 mg of codeine phosphate (equivalent to 40 mg of codeine); and 8 mg of chlorpheniramine maleate (equivalent to 5.6 mg of chlorpheniramine). Each tablet is white to off-white, uncoated, round, debossed with **MP** on one side and **CC** on the other side [*see Description (11)*].

4 CONTRAINDICATIONS

TUXARIN ER is contraindicated for:

- All children younger than 12 years of age [*see Warnings and Precautions (5.2, 5.3, 5.4), Use in Specific Populations (8.4)*].
- Postoperative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy [*see* Warnings and Precautions (*5.2*, *5.3*)].

TUXARIN ER is also contraindicated in patients with:

- Significant respiratory depression [see Warnings and Precautions (*5.2*)]
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [*see Warnings and Precautions (5.5)*].
- Known or suspected gastrointestinal obstruction, including paralytic ileus [*see Warnings and Precautions (5.10)*].
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within 14 days [*see Warnings and Precautions (*5.13*), Drug Interactions (7.7)*].
- Hypersensitivity to codeine, chlorpheniramine, or any of the inactive ingredients in TUXARIN ER [*see Adverse Reactions (6)*]. Persons known to be hypersensitive to certain other opioids may exhibit cross-reactivity to codeine.

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

TUXARIN ER contains codeine, a Schedule III controlled substance. As an opioid, TUXARIN ER exposes users to the risks of addiction, abuse, and misuse [*see Drug Abuse and Dependence (9)*], which can lead to

overdose and death [*see Overdosage (10)*]. **Reserve TUXARIN ER for use in adult patients for whom the benefits of cough suppression are expected to outweigh the risks, and in whom an adequate assessment of the etiology of the cough has been made. Assess each patient's risk prior to prescribing TUXARIN ER, prescribe TUXARIN ER for the shortest duration that is consistent with individual patient treatment goals, monitor all patients regularly for the development of addiction or abuse, and refill only after reevaluation of the need for continued treatment.**

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed TUXARIN ER. Addiction can occur at recommended dosages and if the drug is misused or abused. The risk of opioid-related overdose or overdose-related death is increased with higher opioid doses, and this risk persists over the course of therapy. In postmarketing studies, addiction, abuse, misuse, and fatal and non-fatal opioid overdose were observed in patients with long-term opioid use. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression).

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing TUXARIN ER. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug [*see Patient Counseling Information (17)*]. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, including codeine, one of the active ingredients in TUXARIN ER. Codeine produces dose-related respiratory depression by directly acting on the brain stem respiratory center that controls respiratory rhythm and may produce irregular and periodic breathing. Codeine is subject to variability in metabolism based upon CYP2D6 genotype, which can lead to an increased exposure to the active metabolite morphine [*see Warnings and Precautions (5.3)*]. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression includes discontinuation of TUXARIN ER, close observation, supportive measures, and use of opioid overdose reversal agents ~~antagonists~~ (e.g., naloxone or nalmefene), depending on the patient's clinical status [*see Overdosage (10)*]. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of TUXARIN ER, the risk is greatest during the initiation of therapy, when TUXARIN ER is used concomitantly with other drugs that may cause respiratory depression [*see Warnings and Precautions (5.9)*], in patients with chronic pulmonary disease or decreased respiratory reserve, and in patients with altered pharmacokinetics or altered clearance (e.g. elderly, cachectic, or debilitated patients) [*see Warnings and Precautions (5.5)*].

To reduce the risk of respiratory depression, proper dosing of TUXARIN ER is essential [see Dosage and Administration (*2.1*), Warnings and Precautions (*5.6*)]. Monitor patients closely, especially within the first 24-72 hours of initiating therapy or when used in patients at higher risk.

Overdose of codeine in adults has been associated with fatal respiratory depression, and the use of codeine in children younger than 12 years of age has been associated with fatal respiratory depression when used as recommended [*see Warnings and Precautions (5.3)*]. Accidental ingestion of even one dose of TUXARIN ER, especially by children, can result in respiratory depression and death.

5.3 Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children

Life-threatening respiratory depression and death have occurred in children who received codeine. Codeine is subject to variability in metabolism based upon CYP2D6 genotype (described below), which can lead to an increased exposure to the active metabolite morphine. Based upon post-marketing reports, children younger than 12 years old appear to be more susceptible to the respiratory depressant effects of codeine, particularly if there are risk factors for respiratory depression. For example, many reported cases of death occurred in the post-operative period following tonsillectomy and/or adenoidectomy, and many of the children had evidence of

being ultra-rapid metabolizers of codeine. Furthermore, children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to its respiratory depressant effect. Because of the risk of life-threatening respiratory depression and death:

- TUXARIN ER is contraindicated in all children younger than 12 years of age [*see Contraindications (4)*].
- TUXARIN ER is contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy [*see Contraindications (4)*].
- Avoid the use of TUXARIN ER in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine. Risk factors include conditions associated with hypoventilation, such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression. [*see Warnings and Precautions (5.9), Use in Specific Populations (8.4)*]
- Healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of morphine overdose [*see Warnings and Precautions (5.1), Overdosage (10)*].

Lactation

At least one death was reported in a nursing infant who was exposed to high levels of morphine in breast milk because the mother was an ultra-rapid metabolizer of codeine. Breastfeeding is not recommended during treatment with TUXARIN ER [*see Use in Specific Populations (8.2)*].

CYP2D6 Genetic Variability: Ultra-Rapid Metabolizers

Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (e.g., gene duplications denoted as *1/*1xN or *1/*2xN). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 1 to 10% for Whites (European, North American), 3 to 4% for Blacks (African Americans), 1 to 2% for East Asians (Chinese, Japanese, Korean), and may be greater than 10% in certain /ethnic groups (i.e., Oceanian, Northern African, Middle Eastern, Ashkenazi Jews, Puerto Rican). These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) [*see Overdosage (10)*]. Therefore, individuals who are ultra-rapid metabolizers should not use TUXARIN ER.

5.4 Risks with Use in Pediatric Populations

Children are particularly sensitive to the respiratory depressant effects of codeine [*see Warnings and Precautions (5.2, 5.3)*]. Because of the risk of life-threatening respiratory depression and death, TUXARIN ER is contraindicated in children less than 12 years of age, and in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy [*see Contraindications (4)*].

Use of TUXARIN ER in children also exposes them to the risks of addiction, abuse, and misuse [*see Drug Abuse and Dependence (9)*], which can lead to overdose and death [*see Warnings and Precautions (5.1), Overdosage (10)*]. Because the benefits of symptomatic treatment of cough associated with allergies or the common cold do not outweigh the risks of use of codeine in pediatric patients, TUXARIN ER is not indicated for use in patients younger than 18 years of age [*see Indications (1), Use in Specific Populations (8.4)*].

5.5 Risks with Use in Other At-Risk Populations

Unresponsive Cough

The dosage of TUXARIN ER should not be increased if cough fails to respond; an unresponsive cough should be reevaluated in 5 days or sooner for possible underlying pathology, such as foreign body or lower respiratory tract disease [*see Dosage and Administration (2.3)*].

Asthma and Other Pulmonary Disease

The use of TUXARIN ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated [*see Contraindications (4)*].

Opioid analgesics and antitussives, including codeine, one of the active ingredients in TUXARIN ER, should not be used in patients with acute febrile illness associated with productive cough or in patients with chronic respiratory disease where interference with ability to clear the tracheobronchial tree of secretions would have a deleterious effect on the patient's respiratory function.

TUXARIN ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of TUXARIN ER [*see Warnings and Precautions (5.2)*].

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients [*see Warnings and Precautions (5.2)*].

Because of the risk of respiratory depression, avoid the use of opioid antitussives, including TUXARIN ER in patients with compromised respiratory function, patients at risk of respiratory failure, and in elderly, cachectic, or debilitated patients. If TUXARIN ER is prescribed, monitor such patients closely, particularly when initiating TUXARIN ER and when TUXARIN ER is given concomitantly with other drugs that depress respiration [*see Warnings and Precautions (5.9)*].

5.6 Risk of Accidental Overdose and Death due to Medication Errors

Dosing errors can result in accidental overdose and death. To reduce the risk of overdose and respiratory depression, ensure that the dose of TUXARIN ER is communicated clearly and dispensed accurately [*see Dosage and Administration (2.1)*].

5.7 Activities Requiring Mental Alertness: Risks of Driving and Operating Machinery

Codeine and chlorpheniramine, the active ingredients in TUXARIN ER, may produce marked drowsiness and impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Advise patients to avoid engaging in hazardous tasks requiring mental alertness and motor coordination after ingestion of TUXARIN ER. Avoid concurrent use of TUXARIN ER with alcohol or other central nervous system depressants because additional impairment of central nervous system performance may occur [*See Warnings and Precautions (5.9)*].

5.8 Risks of Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with codeine are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with TUXARIN ER requires careful consideration of the effects on the parent drug, codeine, and the active metabolite, morphine.

Cytochrome P450 3A4 Interaction

The concomitant use of TUXARIN ER with all cytochrome P450 3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir) or discontinuation of a cytochrome P450 3A4 inducer such as rifampin, carbamazepine, and phenytoin, may result in an increase in codeine plasma concentrations with subsequently greater metabolism by cytochrome P450 2D6, resulting in greater morphine levels, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression.

The concomitant use of TUXARIN ER with all cytochrome P450 3A4 inducers or discontinuation of a cytochrome P450 3A4 inhibitor may result in lower codeine levels, greater norcodeine levels, and less metabolism via 2D6 with resultant lower morphine levels. This may be associated with a decrease in efficacy, and in some patients, may result in signs and symptoms of opioid withdrawal.

Avoid the use of TUXARIN ER in patients who are taking a CYP3A4 inhibitor or CYP3A4 inducer. If concomitant use of TUXARIN ER with inhibitors and inducers of CYP3A4 is necessary, monitor patients for signs and symptoms that may reflect opioid toxicity and opioid withdrawal [*see Drug Interactions (7.1, 7.2)*].

Risks of Concomitant Use or Discontinuation of Cytochrome P450 2D6 Inhibitors

The concomitant use of TUXARIN ER with all cytochrome P450 2D6 inhibitors (e.g., amiodarone, quinidine) may result in an increase in codeine plasma concentrations and a decrease in active metabolite morphine plasma concentration which could result in an analgesic efficacy reduction or symptoms of opioid withdrawal.

Discontinuation of a concomitantly used cytochrome P450 2D6 inhibitor may result in a decrease in codeine plasma concentration and an increase in active metabolite morphine plasma concentration which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression.

Avoid the use of TUXARIN ER in patients who are taking a CYP2D6 inhibitor. If concomitant use of TUXARIN ER with inhibitors of CYP2D6 is necessary, monitor patients for signs and symptoms that may reflect opioid toxicity and opioid withdrawal [*see Drug Interactions (7.4)*].

5.9 Risks from Concomitant Use with Benzodiazepines or other CNS Depressants

Concomitant use of opioids, including TUXARIN ER, with benzodiazepines, or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Because of these risks, avoid use of opioid cough medications in patients taking benzodiazepines, gabapentinoids, other CNS depressants, or alcohol [*see Drug Interactions (7.5)*].

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of similar pharmacologic properties, it is reasonable to expect similar risk with concomitant use of opioid cough medications and benzodiazepines, gabapentinoids, other CNS depressants, or alcohol.

Advise both patients and caregivers about the risks of respiratory depression and sedation if TUXARIN ER is used with benzodiazepines, gabapentinoids, alcohol, or other CNS depressants [*see Patient Counseling Information (17)*].

5.10 Risks of ~~Use in Patients with~~ Gastrointestinal ~~Conditions~~Complications

TUXARIN ER is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus [*see Contraindications (4)*]. The use of codeine in TUXARIN ER may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

The concurrent use of anticholinergics with TUXARIN ER may produce paralytic ileus [*see Drug Interactions (7.10)*].

The codeine in TUXARIN ER may result in constipation or obstructive bowel disease, especially in patients with underlying intestinal motility disorders. Use with caution in patients with underlying intestinal motility disorders.

The codeine in TUXARIN ER may cause spasm of the sphincter of Oddi, resulting in an increase in biliary tract pressure. Opioids may cause increases in serum amylase [*see Warnings and Precautions (5.17)*]. Monitor patients with biliary tract disease, including acute pancreatitis for worsening symptoms.

Cases of opioid-induced esophageal dysfunction (OIED) have been reported in patients taking opioids. The risk of OIED may increase as the dose and/or duration of opioids increases. Regularly evaluate patients for signs and symptoms of OIED (e.g., dysphagia, regurgitation, non-cardiac chest pain), and if necessary, adjust opioid therapy as clinically appropriate.

5.11 Risks of Use in Patients with Head Injury, Impaired Consciousness, Increased Intracranial Pressure, or Brain Tumors

Avoid the use of TUXARIN ER in patients with head injury, intracranial lesions, or a pre-existing increase in intracranial pressure. In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), TUXARIN ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Furthermore, opioids produce adverse reactions that may obscure the clinical course of patients with head injuries.

5.12 Increased Risk of Seizures in Patients with Seizure Disorders

The codeine and chlorpheniramine in TUXARIN ER may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during TUXARIN ER therapy.

5.13 Co-administration with Monoamine Oxidase Inhibitors (MAOIs)

Concurrent use of TUXARIN ER is contraindicated in patients receiving monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping such therapy [*see Contraindications (4)*]. MAOIs may potentiate the effects of morphine, codeine's active metabolite, including respiratory depression, coma, and confusion MAOIs [*see Drug Interactions (7.7)*].

5.14 Severe Hypotension

TUXARIN ER may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) [*see Drug Interactions (7.5)*]. Monitor these patients for signs of hypotension after initiating TUXARIN ER.

In patients with circulatory shock, TUXARIN ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of TUXARIN ER in patients with circulatory shock.

5.15 Neonatal Opioid Withdrawal Syndrome

TUXARIN ER is not recommended for use in pregnant women. Prolonged use of TUXARIN ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. [*see Use in Specific Populations (8.1), Patient Counseling Information (17)*]

5.16 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal

function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be

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tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.17 Drug/Laboratory Test Interactions

Because opioid agonists may increase biliary tract pressure, with resultant increase in plasma amylase or lipase levels, determination of these enzyme levels may be unreliable for 24 hours after administration of a dose of TUXARIN ER.

6 ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Addiction, abuse, and misuse [*see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.3)*]
- Life-threatening respiratory depression [*see Warnings and Precautions (5.2, 5.3, 5.4, 5.5, 5.9), Overdosage (10)*]
- Ultra-rapid metabolism of codeine and other risk factors for life-threatening respiratory depression in children [*see Warnings and Precautions (5.3)*]
- Accidental overdose and death due to medication errors [*see Warnings and Precautions (5.6)*]
- Decreased mental alertness with impaired mental and/or physical abilities [*see Warnings and Precautions (5.7)*]
- Interactions with benzodiazepines and other CNS depressants [*see Warnings and Precautions (5.9)*]
- Paralytic ileus, gastrointestinal adverse reactions [*see Warnings and Precautions (5.10)*]
- Increased intracranial pressure [*see Warnings and Precautions (5.11)*]
- Obscured clinical course in patients with head injuries [*see Warnings and Precautions (5.11)*]
- Seizures [*see Warnings and Precautions (5.12)*]
- Interactions with MAOI [*see Warnings and Precautions (5.13)*]
- Severe hypotension [*see Warnings and Precautions (5.14)*]
- Neonatal Opioid Withdrawal Syndrome [*see Warnings and Precautions (5.15)*]
- Adrenal insufficiency [*see Warnings and Precautions (5.16)*]

The following adverse reactions have been identified during clinical studies, or during post-approval use of codeine and/or chlorpheniramine. Because these reactions may be reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The most common adverse reactions to TUXARIN ER include: Sedation (somnolence, mental clouding, lethargy), impaired mental and physical performance, lightheadedness, dizziness, headache, dry mouth, nausea, vomiting, constipation, shortness of breath, and sweating.

Other reactions include:

Anaphylaxis: Anaphylaxis has been reported with codeine, one of the ingredients in TUXARIN ER.

Body as a whole: Coma, death, fatigue, falling injuries, lethargy.

Cardiovascular: Peripheral edema, increased blood pressure, decreased blood pressure, tachycardia, chest pain, palpitation, syncope, orthostatic hypotension, prolonged QT interval, hot flush.

Central Nervous System: Ataxia, facial dyskinesia, insomnia, increased intracranial pressure, migraine, seizure, tremor, tinnitus, vertigo.

Dermatologic: Flushing, hyperhidrosis, pruritus, rash.

Endocrine/Metabolic: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs. Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Cases of androgen deficiency have occurred with chronic use of opioids [*see Clinical Pharmacology (12.2)*].

Gastrointestinal: Abdominal pain, bowel obstruction, decreased appetite, diarrhea, difficulty swallowing, GERD, indigestion, pancreatitis, paralytic ileus, biliary tract spasm (spasm of the sphincter of Oddi).

Genitourinary: Urinary tract infection, ureteral spasm, spasm of vesicle sphincters, urinary retention.

Hematologic: Agranulocytosis, aplastic anemia, and thrombocytopenia have been reported.

Laboratory: Increases in serum amylase.

Musculoskeletal: Arthralgia, backache, muscle spasm.

Ophthalmic: Blurred vision, diplopia, miosis (constricted pupils), visual disturbances.

Psychiatric: Agitation, anxiety, confusion, fear, dysphoria, depression, hallucinations.

Reproductive: Hypogonadism, infertility.

Respiratory: Bronchitis, cough, dry nose, dry throat, dyspnea, nasal congestion, nasopharyngitis, respiratory depression, sinusitis, thickening of bronchial secretions, tightness of chest and wheezing, upper respiratory tract infection.

Other: Drug abuse, drug dependence, opioid withdrawal syndrome.

Hypoglycemia: Cases of hypoglycemia have been reported in patients taking opioids. Most reports were in patients with at least one predisposing risk factor (e.g., diabetes).

Opioid-induced esophageal dysfunction (OIED): Cases of OIED have been reported in patients taking opioids, and may occur more frequently in patients taking higher doses of opioid, and/or in patients taking opioids longer term *[see Warnings and Precautions (5.10)].*

7 DRUG INTERACTIONS

No specific drug interaction studies have been conducted with TUXARIN ER.

7.1 Inhibitors of CYP3A4

The concomitant use of TUXARIN ER with CYP3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), or protease inhibitors (e.g., ritonavir), may result in an increase in codeine plasma concentrations with subsequently greater metabolism by cytochrome CYP2D6, resulting in greater morphine levels, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of TUXARIN ER is achieved [*see Warnings and Precautions (5.8)*]. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, it may result in lower codeine levels, greater norcodeine levels, and less metabolism via CYP2D6 with resultant lower morphine levels [*see Clinical Pharmacology (12.3)*], resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to codeine.

Avoid the use of TUXARIN ER while taking a CYP3A4 inhibitor. If concomitant use is necessary, monitor patients for respiratory depression and sedation at frequent intervals.

7.2 CYP3A4 Inducers

The concomitant use of TUXARIN ER and CYP3A4 inducers, such as rifampin, carbamazepine, or phenytoin, can result in lower codeine levels, greater norcodeine levels, and less metabolism via 2D6 with resultant lower morphine levels [*see Clinical Pharmacology (12.3)*], resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence [*see Warnings and Precautions (5.8)*]. After stopping a CYP3A4 inducer, as the effects of the inducer decline, codeine plasma concentrations may increase with subsequently greater metabolism by cytochrome CYP2D6, resulting in greater morphine levels [*see Clinical Pharmacology (12.3)*], which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.

Avoid the use of TUXARIN ER in patients who are taking CYP3A4 inducers. If concomitant use of a CYP3A4

inducer is necessary, follow the patient for reduced efficacy.

7.3 Phenytoin

Adverse event reports in the literature suggest a possible drug interaction involving increased serum phenytoin levels and phenytoin toxicity when chlorpheniramine and phenytoin are co-administered. The exact mechanism for this interaction is not known, however it is believed that chlorpheniramine may inhibit the hepatic metabolism of phenytoin. Avoid the use of TUXARIN ER while taking phenytoin.

7.4 Inhibitors of CYP2D6

Codeine is metabolized by CYP2D6 to form morphine. The concomitant use of TUXARIN ER and CYP2D6 inhibitors, such as paroxetine, fluoxetine, bupropion, or quinidine, can increase the plasma concentration of codeine, but can decrease the plasma concentration of active metabolite morphine, which could result in reduced efficacy [see *Clinical Pharmacology (12.3)*]. After stopping a CYP2D6 inhibitor, as the effects of the inhibitor decline, the codeine plasma concentration will decrease but the active metabolite morphine plasma concentration will increase, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression [*see Clinical Pharmacology (*12.3*)*].

Avoid the use of TUXARIN ER in patients who are taking inhibitors of CYP2D6.

7.5 Benzodiazepines and Other CNS Depressants

Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids, and other opioids, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death. Avoid the use of TUXARIN ER in patients who are taking benzodiazepines, gabapentinoids, or other CNS depressants. [*see Warnings and Precautions (5.9)*].

7.6 Serotonergic Drugs

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation. Discontinue TUXARIN ER if serotonin syndrome is suspected.

7.7 Monoamine Oxidase Inhibitors (MAOIs)

TUXARIN ER is contraindicated in patients who are taking MAOIs (i.e., certain drugs used for depression, psychiatric or emotional conditions, or Parkinson's disease) or have taken MAOIs within 14 days [*see Contraindications (4)*].

MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) [*see Warnings and Precautions (5.13)*].

7.8 Muscle Relaxants

Codeine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. Avoid the use of TUXARIN ER in patients taking muscle relaxants. If concomitant use is necessary, monitor patients for signs of respiratory depression that may be greater than otherwise expected.

7.9 Diuretics

Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.

7.10 Anticholinergic Drugs

The concomitant use of anticholinergic drugs with TUXARIN ER may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus [*see Warnings and Precautions (*5.10*)*]. Monitor patients

for signs of urinary retention or reduced gastric motility when TUXARIN ER is used concomitantly with anticholinergic drugs.

Additive adverse effects resulting from cholinergic blockade (e.g., xerostomia, blurred vision, or constipation) may occur when anticholinergic drugs are administered with chlorpheniramine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

TUXARIN ER is not recommended for use in pregnant women, including during or immediately prior to labor.

Prolonged use of opioids during pregnancy may cause neonatal opioid withdrawal syndrome [see Warnings and Precautions (*5.15*) and *Clinical Considerations*].

There are no available data with TUXARIN ER use in pregnant women to inform a drug-associated risk for adverse developmental outcomes. Published studies with codeine have reported inconsistent findings and have important methodological limitations (*see Data*). There are reports of respiratory depression when codeine is used during labor and delivery *(see Clinical Considerations)*.

Reproductive toxicity studies have not been conducted with TUXARIN ER; however, studies are available with individual active ingredients (*see Data*).

In animal reproduction studies, codeine administered by the oral route to pregnant rats during the period of organogenesis increased resorptions and decreased fetal weights at a dose approximately 15 times the maximum recommended human dose (MRHD) in the presence of maternal toxicity (*see Data*).

Chlorpheniramine administered by the oral route to mice throughout pregnancy was embryolethal at a dose approximately 9 times the MRHD and decreased postnatal survival when dosing was continued after parturition. Chlorpheniramine administered by the oral route to male and female rats prior to mating produced embryolethality at a dose approximately 9 times the MRHD (*see Data*).

Based on the animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly [*see Warnings and Precautions (5.15)*].

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid overdose reversal agent~~antagonist~~, such as naloxone or nalmefene, must be available for reversal of opioid-induced respiratory depression in the neonate. Opioids, including TUXARIN ER, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be

offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioids during labor for signs of excess sedation and respiratory depression.

Data

Human Data

No new primary pharmacodynamic studies were conducted. Codeine is a well-established antitussive and chlorpheniramine maleate is a recognized antihistamine. Both drugs have been used at these strengths in combination for several years.

Codeine

Published data from case-control and observational studies on codeine use during pregnancy are inconsistent in their findings. Some studies of codeine exposure showed an increased risk of overall congenital malformations while others did not. An increased risk of specific malformations with codeine exposure such as respiratory malformations, spina bifida and congenital heart defects were reported in some studies. Most of the studies, both positive and negative, were limited by small sample size, recall bias and lack of information regarding dose and timing of exposure.

Chlorpheniramine

The majority of studies examining the use of chlorpheniramine in pregnancy did not find an association with an increased risk of congenital anomalies. In the few studies reporting an association, there was no consistent pattern of malformations noted.

Animal Data

Reproductive toxicity studies have not been conducted with TUXARIN ER; however, studies are available with individual active ingredients.

Codeine

In an embryofetal development study in pregnant rats dosed throughout the period of organogenesis, codeine increased resorptions and decreased fetal weights at a dose approximately 15 times the MRHD (on a mg/m^2 basis with a maternal oral dose of 120 mg/kg/day); however, these effects occurred in the presence of maternal toxicity. In embryofetal development studies with pregnant rabbits and mice dosed throughout the period of organogenesis, codeine produced no adverse developmental effects at doses approximately 7 and 35 times, respectively, the MRHD (on a mg/m^2 basis with maternal oral doses of 30 mg/kg/day in rabbits and 600 mg/kg/day in mice).

Chlorpheniramine

In embryofetal development studies with pregnant rats and rabbits dosed throughout the period of organogenesis, chlorpheniramine produced no adverse developmental effects at oral doses up to approximately 35 and 45 times, respectively, the MRHD on a mg/m^2 basis. However, in a reproduction study with pregnant mice dosed throughout pregnancy, chlorpheniramine produced embryolethality at a dose approximately 9 times the MRHD (on a mg/m^2 basis with a maternal oral dose of 20 mg/kg/day) and decreased postnatal survival when dosing was continued after parturition. In a fertility and reproduction study with male and female rats dosed prior to mating, chlorpheniramine produced embryolethality at a dose approximately 9 times the MRHD (on a mg/m^2 basis with an oral parental dose of 10 mg/kg/day).

8.2 Lactation

Risk Summary

Because of the potential for serious adverse reactions, including excess sedation, respiratory depression, and death in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with TUXARIN ER [*see Warnings and Precautions (5.3)*].

There are no data on the presence of TUXARIN ER in human milk, the effects of TUXARIN ER on the breastfed infant, or the effects of TUXARIN ER on milk production; however, data are available with codeine and chlorpheniramine.

Codeine

Codeine and its active metabolite, morphine, are present in human milk. There are published studies and cases that have reported excessive sedation, respiratory depression and death (in one infant) in infants exposed to codeine via breast milk. Women who are ultra-rapid metabolizers of codeine achieve higher than expected serum levels of morphine, potentially leading to higher levels of morphine in breast milk that can be dangerous in their breastfed infants. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent. There is no information on the effects of the codeine on milk production.

Chlorpheniramine

Chlorpheniramine is present in human milk. Chlorpheniramine has not been reported to cause effects on the breastfed infant. The published literature suggests that chlorpheniramine may decrease milk production based on its anticholinergic effects. (*see Clinical Considerations*)

Clinical Considerations

Infants exposed to TUXARIN ER through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid is stopped, or when breastfeeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids, such as codeine, a component of TUXARIN ER, may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [*see Adverse Reactions (6), Clinical Pharmacology (12.2)*].

8.4 Pediatric Use

TUXARIN ER is not indicated for use in patients younger than 18 years of age because the benefits of symptomatic treatment of cough associated with allergies or the common cold do not outweigh the risks for use of codeine in these patients [*see Indications (1), Warnings and Precautions (5.4)*].

Life-threatening respiratory depression and death have occurred in children who received codeine [*see Warnings and Precautions* (*5.2*)]. In most of the reported cases, these events followed tonsillectomy and/or adenoidectomy, and many of the children had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations). Children with sleep apnea may be particularly sensitive to the respiratory depressant effects of codeine.

Because of the risk of life-threatening respiratory depression and death:

- TUXARIN ER is contraindicated in all children younger than 12 years of age *[see Contraindications (4)]*.
- TUXARIN ER is contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy *[see Contraindications (4)]*.
- Avoid the use of TUXARIN ER in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation, such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease,

and concomitant use of other medications that cause respiratory depression. *[see Warnings and Precautions (5.3)]*.

8.5 Geriatric Use

Clinical studies have not been conducted with TUXARIN ER in geriatric populations.

Use caution when considering the use of TUXARIN ER in patients 65 years of age or older. Elderly patients may have increased sensitivity to codeine; greater frequency of decreased hepatic, renal, or cardiac function; or concomitant disease or other drug therapy [*see Warnings and Precautions (5.5)*].

Respiratory depression is the chief risk for elderly patients treated with opioids, including TUXARIN ER. Respiratory depression has occurred after large initial doses of opioids were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration [*see Warnings and Precautions (5.5, 5.9)*].

Codeine is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, monitor these patients closely for respiratory depression, sedation, and hypotension.

8.6 Renal Impairment

The pharmacokinetics of TUXARIN ER has not been characterized in patients with renal impairment. Codeine pharmacokinetics may be altered in patients with renal failure. Clearance may be decreased and the metabolites may accumulate to much higher plasma levels in patients with renal failure as compared to patients with normal renal function. Chlorpheniramine is cleared substantially by the kidney. As such, impaired renal function could potentially lead to the risk of decreased clearance and thereby increased retention or systemic levels of chlorpheniramine. Therefore, TUXARIN ER should be used with caution in patients with severe impairment of renal function, and patients should be monitored closely for signs of hydrocodone toxicity (respiratory depression, sedation, and hypotension) and chlorpheniramine toxicity.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KELLY D STONE
07/31/2025 08:31:08 AM
Signing with the delegated authority of Banu Karimi-Shah, Acting Director, DPACC

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TUXARIN ER™ safely and effectively. See full prescribing information for TUXARIN ER.

TUXARIN ER (codeine phosphate and chlorpheniramine maleate) extended-release tablets, for oral use, CIII
Initial U.S. Approval: 1985

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTIAL INGESTION; ULTRA-RAPID METABOLISM OF CODEINE AND OTHER RISK FACTORS FOR LIFE-THREATENING RESPIRATORY DEPRESSION IN CHILDREN; MEDICATION ERRORS; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; NEONATAL OPOID WITHDRAWAL SYNDROME

See full prescribing information for complete boxed warning.

- **TUXARIN ER exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor closely for these behaviors and conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or when used in patients at higher risk. (5.2)**
- **Accidental ingestion of TUXARIN ER, especially by children, can result in a fatal overdose of codeine. (5.2)**
- **Life-threatening respiratory depression and death have occurred in children who received codeine; most cases followed tonsillectomy and/or adenoidectomy, and many of the children had evidence of being an ultra-rapid metabolizer of codeine due to a CYP2D6 polymorphism. (5.3) TUXARIN ER is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy. (4) Avoid the use of TUXARIN ER in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine.**
- **Ensure accuracy when prescribing, dispensing, and administering TUXARIN ER. Dosing errors can result in accidental overdose and death. (2.1, 5.6)**
- **The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with codeine are complex, requiring careful consideration of the effects on the parent drug, codeine, and the active metabolite, morphine. Avoid the use of TUXARIN ER in these patients. (5.4, 7.1, 7.2, 7.4)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Avoid the use of TUXARIN ER in patients taking benzodiazepines, other CNS depressants, or alcohol. (5.9, 7.5)**
- **TUXARIN ER is not recommended for use in pregnant women. Advise pregnant women using opioids for an extended period of time of the risk of Neonatal Opioid Withdrawal Syndrome, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery (5.15, 8.1). ~~Prolonged use of TUXARIN ER during pregnancy can result in neonatal opioid withdrawal~~**

----------RECENT MAJOR CHANGES----------

Boxed Warning	XX/2025
Indications and Usage (1)	XX/2025
Dosage and Administration (2.3)	XX/2025
Warnings and Precautions (5.1, 5.2, 5.9, 5.10)	XX/2025

----------INDICATIONS AND USAGE----------

TUXARIN ER is a combination of codeine, an opioid agonist; and chlorpheniramine, a histamine-1 (H_1) receptor antagonist, indicated for the temporary relief of cough and upper respiratory symptoms associated with allergy or the common cold in patients 18 years of age and older. (1)

~~Important~~ Limitations of Use ~~(1)~~

- Not indicated for pediatric patients under 18 years of age. (1)
- Because of the risks of addiction, abuse, ~~and~~ misuse, overdose, and death, which can occur at any dosage or duration and persist over the course of therapy, ~~with opioids, even at recommended doses,~~ reserve TUXARIN ER for use in adult patients for whom alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of cough ~~while benefits of cough suppression are expected to outweigh the risks, and in whom an adequate assessment of the etiology of the cough has been made.~~ (1, 5.1)

----------DOSAGE AND ADMINISTRATION----------

- ~~Adults 18 years of age and older: 1 tablet every 12 hours as needed, not to exceed 2 tablets in 24 hours. (2.2)~~
- Do not increase the dose or dosing frequency. (2.1)
- Prescribe for the shortest duration consistent with treatment goals. (2.3)
- Reevaluate patients with unresponsive cough in 5 days or sooner for possible underlying pathology. (2.3)
- Reevaluate patient prior to refilling. (2.3)
- Do not rapidly reduce or abruptly discontinue in a physically-dependent patient. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Extended-release (ER) tablet: contains 54.3 mg of codeine phosphate; and 8 mg of chlorpheniramine maleate. (3)

----------CONTRAINDICATIONS----------

- Children younger than 12 years of age (4)
- Significant respiratory depression. (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment. (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus. (4)
- Concurrent use of monoamine oxidase inhibitor (MAOI) therapy or within the last 14 days. (4)
- Hypersensitivity to codeine or other opiates, chlorpheniramine, or any of the inactive ingredients in TUXARIN ER. (4)

----------WARNINGS AND PRECAUTIONS----------

~~See Boxed WARNINGS~~

- Life-threatening respiratory depression in patients with chronic pulmonary disease or in elderly, cachectic, or debilitated patients: Monitor closely, particularly during initiation of therapy. (5.5)
- Activities requiring mental alertness: Avoid engaging in hazardous tasks requiring mental alertness such as driving or operating machinery. (5.7)
- Risks of use in patients with head injury, impaired consciousness, increased intracranial pressure, or brain tumors: Avoid use. May increase intracranial pressure and obscure the clinical course of head injuries. (5.11)
- Seizures in patients with seizure disorders: Monitor during therapy. (5.12)
- Severe hypotension: Monitor during initiation of therapy. Avoid use in patients with circulatory shock. (5.14)
- Adrenal insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.16)

----------ADVERSE REACTIONS----------

Common adverse reactions of TUXARIN ER include: Sedation (somnolence, mental clouding, lethargy), impaired mental and physical performance, lightheadedness, dizziness, headache, dry mouth, nausea, vomiting, constipation, shortness of breath, and sweating. (6)

To report SUSPECTED ADVERSE REACTIONS, contact MainPointe Pharmaceuticals, LLC at 502-709-7544 or go to mainpointepharmaceuticals.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Phenytoin: Avoid concomitant use; may increase phenytoin levels. (7.4)
- Serotonergic drugs: Concomitant use may result in serotonin syndrome. Discontinue if serotonin syndrome is suspected. (7.6)
- Muscle relaxants: Avoid concomitant use. (7.8)
- Diuretics: Codeine may reduce the efficacy of diuretics. Monitor for reduced effect. (7.9)
- Anticholinergic drugs: Concurrent use may cause paralytic ileus. (5.10, 7.10)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Avoid use in pregnant women. May cause fetal harm. (8.1)
- Lactation: Breastfeeding not recommended. (8.2)
- Renal Impairment: Use with caution in patients with severe renal impairment. (8.6)
- Hepatic Impairment: Use with caution in patients with severe hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

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Revised: 12/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTIAL INGESTION; ULTRA-RAPID METABOLISM OF CODEINE AND OTHER RISK FACTORS FOR LIFE-THREATENING RESPIRATORY DEPRESSION IN CHILDREN; MEDICATION ERRORS; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; NEONATAL OPOID WITHDRAWAL SYNDROME

Addiction, Abuse, and Misuse

TUXARIN ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Reserve TUXARIN ER for use in adult patients for whom the benefits of cough suppression are expected to outweigh the risks, and in whom an adequate assessment of the etiology of the cough has been made. Assess each patient's risk prior to prescribing TUXARIN ER, prescribe TUXARIN ER for the shortest duration that is consistent with individual patient treatment goals, monitor all patients regularly for the development of addition or abuse, and refill only after reevaluation of the need for continued treatment. [*see Warnings and Precautions (5.1)*]

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of TUXARIN ER. Monitor for respiratory depression, especially during initiation of TUXARIN ER therapy or when used in patients at higher risk [*see Warnings and Precautions (5.2)*].

Accidental Ingestion

Accidental ingestion of even one dose of TUXARIN ER, especially by children, can result in a fatal overdose of codeine [*see Warnings and Precautions (5.2)*].

Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children

Life threatening respiratory depression and death have occurred in children who received codeine. Most of the reported cases occurred following tonsillectomy and/or adenoidectomy, and many of the children had evidence of being an ultra-rapid metabolizer of codeine due to a CYP2D6 polymorphism. [*See Warnings and Precautions (5.3)*]. TUXARIN ER is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy [*See Contraindications (4)*]. Avoid the use of TUXARIN ER in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine. [*See Warnings and Precautions (5.1)*].

Risk of Medication Errors

Ensure accuracy when prescribing, dispensing, and administering TUXARIN ER. Dosing errors can result in accidental overdose and death. [*see Dosage and Administration (2.1), Warnings and Precautions (5.6)*].

Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with codeine are complex, requiring careful consideration of the effects on the parent drug, codeine, and the active metabolite, morphine. Avoid the use of TUXARIN ER in patients who are taking a CYP3A4 inhibitor, CYP3A4 inducer, or 2D6 inhibitor [*see Warnings and Precautions (5.8), Drug Interactions (7.1, 7.2, 7.4)*].

Risks from Concomitant Use with Benzodiazepines, CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Avoid use of TUXARIN ER in patients taking benzodiazepines, other CNS depressants, or alcohol. [*see Warning and Precautions (5.9) Drug Interactions (7.5)*].

Neonatal Opioid Withdrawal Syndrome

TUXARIN ER is not recommended for use in pregnant women [*see Use in Specific Populations (8.1)*].
Advise pregnant women using opioids for an extended period of time of the risk of Neonatal Opioid Withdrawal Syndrome, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery ~~Prolonged use of TUXARIN ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If TUXARIN ER is used for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available~~ [*see Warnings and Precautions (5.15)*].

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1 INDICATIONS AND USAGE

TUXARIN ER is indicated for the temporary relief of cough and upper respiratory symptoms associated with allergy or the common cold in patients 18 years of age and older.

~~Important~~ Limitations of Use

- Not indicated for pediatric patients under 18 years of age *[see Use in Specific Population (8.4)]*.
- Contraindicated in pediatric patients under 12 years of age [*see Contraindications (4), Use in Specific Populations (8.4)*].
- Contraindicated in pediatric patients 12 to 18 years of age after tonsillectomy or adenoidectomy *[see Contraindications (4), Use in Specific Populations (8.4)*].
- Because of the risks of addiction, abuse, ~~and~~ misuse, overdose, and death, which can occur at any dosage or duration and persist over the course of therapy ~~with opioids, even at recommended doses~~ [*see Warnings and Precautions (5.1)*], reserve TUXARIN ER for use in adult patients for whom alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of cough~~the benefits of cough suppression are expected to outweigh the risks, and in whom an adequate assessment of the etiology of the cough has been made~~.

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2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

Administer TUXARIN ER by the oral route only.

Advise patients not to increase the dose or dosing frequency of TUXARIN ER because serious adverse events such as respiratory depression may occur with overdosage [*see Warnings and Precautions (5.2), Overdosage (10)*]. The dosage of TUXARIN ER should not be increased if cough fails to respond; an unresponsive cough should be reevaluated for possible underlying pathology [*see Dosage and Administration (2.3), Warnings and Precautions (5.5)*].

2.2 Recommended Dosage

Adults 18 years of age and older: one tablet every 12 hours as needed, not to exceed 2 tablets in 24 hours.

2.3 Monitoring, Maintenance, and Discontinuation of Therapy

Prescribe TUXARIN ER for the shortest duration that is consistent with individual patient treatment goals [*see Warnings and Precautions (5.1)*]

Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy [*see Warnings and Precautions (5.2)*].

Reevaluate patients with unresponsive cough in 5 days or sooner for possible underlying pathology, such as foreign body or lower respiratory tract disease [*see Warnings and Precautions (5.5)*]. If a patient requires a refill, reevaluate the cause of the cough and assess the need for continued treatment with TUXARIN ER, the relative incidence of adverse reactions, and the development of addiction, abuse, or misuse [*see Warnings and Precautions (5.1)*].

Do not rapidly reduce or abruptly discontinue TUXARIN ER in a physically-dependent patient [*see Drug Abuse and Dependence (9.3)*]. When a patient who has been taking TUXARIN ER regularly and may be physically dependent no longer requires therapy with TUXARIN ER, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both.

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3 DOSAGE FORMS AND STRENGTHS

Extended-release tablets: Each tablet contains 54.3 mg of codeine phosphate (equivalent to 40 mg of codeine); and 8 mg of chlorpheniramine maleate (equivalent to 5.6 mg of chlorpheniramine). Each tablet is white to off-white, uncoated, round, debossed with **MP** on one side and **CC** on the other side [*see Description (11)*].

4 CONTRAINDICATIONS

TUXARIN ER is contraindicated for:

- All children younger than 12 years of age [*see Warnings and Precautions (5.2, 5.3, 5.4), Use in Specific Populations (8.4)*].
- Postoperative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy [*see* Warnings and Precautions (*5.2*, *5.3*)].

TUXARIN ER is also contraindicated in patients with:

- Significant respiratory depression [see Warnings and Precautions (*5.2*)]
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [*see Warnings and Precautions (5.5)*].
- Known or suspected gastrointestinal obstruction, including paralytic ileus [*see Warnings and Precautions (5.10)*].
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within 14 days [*see Warnings and Precautions (*5.13*), Drug Interactions (7.7)*].
- Hypersensitivity to codeine, chlorpheniramine, or any of the inactive ingredients in TUXARIN ER [*see Adverse Reactions (6)*]. Persons known to be hypersensitive to certain other opioids may exhibit cross-reactivity to codeine.

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

TUXARIN ER contains codeine, a Schedule III controlled substance. As an opioid, TUXARIN ER exposes users to the risks of addiction, abuse, and misuse [*see Drug Abuse and Dependence (9)*], which can lead to

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overdose and death [*see Overdosage (10)*]. **Reserve TUXARIN ER for use in adult patients for whom the benefits of cough suppression are expected to outweigh the risks, and in whom an adequate assessment of the etiology of the cough has been made. Assess each patient's risk prior to prescribing TUXARIN ER, prescribe TUXARIN ER for the shortest duration that is consistent with individual patient treatment goals, monitor all patients regularly for the development of addiction or abuse, and refill only after reevaluation of the need for continued treatment.**

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed TUXARIN ER. Addiction can occur at recommended dosages and if the drug is misused or abused. The risk of opioid-related overdose or overdose-related death is increased with higher opioid doses, and this risk persists over the course of therapy. In postmarketing studies, addiction, abuse, misuse, and fatal and non-fatal opioid overdose were observed in patients with long-term opioid use *[see Adverse Reactions (6)]*. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression).

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Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing TUXARIN ER. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug [*see Patient Counseling Information (17)*]. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, including codeine, one of the active ingredients in TUXARIN ER. Codeine produces dose-related respiratory depression by directly acting on the brain stem respiratory center that controls respiratory rhythm and may produce irregular and periodic breathing. Codeine is subject to variability in metabolism based upon CYP2D6 genotype, which can lead to an increased exposure to the active metabolite morphine [*see Warnings and Precautions (5.3)*]. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression includes discontinuation of TUXARIN ER, close observation, supportive measures, and use of opioid overdose reversal agents ~~antagonists~~ (e.g., naloxone or nalmefene), depending on the patient's clinical status [*see Overdosage (10)*]. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

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While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of TUXARIN ER, the risk is greatest during the initiation of therapy, when TUXARIN ER is used concomitantly with other drugs that may cause respiratory depression [*see Warnings and Precautions (5.9)*], in patients with chronic pulmonary disease or decreased respiratory reserve, and in patients with altered pharmacokinetics or altered clearance (e.g. elderly, cachectic, or debilitated patients) [*see Warnings and Precautions (5.5)*].

To reduce the risk of respiratory depression, proper dosing of TUXARIN ER is essential [see Dosage and Administration (*2.1*), Warnings and Precautions (*5.6*)]. Monitor patients closely, especially within the first 24-72 hours of initiating therapy or when used in patients at higher risk.

Overdose of codeine in adults has been associated with fatal respiratory depression, and the use of codeine in children younger than 12 years of age has been associated with fatal respiratory depression when used as recommended [*see Warnings and Precautions (5.3)*]. Accidental ingestion of even one dose of TUXARIN ER, especially by children, can result in respiratory depression and death.

5.3 Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children

Life-threatening respiratory depression and death have occurred in children who received codeine. Codeine is subject to variability in metabolism based upon CYP2D6 genotype (described below), which can lead to an increased exposure to the active metabolite morphine. Based upon post-marketing reports, children younger than 12 years old appear to be more susceptible to the respiratory depressant effects of codeine, particularly if there are risk factors for respiratory depression. For example, many reported cases of death occurred in the post-operative period following tonsillectomy and/or adenoidectomy, and many of the children had evidence of

being ultra-rapid metabolizers of codeine. Furthermore, children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to its respiratory depressant effect. Because of the risk of life-threatening respiratory depression and death:

- TUXARIN ER is contraindicated in all children younger than 12 years of age [*see Contraindications (4)*].
- TUXARIN ER is contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy [*see Contraindications (4)*].
- Avoid the use of TUXARIN ER in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine. Risk factors include conditions associated with hypoventilation, such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression. [*see Warnings and Precautions (5.9), Use in Specific Populations (8.4)*]
- Healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of morphine overdose [*see Warnings and Precautions (5.1), Overdosage (10)*].

Lactation

At least one death was reported in a nursing infant who was exposed to high levels of morphine in breast milk because the mother was an ultra-rapid metabolizer of codeine. Breastfeeding is not recommended during treatment with TUXARIN ER [*see Use in Specific Populations (8.2)*].

CYP2D6 Genetic Variability: Ultra-Rapid Metabolizers

Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (e.g., gene duplications denoted as *1/*1xN or *1/*2xN). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 1 to 10% for Whites (European, North American), 3 to 4% for Blacks (African Americans), 1 to 2% for East Asians (Chinese, Japanese, Korean), and may be greater than 10% in certain /ethnic groups (i.e., Oceanian, Northern African, Middle Eastern, Ashkenazi Jews, Puerto Rican). These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) [*see Overdosage (10)*]. Therefore, individuals who are ultra-rapid metabolizers should not use TUXARIN ER.

5.4 Risks with Use in Pediatric Populations

Children are particularly sensitive to the respiratory depressant effects of codeine [*see Warnings and Precautions (5.2, 5.3)*]. Because of the risk of life-threatening respiratory depression and death, TUXARIN ER is contraindicated in children less than 12 years of age, and in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy [*see Contraindications (4)*].

Use of TUXARIN ER in children also exposes them to the risks of addiction, abuse, and misuse [*see Drug Abuse and Dependence (9)*], which can lead to overdose and death [*see Warnings and Precautions (5.1), Overdosage (10)*]. Because the benefits of symptomatic treatment of cough associated with allergies or the common cold do not outweigh the risks of use of codeine in pediatric patients, TUXARIN ER is not indicated for use in patients younger than 18 years of age [*see Indications (1), Use in Specific Populations (8.4)*].

5.5 Risks with Use in Other At-Risk Populations

Unresponsive Cough

The dosage of TUXARIN ER should not be increased if cough fails to respond; an unresponsive cough should be reevaluated in 5 days or sooner for possible underlying pathology, such as foreign body or lower respiratory tract disease [*see Dosage and Administration (2.3)*].

Asthma and Other Pulmonary Disease

The use of TUXARIN ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated [*see Contraindications (4)*].

Opioid analgesics and antitussives, including codeine, one of the active ingredients in TUXARIN ER, should not be used in patients with acute febrile illness associated with productive cough or in patients with chronic respiratory disease where interference with ability to clear the tracheobronchial tree of secretions would have a deleterious effect on the patient's respiratory function.

TUXARIN ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of TUXARIN ER [*see Warnings and Precautions (5.2)*].

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients [*see Warnings and Precautions (5.2)*].

Because of the risk of respiratory depression, avoid the use of opioid antitussives, including TUXARIN ER in patients with compromised respiratory function, patients at risk of respiratory failure, and in elderly, cachectic, or debilitated patients. If TUXARIN ER is prescribed, monitor such patients closely, particularly when initiating TUXARIN ER and when TUXARIN ER is given concomitantly with other drugs that depress respiration [*see Warnings and Precautions (5.9)*].

5.6 Risk of Accidental Overdose and Death due to Medication Errors

Dosing errors can result in accidental overdose and death. To reduce the risk of overdose and respiratory depression, ensure that the dose of TUXARIN ER is communicated clearly and dispensed accurately [*see Dosage and Administration (2.1)*].

5.7 Activities Requiring Mental Alertness: Risks of Driving and Operating Machinery

Codeine and chlorpheniramine, the active ingredients in TUXARIN ER, may produce marked drowsiness and impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Advise patients to avoid engaging in hazardous tasks requiring mental alertness and motor coordination after ingestion of TUXARIN ER. Avoid concurrent use of TUXARIN ER with alcohol or other central nervous system depressants because additional impairment of central nervous system performance may occur [*See Warnings and Precautions (5.9)*].

5.8 Risks of Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with codeine are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with TUXARIN ER requires careful consideration of the effects on the parent drug, codeine, and the active metabolite, morphine.

Cytochrome P450 3A4 Interaction

The concomitant use of TUXARIN ER with all cytochrome P450 3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir) or discontinuation of a cytochrome P450 3A4 inducer such as rifampin, carbamazepine, and phenytoin, may result in an increase in codeine plasma concentrations with subsequently greater metabolism by cytochrome P450 2D6, resulting in greater morphine levels, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression.

The concomitant use of TUXARIN ER with all cytochrome P450 3A4 inducers or discontinuation of a cytochrome P450 3A4 inhibitor may result in lower codeine levels, greater norcodeine levels, and less metabolism via 2D6 with resultant lower morphine levels. This may be associated with a decrease in efficacy, and in some patients, may result in signs and symptoms of opioid withdrawal.

Avoid the use of TUXARIN ER in patients who are taking a CYP3A4 inhibitor or CYP3A4 inducer. If concomitant use of TUXARIN ER with inhibitors and inducers of CYP3A4 is necessary, monitor patients for signs and symptoms that may reflect opioid toxicity and opioid withdrawal [*see Drug Interactions (7.1, 7.2)*].

Risks of Concomitant Use or Discontinuation of Cytochrome P450 2D6 Inhibitors

The concomitant use of TUXARIN ER with all cytochrome P450 2D6 inhibitors (e.g., amiodarone, quinidine) may result in an increase in codeine plasma concentrations and a decrease in active metabolite morphine plasma concentration which could result in an analgesic efficacy reduction or symptoms of opioid withdrawal.

Discontinuation of a concomitantly used cytochrome P450 2D6 inhibitor may result in a decrease in codeine plasma concentration and an increase in active metabolite morphine plasma concentration which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression.

Avoid the use of TUXARIN ER in patients who are taking a CYP2D6 inhibitor. If concomitant use of TUXARIN ER with inhibitors of CYP2D6 is necessary, monitor patients for signs and symptoms that may reflect opioid toxicity and opioid withdrawal [*see Drug Interactions (7.4)*].

5.9 Risks from Concomitant Use with Benzodiazepines or other CNS Depressants

Concomitant use of opioids, including TUXARIN ER, with benzodiazepines, or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Because of these risks, avoid use of opioid cough medications in patients taking benzodiazepines, gabapentinoids (gabapentin or pregabalin), other CNS depressants, or alcohol [*see Drug Interactions (7.5)*].

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Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of similar pharmacologic properties, it is reasonable to expect similar risk with concomitant use of opioid cough medications and benzodiazepines, gabapentinoids (gabapentin or pregabalin), other CNS depressants, or alcohol.

Advise both patients and caregivers about the risks of respiratory depression and sedation if TUXARIN ER is used with benzodiazepines, gabapentinoids (gabapentin or pregabalin), alcohol, or other CNS depressants [*see Patient Counseling Information (17)*].

5.10 Risks of ~~Use in Patients with~~ Gastrointestinal ~~Conditions~~Complications

TUXARIN ER is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus [*see Contraindications (4)*]. The use of codeine in TUXARIN ER may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

The concurrent use of anticholinergics with TUXARIN ER may produce paralytic ileus [*see Drug Interactions (7.10)*].

The codeine in TUXARIN ER may result in constipation or obstructive bowel disease, especially in patients with underlying intestinal motility disorders. Use with caution in patients with underlying intestinal motility disorders.

The codeine in TUXARIN ER may cause spasm of the sphincter of Oddi, resulting in an increase in biliary tract pressure. Opioids may cause increases in serum amylase [*see Warnings and Precautions (5.17)*]. Monitor patients with biliary tract disease, including acute pancreatitis for worsening symptoms.

Cases of opioid-induced esophageal dysfunction (OIED) have been reported in patients taking opioids. The risk of OIED may increase as the dose and/or duration of opioids increases. Regularly evaluate patients for signs and symptoms of OIED (e.g., dysphagia, regurgitation, non-cardiac chest pain) and, if necessary, adjust opioid therapy as clinically appropriate *[see Clinical Pharmacology (12.2)].*

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5.11 Risks of Use in Patients with Head Injury, Impaired Consciousness, Increased Intracranial Pressure, or Brain Tumors

Avoid the use of TUXARIN ER in patients with head injury, intracranial lesions, or a pre-existing increase in intracranial pressure. In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), TUXARIN ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Furthermore, opioids produce adverse reactions that may obscure the clinical course of patients with head injuries.

5.12 Increased Risk of Seizures in Patients with Seizure Disorders

The codeine and chlorpheniramine in TUXARIN ER may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during TUXARIN ER therapy.

5.13 Co-administration with Monoamine Oxidase Inhibitors (MAOIs)

Concurrent use of TUXARIN ER is contraindicated in patients receiving monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping such therapy [*see Contraindications (4)*]. MAOIs may potentiate the effects of morphine, codeine's active metabolite, including respiratory depression, coma, and confusion MAOIs [*see Drug Interactions (7.7)*].

5.14 Severe Hypotension

TUXARIN ER may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) [*see Drug Interactions (7.5)*]. Monitor these patients for signs of hypotension after initiating TUXARIN ER.

In patients with circulatory shock, TUXARIN ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of TUXARIN ER in patients with circulatory shock.

5.15 Neonatal Opioid Withdrawal Syndrome

TUXARIN ER is not recommended for use in pregnant women. Prolonged use of TUXARIN ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. [*see Use in Specific Populations (8.1), Patient Counseling Information (17)*]

5.16 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal

function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be

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tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.17 Drug/Laboratory Test Interactions

Because opioid agonists may increase biliary tract pressure, with resultant increase in plasma amylase or lipase levels, determination of these enzyme levels may be unreliable for 24 hours after administration of a dose of TUXARIN ER.

6 ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Addiction, abuse, and misuse [*see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.3)*]
- Life-threatening respiratory depression [*see Warnings and Precautions (5.2, 5.3, 5.4, 5.5, 5.9), Overdosage (10)*]
- Ultra-rapid metabolism of codeine and other risk factors for life-threatening respiratory depression in children [*see Warnings and Precautions (5.3)*]
- Accidental overdose and death due to medication errors [*see Warnings and Precautions (5.6)*]
- Decreased mental alertness with impaired mental and/or physical abilities [*see Warnings and Precautions (5.7)*]
- Interactions with benzodiazepines and other CNS depressants [*see Warnings and Precautions (5.9)*]
- Paralytic ileus, gastrointestinal adverse reactions [*see Warnings and Precautions (5.10)*]
- Increased intracranial pressure [*see Warnings and Precautions (5.11)*]
- Obscured clinical course in patients with head injuries [*see Warnings and Precautions (5.11)*]
- Seizures [*see Warnings and Precautions (5.12)*]
- Interactions with MAOI [*see Warnings and Precautions (5.13)*]
- Severe hypotension [*see Warnings and Precautions (5.14)*]
- Neonatal Opioid Withdrawal Syndrome [*see Warnings and Precautions (5.15)*]
- Adrenal insufficiency [*see Warnings and Precautions (5.16)*]

The following adverse reactions have been identified during clinical studies, or during post-approval use of codeine and/or chlorpheniramine. Because these reactions may be reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The most common adverse reactions to TUXARIN ER include: Sedation (somnolence, mental clouding, lethargy), impaired mental and physical performance, lightheadedness, dizziness, headache, dry mouth, nausea, vomiting, constipation, shortness of breath, and sweating.

Other reactions include:

Anaphylaxis: Anaphylaxis has been reported with codeine, one of the ingredients in TUXARIN ER.

Body as a whole: Coma, death, fatigue, falling injuries, lethargy.

Cardiovascular: Peripheral edema, increased blood pressure, decreased blood pressure, tachycardia, chest pain, palpitation, syncope, orthostatic hypotension, prolonged QT interval, hot flush.

Central Nervous System: Ataxia, facial dyskinesia, insomnia, increased intracranial pressure, migraine, seizure, tremor, tinnitus, vertigo.

Dermatologic: Flushing, hyperhidrosis, pruritus, rash.

Endocrine/Metabolic: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs. Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Cases of androgen deficiency have occurred with chronic use of opioids [*see Clinical Pharmacology (12.2)*].

Gastrointestinal: Abdominal pain, bowel obstruction, decreased appetite, diarrhea, difficulty swallowing, GERD, indigestion, pancreatitis, paralytic ileus, biliary tract spasm (spasm of the sphincter of Oddi).

Genitourinary: Urinary tract infection, ureteral spasm, spasm of vesicle sphincters, urinary retention.

Hematologic: Agranulocytosis, aplastic anemia, and thrombocytopenia have been reported.

Laboratory: Increases in serum amylase.

Musculoskeletal: Arthralgia, backache, muscle spasm.

Ophthalmic: Blurred vision, diplopia, miosis (constricted pupils), visual disturbances.

Psychiatric: Agitation, anxiety, confusion, fear, dysphoria, depression, hallucinations.

Reproductive: Hypogonadism, infertility.

Respiratory: Bronchitis, cough, dry nose, dry throat, dyspnea, nasal congestion, nasopharyngitis, respiratory depression, sinusitis, thickening of bronchial secretions, tightness of chest and wheezing, upper respiratory tract infection.

Other: Drug abuse, drug dependence, opioid withdrawal syndrome.

Hypoglycemia: Cases of hypoglycemia have been reported in patients taking opioids. Most reports were in patients with at least one predisposing risk factor (e.g., diabetes).

Opioid-induced esophageal dysfunction (OIED): Cases of OIED have been reported in patients taking opioids and may occur more frequently in patients taking higher doses of opioids, and/or in patients taking opioids longer term.

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7 DRUG INTERACTIONS

No specific drug interaction studies have been conducted with TUXARIN ER.

7.1 Inhibitors of CYP3A4

The concomitant use of TUXARIN ER with CYP3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), or protease inhibitors (e.g., ritonavir), may result in an increase in codeine plasma concentrations with subsequently greater metabolism by cytochrome CYP2D6, resulting in greater morphine levels, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of TUXARIN ER is achieved [*see Warnings and Precautions (5.8)*]. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, it may result in lower codeine levels, greater norcodeine levels, and less metabolism via CYP2D6 with resultant lower morphine levels [*see Clinical Pharmacology (12.3)*], resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to codeine.

Avoid the use of TUXARIN ER while taking a CYP3A4 inhibitor. If concomitant use is necessary, monitor patients for respiratory depression and sedation at frequent intervals.

7.2 CYP3A4 Inducers

The concomitant use of TUXARIN ER and CYP3A4 inducers, such as rifampin, carbamazepine, or phenytoin, can result in lower codeine levels, greater norcodeine levels, and less metabolism via 2D6 with resultant lower morphine levels [*see Clinical Pharmacology (12.3)*], resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence [*see Warnings and Precautions (5.8)*]. After stopping a CYP3A4 inducer, as the effects of the inducer decline, codeine plasma concentrations may increase with subsequently greater metabolism by cytochrome CYP2D6, resulting in greater morphine levels [*see Clinical Pharmacology (12.3)*], which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.

Avoid the use of TUXARIN ER in patients who are taking CYP3A4 inducers. If concomitant use of a CYP3A4 inducer is necessary, follow the patient for reduced efficacy.

7.3 Phenytoin

Adverse event reports in the literature suggest a possible drug interaction involving increased serum phenytoin levels and phenytoin toxicity when chlorpheniramine and phenytoin are co-administered. The exact mechanism for this interaction is not known, however it is believed that chlorpheniramine may inhibit the hepatic metabolism of phenytoin. Avoid the use of TUXARIN ER while taking phenytoin.

7.4 Inhibitors of CYP2D6

Codeine is metabolized by CYP2D6 to form morphine. The concomitant use of TUXARIN ER and CYP2D6 inhibitors, such as paroxetine, fluoxetine, bupropion, or quinidine, can increase the plasma concentration of codeine, but can decrease the plasma concentration of active metabolite morphine, which could result in reduced efficacy [see *Clinical Pharmacology (12.3)*]. After stopping a CYP2D6 inhibitor, as the effects of the inhibitor decline, the codeine plasma concentration will decrease but the active metabolite morphine plasma concentration will increase, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression [*see Clinical Pharmacology (12.3)*].

Avoid the use of TUXARIN ER in patients who are taking inhibitors of CYP2D6.

7.5 Benzodiazepines and Other CNS Depressants

Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids (gabapentin or pregabalin), and other opioids, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death. Avoid the use of TUXARIN ER in patients who are taking benzodiazepines, gabapentinoids (gabapentin or pregabalin), or other CNS depressants. [*see Warnings and Precautions (5.9)*].

7.6 Serotonergic Drugs

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation. Discontinue TUXARIN ER if serotonin syndrome is suspected.

7.7 Monoamine Oxidase Inhibitors (MAOIs)

TUXARIN ER is contraindicated in patients who are taking MAOIs (i.e., certain drugs used for depression, psychiatric or emotional conditions, or Parkinson's disease) or have taken MAOIs within 14 days [*see Contraindications (4)*].

MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) [*see Warnings and Precautions (5.13)*].

7.8 Muscle Relaxants

Codeine may enhance the neuromuscular blocking action of skeletal muscle relaxants (e.g., cyclobenzaprine, metaxalone) and produce an increased degree of respiratory depression. Avoid the use of TUXARIN ER in patients taking muscle relaxants. If concomitant use is necessary, monitor patients for signs of respiratory depression that may be greater than otherwise expected.

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These examples should be included per standard opioid class labeling.

7.9 Diuretics

Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.

7.10 Anticholinergic Drugs

The concomitant use of anticholinergic drugs with TUXARIN ER may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus [*see Warnings and Precautions (5.10)*]. Monitor patients

for signs of urinary retention or reduced gastric motility when TUXARIN ER is used concomitantly with anticholinergic drugs.

Additive adverse effects resulting from cholinergic blockade (e.g., xerostomia, blurred vision, or constipation) may occur when anticholinergic drugs are administered with chlorpheniramine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

TUXARIN ER is not recommended for use in pregnant women, including during or immediately prior to labor.

Prolonged use of opioids during pregnancy may cause neonatal opioid withdrawal syndrome [see Warnings and Precautions (*5.15*) and *Clinical Considerations*].

There are no available data with TUXARIN ER use in pregnant women to inform a drug-associated risk for adverse developmental outcomes. Published studies with codeine have reported inconsistent findings and have important methodological limitations (*see Data*). There are reports of respiratory depression when codeine is used during labor and delivery *(see Clinical Considerations)*.

Reproductive toxicity studies have not been conducted with TUXARIN ER; however, studies are available with individual active ingredients (*see Data*).

In animal reproduction studies, codeine administered by the oral route to pregnant rats during the period of organogenesis increased resorptions and decreased fetal weights at a dose approximately 15 times the maximum recommended human dose (MRHD) in the presence of maternal toxicity (*see Data*).

Chlorpheniramine administered by the oral route to mice throughout pregnancy was embryolethal at a dose approximately 9 times the MRHD and decreased postnatal survival when dosing was continued after parturition. Chlorpheniramine administered by the oral route to male and female rats prior to mating produced embryolethality at a dose approximately 9 times the MRHD (*see Data*).

Based on the animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly [*see Warnings and Precautions (5.15)*].

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid overdose reversal agent~~antagonist~~, such as naloxone or nalmefene, must be available for reversal of opioid-induced respiratory depression in the neonate. Opioids, including TUXARIN ER, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be

offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioids during labor for signs of excess sedation and respiratory depression.

Data

Human Data

No new primary pharmacodynamic studies were conducted. Codeine is a well-established antitussive and chlorpheniramine maleate is a recognized antihistamine. Both drugs have been used at these strengths in combination for several years.

Codeine

Published data from case-control and observational studies on codeine use during pregnancy are inconsistent in their findings. Some studies of codeine exposure showed an increased risk of overall congenital malformations while others did not. An increased risk of specific malformations with codeine exposure such as respiratory malformations, spina bifida and congenital heart defects were reported in some studies. Most of the studies, both positive and negative, were limited by small sample size, recall bias and lack of information regarding dose and timing of exposure.

Chlorpheniramine

The majority of studies examining the use of chlorpheniramine in pregnancy did not find an association with an increased risk of congenital anomalies. In the few studies reporting an association, there was no consistent pattern of malformations noted.

Animal Data

Reproductive toxicity studies have not been conducted with TUXARIN ER; however, studies are available with individual active ingredients.

Codeine

In an embryofetal development study in pregnant rats dosed throughout the period of organogenesis, codeine increased resorptions and decreased fetal weights at a dose approximately 15 times the MRHD (on a mg/m^2 basis with a maternal oral dose of 120 mg/kg/day); however, these effects occurred in the presence of maternal toxicity. In embryofetal development studies with pregnant rabbits and mice dosed throughout the period of organogenesis, codeine produced no adverse developmental effects at doses approximately 7 and 35 times, respectively, the MRHD (on a mg/m^2 basis with maternal oral doses of 30 mg/kg/day in rabbits and 600 mg/kg/day in mice).

Chlorpheniramine

In embryofetal development studies with pregnant rats and rabbits dosed throughout the period of organogenesis, chlorpheniramine produced no adverse developmental effects at oral doses up to approximately 35 and 45 times, respectively, the MRHD on a mg/m^2 basis. However, in a reproduction study with pregnant mice dosed throughout pregnancy, chlorpheniramine produced embryolethality at a dose approximately 9 times the MRHD (on a mg/m^2 basis with a maternal oral dose of 20 mg/kg/day) and decreased postnatal survival when dosing was continued after parturition. In a fertility and reproduction study with male and female rats dosed prior to mating, chlorpheniramine produced embryolethality at a dose approximately 9 times the MRHD (on a mg/m^2 basis with an oral parental dose of 10 mg/kg/day).

8.2 Lactation

Risk Summary

Because of the potential for serious adverse reactions, including excess sedation, respiratory depression, and death in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with TUXARIN ER [*see Warnings and Precautions (5.3)*].

There are no data on the presence of TUXARIN ER in human milk, the effects of TUXARIN ER on the breastfed infant, or the effects of TUXARIN ER on milk production; however, data are available with codeine and chlorpheniramine.

Codeine

Codeine and its active metabolite, morphine, are present in human milk. There are published studies and cases that have reported excessive sedation, respiratory depression and death (in one infant) in infants exposed to codeine via breast milk. Women who are ultra-rapid metabolizers of codeine achieve higher than expected serum levels of morphine, potentially leading to higher levels of morphine in breast milk that can be dangerous in their breastfed infants. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent. There is no information on the effects of the codeine on milk production.

Chlorpheniramine

Chlorpheniramine is present in human milk. Chlorpheniramine has not been reported to cause effects on the breastfed infant. The published literature suggests that chlorpheniramine may decrease milk production based on its anticholinergic effects. (*see Clinical Considerations*)

Clinical Considerations

Infants exposed to TUXARIN ER through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid is stopped, or when breastfeeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids, such as codeine, a component of TUXARIN ER, may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [*see Adverse Reactions (6), Clinical Pharmacology (12.2)*].

8.4 Pediatric Use

TUXARIN ER is not indicated for use in patients younger than 18 years of age because the benefits of symptomatic treatment of cough associated with allergies or the common cold do not outweigh the risks for use of codeine in these patients [*see Indications (1), Warnings and Precautions (5.4)*].

Life-threatening respiratory depression and death have occurred in children who received codeine [*see Warnings and Precautions* (*5.2*)]. In most of the reported cases, these events followed tonsillectomy and/or adenoidectomy, and many of the children had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations). Children with sleep apnea may be particularly sensitive to the respiratory depressant effects of codeine.

Because of the risk of life-threatening respiratory depression and death:

- TUXARIN ER is contraindicated in all children younger than 12 years of age *[see Contraindications (4)]*.
- TUXARIN ER is contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy *[see Contraindications (4)]*.
- Avoid the use of TUXARIN ER in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation, such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease,

and concomitant use of other medications that cause respiratory depression. *[see Warnings and Precautions (5.3)]*.

8.5 Geriatric Use

Clinical studies have not been conducted with TUXARIN ER in geriatric populations.

Use caution when considering the use of TUXARIN ER in patients 65 years of age or older. Elderly patients may have increased sensitivity to codeine; greater frequency of decreased hepatic, renal, or cardiac function; or concomitant disease or other drug therapy [*see Warnings and Precautions (5.5)*].

Respiratory depression is the chief risk for elderly patients treated with opioids, including TUXARIN ER. Respiratory depression has occurred after large initial doses of opioids were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration [*see Warnings and Precautions (5.5, 5.9)*].

Codeine is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, monitor these patients closely for respiratory depression, sedation, and hypotension.

8.6 Renal Impairment

The pharmacokinetics of TUXARIN ER has not been characterized in patients with renal impairment. Codeine pharmacokinetics may be altered in patients with renal failure. Clearance may be decreased and the metabolites may accumulate to much higher plasma levels in patients with renal failure as compared to patients with normal renal function. Chlorpheniramine is cleared substantially by the kidney. As such, impaired renal function could potentially lead to the risk of decreased clearance and thereby increased retention or systemic levels of chlorpheniramine. Therefore, TUXARIN ER should be used with caution in patients with severe impairment of renal function, and patients should be monitored closely for signs of hydrocodone toxicity (respiratory depression, sedation, and hypotension) and chlorpheniramine toxicity.

8.7 Hepatic Impairment

No formal studies have been conducted in patients with hepatic impairment so the pharmacokinetics of TUXARIN ER in this patient population are unknown. Chlorpheniramine is extensively metabolized by liver before elimination from the body. As such, impaired hepatic function could potentially lead to the risk of decreased metabolism and thereby increased systemic levels of chlorpheniramine. Therefore, TUXARIN ER should be used with caution in patients with severe impairment of hepatic function, and patients should be monitored closely for signs of hydrocodone toxicity (respiratory depression, sedation, and hypotension) and chlorpheniramine toxicity.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

TUXARIN ER contains codeine, a Schedule III controlled substance.

9.2 Abuse

Codeine

TUXARIN ER contains codeine, a substance with a high potential for abuse similar to other opioids including morphine and codeine. TUXARIN ER can be abused and is subject to misuse, addiction, and criminal diversion [*see Warnings and Precautions (5.1)*].

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

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating health care provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Health care providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

TUXARIN ER, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of TUXARIN ER

TUXARIN ER is for oral use only. Abuse of TUXARIN ER poses a risk of overdose and death. The risk is increased with concurrent use of TUXARIN ER with alcohol and other central nervous system depressants [*see Warnings and Precautions (5.9)*].

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

9.3 Dependence

Psychological dependence, physical dependence, and tolerance may develop upon repeated administration of opioids; therefore, TUXARIN ER should be prescribed and administered for the shortest duration that is consistent with individual patient treatment goals and patients should be reevaluated prior to refills [*see Dosage and Administration (2.3), Warnings and Precautions (5.1)*].

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued oral opioid use, although some mild degree of physical dependence may develop after a few days of opioid therapy.

Do not rapidly reduce or abruptly discontinue TUXARIN ER in a physically-dependent patient. If TUXARIN ER is rapidly reduced or abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [*see Use in Specific Populations (8.1)*].

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10 OVERDOSAGE

Clinical Presentation

Codeine

Acute overdose with codeine is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, partial or complete airway obstruction, atypical snoring, hypotension, hypoglycemia, circulatory collapse, cardiac arrest, and death. Toxic leukoencephalopathy has been reported after opioid overdose and can present hours, days, or weeks after apparent recovery from the initial intoxication.

Codeine may cause miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations [*see Clinical Pharmacology (12.2)*].

Chlorpheniramine

Signs and symptoms of chlorpheniramine overdosage may vary from central nervous system depression to stimulation. Central toxic effects are characterized by agitation, anxiety, delirium, disorientation, hallucinations, hyperactivity, sedation, and seizures. Severe overdosage may produce coma, medullary paralysis, and death. Peripheral toxicity includes hypertension, tachycardia, dysrhythmias, vasodilation, hyperpyrexia, mydriasis, urinary retention, and diminished gastrointestinal motility. Atropine-like signs and symptoms (dry mouth, fixed dilated pupils, flushing, tachycardia, hallucinations, gastrointestinal symptoms, convulsions, urinary retention, cardiac arrhythmias and coma) may be observed.

Impaired secretion from sweat glands following toxic doses of drugs with anticholinergic side effects may predispose to hyperthermia.

Toxic psychosis, a possible class effect from overdose of sedating antihistamines, has been reported.

Treatment of Overdose

Treatment of overdosage is driven by the overall clinical presentation, and consists of discontinuation of TUXARIN ER together with institution of appropriate therapy. Give primary attention to the reestablishment of adequate respiratory exchange through provision of a patent and protected airway and the institution of assisted or controlled ventilation. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques. Gastric emptying may be useful in removing unabsorbed drug.

~~The opioid antagonists, naloxone and nalmefene, are specific antidotes for respiratory depression resulting from opioid overdose.~~ For clinically significant respiratory or circulatory depression secondary to codeine overdose, administer an opioid overdose reversal agent such as naloxone or nalmefene~~antagonist~~. An opioid overdose reversal agent~~antagonist~~ should not be administered in the absence of clinically significant respiratory depression. Because the duration of opioid reversal is expected to be less than the duration of action of codeine in TUXARIN ER, carefully monitor the patient until spontaneous respiration is reliably reestablished. TUXARIN ER will continue to release codeine and add to the codeine load for 4 hours or longer following ingestion, necessitating prolonged monitoring. If the response to an opioid overdose reversal agent~~antagonist~~ is suboptimal or only brief in nature, administer additional reversal agent~~antagonist~~ as directed by the product's prescribing information.

Hemodialysis is not routinely used to enhance the elimination of codeine or chlorpheniramine from the body.

Urinary excretion of chlorpheniramine is increased when the pH of the urine is acidic; however, acid diuresis is NOT recommended to enhance elimination in overdose, as the risks of acidemia and acute tubular necrosis in patients with rhabdomyolysis far outweigh any potential benefits.

11 DESCRIPTION

TUXARIN ER (codeine phosphate and chlorpheniramine maleate) extended-release tablets, contains codeine, an opioid agonist; and chlorpheniramine, a histamine-1 (H_1) receptor antagonist.

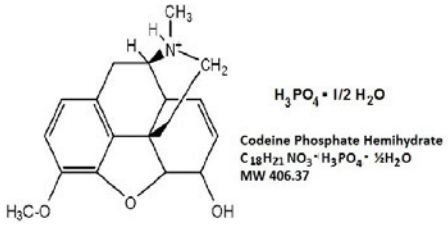
Each tablet of TUXARIN ER contains 54.3 mg of codeine phosphate and 8 mg of chlorpheniramine maleate for oral administration.

TUXARIN ER are white to off-white, uncoated, standard round extended-release matrix tablets.

TUXARIN ER also contains the following inactive ingredients: hypromellose, lactose monohydrate, cellulose microcrystalline, polysorbate 80, magnesium stearate, and colloidal silicon dioxide.

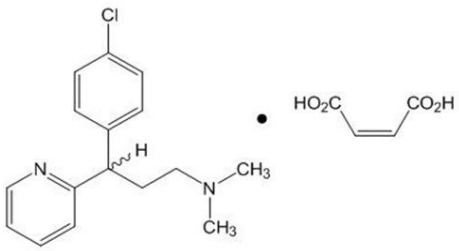
Codeine Phosphate

The chemical name for codeine phosphate is [morphine3methyl ether phosphate (1:1) (salt)] hemihydrate. It has the following structural formula:



Chlorpheniramine Maleate

The chemical name for chlorpheniramine maleate is 2-pyridinepropanamine, γ-(4-chlorophenyl)-*N,N*-dimethyl-, (*Z*)-2-butenedioate (1:1). It has the following structural formula:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Codeine

Codeine is an opioid agonist relatively selective for the mu-opioid receptor, but with a much weaker affinity than morphine. The analgesic and antitussive properties of codeine have been speculated to come from its conversion to morphine. The precise mechanism of action of codeine and other opiates is not known; however, codeine is believed to act centrally on the cough center. In excessive doses, codeine will depress respiration.

Chlorpheniramine

Chlorpheniramine is a propylamine derivative antihistamine (H_1-receptor antagonist) of the alkylamine class that also possesses anticholinergic and sedative activity. It prevents released histamine from dilating capillaries and causing edema of the respiratory mucosa.

12.2 Pharmacodynamics

Codeine

Effects on the Central Nervous System

Codeine produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and to electrical stimulation.

Codeine causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Codeine causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, ~~and~~ transient elevations in serum amylase, and opioid-induced esophageal dysfunction (OIED).

Effects on the Cardiovascular System

Codeine produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans [*see Adverse Reactions (6)*]. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date [*see Adverse Reactions (6)*].

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration–Adverse Reaction Relationships

There is a relationship between increasing codeine plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions.

12.3 Pharmacokinetics

Absorption

Pharmacokinetic (PK) parameters (Mean ± SD) for TUXARIN ER in fasting, healthy volunteers are shown in the table below.

PK Parameter	Single-dose		Multiple-dose (BID for 6.5 days)	
	Codeine Mean (± SD)	Chlorpheniramine Maleate Mean (± SD)	Codeine Mean (± SD)	Chlorpheniramine Maleate Mean (± SD)
Tmax (h) (Range)	3 (2-12)	6 (4-12)	3 (2-5)	5 (3-7)
Cmax (ng/mL)	46 (11)	9 (3)		
AUCinf (ng.h/mL) for single-dose OR AUC12 (ng.h/mL) for multiple-dose	383 (99)	312 (137)		
Half life (h)	4 (1)	21 (7)	Not determined	Not determined

Food Effect

The presence of a high-fat, high-calorie meal did not significantly impact the PK parameters of TUXARIN ER.

Distribution

Codeine has been reported to have an apparent volume of distribution of approximately 3 to 6 L/kg, indicating extensive distribution of the drug into tissues. Codeine has low plasma protein binding with about 7 to 25% of codeine bound to plasma proteins. Codeine passes the blood brain barrier and the placental barrier. Small amounts of codeine and its metabolite, morphine, are transferred to human breast milk.

Chlorpheniramine is widely distributed throughout the tissues of the body, including the central nervous system. It reportedly has an apparent steady-state volume of distribution of approximately 3.2 L/kg in adults and children and is about 70% bound to plasma proteins. Chlorpheniramine and its metabolites likely cross the placental barrier and are excreted into human breast milk.

Elimination

Metabolism

Codeine is metabolized by conjugation with glucuronic acid to codeine-6-glucuronide (about 70 to 80%), by O-demethylation to morphine (about 5 to 10%), and by N-demethylation to norcodeine (about 10%). UDP-glucuronosyltransferase (UGT) 2B7 and 2B4 are the major enzymes mediating glucuronidation of codeine to C6G. Cytochrome P450 2D6 is the major enzyme responsible for conversion of codeine to morphine and P450 3A4 is the major enzyme mediating conversion of codeine to norcodeine. Morphine and norcodeine are further metabolized by conjugation with glucuronic acid. The glucuronide metabolites of morphine are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Morphine and its M6 glucuronide conjugate are

pharmacologically active. Whether C6G has pharmacological activity is unknown. Norcodeine and M3 glucuronide conjugate of morphine are generally not considered to be pharmacologically active.

Chlorpheniramine is rapidly and extensively metabolized via demethylation in the liver, forming mono-and didesmethyl derivatives. Oxidative metabolism of chlorpheniramine is catalyzed by cytochrome P-450 2D6.

Excretion

Approximately 90% of the total dose of codeine is excreted through the kidneys, of which approximately 10% is unchanged codeine. The mean plasma half-life of codeine was about 4 hours with TUXARIN ER.

Chlorpheniramine and its metabolites are primarily excreted through the kidneys, with large individual variation. Urinary excretion depends on urine pH and flow rate. The mean plasma half-life of chlorpheniramine was approximately 21 hours with TUXARIN ER.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity, and fertility studies have not been conducted with TUXARIN ER; however, published information is available for the active ingredients.

Codeine

Carcinogenicity studies were conducted with codeine. Two-year studies in F344/N rats and B6C3F1 mice were conducted to assess the carcinogenic potential of codeine. No evidence of tumorigenicity was observed in male and female rats at codeine dietary doses up to 70 and 80 mg/kg/day (approximately equivalent to 9 and 10 times, the MRHD on a mg/m^2 basis, respectively). No evidence of tumorigenicity was observed in male and female mice at codeine dietary doses up to 400 mg/kg/day (approximately equivalent to 25 times the MRHD on a mg/m^2 basis).

Codeine was not mutagenic in the *in vitro* bacterial reverse mutation assay or clastogenic in the *in vitro* Chinese hamster ovary (CHO) cell chromosomal aberration assay.

Fertility studies with codeine have not been conducted.

Chlorpheniramine

Carcinogenicity studies were conducted with chlorpheniramine maleate. Two-year studies in F344/N rats and B6C3F1 mice were conducted to assess the carcinogenic potential of chlorpheniramine. No evidence of tumorigenicity was observed in male and female rats at chlorpheniramine oral doses up to 30 and 60 mg/kg/day for 5 days/week (approximately equivalent to 25 and 50 times the MRHD on a mg/m^2 basis, respectively). No evidence of tumorigenicity was observed in male and female mice at chlorpheniramine oral doses up to 50 and 200 mg/kg/day for 5 days/week (approximately equivalent to 20 and 85 times the MRHD on a mg/m^2 basis, respectively).

Chlorpheniramine maleate was not mutagenic in the *in vitro* bacterial reverse mutation assay or the *in vitro* mouse lymphoma forward mutation assay. Chlorpheniramine maleate was clastogenic in the *in vitro* Chinese hamster ovary (CHO) cell chromosomal aberration assay.

Chlorpheniramine maleate had no effects on fertility in rats and rabbits at oral doses approximately 35 and 45 times the MRHD on a mg/m^2 basis, respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

TUXARIN ER (codeine phosphate and chlorpheniramine maleate) 54.3 mg/ 8 mg extended-release tablets, are white to off-white, uncoated, standard round tablets, debossed with **MP** on one side and **CC** on the other side. Supplied in bottles of 30 tablets (NDC 71269-040-30) and 100 tablets (NDC 71269-040-10).

Store at 20 to 25°C (68 to 77°F) [see USP Controlled Room Temperature].

Dispense in a tight, light-resistant container, as defined in the USP, with a child-resistant closure.

Keep this and all medicine out of reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Addiction, Abuse, and Misuse

Inform patients that the use of TUXARIN ER, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death [*see Warnings and Precautions (5.1)*]. Instruct patients not to share TUXARIN ER with others and to take steps to protect TUXARIN ER from theft or misuse.

Important Dosing and Administration Instructions

Advise patients take TUXARIN ER exactly as prescribed. Advise patients not to increase the dose or dosing frequency of TUXARIN ER because serious adverse events such as respiratory depression may occur with overdosage [*see Warnings and Precautions (5.2), Overdosage (10)*].

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting TUXARIN ER and that it can occur even at recommended dosages [*see Warnings and Precautions (5.2)*]. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death [*see Warnings and Precautions (5.2)*]. Instruct patients to take steps to store TUXARIN ER securely and to properly dispose of unused TUXARIN ER in accordance with the local state guidelines and/or regulations.

Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children

Advise caregivers that TUXARIN ER is not indicated for pediatric patients under 18 years of age and is contraindicated in all children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy.

Activities Requiring Mental Alertness

Advise patients to avoid engaging in hazardous tasks that require mental alertness and motor coordination such as operating machinery or driving a motor vehicle as TUXARIN ER may produce marked drowsiness [*see Warnings and Precautions (5.7)*].

Interactions with Benzodiazepines and Other Central Nervous System Depressants, Including Alcohol

Inform patients and caregivers that potentially fatal additive effects may occur if TUXARIN ER is used with benzodiazepines or other CNS depressants, including alcohol (e.g., non-benzodiazepine sedative/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids [gabapentin or pregabalin], and other opioids). Advise patients to avoid concomitant use of TUXARIN ER with benzodiazepines or other CNS depressants and to not use alcohol while taking TUXARIN ER [*see Warnings and Precautions (5.9), Drug Interactions (7.5)*].

Constipation

Advise patients of the potential for severe constipation [*see Warnings and Precautions (5.10), Adverse Reactions (6)*].

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in TUXARIN ER. Advise patients how to recognize such a reaction and when to seek medical attention [*see Contraindications (4), Adverse Reactions (6)*].

MAOI Interaction

Inform patients not to take TUXARIN ER while using or within 14 days of stopping any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking TUXARIN ER [*see Warnings and Precautions (5.13), Drug Interactions (7.7)*].

Hypotension

Inform patients that TUXARIN ER may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) [*see Warnings and Precautions (5.14)*].

Pregnancy

Advise patients that use of TUXARIN ER is not recommended during pregnancy [*see Use in Specific Populations (8.1)*].

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that use of TUXARIN ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated [*see Warnings and Precautions (5.15), Use in Specific Populations (8.1)*].

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that TUXARIN ER can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy [*see Use in Specific Populations (8.1)*].

Lactation

Advise women that breastfeeding is not recommended during treatment with TUXARIN ER [*see Use in Specific Populations (8.2)*].

Infertility

Inform patients that chronic use of opioids, such as codeine, a component of TUXARIN ER, may cause reduced fertility. It is not known whether these effects on fertility are reversible [*see Use in Specific Populations (8.3)*].

Adrenal Insufficiency

Inform patients that TUXARIN ER could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms [*see Warnings and Precautions (5.16)*].

Serotonin Syndrome

Inform patients that TUXARIN ER could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their physicians if they are taking, or plan to take serotonergic medications. [*see Adverse Reactions (6), Drug Interactions (7.6)*].

Disposal of Unused TUXARIN ER

Advise patients to properly dispose of unused TUXARIN ER. Advise patients to throw the drug in the household trash following these steps. 1) Remove them from their original containers and mix them with an undesirable substance, such as used coffee grounds or kitty litter (this makes the drug less appealing to children and pets, and unrecognizable to people who may intentionally go through the trash seeking drugs). 2) Place the mixture in a sealable bag, empty can, or other container to prevent the drug from leaking or breaking out of a garbage bag, or to dispose of in accordance with local state guidelines and/or regulations.

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Medication Guide
TUXARIN® ER (Tuks-a-ren)
(codeine phosphate and chlorpheniramine maleate)
extended-release tablets, C-III

What is the most important information I should know about TUXARIN ER?

TUXARIN ER is not for children under 18 years of age.

TUXARIN ER can cause serious side effects, including:

- **Addiction, abuse and misuse.** Taking TUXARIN ER or other medications that contain an opioid can cause addiction, abuse, and misuse, which can lead to overdose and death. This can happen even if you take TUXARIN ER exactly as prescribed by your healthcare provider. Your risk of addiction, abuse, and misuse is increased if you or a family member has a history of drug or alcohol abuse or addiction, or mental health problems.
  - **Do not** share your TUXARIN ER with other people.
  - Keep TUXARIN ER in a safe place away from children.
- **Life-threatening breathing problems (respiratory depression).** TUXARIN ER can cause breathing problems (respiratory depression) that can happen at any time during treatment and can lead to death. Your risk of breathing problems is greatest when you first start taking TUXARIN ER, are taking other medicines that can cause breathing problems, have certain lung problems, are elderly or have certain other health problems. **Children are at higher risk for respiratory depression.** Breathing problems can happen even if you take TUXARIN ER exactly as prescribed by your healthcare provider.

  Call your healthcare provider or get emergency medical help right away if anyone taking TUXARIN ER has any of the symptoms below:
  - increased sleepiness
  - confusion
  - difficulty breathing
  - shallow breathing
  - limpness

  Keep TUXARIN ER in a safe place away from children. Accidental use of even 1 dose of TUXARIN ER, especially by a child, is a medical emergency and can cause breathing problems (respiratory depression) which can lead to death. If a child accidentally takes TUXARIN ER, get emergency help right away.
- **Overdose and death due to medicine dosing errors.** Overdose and death can happen if you take the wrong dose of TUXARIN ER. **Do not** increase the dose or dosing frequency of TUXARIN ER. See "**How should I take TUXARIN ER?"**
- **Breathing problems (respiratory depression) that can lead to death and opioid withdrawal** can happen if you start taking or stop taking other medicines while taking TUXARIN ER, including:
  - certain antibiotics
  - certain medicines to treat a fungal infection
  - certain medicines to treat Human Immunodeficiency Virus (HIV)-1 infection, Acquired Immune Deficiency Syndrome (AIDS), or Hepatitis C
  - rifampin
  - carbamazepine
  - phenytoin
- **Severe drowsiness, breathing problems (respiratory depression), coma, and death** can happen in adults and children who take TUXARIN ER with benzodiazepines, gabapentinoids (gabapentin or pregabalin), or other central nervous system depressants, including alcohol.
  - **Do not** take any benzodiazepines or medicines that can cause drowsiness or sleepiness during treatment with TUXARIN ER. Ask your healthcare provider for a list of these medicines if you are not sure.
  - **Do not** drink alcohol during treatment with TUXARIN ER.
- **Opioid withdrawal in a newborn.** Use of TUXARIN ER during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated. You should not take TUXARIN ER if you are pregnant. Tell your healthcare provider right away if you are pregnant or think you may be pregnant.

What is TUXARIN ER?

- TUXARIN ER is a prescription medicine used to treat cough and upper respiratory symptoms that you can have with allergies or a common cold. TUXARIN ER contains 2 medicines, codeine and chlorpheniramine. Codeine is an opioid (narcotic) cough suppressant. Chlorpheniramine is an antihistamine.
- **TUXARIN ER is a federal controlled substance (C-III) because it contains codeine that can be abused or lead to dependence.** Keep TUXARIN ER in a safe place to prevent misuse and abuse. Selling or giving away TUXARIN ER may harm others and is against the law. Tell your healthcare provider if you have abused or been

dependent on alcohol, prescription medicines or street drugs.

Who should not take TUXARIN ER?

TUXARIN ER is not for children under 18 years of age. See "What is the most important information I should know about TUXARIN ER?"

Do not take TUXARIN ER if you:

- have severe breathing problems (respiratory depression). See "**What is the most important information I should know about TUXARIN ER?"**
- have a blockage (obstruction) in your bowel such as a paralytic ileus.
- take a medicine for depression called a Monoamine Oxidase Inhibitor (MAOI**).**
  - **Do not** take an MAOI within 14 days after you stop taking TUXARIN ER.
  - **Do not** start taking TUXARIN ER if you stopped taking an MAOI in the last 14 days.
- are allergic to codeine, chlorpheniramine, or any of the ingredients in TUXARIN ER. See the end of this Medication Guide for a complete list of ingredients in TUXARIN ER. You may have an increased risk of having an allergic reaction to TUXARIN ER if you are allergic to certain other opioid medicines.

Ask your healthcare provider if you have any questions about this information.

Before taking TUXARIN ER, tell your healthcare provider about all of your medical conditions, including if you:

- have a drug addiction
- have lung or breathing problems
- have a fever and are coughing up mucus
- have had a recent head injury
- have had a brain tumor or other brain problems
- have or have had seizures
- have pain in your stomach-area (abdomen)
- have constipation or other bowel problems
- have bile duct or pancreas problems
- have prostate problems
- have problems with your urinary tract or difficulty urinating
- have kidney or liver problems
- have adrenal gland problems
- have low blood pressure (hypotension)
- plan to have surgery
- are pregnant or plan to become pregnant. TUXARIN ER can harm your unborn baby. See **"What is the most important information I should know about TUXARIN ER?"**
- are breastfeeding or plan to breastfeed. Codeine and chlorpheniramine pass into your breast milk and can cause serious side effects in your baby including increased sleepiness, breathing problems (respiratory depression) and death. You and your healthcare provider should decide if you will take TUXARIN ER or breastfeed. You should not do both. See **"What should I avoid while taking TUXARIN ER?"**
- plan to have children. TUXARIN ER may affect the ability to have a child in females and males (fertility problems). It is not known if these fertility problems will be reversible, even after you stop taking TUXARIN ER.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Taking TUXARIN ER with certain other medicines can cause side effects or affect how well TUXARIN ER or the other medicines work. Do not start or stop taking other medicines without talking to your healthcare provider.

Especially tell your healthcare provider if you:

- See "**What is the most important information I should know about TUXARIN ER?"**
- take pain medicines such as opioids (narcotics).
- take cold or allergy medicines that contain antihistamines or cough suppressants.
- drink alcohol.
- take muscle relaxants.
- take certain medicines used to treat mood, anxiety, psychotic or thought disorders, or depression, including monoamine oxidase inhibitors (MAOIs), tricyclics, selective serotonin reuptake inhibitors (SSRIs), selective serotonin-norepinephrine reuptake inhibitors (SNRIs), or antipsychotics.
- take medicines to lower your blood pressure.
- water pills (diuretics).
- take medicines called "anticholinergics" used to treat health problems such as asthma, chronic obstructive pulmonary disease (COPD), or stomach problems.
- take a medicine called "phenytoin" used to treat seizures or epilepsy.

Ask your healthcare provider if you are not sure if you take one of these medicines.

How should I take TUXARIN ER?

- See "**What is the most important information I should know about TUXARIN ER?**"
- Take TUXARIN ER exactly as your healthcare provider tells you to take it. Do not change your dose without talking to your healthcare provider.
- Take TUXARIN ER by mouth only. TUXARIN ER is usually taken every 12 hours. **Do not** take more than 2 TUXARIN ER tablets in 24 hours.
- If you take too much TUXARIN ER, call your healthcare provider or go to the nearest hospital emergency room right away.

- Tell your healthcare provider if your cough does not get better within 5 days of treatment with TUXARIN ER.

What should I avoid doing while taking TUXARIN ER?

- Avoid driving a car or operating machinery during treatment with TUXARIN ER. TUXARIN ER can cause you to be drowsy, slow your thinking and motor skills, and affect your vision.
- **Do not** drink alcohol during treatment with TUXARIN ER. Drinking alcohol with TUXARIN ER can increase your chances of having serious side effects.

Avoid the use of TUXARIN ER if you:

- are pregnant. Use of TUXARIN ER during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated. Tell your healthcare provider right away if you are pregnant or think you may be pregnant.
- are breastfeeding. Use of TUXARIN ER while breastfeeding can cause severe breathing problems (respiratory depression) in your breastfed infant that could be life-threatening.

What are the possible side effects of TUXARIN ER?

TUXARIN ER can cause serious side effects, including:

- See **"What is the most important information I should know about TUXARIN ER?"**
- **Bowel problems including severe constipation or stomach pain.** See, **"Who should not take TUXARIN ER?"**
- **Increased pressure in your head (intracranial).** Avoid the use of TUXARIN ER if you have a head injury or have been told that you have changes in the tissue of your brain (brain lesions) or increased pressure in your head.
- **Increased risk of seizures in people with seizure disorders.** If you have a seizure disorder, TUXARIN ER may increase how often you have seizures.
- **Low blood pressure.** A sudden drop in blood pressure can happen in some people during treatment with TUXARIN ER and this may cause you to feel dizzy, faint, lightheaded, or weak, especially when you stand up (orthostatic hypotension). Your risk of having this problem may be increased if you take TUXARIN ER with certain other medicines that lower blood pressure. If you have any of these symptoms while taking TUXARIN ER, sit or lie down. Do not change your body position too fast. Get up slowly from sitting or lying down.
- **Adrenal gland problems.** TUXARIN ER can cause serious and life-threatening adrenal gland problems. Your healthcare provider may do blood tests to check for adrenal gland problems. Call your healthcare provider right away if you have any of these symptoms:
  - nausea
  - vomiting
  - not wanting to eat (anorexia)
  - fatigue
  - weakness
  - dizziness
  - low blood pressure

The most common side effects of TUXARIN ER include:

- sleepiness
- confusion
- coordination problems
- decrease in mental and physical performance
- lack of energy
- lightheadedness
- dizziness
- headache
- dry mouth
- sweating
- nausea
- vomiting
- constipation

These are not all the possible side effects of TUXARIN ER.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TUXARIN ER?

- Store TUXARIN ER at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep TUXARIN ER in a tightly closed container, in a dry, cool place away from heat or direct sunlight.
- **Keep TUXARIN ER and all medicines out of the reach of children.**

How should I dispose of TUXARIN ER?

Remove unused TUXARIN ER from the container and mix it with an undesirable, non-toxic substance such as cat litter or used coffee grounds to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and throw it away in the household trash. You can also follow your state or local guidelines on how to safely throw away TUXARIN ER.

General information about the safe and effective use of TUXARIN ER.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TUXARIN ER for a condition for which it was not prescribed. Do not give TUXARIN ER to other people, even if they have the same symptoms that you have. It may harm them.
You can ask your pharmacist or healthcare provider for information about TUXARIN ER that is written for health professionals.

What are the ingredients in TUXARIN ER?
Active ingredients: codeine phosphate and chlorpheniramine maleate
Inactive ingredients: Hypromellose, lactose monohydrate, cellulose microcrystalline, polysorbate 80, magnesium stearate, and colloidal silicon dioxide.

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