HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SYNALGOS®-DC safely and effectively. See full prescribing information for SYNALGOS®-DC.

SYNALGOS®-DC (aspirin, caffeine, and dihydrocodeine bitartrate) capsules, for oral use, CIII
Initial U.S. Approval: 1958

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF SYNALGOS-DC

See full prescribing information for complete boxed warning.

- **SYNALGOS-DC exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and reassess regularly for these behaviors and conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur, especially upon initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of SYNALGOS-DC are essential. (5.2)**
- **Accidental ingestion of SYNALGOS-DC, especially by children, can result in a fatal overdose of dihydrocodeine. (5.2)**
- **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. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate. (5.3, 7)**
- **If opioid use is required for an extended period of time in a pregnant woman, advise the patient 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. (5.4)**
- **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. (5.6) SYNALGOS-DC 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 SYNALGOS-DC in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of dihydrocodeine.**
- **The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with dihydrocodeine are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with SYNALGOS-DC requires careful consideration of the effects on the parent drug, dihydrocodeine, and the active metabolite, dihydromorphine. (5.7), (7)**

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

Boxed Warning	12/2023
Indications and Usage (1)	12/2023
Dosage and Administration (2.1, 2.3, 2.4, 2.5)	12/2023
Warnings and Precautions (5.8)	12/2023

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

SYNALGOS-DC is a combination of dihydrocodeine, an opioid agonist, aspirin, a nonsteroidal anti-inflammatory drug, and caffeine, a methylxanthine, and is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. (1)

Limitations of Use (1)

Because of the risks of addiction, abuse, and misuse with opioids, which can occur at any dosage or duration (5.1), reserve SYNALGOS-DC for use in patients for whom alternative treatment options (e.g., non-opioid analgesics):

- Have not been tolerated or are not expected to be tolerated,
- Have not provided adequate analgesia or are not expected to provide adequate analgesia.

SYNALGOS-DC should not be used for an extended period of time unless the pain remains severe enough to require an opioid analgesic and for which alternative treatment options continue to be inadequate.

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

- SYNALGOS-DC should be prescribed only by healthcare professionals who are knowledgeable about the use of opioids and how to mitigate the associated risks. (2.1)
- Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals. Reserve titration to higher doses of SYNALGOS-DC for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks. (2.1, 5)
- Many acute pain conditions (e.g., the pain that occurs with a number of surgical procedures or acute musculoskeletal injuries) require no more than a few days of an opioid analgesic. Clinical guidelines on opioid prescribing for some acute pain conditions are available. (2.1)
- Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, prior analgesic treatment and response, and risk factors for addiction, abuse, and misuse. (2.1, 5.1)
- Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with SYNALGOSDC. Consider this risk when selecting an initial dose and when making dose adjustments. (2.1, 5.2)
- Discuss availability of naloxone with the patient and caregiver and assess each patient's need for access to naloxone, both when initiating and renewing treatment with SYNALGOS-DC. Consider prescribing naloxone based on the patient's risk factors for overdose (2.2, 5.1, 5.3, 5.7).
- Initiate treatment with two capsules every 4 hours as needed for pain, and at the lowest dose necessary to achieve adequate analgesia. Titrate the dose based upon the individual patient's response to their initial dose of SYNALGOS-DC. (2.1, 5)
- Administer SYNALGOS-DC with food or a full glass of water to minimize gastrointestinal (GI) distress. (2.1)
- Do not abruptly discontinue SYNALGOS-DC in a physically dependent patient because rapid discontinuation of opioid analgesics has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. (2.5, 5.16)

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

Capsules: 356.4 mg aspirin, 30 mg caffeine, and 16 mg dihydrocodeine bitartrate (3)

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

- Children younger than 12 years of age (4)
- Post-operative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy (4)

- Significant respiratory depression (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment (4)
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus (4)
- Hypersensitivity to dihydrocodeine, codeine, or aspirin (4)
- Hemophilia (4)
- Reye's Syndrome (4)
- Known allergy to NSAIDs (4)
- Syndrome of asthma, rhinitis, and nasal polyps (4)

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

- Opioid-Induced Hyperalgesia and Allodynia: Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. If OIH is suspected, carefully consider appropriately decreasing the dose of the current opioid analgesic or opioid rotation. (5.8)
- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.9)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.11)
- Severe Hypotension: Regularly evaluate during dosage initiation and titration. Avoid use of SYNALGOS-DC in patients with circulatory shock. (5.12)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of SYNALGOS-DC in patients with impaired consciousness or coma. (5.13)
- Risks of Use in Patients with Gastrointestinal Conditions Including Peptic Ulcer Disease: Aspirin can cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events. (5.14)
- Fetal Toxicity: Limit use of NSAIDs, including SYNALGOS-DC, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of the fetal ductus arteriosus (5.17, 8.1).
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Discontinue and evaluate clinically (5.21)

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

Most common adverse reactions were lightheadedness, dizziness, drowsiness, sedation, nausea, vomiting, constipation, pruritus, and skin reactions. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-406-7984 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue SYNALGOS-DC if serotonin syndrome is suspected. (7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with SYNALGOS-DC because they may reduce analgesic effect of SYNALGOS-DC or precipitate withdrawal symptoms. (7)

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

- Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF SYNALGOS-DC

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

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF SYNALGOS-DC

Addiction, Abuse, and Misuse

Because the use of SYNALGOS-DC exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death, assess each patient's risk prior to prescribing and reassess all patients regularly for the development of these behaviors and conditions [*see Warnings and Precautions (5.1)*].

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of SYNALGOS-DC, especially during initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of SYNALGOS-DC are essential [*see Warnings and Precautions (5.2)*].

Accidental Ingestion

Accidental ingestion of even one dose of SYNALGOS-DC, especially by children, can result in a fatal overdose of dihydrocodeine *[see Warnings and Precautions (5.2)]*.

Risks From Concomitant Use With Benzodiazepines Or Other 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. Reserve concomitant prescribing of SYNALGOS-DC and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate *[*see *Warnings and Precautions (5.3), Drug Interactions (7)]*

Neonatal Opioid Withdrawal Syndrome (NOWS)

If opioid use is required for an extended period of time in a pregnant woman, advise the patient of the risk of NOWS, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery [*see Warnings and Precautions (5.4)*].

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS):

Healthcare providers are strongly encouraged to complete a REMS-compliant education program and to counsel patients and caregivers on serious risks, safe use, and the importance of reading the Medication Guide with each prescription [*see Warnings and Precautions (5.5)*].

Ultra-Rapid Metabolism of Dihydrocodeine 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 (5.4)]. SYNALGOS-DC 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 SYNALGOS-DC in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of dihydrocodeine.

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 dihydrocodeine are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with SYNALGOS-DC requires careful consideration of the effects on dihydrocodeine, and the active metabolite, dihydromorphine *[see Warnings and Precautions (5.7), Drug Interactions (7)]*.

1. INDICATIONS AND USAGE

SYNALGOS-DC is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use
Because of the risks of addiction, abuse, and misuse with opioids, which can occur at any dosage or duration *[see Warnings and Precautions (5.1)]*, reserve SYNALGOS-DC for use in patients for whom alternative treatment options [e.g., non-opioid analgesics]:

- Have not been tolerated or are not expected to be tolerated,
- Have not provided adequate analgesia or are not expected to provide adequate analgesia

SYNALGOS-DC should not be used for an extended period of time unless the pain remains severe enough to require an opioid analgesic and for which alternative treatment options continue to be inadequate.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

SYNALGOS-DC should be prescribed only by healthcare professionals who are knowledgeable about the use of opioids and how to mitigate the associated risks.

Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*. Because the risk of overdose increases as opioid doses increase, reserve titration to higher doses of SYNALGOS-DC for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks.

Many acute pain conditions (e.g., the pain that occurs with a number of surgical procedures or acute musculoskeletal injuries) require no more than a few days of an opioid analgesic. Clinical guidelines on opioid prescribing for some acute pain conditions are available.

There is variability in the opioid analgesic dose and duration needed to adequately manage pain due both to the cause of pain and to individual patient factors. Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, prior analgesic treatment and response, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*.

Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with SYNALGOS-DC. Consider this risk when selecting an initial dose and when making dose adjustments *[see Warnings and Precautions (5.2)]*.
Administer SYNALGOS-DC with food or a full glass of water to minimize GI distress.

2.2 Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with SYNALGOS-DC *[see Warnings and Precautions (5.2)]*

Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program).

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient *[see Warnings and Precautions (5.1, 5.2, 5.3)]*.

Consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose.

2.3 Initial Dosage

Initiating Treatment with SYNALGOS-DC

Initiate treatment in adults with two capsules of SYNALGOS-DC orally every 4 hours as needed for pain, and at the lowest dose necessary to achieve adequate analgesia. Titrate the dose based upon the individual patient's response to their initial dose of SYNALGOS-DC.

Conversion from Other Opioids to SYNALGOS-DC

There is inter-patient variability in the potency of opioid drugs and opioid formulations. Therefore, a conservative approach is advised when determining the total daily dosage of SYNALGOS-DC. It is safer to underestimate a patient's 24-hour SYNALGOS-DC dosage than to overestimate the 24-hour SYNALGOS-DC dosage and manage an adverse reaction due to overdose.

2.4 Titration and Maintenance of Therapy

Individually titrate SYNALGOS-DC to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving SYNALGOS-DC to assess the maintenance of pain control, signs and symptoms of opioid withdrawal, and other adverse reactions, as well as reassessing for the development of addiction, abuse, or misuse *[see Warnings and Precautions (5.1, 5.16)]*. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration.

If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the SYNALGOS-DC dosage. If after increasing the dosage, unacceptable opioid-related adverse reactions are observed (including an increase in pain after dosage increase), consider reducing the dosage *[see Warnings and Precautions (5)]*. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.5 Safe Reduction or Discontinuation of SYNALGOS-DC

Do not abruptly discontinue SYNALGOS-DC in patients who may be physically dependent on opioids. Rapid discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse. Patients may also attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin, and other substances.

When a decision has been made to decrease the dose or discontinue therapy in an opioid-dependent patient taking SYNALGOS-DC, there are a variety of factors that should be considered, including the total daily dose of opioid (including SYNALGOS-DC) the patient has been taking, the duration of treatment, the type of pain being treated, and the physical and psychological attributes of the patient. It is important to ensure ongoing care of the patient and to agree on an appropriate tapering schedule

and follow-up plan so that patient and provider goals and expectations are clear and realistic. When opioid analgesics are being discontinued due to a suspected substance use disorder, evaluate and treat the patient, or refer for evaluation and treatment of the substance use disorder. Treatment should include evidence-based approaches, such as medication assisted treatment of opioid use disorder. Complex patients with comorbid pain and substance use disorders may benefit from referral to a specialist.

There are no standard opioid tapering schedules that are suitable for all patients. Good clinical practice dictates a patient-specific plan to taper the dose of the opioid gradually. For patients on SYNALGOS-DC who are physically opioid-dependent, initiate the taper by a small enough increment (e.g., no greater than 10% to 25% of the total daily dose) to avoid withdrawal symptoms, and proceed with dose-lowering at an interval of every 2 to 4 weeks. Patients who have been taking opioids for briefer periods of time may tolerate a more rapid taper.

It may be necessary to provide the patient with lower dosage strengths to accomplish a successful taper. Reassess the patient frequently to manage pain and withdrawal symptoms, should they emerge. Common withdrawal symptoms include 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. If withdrawal symptoms arise, it may be necessary to pause the taper for a period of time or raise the dose of the opioid analgesic to the previous dose, and then proceed with a slower taper. In addition, evaluate patients for any changes in mood, emergence of suicidal thoughts, or use of other substances.

When managing patients taking opioid analgesics, particularly those who have been treated for an extended period of time and/or with high doses for chronic pain, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper. A multimodal approach to pain management may optimize the treatment of chronic pain, as well as assist with the successful tapering of the opioid analgesic *[see Warnings and Precautions (5.2), Drug Abuse and Dependence (9.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Capsules: 356.4 mg aspirin, 30 mg caffeine, and 16 mg dihydrocodeine bitartrate (blue and gray, marked “CP” and “419”)

4 CONTRAINDICATIONS

SYNALGOS-DC is contraindicated for:

- All children younger than 12 years of age *[see Warnings and Precautions (5.6)]*

- Post-operative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy *[see Warnings and Precautions (5.6)]*

SYNALGOS-DC 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 (5.9)]*
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days *[see Warnings and Precautions (5.10), Drug Interactions (7)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.14)]*
- Hypersensitivity to dihydrocodeine, codeine, or aspirin, or NSAIDs *[see Adverse Reactions (6)]*
- Hemophilia *[see Warnings and Precautions (5.19)]*
- Reye's Syndrome *[see Warnings and Precautions (5.20)]*
- Known allergy to nonsteroidal anti-inflammatory drugs (NSAIDs) *[see Warnings and Precautions (5.22)]*
- Syndrome of asthma, rhinitis, and nasal polyps *[see Warnings and Precautions (5.21)]*

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

SYNALGOS-DC contains dihydrocodeine bitartrate, a Schedule III controlled substance. As an opioid, SYNALGOS-DC exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed SYNALGOS-DC. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing SYNALGOS-DC, and reassess all patients receiving SYNALGOS-DC for the development of these behaviors and conditions. 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). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as SYNALGOS-DC, but use in such patients necessitates intensive counseling about the risks and proper use of SYNALGOS-DC along with frequent reevaluation for signs of addiction, abuse, and misuse. Consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.2)]*.

Opioids are sought for nonmedical use and are subject to diversion from legitimate prescribed use. Consider these risks when prescribing or dispensing SYNALGOS-DC. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on careful storage of the drug during the course of treatment and the proper disposal of unused drug. 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, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, 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 SYNALGOS-DC, the risk is greatest during the initiation of therapy or following a dosage increase.

To reduce the risk of respiratory depression, proper dosing and titration of SYNALGOS-DC are essential *[see Dosage and Administration (2)]*. Overestimating the SYNALGOS-DC dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of even one dose of SYNALGOS-DC, especially by children, can result in respiratory depression and death due to an overdose of dihydrocodeine.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose.

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper *[see Dosage and Administration (2.5)]*.

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient

and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with SYNALGOS-DC. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered.

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone *[see Warnings and Precautions (5.1, 5.3), Overdosage (10)]*.

5.3 Risks from Concomitant Use with Benzodiazepines or Other Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of SYNALGOS-DC with benzodiazepines and/or other CNS depressants, including alcohol (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug- related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics *[see Drug Interactions (7)]*.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Inform patients and caregivers of this potential interaction and educate them on the signs and symptoms of respiratory depression (including sedation).

If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.2)]*.

Advise both patients and caregivers about the risks of respiratory depression and sedation when

SYNALGOS-DC is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs *[see Drug Interactions (7)]*.

5.4 Neonatal Opioid Withdrawal Syndrome

Use of SYNALGOS-DC for an extended period of time 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 for an extended period of time of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1)]*.

5.5 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG.
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

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

Because of comparable metabolic pathways for codeine and dihydrocodeine and similar potencies for codeine and dihydrocodeine and morphine and dihydromorphine, the risks associated with ultra-rapid metabolism of codeine are present for dihydrocodeine.

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 postmarketing 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 opioids for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to their respiratory depressant effect. Because of the risk of life-threatening respiratory depression and death:

- SYNALGOS-DC is contraindicated for all children younger than 12 years of age *[see Contraindications (4)]*.
- SYNALGOS-DC 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 SYNALGOS-DC in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of dihydrocodeine unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation, such as post-operative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression.
- As with adults, when prescribing opioids for adolescents, 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 opioid overdose *[see Use in Specific Populations (8.4), Overdosage (10)]*.

Nursing Mothers

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 SYNALGOS-DC *[see Use in Specific Populations (8.2)]*.

CYP2D6 Genetic Variability: Ultra-rapid metabolizer

Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (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 racial/ethnic groups (i.e., Oceanian, Northern African, Middle Eastern, Ashkenazi Jews, Puerto Rican). Data are not available for other ethnic groups. These individuals convert

dihydrocodeine into its active metabolite, dihydromorphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum dihydromorphine 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 SYNALGOS-DC.

5.7 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 dihydrocodeine are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with SYNALGOS-DC requires careful consideration of the effects on dihydrocodeine and the active metabolite, dihydromorphine.

- Cytochrome P450 3A4 Interaction

  The concomitant use of SYNALGOS-DC 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 dihydrocodeine plasma concentrations with subsequently greater metabolism by cytochrome P450 2D6, resulting in greater dihydromorphine levels, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression.

  The concomitant use of SYNALGOS-DC with all cytochrome P450 3A4 inducers or discontinuation of a cytochrome P450 3A4 inhibitor may result in lower dihydrocodeine levels, greater dihydronorcodeine levels, and less metabolism via 2D6 with resultant lower dihydromorphine levels. This may be associated with a decrease in efficacy, and in some patients, may result in signs and symptoms of opioid withdrawal. Evaluate patients receiving SYNALGOS-DC and any CYP3A4 inhibitor or inducer at frequent intervals for signs and symptoms that may reflect opioid toxicity and opioid withdrawal when SYNALGOS-DC is used in conjunction with inhibitors and inducers of CYP3A4.

  If concomitant use of a CYP3A4 inhibitor is necessary or if a CYP3A4 inducer is discontinued, consider dosage reduction of SYNALGOS-DC until stable drug effects are achieved. Evaluate patients at frequent intervals for respiratory depression and sedation.

  If concomitant use of a CYP3A4 inducer is necessary or if a CYP3A4 inhibitor is discontinued, consider increasing the SYNALGOS-DC dosage until stable drug effects are achieved. Evaluate patients at frequent intervals for signs of opioid withdrawal *[see Drug Interactions (7)]*.

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

  The concomitant use of SYNALGOS-DC with all cytochrome P450 2D6 inhibitors (e.g., amiodarone, quinidine) may result in an increase in dihydrocodeine plasma concentrations and a decrease in active metabolite dihydromorphine 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 dihydrocodeine plasma concentration and an increase in active metabolite dihydromorphine plasma concentration which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression.

  Evaluate patients receiving SYNALGOS-DC and any CYP2D6 inhibitor at frequent intervals for signs and symptoms that may reflect opioid toxicity and opioid withdrawal when SYNALGOS-DC is used in conjunction with inhibitors of CYP2D6.

  If concomitant use with a CYP2D6 inhibitor is necessary, evaluate patients at frequent intervals for signs of reduced efficacy or opioid withdrawal and consider increasing the SYNALGOS-DC dosage. After stopping use of a CYP2D6 inhibitor, consider reducing the SYNALGOS-DC dosage and evaluate the patients at frequent intervals for signs and symptoms of respiratory depression or sedation *[see Drug Interactions (7)]*.

5.8 Opioid-Induced Hyperalgesia and Allodynia

Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect [*see Dependence (9.3)*]. Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). These symptoms may suggest OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behavior.

Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been implicated. Medical literature suggests a strong biologic plausibility between opioid analgesics and OIH and allodynia. If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic or opioid rotation (safely switching the patient to a different opioid moiety) [*see Dosage and Administration (2), Warnings and Precautions (5)*].

5.9 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of SYNALGOS-DC in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: SYNALGOS-DC-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 SYNALGOS-DC *[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)]*.

Monitor patients, particularly when initiating and titrating SYNALGOS-DC and when SYNALGOS-DC is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.3)]*. Alternatively, consider the use of non- opioid analgesics in these patients.

5.10 Interaction with Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) may potentiate the effects of dihydromorphine, dihydrocodeine's active metabolite, including respiratory depression, coma, and confusion. SYNALGOS-DC should not be used in patients taking MAOIs or within 14 days of stopping such treatment.

5.11 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 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.

5.12 Severe Hypotension

SYNALGOS-DC 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)]*. Regularly evaluate these patients for signs of hypotension after initiating or titrating the dosage of SYNALGOS-DC. In patients with circulatory shock, SYNALGOS-DC may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of SYNALGOS-DC in patients with circulatory shock.

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

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), SYNALGOS-DC may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with SYNALGOS-DC.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of SYNALGOS-DC in patients with impaired consciousness or coma.

5.14 Risks of Use in Patients with Gastrointestinal Conditions Including Peptic Ulcer Disease

SYNALGOS-DC is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The dihydrocodeine in SYNALGOS-DC may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Regularly evaluate patients with biliary tract disease, including acute pancreatitis for worsening symptoms.

Patients with a history of active peptic ulcer disease should avoid using aspirin, which can cause gastric mucosal irritation and bleeding.

Gastrointestinal Bleeding, Ulceration, and Perforation: The aspirin in SYNALGOS-DC can cause GI side effects including stomach pain, heartburn, nausea, vomiting, and gross GI bleeding. Although minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy, physicians should remain alert for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Physicians should inform patients about the signs and symptoms of GI side effects and what steps to take if they occur.

Risk Factors for GI Bleeding, Ulceration, and Perforation
Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a

greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk for of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Strategies to Minimize the GI Risks in NSAID-treated patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such high-risk patients, as well as those with active GI bleeding, consider alternate therapies other than SYNALGOS-DC.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue SYNALGOS-DC until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding *[see Drug Interactions (7)]*.

5.15 Increased Risk of Seizures in Patients with Seizure Disorders

The dihydrocodeine in SYNALGOS-DC 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. Regularly evaluate patients with a history of seizure disorders for worsened seizure control during SYNALGOS-DC therapy.

5.16 Withdrawal

Do not abruptly discontinue SYNALGOS-DC in a patient physically dependent on opioids. When discontinuing SYNALGOS-DC in a physically dependent patient, gradually taper the dosage. Rapid tapering of SYNALGOS-DC in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain *[see Dosage and Administration (2.5), Drug Abuse and Dependence (9.3)]*.

Additionally, avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including SYNALGOS-DC. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms.

5.17 Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus

Avoid use of NSAIDs, including SYNALGOS-DC, in pregnant women at about 30 weeks gestation and later. NSAIDs, including SYNALGOS-DC, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs, including SYNALGOS-DC, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation.
Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit SYNALGOS-DC use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if SYNALGOS-DC treatment extends beyond 48 hours. Discontinue SYNALGOS-DC if oligohydramnios occurs and follow up according to clinical practice *[see Use in Specific Populations (8.1)]*.

5.18 Risks of Driving and Operating Machinery

SYNALGOS-DC may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of SYNALGOS-DC and know how they will react to the medication.

5.19 Coagulation Abnormalities and Bleeding Risks

Even low doses of aspirin can inhibit platelet function leading to an increase in bleeding time. This can adversely affect patients with inherited (i.e. hemophilia) or acquired (i.e. liver disease or vitamin K deficiency) bleeding disorders. Aspirin is contraindicated in patients with hemophilia.

Aspirin administered pre-operatively may prolong the bleeding time.

Patients who consume three or more alcoholic drinks every day should be counseled about the bleeding risks involved with chronic, heavy alcohol use while taking aspirin.

5.20 Reye's Syndrome

Aspirin should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye syndrome with concomitant use of aspirin in certain viral illnesses.

5.21 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as SYNALGOS-DC. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue SYNALGOS-DC and evaluate the patient immediately.

5.22 Allergy

Aspirin is contraindicated in patients with known allergy to nonsteroidal anti-inflammatory drug products (NSAIDs) and in patients with the syndrome of asthma, rhinitis, and nasal polyps. Aspirin may cause severe urticaria, angioedema, or bronchospasm (asthma).

5.23 Renal Toxicity and Hyperkalemia

Renal Toxicity

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.

Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy was is usually followed by recovery to the pretreatment state.

No information is available from controlled clinical studies regarding the use of SYNALGOS-DC in patients with advanced renal disease. The renal effects of SYNALGOS-DC may hasten the progression of renal dysfunction in patients with pre-existing renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating SYNALGOS-DC. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of SYNALGOS-DC *[see Drug Interactions (7)]*. Avoid the use of SYNALGOS-DC in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If SYNALGOS-DC is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

Hyperkalemia

Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic- hypoaldosteronism state.

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)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]*
- Interactions with Benzodiazepines or Other CNS Depressants *[see Warnings and Precautions (5.3)]*
- Ultra-Rapid Metabolism of Dihydrocodeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children *[see Warnings and Precautions (5.6)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.4)]*
- Opioid-Induced Hyperalgesia and Allodynia *[see Warnings and Precautions (5.8)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.11)]*
- Severe Hypotension *[see Warnings and Precautions (5.12)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.14)]*
- Seizures *[see Warnings and Precautions (5.15)]*
- Withdrawal *[see Warnings and Precautions (5.16)]*
- Coagulation Abnormalities and Bleeding *[see Warnings and Precautions (5.19)]*
- Reye's Syndrome *[see Warnings and Precautions (5.20)]*
- Allergy *[see Warnings and Precautions (5.22)]*
- Renal Toxicity and Hyperkalemia *[see Warnings and Precautions (5.23)]*

The following adverse reactions associated with the use of SYNALGOS-DC were identified in clinical

studies or postmarketing reports. Because some of these reactions were 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.

Many adverse reactions due to aspirin ingestion are dose-related. The following is a list of adverse reactions that have been reported in the literature *[see Warnings and Precautions (5)]*.

Body as a Whole: Fever, hypothermia, thirst.

Cardiovascular: Dysrhythmias, hypotension, tachycardia.

Central Nervous System: Agitation, cerebral edema, coma, confusion, dizziness, headache, subdural or intracranial hemorrhage, lethargy, seizures.

Fluid and Electrolyte: Dehydration, hyperkalemia, metabolic acidosis, respiratory alkalosis.

Gastrointestinal: Dyspepsia, GI bleeding, ulceration and perforation, nausea, vomiting, transient elevations of hepatic enzymes, hepatitis, Reye's syndrome, pancreatitis.

Hematologic: Prolongation of the prothrombin time, disseminated intravascular coagulation, coagulopathy, thrombocytopenia.

Hypersensitivity: Acute anaphylaxis, angioedema, asthma, bronchospasm, laryngeal edema, urticaria.

Musculoskeletal: Rhabdomyolysis.

Metabolism: Hypoglycemia (in children), hyperglycemia.

Reproductive: Prolonged pregnancy and labor, stillbirths, lower birth weight infants, antepartum and postpartum bleeding.

Respiratory: Hyperpnea, pulmonary edema, tachypnea.

Special Senses: Hearing loss, tinnitus. Patients with high frequency hearing loss may have difficulty perceiving tinnitus. In these patients, tinnitus cannot be used as a clinical indicator of salicylism.

Urogenital: Interstitial nephritis, papillary necrosis, proteinuria, renal insufficiency and failure.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in SYNALGOS-DC.

Androgen Deficiency: Cases of androgen deficiency have occurred with use of opioids for an extended period of time.

Hyperalgesia and Allodynia: Cases of hyperalgesia and allodynia have been reported with opioid therapy of any duration *[see Warnings and Precautions (5.8)]*

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).

7 DRUG INTERACTIONS

Table 1 includes clinically significant drug interactions with SYNALGOS-DC.

Table 1: Clinically Significant Drug Interactions with SYNALGOS-DC

Inhibitors of CYP3A4	
Clinical Impact:	The concomitant use of SYNALGOS-DC with CYP3A4 inhibitors may result in an increase in dihydrocodeine plasma concentration with subsequently greater metabolism by cytochrome CYP2D6, resulting in greater dihydromorphine 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 SYNALGOS-DC is achieved. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, it may result in lower dihydrocodeine plasma levels, greater dihydronorcodeine levels, and less metabolism via 2D6 with resultant lower dihydromorphine levels *[see Clinical Pharmacology (12.3)]*, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to dihydrocodeine.

Intervention:	If concomitant use with CYP3A4 inhibitor is necessary, consider dosage reduction of SYNALGOS-DC until stable drug effects are achieved. Evaluate at frequent time intervals patients for respiratory depression and sedation. If a CYP3A4 inhibitor is discontinued, consider increasing the SYNALGOS-DC dosage until stable drug effects are achieved. Assess for signs of opioid withdrawal.
Examples:	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir)

CYP3A4 Inducers	
Clinical Impact:	The concomitant use of SYNALGOS-DC and CYP3A4 inducers can result in lower dihydrocodeine levels, greater dihydronorcodeine levels, and less metabolism via 2D6 with resultant lower dihydromorphine levels *[see Clinical Pharmacology (12.3)]*, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to dihydrocodeine *[see Warnings and Precautions (5.16)]*. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the dihydrocodeine plasma concentration may increase with subsequently greater metabolism by cytochrome CYP2D6, resulting in greater dihydromorphine levels *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both the therapeutic effects and adverse reactions and may cause serious respiratory depression.
Intervention:	If concomitant use of a CYP3A4 inducer is necessary, evaluate patients at frequent intervals for reduced efficacy and signs of opioid withdrawal and consider increasing the SYNALGOS-DC dosage as needed. If a CYP3A4 inducer is discontinued, consider SYNALGOS-DC dosage reduction, and evaluate for signs of respiratory depression and sedation at frequent intervals.
Examples:	Rifampin, carbamazepine, phenytoin
Inhibitors of CYP2D6	
Clinical Impact:	The dihydrocodeine in SYNALGOS-DC is metabolized by CYP2D6 to form dihydromorphine. The concomitant use of SYNALGOS-DC and CYP2D6 inhibitors can increase the plasma concentration of dihydrocodeine, and decrease the plasma concentration of the active metabolite dihydromorphine. This could result in reduced analgesic efficacy or symptoms of opioid withdrawal, particularly when an inhibitor is added after a stable dose of SYNALGOS-DC is achieved *[see Clinical Pharmacology (12.3)]*. After stopping a CYP2D6 inhibitor, as the effects of the inhibitor decline, the

	dihydrocodeine plasma concentration will decrease but the active metabolite dihydromorphine plasma concentration will increase, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression *[see Clinical Pharmacology (12.3)]*.
Intervention:	If concomitant use with a CYP2D6 inhibitor is necessary or if a CYP2D6 inhibitor is discontinued after concomitant use, consider dosage adjustment of SYNALGOS-DC and evaluate patients at frequent intervals. If concomitant use with CYP2D6 inhibitors is necessary, evaluate patients at frequent intervals for reduced efficacy or signs and symptoms of opioid withdrawal and consider increasing the SYNALGOS-DC as needed. After stopping use of a CYP2D6 inhibitor, consider reducing the SYNALGOS-DC and follow the patient for signs and symptoms of respiratory depression or sedation.
Examples:	Quinidine, fluoxetine, paroxetine, bupropion
Benzodiazepines and other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Inform patients and caregivers of this potential interaction and educate them on the signs and symptoms of respiratory depression (including sedation). If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose [see Dosage and Administration (2.2, 2.5), Warnings and Precautions (5.1, 5.2, 5.3)].
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, frequently evaluate the patient, particularly during treatment initiation and dose adjustment. Discontinue SYNALGOS-DC if serotonin syndrome is suspected.

Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue)
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.2)]*
Intervention:	Do not use SYNALGOS-DC in patients taking MAOIs or within 14 days of stopping such treatment. If urgent use of an opioid is necessary, use test doses and frequent titration of small doses of <u>other</u> opioids (such as oxycodone, hydrocodone, oxymorphone, hydromorphone, or buprenorphine) to treat pain while closely following blood pressure and signs and symptoms of CNS and respiratory depression.
Examples:	Phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of SYNALGOS-DC and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	Butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Dihydrocodeine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Because respiratory depression may be greater than otherwise expected, decrease the dosage of SYNALGOS-DC and/or the muscle relaxant as necessary. Due to the risk of respiratory depression with concomitant use of skeletal muscle relaxants and opioids, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.2, 5.3)]*.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. The effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow and salt and fluid retention.
Intervention:	Evaluate patients for signs of diminished diuresis and/or effects on blood pressure and

	increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Evaluate patients for signs of urinary retention or reduced gastric motility when SYNALGOS-DC is used concomitantly with anticholinergic drugs.
Anticoagulants	
Clinical Impact:	Aspirin may enhance the effects of anticoagulants. Concurrent use may increase the risk of bleeding. Aspirin can also displace warfarin from protein binding sides, leading to prolongation of both the prothrombin time and the bleeding time.
Intervention:	Inform patients of this interaction and frequently evaluate for signs of bleeding.
Examples:	Warfarin, heparin, enoxaparin, clopidogrel, prasugrel, rivaroxaban, apixaban
Uricosuric Agents	
Clinical Impact:	Aspirin inhibits the uricosuric effects of uricosuric agents.
Intervention:	Avoid concomitant use.
Examples:	Probenecid
Carbonic Anhydrase Inhibitors	
Clinical Impact:	Concurrent use with aspirin can lead to high serum concentrations of the carbonic anhydrase inhibitor and cause toxicity due to competition at the renal tubule for secretion.
Intervention:	Consider reducing the dose of the carbonic anhydrase inhibitor and assess the patient for any adverse effects from the carbonic anhydrase inhibitor.
Examples:	Acetazolamide, methazolamide
Methotrexate	
Clinical Impact:	Aspirin may enhance the toxicity of methotrexate by displacing it from its plasma protein binding sites and/or reducing its renal clearance.
Intervention:	Use caution if using concomitantly, especially in elderly patients or patients with renal impairment. Reevaluate patients for methotrexate toxicity.
Nephrotoxic Agents	
Clinical Impact:	Concomitant use with aspirin may lead to additive nephrotoxicity due to the inhibition of renal prostaglandins by aspirin. Also, the plasma concentration of aspirin is increased by conditions that reduce the glomerular filtration rate or tubular secretion.
Intervention:	Use SYNALGOS-DC with caution if used concomitantly with nephrotoxic agents. Frequently reevaluate the renal function of patients.
Examples:	Aminoglycosides, amphotericin B, systemic bacitracin, cisplatin, cyclosporine, foscarnet, or parenteral vancomycin
Angiotensin Converting Enzyme (ACE) Inhibitors	
Clinical Impact:	The hyponatremic and hypotensive effects of ACE inhibitors may be diminished by the concomitant administration of aspirin due to its indirect effect on the renin-angiotensin

	conversion pathway.
Intervention:	Use caution if using concomitantly. Reevaluate the blood pressure and renal function of patients.
Examples:	Ramipril, captopril
Beta Blockers	
Clinical Impact:	The hypotensive effects of beta blockers may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow, and salt and fluid retention.
Intervention:	Use caution if using concomitantly. Follow the blood pressure and renal function of patients.
Examples:	Metoprolol, propranolol
Hypoglycemic Agents	
Clinical Impact:	Aspirin may increase the serum glucose-lowering action of insulin and sulfonylureas leading to hypoglycemia.
Intervention:	Patients should be advised to consult a physician if any signs or symptoms of hypoglycemia occur.
Examples:	Insulin, glimepiride, glipizide
Anticonvulsants	
Clinical Impact:	Aspirin can displace protein-bound phenytoin and valproic acid, leading to a decrease in the total concentration of phenytoin and an increase in serum valproic acid levels.
Intervention:	Use caution if using concomitantly.
Examples:	Phenytoin, valproic acid
Nonsteroidal Anti-inflammatory Drugs (NSAIDs)	
Clinical Impact:	Concurrent use with aspirin may increase the risk of bleeding or lead to decreased renal function. Aspirin may enhance serious side effects and toxicity of ketoralac by displacing it from its plasma protein binding sites and/or reducing its renal clearance.
Intervention:	Avoid concomitant use.
Examples:	Ketorolac, ibuprofen, naproxen, diclofenac
Corticosteroids	
Clinical Impact:	In patients receiving concomitant corticosteroids and chronic use of aspirin, withdrawal of corticosteroids may result in salicylism because corticosteroids enhance renal clearance of salicylates and their withdrawal is followed by return to normal rates of renal clearance.
Intervention:	Avoid concomitant use.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of opioid analgesics for an extended period of time during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.4)]*. Use of NSAIDs, including aspirin, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of SYNALGOSDC use between about 20 and 30 weeks of gestation, and avoid SYNALGOS-DC use at about 30 weeks of gestation and later in pregnancy (see *Clinical Considerations, Data*).

Premature Closure of Fetal Ductus Arteriosus

Use of NSAIDs, including aspirin, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as aspirin, resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

The 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

Use of opioid analgesics for an extended period of time 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 (5.4)]*.

Premature Closure of Fetal Ductus Arteriosus:
Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including SYNALGOS-DC, can cause premature closure of the fetal ductus arteriosus (see *Data*).

Oligohydramnios/Neonatal Renal Impairment:
If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If SYNALGOS-DC treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue SYNALGOS-DC and follow up according to clinical practice (see *Data*).

Labor or Delivery
Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. SYNALGOS-DC is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including SYNALGOS-DC, 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 opioid analgesics during labor for signs of excess sedation and respiratory depression.

Aspirin should be avoided one week prior to and during labor and delivery because it can result in excessive blood loss at delivery. Prolonged gestation and prolonged labor due to prostaglandin inhibition have been reported.

Data

Human Data

Premature Closure of Fetal Ductus Arteriosus
Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment
Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some

cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.

Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.

Animal Data
Animal reproduction studies have not been conducted with the combination of aspirin, caffeine, and dihydrocodeine capsules or with dihydrocodeine alone.

In studies performed in adult animals, caffeine (as caffeine base) administered to pregnant mice as sustained release pellets at 50 mg/kg (0.7 times the human daily dose of 360 mg caffeine on a mg/m^2 basis), during the period of organogenesis, caused a low incidence of cleft palate and exencephaly in the fetuses.

8.2 Lactation

Risk Summary

SYNALGOS-DC is not recommended for use in nursing women.

Dihydrocodeine and its active metabolite, dihydromorphine, are present in human milk. There are published studies and cases that have reported excessive sedation, respiratory depression, and death 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; this would be expected to occur with dihydrocodeine as well. In women with normal dihydrocodeine metabolism (normal CYP2D6 activity), the amount of dihydrocodeine secreted into human milk is low and dose-dependent.

There is no information on the effects of the dihydrocodeine on milk production. 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

SYNALGOS-DC *[see Warnings and Precautions (5.6)]*.

Aspirin and caffeine are also excreted in breast milk in small amounts. Adverse effects on platelet function in the nursing infant exposed to aspirin in breast milk may be a potential risk. Use of high doses of aspirin may lead to rashes, platelet abnormalities, and bleeding in nursing infants.

Nursing women are advised against aspirin use because of the possible development of Reye's Syndrome in their babies. The risk of Reye's Syndrome caused by salicylate in breast milk is unknown *[see Warnings and Precautions (5.20)]*.

Because of the potential for serious adverse reactions, including excess sedation and respiratory depression, rashes, platelet abnormalities, bleeding, and the possibility of Reye Syndrome in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with SYNALGOS-DC.

Clinical Considerations

If infants are exposed to SYNALGOS-DC through breast milk, they should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breastfeeding is stopped.

Aspirin and caffeine are also excreted in breast milk in small amounts. Adverse effects on platelet function in the nursing infant exposed to aspirin in breast milk may be a potential risk.

8.3 Females and Males of Reproductive Potential

Infertility

Use of opioids for an extended period of time 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)], Nonclinical Toxicology (13.1)]*.

Females
Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including aspirin, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including aspirin, in women who have difficulties conceiving or who are undergoing investigation of infertility.

8.4 Pediatric Use

Preparations containing aspirin should be kept out of the reach of children. Reye's Syndrome is a rare condition that affects the brain and liver and is most often observed in children given aspirin during a viral illness. The safety and effectiveness of SYNALGOS-DC in pediatric patients below 12 years of age have not been established.

Life-threatening respiratory depression and death have occurred in children who received codeine *[see Warnings and Precautions (5.6)]*. 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 opioids. Because of the risk of life-threatening respiratory depression and death:

- SYNALGOS-DC is contraindicated for all children younger than 12 years of age *[see Contraindications (4)]*.
- SYNALGOS-DC 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 SYNALGOS-DC in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of dihydrocodeine unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation, such as post-operative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression *[see Warnings and Precautions (5.6)]*.

8.5 Geriatric Use

Clinical studies of SYNALGOS-DC did not include sufficient numbers of subjects 65 years of age and older to determine whether elderly subjects respond differently from younger subjects.

Elderly patients (aged 65 years or older) may have increased sensitivity to dihydrocodeine. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of SYNALGOS-DC slowly in geriatric patients and frequently reevaluate the patient for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.9)]*.

Component of this drug product are 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, care should be taken in dose selection, and it may be useful to regularly evaluate renal function.

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, dose selection should start at the low end of the dosing range, and regularly evaluate patients for adverse effects *[see Warnings and Precautions (5.9)]*.

8.6 Hepatic Impairment

SYNALGOS-DC contains aspirin, which should be avoided in patients with severe hepatic impairment.

No formal studies have been conducted in patients with hepatic impairment so the pharmacokinetics of dihydrocodeine in this patient population is unknown. Start these patients cautiously with lower doses of SYNALGOS-DC or with longer dosing intervals and titrate slowly while carefully following for side effects. In patients with severe hepatic disease, follow effects of therapy with serial liver function tests.

8.7 Renal Impairment

SYNALGOS-DC contains aspirin, which should be avoided in patients with severe renal failure (glomerular filtration rate less than 10 mL/minute).

Dihydrocodeine 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. Start these patients cautiously with lower doses of SYNALGOS-DC or with longer dosing intervals and titrate slowly while carefully following for side effects. In patients with renal disease, follow effects of therapy with serial renal function tests.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

SYNALGOS-DC contains dihydrocodeine, a Schedule III controlled substance.

9.2 Abuse

SYNALGOS-DC contains dihydrocodeine, a substance with high potential for misuse and abuse, which can lead to the development of substance use disorder, including addiction *[see Warnings and Precautions (5.1)]*.

Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed.

Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of SYNALGOS-DC increases risk of overdose, which may lead to central nervous system and respiratory depression, hypotension, seizures, and death. The risk is increased with concurrent abuse of SYNALGOS-DC with alcohol and other CNS depressants. Abuse of and addiction to opioids in some individuals may not be accompanied by concurrent tolerance and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of addiction.

All patients treated with opioids require careful and frequent reevaluation for signs of misuse, abuse, and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Patients at high risk of SYNALGOS-DC abuse include those with a history of prolonged use of any opioid, including products containing dihydrocodeine, those with a history of drug or alcohol abuse, or those who use SYNALGOS-DC in combination with other abused drugs.

“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 healthcare provider(s). “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among people who abuse drugs and people with substance use disorder. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with inadequate pain control.

SYNALGOS-DC, like other opioids, can be diverted for nonmedical 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 reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of SYNALGOS-DC

Abuse of SYNALGOS-DC poses a risk of overdose and death. The risk is increased with concurrent use of SYNALGOS-DC with alcohol and/or other CNS depressants.

SYNALGOS-DC is approved for oral use only.

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

9.3 Dependence

Both tolerance and physical dependence can develop during use of opioid therapy.

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

Physical dependence is a state that develops as a result of a physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued use.

Do not abruptly discontinue SYNALGOS-DC in a patient physically dependent on opioids. Rapid tapering of SYNALGOS-DC in a patient physically dependent on opioids may lead to serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse.

When discontinuing SYNALGOS-DC, gradually taper the dosage using a patient-specific plan that considers the following: the dose of SYNALGOS-DC the patient has been taking, the duration of treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for an extended period of time at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper *[see Dosage and Administration (2.5), and Warnings and Precautions (5.17)]*.

10 OVERDOSAGE

Clinical Presentation

Serious overdose with SYNALGOS-DC is characterized by signs and symptoms of opioid and salicylate overdose.

Acute overdose with dihydrocodeine can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, hypoglycemia, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*.

Early signs of acute aspirin (salicylate) overdose including tinnitus occur at plasma concentrations approaching 200 mcg/mL. Plasma concentrations of aspirin above 300 mcg/mL are toxic. Severe toxic effects are associated with levels above 400 mcg/mL. A single lethal dose of aspirin in adults is not known with certainty but death may be expected at 30 g. For real or suspected overdose, a Poison Control Center should be contacted immediately.

In acute salicylate overdose, severe acid-base and electrolyte disturbances may occur and are complicated by hyperthermia and dehydration, and coma. Respiratory alkalosis occurs early while hyperventilation is present, but is quickly followed by metabolic acidosis. Serious symptoms such as depression, coma, and respiratory failure progress rapidly.

Salicylism (chronic salicylate toxicity) may be noted by symptoms such as dizziness, tinnitus, difficulty hearing, nausea, vomiting, diarrhea, and mental confusion. More severe salicylism may result in respiratory alkalosis.

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. 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 measures. Treatment of acid- base disturbances and electrolyte disorders is also important. Because of the concern over salicylate toxicity, acid-base status should be followed closely with serial blood gas and serum pH determinations.

Opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to dihydrocodeine overdose, administer an opioid antagonist.

Because the duration of opioid reversal is expected to be less than the duration of action of dihydrocodeine in SYNALGOS-DC, carefully monitor the patient until spontaneous respiration is reliably reestablished. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

In severe cases of salicylate overdose, hyperthermia and hypovolemia are the major immediate threats to life. Children should be sponged with tepid water. Replacement fluid should be administered intravenously and augmented with correction of acidosis. Plasma electrolytes and pH should be monitored to promote alkaline diuresis of salicylate if renal function is normal. Infusion of glucose may be required to control hypoglycemia. With more severe acute toxicity respiratory alkalosis may occur.

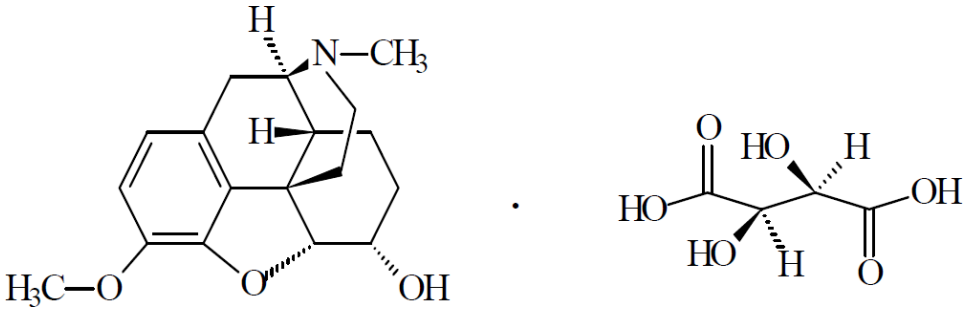
Hemodialysis and peritoneal dialysis can be performed to reduce the body content of aspirin. In patients with renal insufficiency or in cases of life-threatening salicylate intoxication dialysis is usually required. Exchange transfusion may be indicated in infants and young children.

In case of real or suspected overdose, a poison control center should be consulted for the treatment of salicylism.

11 DESCRIPTION

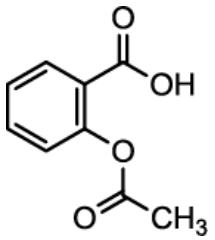
SYNALGOS-DC (aspirin, caffeine, and dihydrocodeine bitartrate) capsules are a three-drug combination of dihydrocodeine, an opioid agonist, aspirin, a nonsteroidal anti-inflammatory drug, and caffeine, a methylxanthine. SYNALGOS-DC capsules are available as,
356.4 mg aspirin, 30 mg caffeine, and 16 mg dihydrocodeine bitartrate for oral administration.

The chemical name for dihydrocodeine bitartrate is morphinan-6-ol, 4,5-epoxy-3-methoxy-17-methyl-, (5α,6α)-2,3- dihydroxybutanedioate (1:1) (salt). It is also known as 4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol (+)-tartrate (salt). The molecular weight for dihydrocodeine bitartrate is 451.48. Its molecular formula is $C_{18}H_{23}NO_3 \cdot C_4H_6O_6$, and it has the following chemical structure.



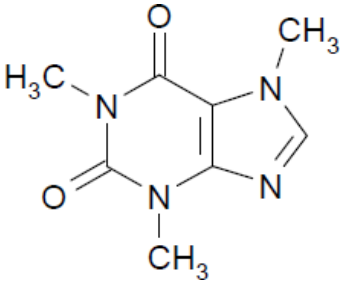
Dihydrocodeine is a fine, white, odorless, crystalline powder that is synthesized from codeine. Dihydrocodeine bitartrate dissolves in water (1 g in 4.5 g) and turns into a clear, colorless solution. It has a dissociation constant of pKa 8.89 at 25°C and pKa 8.67 at 37°C. Dihydrocodeine bitartrate has partition coefficient of logP 1.16 and a pH of 3.2 to 4.2.

The chemical name for aspirin is 2-(acetyloxy)benzoic acid. The molecular weight for aspirin is 180.16. Its molecular formula is $C_9H_8O_4$, and it has the following chemical structure.



Aspirin is a white, crystalline powder, or white crystals (usually needle-like). It is odorless or has a faint odor, and is stable in dry air. In moist air, it gradually hydrolyzes to salicylic and acetic acids. Aspirin is slightly soluble in water, freely soluble in alcohol, soluble in chloroform and ether, and sparingly soluble in absolute ether. Aspirin has a dissociation constant of 1.8×10^{-4} at 25°C.

The chemical name for caffeine is 1,3,7-trimethylxanthine. The molecular weight for caffeine is 194.19. Its molecular formula is $C_8H_{10}N_4O_2$, and it has the following chemical structure.



Caffeine is a white, crystalline substance or granules. It is freely soluble in boiling water, sparingly soluble in water at 20°C, and slightly soluble in ethanol. It has a pH of 6.9 (1% solution) and a pKa of 14.0 at 25°C. Caffeine has a partition coefficient of Kp 0.96 (n-octanol/aqueous solution pH 7.41) and Kp 0.72 (n-octanol/0.1 M HCl).

The inactive ingredients in SYNALGOS-DC include: alginic acid, cellulose, D&C Red 28, FD&C Blue 1, gelatin, iron oxides, stearic acid, and titanium dioxide.

SYNALGOS-DC is available as blue and gray capsules that are marked "CP" and "419".

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SYNALGOS-DC contains dihydrocodeine, a full opioid agonist, aspirin, a nonsteroidal anti-inflammatory drug, and caffeine, a methylxanthine.

Dihydrocodeine is an opioid agonist relatively selective for the μ-opioid receptor, but with a much weaker affinity than dihydromorphine. The analgesic properties of dihydrocodeine have been speculated to come from its conversion to dihydromorphine, although the exact mechanism of analgesic action remains unknown.

Aspirin is a nonsteroidal anti-inflammatory drug and a non-selective irreversible inhibitor of cyclooxygenases.

Caffeine is a methylxanthine and CNS stimulant. The exact mechanism with respect to the indication is not clear; however, the effects of caffeine may be due to antagonism of adenosine receptors.

12.2 Pharmacodynamics

Effects on the Central Nervous System

Dihydrocodeine 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 electrical stimulation.

Dihydrocodeine 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.

Aspirin works by inhibiting the body's production of prostaglandins, including prostaglandins involved in inflammation. Prostaglandins cause pain sensations by stimulating muscle contractions and dilating blood vessels throughout the body. In the CNS, aspirin works on the hypothalamus heat-regulating center to reduce fever, however, other mechanisms may be involved.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Dihydrocodeine 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.

Aspirin can produce gastrointestinal injury (lesions, ulcers) through a mechanism that is not yet completely understood, but may involve a reduction in eicosanoid synthesis by the gastric mucosa. Decreased production of prostaglandins may compromise the defenses of the gastric mucosa and the activity of substances involved in tissue repair and ulcer healing.

Effects on the Cardiovascular System

Dihydrocodeine 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, sweating, and/or orthostatic hypotension.

Aspirin affects platelet aggregation by irreversibly inhibiting prostaglandin cyclooxygenase. This effect lasts for the life of the platelet and prevents the formation of the platelet aggregating factor, thromboxane A_2. Nonacetylated salicylates do not inhibit this enzyme and have no effect on platelet aggregation. At somewhat higher doses, aspirin reversibly inhibits the formation of prostaglandin 12 (prostacyclin), which is an arterial vasodilator and inhibits platelet aggregation.

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.

Use of opioids for an extended period of time 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)]*.

Effect 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-Efficacy Relationship

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with opioid agonists *[see Dosage and Administration (2.1)]*. The minimum effective analgesic concentration of dihydrocodeine for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance *[see Dosage and Administration (2.1)]*.

Concentration-Adverse Reaction Relationships

There is a relationship between increasing dihydrocodeine 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 *[see Dosage and Administration (2.1), (2.3), (2.4)]*.

12.2 Pharmacokinetics

Aspirin

Absorption

In general, immediate-release aspirin is well and completely absorbed from the gastrointestinal (GI) tract. Following absorption, aspirin is hydrolyzed to salicylic acid with peak plasma levels of salicylic acid occurring within 1 to 2 hours of dosing. The rate of absorption from the GI tract is dependent upon the dosage form, the presence or absence of food, gastric pH (the presence or absence of GI antacids or buffering agents), and other physiologic factors.

Distribution

Salicylic acid is widely distributed to all tissues and fluids in the body including the central nervous system (CNS), breast milk, and fetal tissues. The highest concentrations are found in the plasma, liver, renal cortex, heart, and lungs. The protein binding of salicylate is concentration-dependent, *i.e.*,

nonlinear. At low concentrations (< 100 micrograms/milliliter (µg/mL)), approximately 90 percent of plasma salicylate is bound to albumin while at higher concentrations (> 400 µg/mL), only about 75 percent is bound.

Elimination

Metabolism

Aspirin is rapidly hydrolyzed in the plasma to salicylic acid such that plasma levels of aspirin are essentially undetectable 1 to 2 hours after dosing. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites. Salicylic acid has a plasma half-life of approximately 6 hours. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. Following toxic doses (10 to 20 grams (g)), the plasma half-life may be increased to over 20 hours.

Excretion

The elimination of salicylic acid follows zero order pharmacokinetics; (*i.e.*, the rate of drug elimination is constant in relation to plasma concentration). Renal excretion of unchanged drug depends upon urine pH. The renal clearance is greatly augmented by an alkaline urine as is produced by concurrent administration of sodium bicarbonate or potassium citrate. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from < 5 percent to > 80 percent.

Following therapeutic doses, approximately 10 percent is found excreted in the urine as salicylic acid, 75 percent as salicyluric acid, and 10 percent phenolic and 5 percent acyl glucuronides of salicylic acid.

Dihydrocodeine

Metabolism

CYP3A4 and CYP2D6 are involved in the metabolism of dihydrocodeine. Dihydrocodeine is mainly metabolized by CYP2D6 to its active metabolite dihydromorphine.

Caffeine

Absorption

Like most xanthines, caffeine is rapidly absorbed.

Distribution

Caffeine is distributed in all body tissues and fluids, including the CNS, fetal tissues, and breast milk.

Elimination

Caffeine is cleared rapidly through metabolism and excretion in the urine.

Metabolism
Caffeine is mainly metabolized by CYP1A2. Other enzymes, including CYP2E1, CYP3A4, CYP2C8 and CYP2C9 may play a minor role in its metabolism. Hepatic biotransformation prior to excretion results in about equal amounts of 1-methylxanthine and 1- methyluric acid.

Excretion
Of the 70% of the dose that has been recovered in the urine, only 3% was unchanged drug. The plasma half-life is about 3 hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Long-term studies in animals to evaluate the carcinogenic potential of the combination of aspirin, caffeine, and dihydrocodeine bitartrate or dihydrocodeine alone have not been conducted.

Administration of aspirin for 68 weeks at 0.5 percent in the feed of rats was not carcinogenic.

In a 2-year study in Sprague-Dawley rats, caffeine (as caffeine base) administered in drinking water was not carcinogenic in male rats at doses up to 102 mg/kg or in female rats at doses up to 170 mg/kg (approximately 2.8 and 4.6 times, respectively, the daily dose of 360 mg caffeine on a mg/m^2 basis). In an 18-month study in C57BL/6 mice, no evidence of tumorigenicity was seen at dietary doses up to 55 mg/kg (0.7 times the daily dose of 360 mg caffeine on a mg/m^2 basis).

Mutagenesis
The combination of aspirin, caffeine, and dihydrocodeine or dihydrocodeine alone has not been evaluated for mutagenicity.

Aspirin is not mutagenic in the Ames Salmonella assay; however, aspirin did induce chromosome aberrations in cultured human fibroblasts.

Caffeine (as caffeine base) increased the sister chromatid exchange (SCE) SCE/cell metaphase (exposure time dependent) in an *in vivo* mouse metaphase analysis. Caffeine also potentiated the genotoxicity of known mutagens and enhanced the micronuclei formation (5-fold) in folate-deficient mice. However, caffeine did not increase chromosomal aberrations in *in vitro* Chinese hamster ovary cell (CHO) and human lymphocyte assays and was not mutagenic in an *in vitro* CHO/hypoxanthine guanine phosphoribosyltransferase (HGPRT) gene mutation assay, except at cytotoxic concentrations. In addition, caffeine was not clastogenic in an *in vivo* mouse micronucleus assay. Caffeine was negative in the *in vitro* bacterial reverse mutation assay (Ames test).

Impairment of Fertility

Animal studies to evaluate the effects of the combination of aspirin, caffeine, and dihydrocodeine or dihydrocodeine alone on fertility have not been performed.

Aspirin has been shown to inhibit ovulation in rats.

Caffeine (as caffeine base) administered to male rats at 50 mg/kg/day subcutaneously (0.7 times the daily dose of 360 mg caffeine on a mg/m^2 basis) for 4 days prior to mating with untreated females, caused decreased male reproductive performance in addition to causing embryotoxicity. In addition, long-term exposure to high oral doses of caffeine (3 g over 7 weeks) was toxic to rat testes as manifested by spermatogenic cell degeneration.

16 HOW SUPPLIED/STORAGE AND HANDLING

SYNALGOS-DC (aspirin, caffeine, and dihydrocodeine bitartrate) are blue and gray capsules marked with "CP" and "419", and are supplied as:

NDC 49708-419-88 (356.4 mg aspirin/30 mg caffeine/16 mg dihydrocodeine bitartrate): 100 capsules per bottle

Store at room temperature, approx. 25°C (77°F). Keep tightly closed. Dispense in tight container. Store SYNALGOS-DC securely and dispose of properly.

17 PATIENT COUNSELING INFORMATION

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

Storage and Disposal

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store SYNALGOS-DC securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home. Inform patients that leaving SYNALGOS-DC unsecured can pose a deadly risk to others in the home *[see Warnings and Precautions (5.1, 5.2), Drug Abuse and Dependence (9.2)]*.

Advise patients and caregivers that when medicines are no longer needed, they should be disposed of promptly. Inform patients that medicine take-back options are the preferred way to safely dispose of most types of unneeded medicines. If no take back programs or DEA-registered collectors are available, instruct patients to dispose of SYNALGOS-DC by following these four steps:

- Mix SYNALGOS-DC (do not crush) with an unpalatable substance such as dirt, cat litter, or used

coffee grounds;

- Place the mixture in a container such as a sealed plastic bag;
- Throw the container in the household trash;
- Remove all personal information on the prescription label of the empty bottle.

Inform patients that they can visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

Addiction, Abuse, and Misuse

Inform patients that the use of SYNALGOS-DC, 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 SYNALGOS-DC with others and to take steps to protect SYNALGOS-DC from theft or misuse.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting SYNALGOS-DC or when the dosage is increased, and that it can occur even at recommended dosages.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death *[see Warnings and Precautions (5.2)]*.

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if SYNALGOS-DC is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider *[see Warnings and Precautions (5.3), Drug Interactions (7)]*.

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss with the patient and caregiver the availability of naloxone for the emergency treatment of opioid overdose, both when initiating and renewing treatment with SYNALGOS-DC. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program) *[see Dosage and Administration (2.2), Warnings and Precautions (5.2)]*.

Educate patients and caregivers on how to recognize the signs and symptoms of an overdose.

Explain to patients and caregivers that naloxone's effects are temporary, and that they must call 911 or get emergency medical help right away in all cases of known or suspected opioid overdose, even if naloxone is administered *[see Overdosage (10)]*.

If naloxone is prescribed, also advise patients and caregivers:

- How to treat with naloxone in the event of an opioid overdose
- To tell family and friends about their naloxone and to keep it in a place where family and friends can access it in an emergency
- To read the Patient Information (or other educational material) that will come with their naloxone. Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver will know what to do.

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

Advise caregivers that SYNALGOS-DC 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. Advise caregivers of children 12 to 18 years of age receiving SYNALGOS-DC to monitor for signs of respiratory depression *[see Warnings and Precautions (5.6)]*.

Hyperalgesia and Allodynia

Inform patients and caregivers not to increase opioid dosage without first consulting a clinician. Advise patients to seek medical attention if they experience symptoms of hyperalgesia, including worsening pain, increased sensitivity to pain, or new pain *[see Warnings and Precautions (5.8), Adverse Reactions (6.2)]*.

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition called serotonin syndrome 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 healthcare providers if they are taking, or plan to take serotonergic medications *[see Drug Interactions (7)]*.

MAOI Interaction

Inform patients not to take SYNALGOS-DC while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking SYNALGOS-DC *[see Drug Interactions (7)]*.

Important Administration Instructions

Instruct patients how to properly take SYNALGOS-DC.
Administer SYNALGOS-DC with food or a full glass of water to minimize GI distress *[see Dosage and Administration (2.1)]*.

Important Discontinuation Instructions
In order to avoid developing withdrawal symptoms, instruct patients not to discontinue SYNALGOS-DC without first discussing a tapering plan with the prescriber *[see Dosage and Administration (2.5)]*

Driving or Operating Heavy Machinery
Inform patients that SYNALGOS-DC may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication *[see Warnings and Precautions (5.17)]*.

Constipation
Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention *[see Adverse Reactions (6)]*.

Adrenal Insufficiency
Inform patients that opioids 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 (5.11)]*.

Hypotension
Inform patients that SYNALGOS-DC 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 (5.12)]*.

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

Serious Skin Reactions, including DRESS
Advise patients to stop taking SYNALGOS-DC immediately if they develop any type of rash or fever and to contact their healthcare provider as soon as possible *[see Warnings and Precautions (5.20)]*.

Aspirin Allergy
Patients should be informed that SYNALGOS-DC contains aspirin and should not be taken by patients

with an aspirin or NSAID allergy.

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that use of SYNALGOS-DC for an extended period of time during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.5), Use in Specific Populations (8.1)]*.

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that SYNALGOS-DC can cause fetal harm and to inform the healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*. Inform pregnant women to avoid use of aspirin and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with SYNALGOS-DC is needed for a pregnant woman between about 20 to
30 weeks gestation, advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours *[see Warnings and Precautions (5.17) and Use in Specific Populations (8.1)]*.

Lactation

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

Infertility

Inform patients that use of opioids for an extended period of time may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6)]*. Advise females of reproductive potential who desire pregnancy that NSAIDs, including SYNALGOS- DC, may be associated with a reversible delay in ovulation *[see Use in Specific Populations (8.3)]*.

Risk of Bleeding

Inform patients about the signs and symptoms of bleeding. Tell patients to notify their physician if they are prescribed any drug which may increase risk of bleeding.

Counsel patients who consume three or more alcoholic drinks daily about the bleeding risks involved with chronic, heavy alcohol use while taking aspirin *[see Warnings and Precautions (5.18)]*.

Avoid Concomitant Use of NSAIDs

Inform patients that the concomitant use of SYNALGOS-DC with NSAIDs or other salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little

or no increase in efficacy *[see Warnings and Precautions (5.14) and Drug Interactions (7)]*. Alert patients that NSAIDs may be present in "over the counter" medications for treatment of colds, fever, or insomnia.

Manufactured by:

Mikart, Inc.
Atlanta, Georgia 30318

Distributed by:

Sun Pharmaceutical Industries, Inc.
Cranbury, NJ 08512
Rev. 12/2023

Medication Guide
SYNALGOS®-DC (sin-AAL-gus-dee-see)
(aspirin, caffeine, and dihydrocodeine bitartrate) capsules, CIII

SYNALGOS-DC is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain, when other pain treatments such as non-opioid pain medicines do not treat your pain well enough or you cannot tolerate them.
- An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.

Important information about SYNALGOS-DC:

- **Get emergency help or call 911 right away if you take too much SYNALGOS-DC (overdose).** When you first start taking SYNALGOS-DC, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur. Talk to your healthcare provider about naloxone, a medicine for the emergency treatment of an opioid overdose.
- Taking SYNALGOS-DC with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Increases risk of bleeding and ulcers.
- Never give anyone else your SYNALGOS-DC. They could die from taking it. Selling or giving away SYNALGOS- DC is against the law.
- Store SYNALGOS-DC securely, out of sight and reach of children, and in a location not

accessible by others, including visitors to the home.

Important Information Guiding Use in Pediatric Patients:

- Do not give SYNALGOS-DC to a child younger than 12 years of age.
- Do not give SYNALGOS-DC to a child younger than 18 years of age after surgery to remove the tonsils and/or adenoids.
- Avoid giving SYNALGOS-DC to children between 12 to 18 years of age who have risk factors for breathing problems such as obstructive sleep apnea, obesity, or underlying lung problems.

Do not give SYNALGOS-DC to a child or teenager with a viral illness. Reye's Syndrome, a life-threatening condition, can happen when aspirin (an ingredient in SYNALGOS-DC) is used in children and teenagers who have certain viral illnesses.

Do not take SYNALGOS-DC if you have:

- severe asthma, asthma in combination with runny nose and nasal polyps, trouble breathing, or other lung problems
- a bowel blockage or have narrowing of the stomach or intestines
- allergic to any of the ingredients in SYNALGOS-DC
- known allergy to nonsteroidal anti-inflammatory drug products (NSAIDs)
- a rare disorder in which your blood doesn't clot normally (hemophilia)

Before taking SYNALGOS-DC, tell your healthcare provider if you have a history of:

- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, opioid overdose, or mental health problems
- have been told by your healthcare provider that you are a "rapid metabolizer" of certain medicines
- stomach ulcers, or stomach or intestinal bleeding with use of acetylsalicylic acid (ASA) or NSAIDs

Tell your healthcare provider if you are:

- **noticing your pain getting worse**. If your pain gets worse after you take SYNALGOS-DC, do not take more of SYNALGOS-DC without first talking to your healthcare provider. Talk to your healthcare provider if the pain that you have increases, if you feel more sensitive to pain, or if you have new pain after taking SYNALGOS-DC.
- **pregnant or planning to become pregnant**. Use of SYNALGOS-DC for an extended period of time during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated. Taking NSAID-containing products like SYNALGOS-

DC at about 20 weeks of pregnancy or later may harm your unborn baby. If you need to take NSAIDs for more than 2 days when you are between 20 and 30 weeks of pregnancy, your healthcare provider may need to monitor the amount of fluid in your womb around your baby. **You should not take NSAIDs after about 30 weeks of pregnancy**.

- **breastfeeding.** Not recommended during treatment with SYNALGOS-DS; may harm your baby.
- **develop any type of rash or fever**. Contact your healthcare provider as soon as possible and stop taking SYNALGOS-DC.
- living in a household where there are small children or someone who has abused street or prescription drugs.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking SYNALGOS-DC with certain other medicines can cause serious side effects that could lead to death. Taking with corticosteroids or anticoagulants increases risk of ulcers and stomach/intestinal bleeding.

When taking SYNALGOS-DC:

- Do not change your dose. Take SYNALGOS-DC exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- For acute (short-term) pain, you may only need to take SYNALGOS-DC for a few days. You may have some SYNALGOS-DC left over that you did not use. See disposal information at the bottom of this section for directions on how to safely throw away (dispose of) your unused SYNALGOS-DC.
- Take your prescribed dose every 4 hours as needed for pain. Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time.
- Call your healthcare provider if the dose you are taking does not control your pain.
- If you have been taking SYNALGOS-DC regularly, do not stop taking SYNALGOS-DC without talking to your healthcare provider.
- After you stop taking SYNALGOS-DC, dispose the unused SYNALGOS-DC in accordance with the local state guidelines and/or regulations.
- Dispose of expired, unwanted, or unused SYNALGOS-DC by taking your drug to an authorized DEA-registered collector or drug take-back program. If one is not available, you can dispose of SYNALGOS-DC by mixing the product with dirt, cat litter, or coffee grounds; placing the mixture in a sealed plastic bag, and throwing the bag in your trash. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

While taking SYNALGOS-DC DO NOT:

- Drive or operate heavy machinery, until you know how SYNALGOS-DC affects you. SYNALGOS-DC can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with SYNALGOS-DC may cause you to overdose and die.

The possible side effects of SYNALGOS-DC:

- bleeding, constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain, rash, or fever. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help or call 911 right away if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.
- if you are a nursing mother taking SYNALGOS-DC and your breastfeeding baby has increased sleepiness, confusion, difficulty breathing, shallow breathing, limpness, or difficulty breastfeeding.

These are not all the possible side effects of SYNALGOS-DC. Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov.**

Manufactured by: **Mikart, Inc., Atlanta, Georgia 30318** and Distributed by: **Sun Pharmaceutical Industries, Inc., Cranbury, NJ 08512**, www.SYNALGOSDC.com or call 1-800-406-7984

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

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