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: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; ULTRA-RAPID METABOLISM OF DIHYDROCODEINE AND OTHER RISK FACTORS FOR LIFE-THREATENING RESPIRATORY DEPRESSION IN CHILDREN; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

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 monitor regularly for these behaviors and conditions. (5.1)**
- **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. (5.2)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. (5.3)**
- **Accidental ingestion of SYNALGOS-DC, especially by children, can result in a fatal overdose of dihydrocodeine. (5.3)**
- **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. (5.4) 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. (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.**
- **Prolonged use of SYNALGOS-DC during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.5)**
- **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. (5.6), (7)**
- **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; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.7), (7)**

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

Dosage and Administration (2.4)	10/2019
Warnings and Precautions (5.3, 5.15)	10/2019

----------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
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, 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

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

- Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. (2.1)
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Initiate treatment with two capsules orally every 4 hours as needed for pain. (2.2)
- 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. (2.4)

----------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----------

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.8)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.10)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of SYNALGOS-DC in patients with circulatory shock. (5.11)
- 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. (5.12)
- 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. (5.13)

----------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----------

- Pregnancy: May cause fetal harm. Use of aspirin, including SYNALGOS-DC, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. (8.1)
- Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; ULTRA-RAPID METABOLISM OF DIHYDROCODEINE AND OTHER RISK FACTORS FOR LIFE-THREATENING RESPIRATORY DEPRESSION IN CHILDREN; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

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 SYNALGOS-DC, and monitor all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.1)]*.

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 REMS for these products *[see Warnings and Precautions (5.2)]*. 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

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of SYNALGOS-DC. Monitor for respiratory depression, especially during initiation of SYNALGOS-DC or following a dose increase *[see Warnings and Precautions (5.3)]*.

Accidental Ingestion

Accidental ingestion of even one dose of SYNALGOS-DC, especially by children, can result in a fatal overdose of SYNALGOS-DC *[see Warnings and Precautions (5.3)]*.

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.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of SYNALGOS-DC during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.5)]*.

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 (5.6), Drug Interactions (7)]*.

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 *[see Warnings and Precautions (5.7), Drug Interactions (7)]*.

- **Reserve concomitant prescribing of SYNALGOS-DC and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

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, even at recommended doses *[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

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*.

Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*.

Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy and following dosage increases with SYNALGOS-DC and adjust the dosage accordingly *[see Warnings and Precautions (5.3)]*.

Administer SYNALGOS-DC with food or a full glass of water to minimize GI distress.

2.2 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.

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.

2.3 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 and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse *[see Warnings and Precautions (5.1)]*. 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 unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.4 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 dose of 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, monitor 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 a long duration 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 (5.3), 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 (5.4)]*
- Post-operative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy *[see Warnings and Precautions (5.4)]*

SYNALGOS-DC is also contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.3)]*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.8)]*
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days *[see Warnings and Precautions (5.9), Drug Interactions (7)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.13)]*
- Hypersensitivity to dihydrocodeine, codeine, or aspirin, or NSAIDs *[see Adverse Reactions (6)]*
- Hemophilia *[see Warnings and Precautions (5.17)]*
- Reye’s Syndrome *[see Warnings and Precautions (5.18)]*
- Known allergy to nonsteroidal anti-inflammatory drugs (NSAIDs) *[see Warnings and Precautions (5.19)]*
- Syndrome of asthma, rhinitis, and nasal polyps *[see Warnings and Precautions (5.19)]*

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 monitor 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 intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. 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 the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 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.

5.3 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. Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy with and following dosage increases of SYNALGOS-DC.

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.

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 (2.4)]*.

5.4 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.

5.5 Neonatal Opioid Withdrawal Syndrome

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

5.6 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. Follow patients receiving SYNALGOS-DC and any CYP3A4 inhibitor or inducer 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. Monitor patients for respiratory depression and sedation at frequent intervals.

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. Monitor 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.

  Follow patients receiving SYNALGOS-DC and any CYP2D6 inhibitor 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, follow the patient 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 follow the patient for signs and symptoms of respiratory depression or sedation *[see Drug Interactions (7)]*.

5.7 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 or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). 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. Follow patients closely for signs and symptoms of respiratory depression and sedation.

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), Patient Counseling Information (17)]*.

5.8 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 (5.3)]*.

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 (5.3)]*.

Monitor such patients closely, particularly when initiating and titrating SYNALGOS-DC and when SYNALGOS-DC is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.7)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.9 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.

5.10 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.

5.11 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)]*. Monitor 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.

5.12 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.

5.13 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. Monitor 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)]*.

5.14 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. Monitor patients with a history of seizure disorders for worsened seizure control during SYNALGOS-DC therapy.

5.15 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 (2.4), 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.

5.16 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 *[see Patient Counseling Information (17)]*.

5.17 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.

5.18 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.

5.19 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).

5.20 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.

5.21 Premature Closure of Fetal Ductus Arteriosus

Aspirin may cause premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including SYNALGOS-DC, in pregnant women starting at 30 weeks of gestation (third trimester) *[see Use in Specific Populations (8.1)]*.

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 (5.3)]*
- Ultra-Rapid Metabolism of Dihydrocodeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children *[see Warnings and Precautions (5.4)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.5)]*
- Interactions with Benzodiazepines or Other CNS Depressants *[see Warnings and Precautions (5.7)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.10)]*
- Severe Hypotension *[see Warnings and Precautions (5.11)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.13)]*
- Seizures *[see Warnings and Precautions (5.14)]*
- Withdrawal *[see Warnings and Precautions (5.15)]*
- Coagulation Abnormalities and Bleeding *[see Warnings and Precautions (5.17)]*
- Reye's Syndrome *[see Warnings and Precautions (5.18)]*
- Allergy *[see Warnings and Precautions (5.19)]*
- Renal Toxicity and Hyperkalemia *[see Warnings and Precautions (5.20)]*
- Premature Closure of Fetal Ductus Arteriosus *[see Warnings and Precautions (5.21)]*

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 chronic use of opioids *[see Clinical Pharmacology (12.2)]*.

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. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the SYNALGOS-DC dosage until stable drug effects are achieved. Monitor 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 (5.15)]*. 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, follow the patient 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 monitor 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 monitor patients closely at frequent intervals. If concomitant use with CYP2D6 inhibitors is necessary, follow the patient 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. Follow patients closely for signs of respiratory depression and sedation *[see Warnings and Precautions (5.7)]*.
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, carefully observe 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 (5.3)]*
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:	Follow patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of SYNALGOS-DC and/or the muscle relaxant as necessary.
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:	Follow 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:	Follow 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:	Follow patients 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 follow 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. Follow 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. Closely follow 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. Follow 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:	Ketoralac, 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

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.5)]*. Use of aspirin, including SYNALGOS-DC, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including SYNALGOS-DC, in pregnant women starting at 30 weeks of gestation (third trimester). Salicylates readily cross the placenta and by inhibiting prostaglandin synthesis, may cause constriction of ductus arteriosus resulting in pulmonary hypertension and increased fetal mortality and, possibly other untoward fetal effects. Aspirin use in pregnancy can also result in alteration in maternal and neonatal hemostasis mechanisms. Maternal aspirin use during later stages of pregnancy may cause low birth weight, increased incidence of intracranial hemorrhage in premature infants, stillbirths and neonatal death.

Studies of aspirin use in pregnant women have not shown that aspirin increases the risk of abnormalities when administered during the first trimester of pregnancy. In controlled studies involving 41,337 pregnant women and their offspring, there was no evidence that aspirin taken during pregnancy caused stillbirth, neonatal death or reduced birth weight. In controlled studies of 50,282 pregnant women and their offspring, aspirin administration in moderate and heavy doses during the first four lunar months of pregnancy showed no teratogenic effect.

Therapeutic doses of aspirin in pregnant women close to term may cause bleeding in mother, fetus, or neonate. During the last 6 months of pregnancy, regular use of aspirin in high doses may prolong pregnancy and delivery.

Available data with SYNALGOS-DC in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage. Reproduction studies for the combination of aspirin, caffeine, and dihydrocodeine have not been performed in animals. In animal studies, caffeine administration to pregnant mice increased the incidence of cleft palate and exencephaly at 0.7 times and 2 times the daily dose of 360 mg caffeine. 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.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4 % and 15 to 20%, respectively.

Clinical Considerations

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

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.5)]*.

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.

Salicylates readily cross the placenta and by inhibiting prostaglandin synthesis, may cause constriction of ductus arteriosus resulting in pulmonary hypertension and increased fetal mortality and, possibly other untoward fetal effects. Aspirin use in pregnancy can also result in alteration in maternal and neonatal hemostasis mechanisms. Maternal aspirin use during later stages of pregnancy may cause low birth weight, increased incidence of intracranial hemorrhage in premature infants, stillbirths and neonatal death. Use during pregnancy, especially in the third trimester, should be avoided.

Data

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 (5.4)]*.

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 (5.18)]*.

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

Chronic use of opioids 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 (5.4)]*. 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 (5.4)]*.

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 follow closely for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.8)]*.

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 monitor 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 follow patients for adverse effects *[see Warnings and Precautions (5.8)]*.

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 a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol. SYNALGOS-DC can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1)]*.

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

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

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

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

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

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

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

Risks Specific to Abuse of SYNALGOS-DC

SYNALGOS-DC is for oral use only. Abuse of SYNALGOS-DC poses a risk of overdose and death. The risk is increased with concurrent use of SYNALGOS-DC with alcohol and other central nervous system depressants.

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 chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence is a physiological state in which the body adapts to the drug after a period of regular exposure, resulting in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

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 a long duration 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 (2.4), Warnings and Precautions (5.15)]*.

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

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, 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 techniques. 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.

The opioid antagonists, naloxone or nalmefene, 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. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to dihydrocodeine overdose.

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.

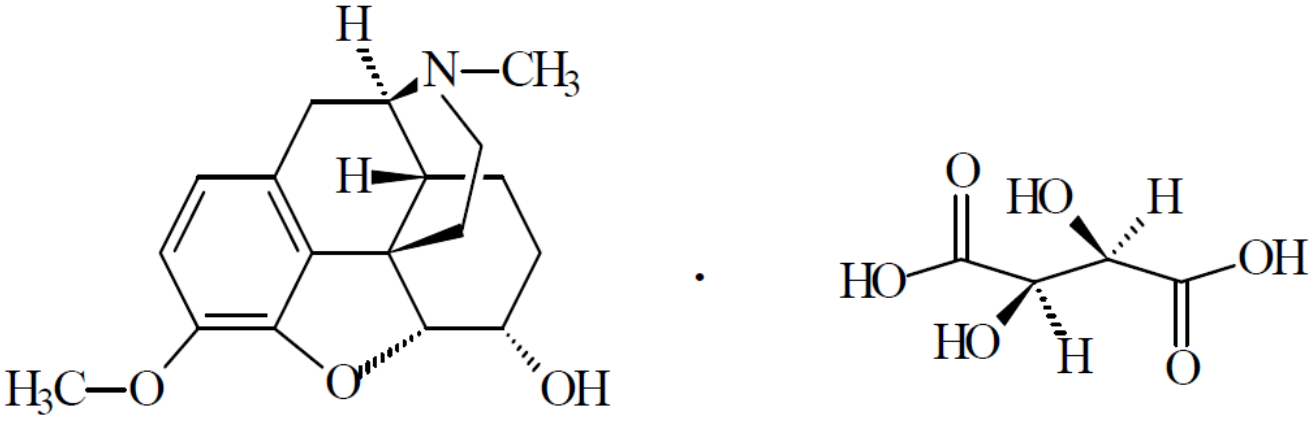
Hemodialysis and peritoneal dialysis can be performed to reduce the body content of aspirin. In patients with renal insufficiency or in cases of life-threatening salicylate intoxication dialysis is usually required. Exchange transfusion may be indicated in infants and young children.

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

11 DESCRIPTION

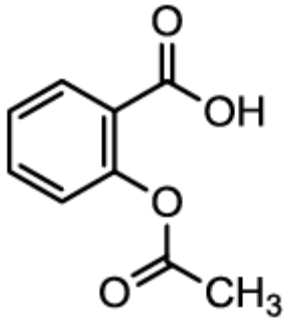
SYNALGOS-DC (aspirin, caffeine, and dihydrocodeine bitartrate) capsules are a three-drug combination of dihydrocodeine, an opioid agonist, aspirin, a nonsteroidal anti-inflammatory drug, and caffeine, a methylxanthine. SYNALGOS-DC capsules are available as, 356.4 mg aspirin, 30 mg caffeine, and 16 mg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



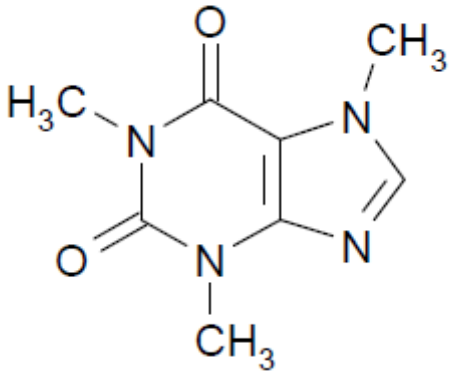
Dihydrocodeine is a fine, white, odorless, crystalline powder that is synthesized from codeine. Dihydrocodeine bitartrate dissolves in water (1 g in 4.5 g) and turns into a clear, colorless solution. It has a dissociation constant of pKa 8.89 at 25°C and pKa 8.67 at 37°C. Dihydrocodeine bitartrate has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

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of

hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6)]*.

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 potent agonist opioids *[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), (2.2), (2.3)]*.

12.3 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 *[see Patient Counseling Information (17)]*.

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 *[see Warnings and Precautions (5.1, 5.3), Drug Abuse and Dependence (9.2)]*. Inform patients that leaving SYNALGOS-DC unsecured can pose a deadly risk to others in the home.

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;
- Delete 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 *[see Warnings and Precautions (5.3)]*. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Ingestion
Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death *[see Warnings and Precautions (5.3)]*.

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 (5.4)]*.

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 (5.7), Drug Interactions (7)]*.

Serotonin Syndrome
Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms

develop. Instruct patients to inform their 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)]*.

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 (5.10)]*.

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 (2.4)]*

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 (5.11)]*.

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)]*.

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 prolonged use of SYNALGOS-DC 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)]*. Avoid use of SYNALGOS-DC and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus *[see Warnings and Precautions (5.21), 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 chronic use of opioids 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 (5.17)]*.

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 (5.16)]*.

Constipation

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

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 (5.13) 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

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 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.
- 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, 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:

- **pregnant or planning to become pregnant.** Prolonged use of SYNALGOS-DC during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated. **You should not take SYNALGOS-DC after 29 weeks of pregnancy as it can cause serious heart conditions in newborns.**
- **breastfeeding.** Not recommended; may harm your baby.
- 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.
- 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.

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. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help 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 doctor 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. Revised: 10/2019