SYNERA (lidocaine and tetracaine) Topical Patch

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SYNERA safely and effectively. See full prescribing information for SYNERA.

SYNERA (lidocaine and tetracaine) topical patch

Indications and Usage
SYNERA is a combination amide and ester local anesthetic indicated for use on intact skin to provide local dermal analgesia for superficial venous access and superficial dermatological procedures such as excision, electrodesiccation and shave biopsy of skin lesions. (1)

Important Limitations:
• For use on intact skin only (1, 2)
• For external use only (5)

Dosage and Administration
SYNERA should only be applied to intact skin. (2)
• Apply SYNERA for 20 to 30 minutes prior to venipuncture or intravenous cannulation, and for 30 minutes prior to superficial dermatological procedures. (2)

Dosage Forms and Strengths
SYNERA topical patch contains 70 mg lidocaine and 70 mg tetracaine and has an entire skin contact area of 50 cm², of which 10 cm² contains lidocaine and tetracaine. (3)

Contraindications
• Patients with a known history of sensitivity to lidocaine, tetracaine, or local anesthetics of the amide or ester type. (4)
• Patients with para-aminobenzoic acid (PABA) hypersensitivity. (4)

Warnings and Precautions
Application of SYNERA for longer duration than recommended or the simultaneous or sequential application of multiple SYNERA patches could result in serious adverse effects. (5.1, 10)

Store and dispose of SYNERA out of the reach of children and pets due to the large amount of lidocaine and tetracaine (at least 90% of the initial amount) present in used patches. (5.2)

Use with caution in patients who may be more sensitive to the systemic effects of lidocaine and tetracaine, including the acutely ill or those with severe hepatic disease or pseudocholinesterase deficiency. (5.7)

Allergic or anaphylactoid reactions associated with lidocaine and tetracaine can occur. (5.6)

Avoid contact with the eyes. (5.3)

Not recommended for use on mucous membranes or on areas with a compromised skin barrier. (5.3)

The SYNERA patch must be removed before a patient undergoes magnetic resonance imaging. (5.4)

Adverse Reactions
The most common adverse reactions (>10%) were localized adverse effects from chewing or ingesting a new or used SYNERA patch. It is important for patients to store and dispose of SYNERA out of the reach of children and pets.

5.3 Avoidance of Exposure to Eyes and Mucous Membranes
5.4 Magnetic Resonance Imaging
5.5 Methemoglobinemia
5.6 Allergic Reactions
5.7 Special Patient Populations

5.8 Vaccinations
Lidocaine has been shown to inhibit viral and bacterial growth. The effect of SYNERA on intradermal injections of live vaccines has not been determined.

6.1 Clinical Studies Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Three different formulations were studied during clinical development of SYNERA: Developmental A (n=138), Developmental B (n=30), and the SYNERA final formulation (n=1281). The developmental patch formulations each contained the same amount of the active drug (70 mg each of lidocaine and tetracaine) as the final patch formulation, but varying amounts of excipients, principally polyvinyl alcohol, methoceloid, nitroprusside, pamaquine, para-aminosalicylic acid, methemoglobin-inducing agents. However, providers are cautioned to carefully apply SYNERA to ensure that the areas of application and duration of application are consistent with those recommended for the intended population.

5.6 Allergic Reactions
Allergic or anaphylactoid reactions associated with lidocaine, tetracaine, or local anesthetics of the amide or ester type can occur. They are characterized by urticaria, angioedema, bronchospasm, and shock. If an allergic reaction occurs, it should be managed by conventional means.

5.7 Special Patient Populations
SYNERA should be used with caution in patients who may be more sensitive to the effects of lidocaine and tetracaine particularly the acutely ill or debilitated.

Patients with severe hepatic disease or pseudocholinesterase deficiency, because of their inability to metabolize local anesthetics normally, are at greater risk for developing toxic plasma concentrations of lidocaine and tetracaine.

5.8 Vaccinations
Lidocaine has been shown to inhibit viral and bacterial growth. The effect of SYNERA on intradermal injections of live vaccines has not been determined.
SYNERA® (lidocaine and tetracaine) Topical Patch

(12%). These reactions were generally mild, resolving spontaneously soon after patch removal. There were no treatment-related serious adverse events.

Other application site reactions of various types (contact dermatitis, rash, skin thickening) occurred in less than 4% of SYNERA-treated patients during clinical trials. Of these adverse events, 75% were mild, resolving spontaneously soon after patch removal.

Application site-related adverse events that occurred in 1% or less of SYNERA-treated subjects included rash, pruritus, pain, contact dermatitis, allergic reaction, blister, paresthesia, urticaria, and vesiculobullous rash.

Allergic Reactions

Allergic or anaphylactoid reactions can occur with the active or inactive components of SYNERA. They may be characterized by urticaria, angioedema, bronchospasm, and shock. Allergic reactions to the patch should be managed by conventional means.

Systemic (Dose-Related) Reactions

Systemic adverse reactions that occurred in 1% or less of SYNERA-treated subjects included dizziness, headache, nausea, somnolence, and vomiting. Systemic adverse effects of lidocaine and tetracaine are similar in nature to those observed with other amide- and ester local anesthetic agents, including CNS excitation and/or depression (light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, blurred vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression). Excitatory CNS reactions may be brief or not occur at all, in which case the first manifestation may be drowsiness merging into unconsciousness. Signs of CNS toxicity may start at plasma concentrations of lidocaine as low as 1000 ng/mL. The plasma concentrations at which tetracaine toxicity may occur are less well characterized; however, systemic toxicity with tetracaine is thought to occur with much lower plasma concentrations compared with lidocaine. The toxicity of co-administered local anesthetics is thought to be at least additive. Cardiovascular manifestations may include bradycardia, hypotension and cardiovascular collapse leading to arrest.

7 Drug Interactions

7.1 Antiarrhythmic Drugs

SYNERA should be used with caution in patients receiving Class I antiarrhythmics such as quinidine (e.g., procainamide and meclofenoxate) since the systemic toxic effects are thought to be additive and potentially synergistic with lidocaine and tetracaine.

7.2 Local Anesthetics

When SYNERA is used concomitantly with other products containing local anesthetics, the amount absorbed from all formulations should be considered since the systemic toxic effects are thought to be additive and potentially synergistic with lidocaine and tetracaine.

8 Use in Specific Populations

8.1 Pregnancy

Pregnancy Category B. Lidocaine was not teratogenic in rats given subcutaneous doses up to 60 mg/kg (360 mg/m²) or 8-fold the Single Dermal Administration (SDA) or in rabbits up to 15 mg/kg (180 mg/m² or 4-fold the SDA). Tetracaine was not teratogenic in rats given subcutaneous doses up to 10 mg/kg (60 mg/m² or 1-fold the SDA) or in rabbits up to 5 mg/kg (60 mg/m² or 1-fold the SDA). In clinical studies of SYNERA components (lidocaine and tetracaine) given as a 1:1 eutectic mixture were not teratogenic in rats (60 mg/m² or 1-fold the SDA) or rabbits (120 mg/m² or 3-fold the SDA).

Lidocaine, contained 1:100,000 epinephrine, at a dose of 6 mg/kg (3.6 mg/m²) (the SDA) injected into the masseter muscle of the jaw or into the gum of the lower jaw of Long-Evans hooded pregnant rats on Gestation Day 11 led to developmental delays in neonatal behavior among offspring. The entire SYNERA patch is approximately 50 cm², 10 cm² of which is active.

Lidocaine is chemically designated as acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl), has an octanol/water partition ratio of 182 at pH 7.3 and has the following structure:

Each SYNERA patch contains lidocaine 70 mg and tetracaine 70 mg in a eutectic mixture. The SYNERA formulation also contains important admixing agents, such as polyvinyl alcohol, sorbitan monopalmitate, water, methylparaben and propylparaben.

The SYNERA heating component generates a mild warming that is intended to enhance the delivery of the local anesthetic. SYNERA is not to be heat removed from the pouch and is exposed to oxygen in the air. Although the patch may increase skin temperature by up to approximately 5°C, maximum skin temperature will not exceed 40°C. The heating component can cause skin irritation, skin burning, activation of any active cutaneous inflammation, and is not recommended for long-term skin contact.

12 Clinical Pharmacology

12.1 Mechanism of Action

SYNERA applied to intact skin provides local dermal analgesia by the release of lidocaine and tetracaine from the patch into the skin. Lidocaine is an amide-type local anesthetic agent and tetracaine is an ester-type local anesthetic agent. The two local anesthetics block sodium ion channels required for the initiation and conduction of neuronal impulses, resulting in local anesthesia.

12.3 Pharmacokinetics

Absorption—Application of one SYNERA patch for 30 minutes in adults produced peak plasma concentrations of lidocaine less than 5 ng/mL, while plasma levels of tetracaine were below the limit of quantitation (<0.9 ng/mL) in all subjects tested (n = 12, see Table 1). SYNERA application up to 60 minutes did not significantly increase plasma levels of lidocaine or tetracaine compared to a 30-minute application.

Table 1

<table>
<thead>
<tr>
<th>Number of SYNERA Patches</th>
<th>Age Range (yr)</th>
<th>Application Time (min)</th>
<th>Drug Content (mg)</th>
<th>Estimated Amount Absorbed (mg)</th>
<th>Lidocaine, %</th>
<th>Tetracaine, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18 - 65</td>
<td>30</td>
<td>20</td>
<td>1.7</td>
<td>&lt;0.9</td>
<td>&lt;0.9</td>
</tr>
</tbody>
</table>

Table 1. Absorption of Lidocaine and Tetracaine from SYNERA in Normal Adult Volunteers (n = 12)

 Application of SYNERA to broken or inflamed skin or more than four simultaneous or sequentially applied SYNERA patches could result in higher plasma levels of local anesthetic that carries the risk of systemic toxicity.

Simultaneous or sequential application of multiple SYNERA patches is not recommended. However, plasma levels of lidocaine and tetracaine have been determined in clinical pharmacology studies following multiple successive and simultaneous applications of SYNERA patches on intact skin. Maximum plasma levels of lidocaine after the application of a) four successive SYNERA patches for 30 minutes each with a 30-minute interval between each patch application, and b) three SYNERA patches for 6 minutes each with a 60-minute interval between each application were <12 ng/mL and 8 ng/mL, respectively. Tetracaine was not detected in plasma following either treatment. Simultaneous application of two or four SYNERA patches for 60 minutes produced peak plasma concentrations of lidocaine of less than 9 ng/mL, while tetracaine plasma concentrations were not detectable in all subjects (n=22). Sequential 30-minute applications of four SYNERA patches at 60-minute intervals...
Impairment of Fertility—Lidocaine did not affect fertility in female rats when given via continuous subcutaneous infusion via osmotic minipumps in doses of 250 mg/kg/day (1500 mg/m² or 43-fold higher than the SDA). Although lidocaine treatment of male rats increased the copulatory index and lead to a dose-related decreased homogonization resistant sperm head count, daily sperm production, and spermagomeric efficiency, the treatment did not affect overall fertility of rats when given subcutaneous doses up to 60 mg/kg (360 mg/m² or 8-fold the SDA). Tetracaine did not affect fertility in male or female rats when given subcutaneous doses up to 7.5 mg/kg (45 mg/m² or 1-fold the SDA). Multiples of exposure were based on an SDA of 70 mg each of lidocaine and tetracaine in SYNERA patch for 30 minutes to a 60 kg person (43 mg/m²).

14 Clinical Studies

14.1 Superficial Venous Access

Three randomized, double-blind placebo controlled clinical trials in adult and geriatric subjects evaluated the degree of dermal analgesia upon venipuncture following a 20-minute treatment with SYNERA or a placebo patch (patch with heating component but no drug). In each trial, subjects received SYNERA on one arm and placebo patch on the other. In all three studies pain was measured by a 100-mm VAS in which a lower VAS score corresponds to less pain. In the first study in 21 subjects, median VAS scores for SYNERA and placebo treatments were 1 mm and 9 mm, respectively. In the second study in 40 subjects, median VAS scores were 5 mm and 28 mm for SYNERA and placebo treatments, respectively. In the third study, in 40 subjects over the age of 65 median VAS scores were 5 mm and 28 mm for SYNERA and placebo treatments were 8 mm and 14 mm, respectively. In a randomized, double-blind, placebo controlled study, 61 pediatric patients received either SYNERA or placebo for 20 minutes prior to venipuncture or IV cannulation in the antecubital fossa or dorsum of the hand. Subjects were stratified by age group (2 to 3 years and 4 to 12 years). Children in the younger group reported less pain on IV cannulation with SYNERA than with placebo, as rated using a six-point Oucher pain scale with faces. Children in the older group rated their pain using an eleven-point Oucher pain scale that contained both faces and numbers. Pain scores on IV cannulation in the older group for SYNERA were not significantly different from pain scores in those treated with placebo.

In a double-blind trial in 250 adults, subjects were randomized to receive either SYNERA without heating element or SYNERA with heating element, prior to venipuncture. Median VAS scores for the patch with the heating element and without the heating element were 17 mm and 22 mm, respectively.

14.2 Superficial Dermatological Procedures

In one randomized, double-blind, placebo controlled study, 24 subjects received a single 20 minute SYNERA treatment. A single SYNERA patch for 30 minutes prior to a superficial dermatological procedure such as superficial excision, shave biopsy or electrodessication were removed. Median VAS scores were 5 mm and 28 mm for SYNERA and placebo treatments were 5 mm and 31 mm, respectively. In a similarly designed study in 74 subjects over the age of 65 median VAS scores were 5 mm and 28 mm for SYNERA treatment compared to placebo with median VAS scores for SYNERA and placebo treatments were 10 mm and 23 mm, respectively.

In a randomized, double-blind, placebo controlled study, 88 pediatric patients were stratified by age group (3 to 6 years and 7 to 17 years) to receive a 30-minute application of either SYNERA or placebo patch, prior to lidocaine injection. In younger children who used the Oucher pain scale with faces, those receiving SYNERA reported less pain from lidocaine injection than those receiving placebo. Older children used the numerical Oucher pain scale to report pain intensity. There was no difference between treatments observed in the older children.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 HOW SUPPLIED

SYNERA is available as the following:

NDC 10885-002-01 One individually packaged SYNERA patch
NDC 10885-002-10 Box of 10 individually packaged SYNERA patches

16.2 Storage and Handling

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

Keep out of reach of children and pets.

Apply SYNERA immediately upon removal from the protective pouch.

Do not cut the patch or otherwise remove the top cover so that this could cause the patch to heat to temperatures that could cause thermal injury. Do not cover the holes on the top side of the patch as this could cause the patch not to heat.

Hands should be washed after handling SYNERA, and eye contact should be avoided immediately. The used patch should be disposed of immediately. The adhesive sides of the patch should be folded together and the patch should then be thrown away in a location that is out of the reach of children and pets.

17 Patient Counseling Information

• Advise patients to read the FDA-approved patient labeling (Instructions for Use).
• Advise patients that SYNERA is a patch containing two medicaments (lidocaine and tetracaine) that are known as local anesthetics, and a heating component. These medicines are used to lessen the pain associated with superficial venous access and superficial dermatological procedures such as excision, electrodessication and shave biopsy of skin lesions.
• Advise patients that SYNERA should be applied immediately after opening the pouch. Instruct patients not to cut or remove the top cover of the patch as this could result in thermal injury.
• Advise patients that keeping a patch on longer than recommended or applying multiple patches simultaneously or sequentially could result in systemic absorption sufficient to result in serious adverse effects that are typical of drugs in this class.
• Advise patients that the patch must be removed before undergoing other local anesthesia, or any other component of the product and in patients with para-aminobenzoic acid (PABA) hypersensitivity.
• Advise patients that SYNERA should be used with caution in patients who may be more sensitive to the systemic effects of lidocaine and tetracaine, including the acute ill, the debilitated, and those with compromised hepatic function. Patients with severe hepatic disease or pseudocholinesterase deficiency are at greater risk of developing toxic plasma concentrations.
• Advise patients that SYNERA should be used with caution in patients receiving class I antiarrhythmics and/or other local anesthetics, because the systemic toxic effects may be additive and potentially synergistic with lidocaine and tetracaine.
• Advise patients not to use SYNERA if they have a history of methemoglobinemia.
• Advise patients to avoid contact of SYNERA with the eyes due to potential irritation or abrasion. If contact occurs, immediately wash the eye with water or saline, and protect it until sensation returns.
• Advise patients that SYNERA should only be applied to intact skin. Inform patients that exposure of the skin to SYNERA may result in erythema, blanching and edema; these reactions are generally mild, resolving spontaneously shortly after removal of the product.
• Advise patients that SYNERA is not for use on mucous membranes or on areas with broken skin.
• Advise patients not to use SYNERA if the skin sensation or a burning sensation occurs during application, the product should be removed.
• Inform patients of the signs of an allergic or anaphylactoid reaction (urticaria, angioedema, bronchospasm, and shock). Instruct patients to seek immediate emergency help if these occur.
• Advise patients that SYNERA may lead to diminished or blocked sensation in the treated skin; therefore, patients should avoid inadvertent trauma (rubbing, scratching, or allowing skin to heat or cool) before complete sensation returns.
• Advise patients to contact their healthcare professional if they do not recognize the signs of an allergic or anaphylactoid reaction or if their skin irritation does not resolve.
• Instruct patients to store SYNERA and to discard used patches out of the reach of children and pets.
• The effect of SYNERA on intradermal injections of live vaccines has not been determined.
INSTRUCTIONS FOR USE

Leave the patch in the foil pouch until you read this leaflet

STEP 1: Check the skin where the patch will be worn
• Keep the patch in the unopened foil pouch until you are ready to put it on.
• Check the skin where your doctor or health care professional told you to wear it.
• Do not put the patch on skin that is cut, scratched or red (like a rash).
• Do not shave the area or you may hurt the skin.

STEP 2: Open the foil pouch and remove the patch. Save the foil pouch.
• TO TEAR OPEN THE FOIL POUCH - fold the upper right corner toward you. (See picture A)
  • Press the corner flat to form a small triangle.
  • Tear the foil pouch in the middle of the fold along the pre-cut slit. (See picture B)
• TO CUT OPEN WITH SCISSORS - cut carefully along the edge of the package.
  • SAVE THE FOIL POUCH.

STEP 3: Put the patch on your skin
• DO NOT TOUCH THE MEDICINE IN THE MIDDLE - touch only the sticky edges of the patch. Never touch the center area.
• Peel the patch off of the hard plastic backing.
• Put the sticky side of the patch on your skin, where you were told to wear it. Press the edges to make sure the patch will stick to your skin.
• Wash your hands.

STEP 4: IMPORTANT — How to remove and discard the patch
• Do not leave the patch on the skin for longer than 30 minutes.
• Carefully peel the patch off your skin, touching only the sticky edges of the patch - DO NOT TOUCH THE MEDICINE IN THE MIDDLE.
• PRESS THE STICKY SIDE OF THE USED PATCH ONTO THE FOIL POUCH.
• THROW FOIL POUCH WITH PATCH ATTACHED, AND HARD PLASTIC BACKING, IN THE GARBAGE so children and pets cannot reach it.
• Wash your hands.

While wearing the patch:
• Do not put the patch on your lips or near your eyes.
  If you get medicine from the patch in your eye, rinse your eye with water and protect it until the numbness goes away.
• Do not cut or tear the patch.
• Do not get water on the patch.
• Do not get water on the patch. Keep the patch dry. Do not cover the small holes on the outside of the patch.
• If you applied the patch to the back of your hand, wash your hands carefully.
• If your skin hurts or burns too much, you should take the patch off.
  It is normal for the skin to feel warm, but it should not burn.

After the patch is removed:
Be careful with your skin after the patch is removed. The skin that was covered by the patch stays numb and you won’t be able to feel pain right away. Do not scratch or let this skin touch hot or cold things.

WHAT THE PATCH DOES:
The medicine on this patch is used to numb the skin that it covers. The safety and effectiveness of Synera® have been established in adults and children 3 years of age and older.

FOLLOW THE INSTRUCTIONS BELOW, AND THESE SAFETY TIPS:
• Do not put the patch on your lips or near your eyes. If you get medicine from the patch in your eye, rinse your eye with water and protect it until the numbness goes away.
• Do not cut or tear the patch.
• Do not get water on the patch.
• Keep the patch away from children and pets at all times.