

Approval Date: OCT 28 2004

FREEDOM OF INFORMATION SUMMARY
SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION
NADA 009-576

SYNOVEX C and SYNOVEX S
(Progesterone and Estradiol Benzoate)

This supplement provides for addition to the labeling of the statements “A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.” to the warning section and “Do not use in veal calves. Effectiveness and animal safety in veal calves have not been established.” immediately following the indications.

Sponsored by:

Fort Dodge Animal Health
Division of Wyeth
800 Fifth St. NW.
Fort Dodge, IA 50501

FREEDOM OF INFORMATION SUMMARY

SYNOVEX C Ear Implant for Suckling Beef Calves and SYNOVEX S Ear Implant for Steers Fed in Confinement for Slaughter

1. GENERAL INFORMATION:

- a. File Number: NADA 009-576
- b. Sponsor: Fort Dodge Animal Health
Division of Wyeth
800 Fifth St. NW.
Fort Dodge, IA 50501
Drug Labeler Code: 000856
- c. Established Names: Progesterone and Estradiol Benzoate
- d. Proprietary Names: SYNOVEX C and SYNOVEX S
- e. Dosage Form: Implantation (ear implant) as per 21 CFR 522.1940
- f. How Supplied: SYNOVEX C: Each box contains 2 or 10 foil pouches each containing 1 cartridge belt with 10 doses. Each implant dose consists of 4 pellets containing 100 mg progesterone and 10 mg estradiol benzoate.
- SYNOVEX S: Each box contains 10 foil pouches each containing 1 cartridge belt with 10 doses. Each implant dose consists of 8 pellets containing 200 mg progesterone and 20 mg estradiol benzoate.
- g. How Dispensed: OTC
- h. Amount of Active Ingredients: SYNOVEX C:
100 mg progesterone.
10 mg estradiol benzoate.
- SYNOVEX S:
200 mg progesterone.
20 mg estradiol benzoate.
- i. Route of Administration: Subcutaneous implantation on the posterior aspect of the middle one-third of the ear by means of an implant gun.

- j. Species/Class: Suckling beef calves and steers fed in confinement for slaughter
- k. Recommended Dosage: SYNOVEX C: One implant containing 100 mg progesterone and 10 mg estradiol benzoate.
SYNOVEX S: One implant containing 200 mg progesterone and 20 mg estradiol benzoate. May be re-implanted at approximately 70 days.
- l. Pharmacological Category: Steroid hormones
- m. Indications: SYNOVEX C: For increased rate of weight gain SYNOVEX C is recommended for use in suckling beef calves (at least 45 days of age) up to approximately 400 pounds of body weight. SYNOVEX C is also recommended for improvement in rate of weight gain in steers weighing greater than 400 pounds and fed in confinement for slaughter when used as part of a re-implant program in which an initial SYNOVEX C implant is followed at approximately 70 days by SYNOVEX S.
SYNOVEX S: For increased rate of weight gain and improved feed efficiency in steers weighing 400 pounds or more. For additional improvement in rate of weight gain in steers fed in confinement for slaughter, SYNOVEX S may be used as part of a re-implant program where an initial SYNOVEX C or SYNOVEX S implant is followed by SYNOVEX S at approximately 70 days.
- n. Effect of Supplement: This supplement provides for addition to the labeling of the statements "A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal." to the warning section and "Do not use in veal calves. Effectiveness and animal safety in veal calves have not been established." immediately following the label indications.

2. DRUG EFFECTIVENESS:

No new effectiveness data are required for the approval of this supplement. The products' effectiveness has been established in the Freedom of Information (FOI) Summaries for the parent new animal drug applications for SYNOVEX C and SYNOVEX S (NADA 009576).

3. TARGET ANIMAL SAFETY:

No new target animal safety data are required for the approval of this supplement. The products' target animal safety has been established in the Freedom of Information (FOI) Summaries for the parent new animal drug applications for SYNOVEX C and SYNOVEX S (NADA 009576).

4. HUMAN SAFETY:

No new human food safety data are required for the approval of this supplement. The products' human food safety has been established in the Freedom of Information (FOI) Summaries for the parent new animal drug applications for SYNOVEX C and SYNOVEX S (NADA 009576).

5. AGENCY CONCLUSIONS:

The information submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations providing for the addition to the labeling of the statements "A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal." to the warning section and "Do not use in veal calves. Effectiveness and animal safety in veal calves have not been established." immediately following the indications. The labeling is modified to conform to agency policy (69 FR 135 pages 42443-42444 dated July 15, 2004, and 69 FR 68 page 18594 dated April 8, 2004.)

The Center for Veterinary Medicine has concluded that, for these products, adequate directions for use by the layperson have been provided and the product will have over-the-counter (OTC) status. Label directions are accompanied by pictorial diagrams and detailed instruction in plain language. The drugs are not controlled substances. The products' status remains OTC. The labeling is adequate for the intended use and has sufficient warnings/statements to prevent illegal use in veal calves.

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act.

Under the Center's supplemental approval policy (21 CFR 514.106(b)(2)), this is a Category II change. The approval of this change is not expected to have any adverse effect on the

safety or effectiveness of this new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

No patent information was submitted with this application.

6. ATTACHMENTS:

Facsimile Labeling is attached as indicated below:

SYNOVEX C 20 Dose Carton Label
SYNOVEX C 20 Dose Package Insert (Front and Back)
SYNOVEX C 100 Dose Carton Label
SYNOVEX C 100 Dose Package Insert (Front and Back)
SYNOVEX S Carton Label
SYNOVEX S Package Insert (Front and Back)

HOW TO IMPLANT WITH SYNOVEX[®] PELLETS

Study the following instructions carefully, then proceed step by step until the technique becomes routine. Many hands can be implanted per hour by an experienced team, one member of which should be assigned to do nothing but the implantation. This person should maintain hand cleanliness and use sanitary instruments only.

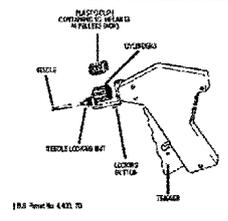
SYNOVEX[®] C Implant

Synovex C is recommended for use in making feed rations for a specific animal. All lots of heavy weight Synovex C is also recommended for application to lots of animals with the same feeding schedule. All lots of heavy weight Synovex C is also recommended for application to lots of animals with the same feeding schedule. All lots of heavy weight Synovex C is also recommended for application to lots of animals with the same feeding schedule.

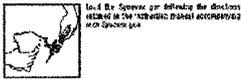
WARNING
Do not, under any conditions, use Synovex C in any feed ration unless it is specifically recommended for that purpose. Do not use Synovex C in any feed ration unless it is specifically recommended for that purpose.

CAUTION
Do not use Synovex C in any feed ration unless it is specifically recommended for that purpose. Do not use Synovex C in any feed ration unless it is specifically recommended for that purpose.

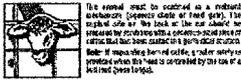
SYNOVEX[®] Tube



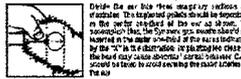
STEP 1 Loading the SYNOVEX Tube



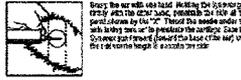
STEP 2 Assembling



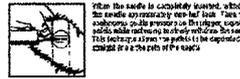
STEP 3 Positioning Site



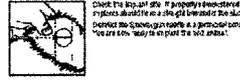
STEP 4 Insert Needle



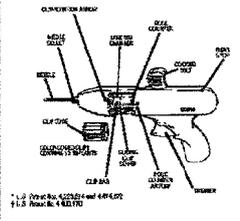
STEP 5 Pellet Implantation



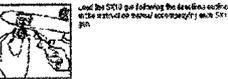
STEP 6 Inspection



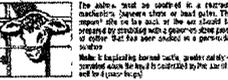
SYNOVEX[®] 5X10³ Unit



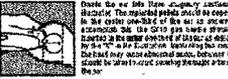
STEP 1 Loading the SYNOVEX Tube



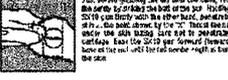
STEP 2 Assembling



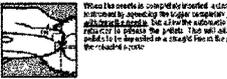
STEP 3 Positioning Site



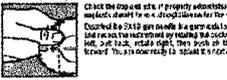
STEP 4 Insert Needle



STEP 5 Pellet Implantation



STEP 6 Inspection



HOW SUPPLIED

100-0000-00-00-00-00
100-0000-00-00-00-00

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Fort Dodge Animal Health
Fort Dodge, Iowa 50501 USA

SYNOVEX C

FOR INCREASED RATE OF WEIGHT GAIN

Each dosage contains 4 pellets containing 100 mg progesterone and 10 mg estradiol benzoate per implantation. This product may be administered by intramuscular injection.

Do Not Use in Veal Calves, Pigs, or Horses and For Animals Under One Year of Age.

BACK
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FORT DODGE

FORT DODGE ANIMAL HEALTH

Revision .7
Operator Ish
Date 08Sep04
Product ID# 6034C
Revision # 889
Product Name Synovex C
Type/Size - Boxset Carton/Insert
FDA# Template 815
Template Dimensions
Carton 3-5/16 x 1-1/8 x 5-7/16
Insert (Inch) 1-7/8 x 1-1/4
Insert (Folded) 2-7/8 x 1-1/4
File Path V:\P\ 6034C\034C
To Disk
Rev Level

ALL ELECTRONIC artwork is the PROPERTY OF AND MUST BE RETURNED TO FORT DODGE ANIMAL HEALTH.

PMS 292



NET CONTENTS: 10 CARTRIDGES (100 DOSES)
Each Cartridge Contains 10 Doses of 1 Dose



Do Not Use in Your Country
Not For Use in Humans
For Animal Use Only
Do Not Use in Your Country
Not For Use in Humans
For Animal Use Only
Do Not Use in Your Country
Not For Use in Humans
For Animal Use Only

SYNOVEX C

Lot:
Exp. Date:



SYNOVEX C

CALF IMPLANTS
For increased rate of weight gain
Each syringe consists of 4 pellets containing 100 mg progesterone and 10 mg estradiol benzoate per implantation. The product was manufactured by a hot-sterilizing process.
NEC 1993-1-202-1310

NET CONTENTS: 10 CARTRIDGES (100 DOSES)
Each Cartridge Contains 10 Doses of 1 Dose

WARNING: Not for use in humans. For animal use only. Inject only in the ear vein. All other locations are prohibited. Do not allow leakage of injected solution or contact of a well-ventilated area has not been established for the product. Do not use unless the label is to be processed for use.
HAZARDOUS: Keep out of reach of children.
CAUTION: Blind, fever and vaccine reactions, uterine development, ventral edema and prostatic hypertrophy have been reported in calves administered with Synovex C implants.

NET CONTENTS: 10 CARTRIDGES (100 DOSES)
Each Cartridge Contains 10 Doses of 1 Dose



Do Not Use in Your Country
Not For Use in Humans
For Animal Use Only
Do Not Use in Your Country
Not For Use in Humans
For Animal Use Only
Do Not Use in Your Country
Not For Use in Humans
For Animal Use Only

SYNOVEX C

SYNOVEX C
Do Not Use in Your Country
Not For Use in Humans
For Animal Use Only

HOW TO IMPLANT WITH SYNOVEX[®] PELLETS

Study the following instructions carefully, then proceed step by step, until the technique becomes routine. Many head can be implanted per hour by an experienced team one member of which should be assigned to do nothing but the implantation. This person should maintain hand cleanliness and use sanitary instruments only.

HOW SUPPLIED

NDC 0856-3903-02 - 20 Dose
NDC 0856-3903-43 - 100 Dose

SYNOVEX[®] C Implants

Synovex C is recommended for use in castrating beef calves up to approximately 400 lbs. of body weight. Synovex C is also recommended for improvement in rate of weight gain in steers weighing greater than 400 pounds and fed in confinement for slaughter, when used as part of a re-implant program in which an initial Synovex C implant is followed at approximately 70 days by Synovex S. Control use in veal calves. Effectiveness and animal safety in veal calves have not been established. Do not use in bull calves intended for reproduction, or in calves less than 45 days old. Store at our rolled room temperature (15° to 30°C (59° to 85°F)). Avoid excessive heat or humid by.

WARNING

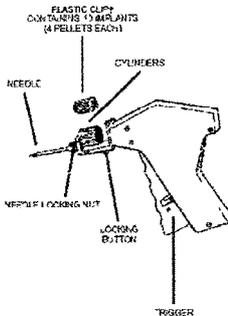
Not to use in humans. For animals, use only inside the pelvis in the ear only. Any other location is in violation of federal law. Do not attempt salvage of implanted site for human or animal use.

After the seal cannot has not been established for the product in pre-sterilizing solution. Do not use in calves to be processed for veal.

CAUTION

Bulling, rotal and vaginal ordises, udder development, ventral edema and elevated fat pads may be reduced in calves administered Synovex C in pre-sterilizing solution. Keep live and drugs out of the reach of children. Restricted Drug (California)—Use Only as Directed.

SYNOVEX[®] Gun



U.S. Patent No. 4,400,170

STEP 1 Loading The SYNOVEX Gun



Load the Synovex gun following the directions outlined in the instruction manual accompanying each Synovex gun.

STEP 2 Restraint



The animal must be confined in a restraint mechanism (squeeze chute or head gate). The implant site on the back of the ear should be prepared by scrubbing with a generous piece of cotton that has been soaked in a germicidal solution.

Note: If implanting horned cattle, greater safety is provided when the head is controlled by the use of a bull lead (nose tongs).

STEP 3 Implant Site



Divide the ear into three imaginary sections as illustrated. The implanted pellets should be deposited in the center one-third of the ear as shown. To accomplish this, the Synovex gun needle should be inserted in the outer one-third of the ear as indicated by the "X" in the illustration. Implanting too close to the head may cause abnormal sexual behavior. Care should be taken to avoid severing the major arteries of the ear.

STEP 4 Insert Needle



Grasp the ear with one hand. Holding the Synovex gun firmly with the other hand, penetrate the skin at the point shown by the "X". Thrust the needle under the skin taking care not to penetrate the cartilage. Ease the Synovex gun forward (toward the base of the ear) until the full needle length is beneath the skin.

STEP 5 Pellet Implantation



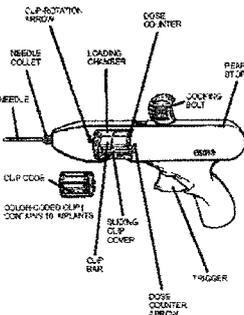
When the needle is completely inserted, withdraw the needle approximately one-half inch. Then with continuous gentle pressure on the trigger, expel the pellets while continuing to slowly withdraw the needle. This technique allows the pellets to be deposited in a straight line in the path of the needle.

STEP 6 Inspection



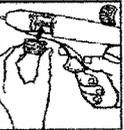
Check the implant site. If properly administered, the implants should lie in a straight line under the skin. Disinfect the Synovex gun needle in a germicidal solution. You are now ready to implant the next animal.

SYNOVEX[®] SX10[™] Gun



* U.S. Patent Nos. 4,371,676 and 4,474,577
† U.S. Patent No. 4,496,170

STEP 1 Loading the SX10 Gun



Load the SX10 gun following the directions outlined in the instruction manual accompanying each SX10 gun.

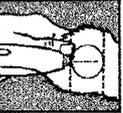
STEP 2 Restraint



The animal must be confined in a restraint mechanism (squeeze chute or head gate). The implant site on the back of the ear should be prepared by scrubbing with a generous piece of cotton that has been soaked in a germicidal solution.

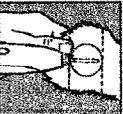
Note: If implanting horned cattle, greater safety is provided when the head is controlled by the use of a bull lead (nose tongs).

STEP 3 Implant Site



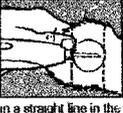
Divide the ear into three imaginary sections as illustrated. The implanted pellets should be deposited in the center one-third of the ear as shown. To accomplish this, the SX10 gun needle should be inserted in the outer one-third of the ear as indicated by the "X" in the illustration. Implanting too close to the head may cause abnormal sexual behavior. Care should be taken to avoid severing the major arteries of the ear.

STEP 4 Insert Needle



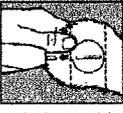
Just before grasping the ear with one hand, release the safety by striking the butt of the gun. Holding the SX10 gun firmly with the other hand, penetrate the skin at the point shown by the "X". Thrust the needle under the skin taking care not to penetrate the cartilage. Ease the SX10 gun forward (toward the base of the ear) until the full needle length is beneath the skin.

STEP 5 Pellet Implantation



When the needle is completely inserted, advance the instrument by squeezing the trigger completely. Do not withdraw the needle, but allow the automatic needle retractor to release the pellets. This will allow the pellets to be deposited in a straight line in the path of the retracted needle.

STEP 6 Inspection



Check the implant site. If properly administered, the implants should lie in a straight line under the skin. Disinfect the SX10 gun needle in a germicidal solution and cock the instrument by rotating the cocking grip left. You are now ready to implant the next animal.

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Fort Dodge Animal Health
Fort Dodge, Iowa 50501 USA

NADA 9-576 Approved by FDA



CALF IMPLANTS

For Increased Rate of Weight Gain

Each dosage consists of 4 pellets containing 100 mg progesterone and 10 mg estradiol benzoate per implantation. This product was manufactured by a non-sterilizing process.

Do Not Use In Veal Calves
Not For Use In Humans
For Animal Use Only

SYNOVEX[®] C

BACK
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HOW TO IMPLANT WITH SYNOVEX[®] PELLETS

Study the following instructions carefully, then proceed step by step, until the technique becomes routine. Many heads can be implanted per hour by an experienced team, one member of which should be assigned to do nothing but the implantation. This person should maintain hand cleanliness and use sanitary instruments only.

HOW SUPPLIED

NDC 0856-3902-40 - 100 Dose

- 2 -

SYNOVEX[®] S Implants

Synovex S is recommended for use in steers weighing 400 lbs or more. When properly administered, Synovex S implants increase rate of weight gain and improve feed efficiency. Do not use in veal calves. Effectiveness and animal safety in veal calves have not been established. Store at uncontrolled room temperature 15° to 30°C (59° to 86°F). Avoid excessive heat or humidity.

WARNING

Not for use in humans. For animal use only. Implant pellets in the ear only. Any other location is in violation of federal law. Do not attempt salvaging of implanted site for human or animal food.

A withdrawal period has not been established for this product in pro-ruminating calves. Do not use in calves to be processed for veal.

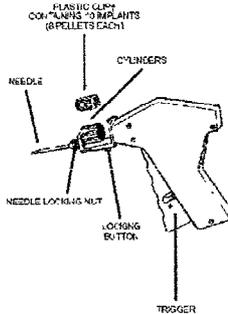
CAUTION

Butting, rectal prolapse, ventral edema and elevated tailheads have been occasionally reported in steers administered with Synovex S implants.

Keep this and all drugs out of the reach of children. Restricted Drug (California)—Use Only as Directed.

- 3 -

SYNOVEX[®] Gun



U.S. Patent No. 4,400,170

- 4 -

STEP 1 Loading The SYNOVEX Gun



Load the Synovex gun following the directions outlined in the instruction manual accompanying each Synovex gun.

STEP 2 Restraint



The animal must be confined in a restraint mechanism (squeeze chute or head gate). The implant site on the back of the ear should be prepared by scrubbing with a generous-sized piece of cotton that has been soaked in a germicidal solution.

Note: If implanting horned cattle, greater safety is provided when the head is controlled by the use of a bull lead (nose tongs).

- 5 -

STEP 3 Implant Site



Divide the ear into three imaginary sections as illustrated. The implanted pellets should be deposited in the center one-third of the ear as shown. To accomplish this, the Synovex gun needle should be inserted in the outer one-third of the ear as indicated by the "X" in the illustration. Implanting too close to the head may cause abnormal sexual behavior. Care should be taken to avoid severing the major arteries of the ear.

STEP 4 Insert Needle



Grasp the ear with one hand. Holding the Synovex gun firmly with the other hand, penetrate the skin at the point shown by the "X". Thrust the needle under the skin taking care not to penetrate the cartilage. Ease the Synovex gun forward (toward the base of the ear) until the full needle length is beneath the skin.

- 6 -

STEP 5 Pellet Implantation



When the needle is completely inserted, withdraw the needle approximately one-half inch. Then with continuous gentle pressure on the trigger, expel the pellets while continuing to slowly withdraw the needle. This technique allows the pellets to be deposited in a straight line in the path of the needle.

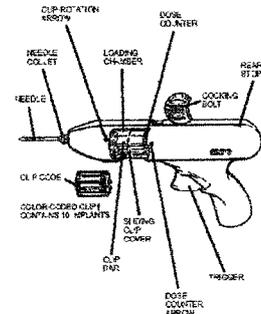
STEP 6 Inspection



Check the implant site. If properly administered, the implants should lie in a straight line under the skin. Disinfect the Synovex gun needle in a germicidal solution. You are now ready to implant the next animal.

- 7 -

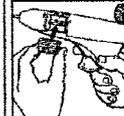
SYNOVEX[®] SX10 Gun



* U.S. Patent Nos. 4,227,274 and 4,474,572
U.S. Patent No. 4,694,170

- 8 -

STEP 1 Loading the SX10 Gun



Load the SX10 gun following the directions outlined in the instruction manual accompanying each SX10 gun.

STEP 2 Restraint

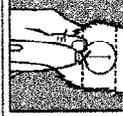


The animal must be confined in a restraint mechanism (squeeze chute or head gate). The implant site on the back of the ear should be prepared by scrubbing with a generous-sized piece of cotton that has been soaked in a germicidal solution.

Note: If implanting horned cattle, greater safety is provided when the head is controlled by the use of a bull lead (nose tongs).

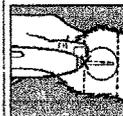
- 9 -

STEP 3 Implant Site



Divide the ear into three imaginary sections as illustrated. The implanted pellets should be deposited in the center one-third of the ear as shown. To accomplish this, the SX10 gun needle should be inserted in the outer one-third of the ear as indicated by the "X" in the illustration. Implanting too close to the head may cause abnormal sexual behavior. Care should be taken to avoid severing the major arteries of the ear.

STEP 4 Insert Needle



Just before grasping the ear with one hand, release the safety by shaking the butt of the gun. Holding the SX10 gun firmly with the other hand, penetrate the skin at the point shown by the "X". Thrust the needle under the skin taking care not to penetrate the cartilage. Ease the SX10 gun forward (toward the base of the ear) until the full needle length is beneath the skin.

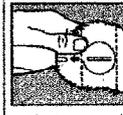
- 10 -

STEP 5 Pellet Implantation



When the needle is completely inserted, activate the instrument by squeezing the trigger completely. Do not withdraw the needle, but allow the automatic needle retractor to release the pellets. This will allow the pellets to be deposited in a straight line in the path of the retracted needle.

STEP 6 Inspection



Check the implant site. If properly administered the implants should lie in a straight line under the skin.

Disinfect the SX10 gun needle in a germicidal solution and cock the instrument by rotating the cocking gun left, pull back, rotate right, then push all the way forward. You are now ready to implant the next animal.

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Fort Dodge Animal Health
Fort Dodge, Iowa 50501 USA

62474

- 11 -

6062F

NADA 2-576 Approved by FDA



STEER IMPLANTS

For Increased Rate of Weight Gain and Improved Feed Efficiency

For additional improvement in rate of weight gain in steers fed in confinement for slaughter, reimplant at approximately 70 days.

NOTE: Studies have demonstrated that reimplantation of Synovex S can decrease marbling scores when compared to non-implanted controls.

Each dosage consists of 6 pellets containing 200 mg progesterone and 50 mg estradiol benzoate per implantation. This product was manufactured by a non-member of the company.

Do Not Use in Veal Calves
Not for Use in Humans
For Animal Use Only

SYNOVEX[®] S

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