

A. Package insert

HOW SUPPLIED

Serostim can be administered using (1) a standard sterile, disposable syringe and needle, (2) the Serojet™ needle-free growth hormone delivery device or (3) the one.click autoinjector pen with the click.easy reconstitution device. For proper use, refer to the Instructions for Use provided with either the Serojet™ needle-free device or the one.click™ autoinjector pen/click.easy™ reconstitution device.

B. Click.easy Reconstitution Device Instructions for Use (for Serostim and Saizen)

click.easy® Reconstitution Device

Serostim® [somatotropin (rDNA origin) for injection] 8mg click.easy®

INSTRUCTIONS FOR USE

FOR COMPLETE DOSING AND SAFETY INFORMATION, PLEASE REFER TO THE SEROSTIM® [SOMATROPIN (RDNA ORIGIN) FOR INJECTION] PACKAGE INSERT.

COMPOSITION

Each vial of Serostim® 8 mg click.easy® contains the following ingredients:

- Active substance: Somatotropin (Recombinant Human Growth Hormone) 8mg.
- Excipients: Sucrose, Phosphoric acid, Sodium Hydroxide 1 ml of the reconstituted solution for injection contains 5.83 mg of somatotropin when reconstituted with the contents of the bacteriostatic solvent cartridge.

PHARMACEUTICAL FORM

Powder and solvent for solution for injection: Powder and bacteriostatic solvent (0.3% (w/v) metacresol in water for injections) for parenteral use.

METHOD AND ROUTE OF ADMINISTRATION

The product (powder in vials) must be reconstituted with the enclosed bacteriostatic solvent (0.3% (w/v) metacresol in water for injections) using the click.easy® reconstitution device.

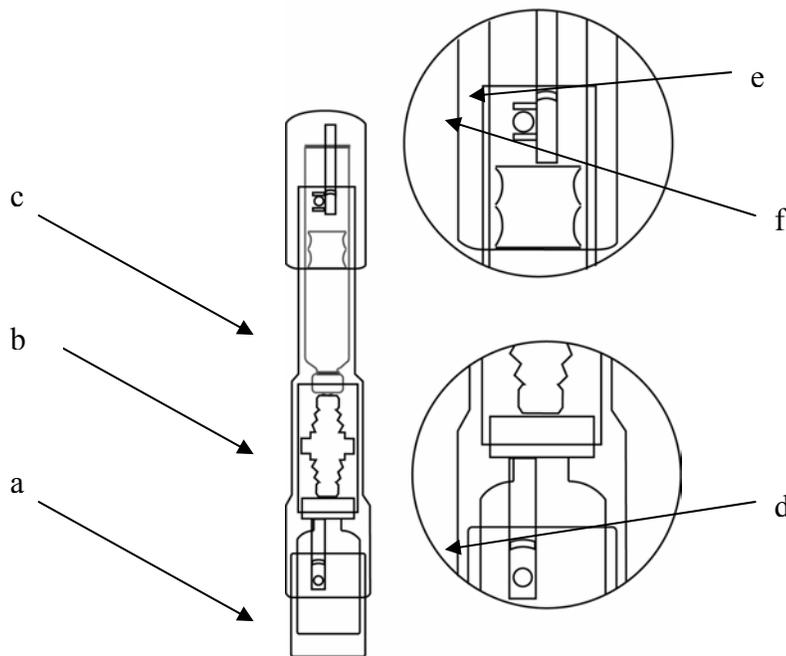
The reconstituted solution is intended for subcutaneous administration (under the skin) and should be clear with no particles. If the solution contains particles, it must not be injected. The reconstituted solution contains 8 mg of Serostim® [5.83 mg/ml].

IMPORTANT INFORMATION

Patients should be thoroughly instructed in the reconstitution procedure.

For young children, the reconstitution process should be supervised by an adult.

For administration of Serostim[®] 8 mg click.easy[®] please read the following instruction carefully. Please consult your doctor or nurse or pharmacist if you have any questions concerning the reconstitution process.



- Make sure the click.easy[®] reconstitution device is complete by checking that the Serostim[®] vial (a), the sterile transfer cannula (b), and the solvent cartridge (c) are present.
- Check that the tamper evident seals on the vial container (d) and on the cap (e) are not broken. Do not use the device if one of the tamper evident seal is broken, but return it to your pharmacist or doctor.
- Place all elements needed for the preparation of the solution on a clean surface.
- Wash your hands with soap and water.

HOW TO PREPARE YOUR SOLUTION OF SEROSTIM[®]

1. Place the click.easy[®] vertically on a flat surface with the vial at the bottom and the cap facing upward.

2. Push on the cap firmly until the vial container is completely inside the main body (Note: the tamper evident seal on the vial container is now broken).
3. Turn the cap clockwise until the green button (f) is visible. Push the cap down very slowly until it will go no further to transfer the solvent from the cartridge into the vial (Note: The tamper evident seal on the cap is now broken).
Check that all the solvent has been transferred into the vial. Dissolve the powder with the solvent by gently swirling the click.easy[®] (Note: A fast transfer of the solvent or shaking will create more foam). Let the solution stand for 2-5 minutes until the powder is completely dissolved.
4. Push the cap back down until it will go no further and keep it in position. Turn the click.easy[®] upside down and pull the cap slowly downwards until the solution is completely drawn back into the cartridge. Check that no more than one or two drops of solution remain in the vial. If there are more than one or two drops of solution remaining in the vial, slowly push the cap up until some of the solution is back in the vial and gently tap the click.easy[®]. Then draw the solution slowly again back into the cartridge. Remove any excess air that has been drawn into the cartridge by pushing slowly the cap up until no air is visible in the cartridge (Note: Avoid pulling the cap down too fast, as this will draw air into the cartridge).
5. Turn the click.easy[®] so that the cap is again on the top. Unscrew the cap and remove it.
6. Remove the cartridge containing the reconstituted solution for injection from the click.easy[®] and carefully peel off the outer label using the tab provided. Write the reconstitution date on the transparent inner label on the cartridge.
7. Discard the click.easy[®] safely in accordance with your local requirements. The cartridge containing the reconstituted solution of Serostim[®] is now ready to be used with the one.click[®] auto-injector (Note: Please read the instruction manual provided with the injection device for instruction on how to inject the reconstituted solution of Serostim[®] from the cartridge).

Injections should be given in different parts of your body. Do not use any areas in which you feel lumps, firm knots, depressions, or pain; talk to your doctor or healthcare professional about anything you find. Clean the skin at the injection site with soap and water.

STABILITY AND STORAGE

Serostim[®] 8 mg click.easy[®] is stable for 3 years in unopened vials.

Vials of Serostim[®] 8 mg click.easy[®] pre-assembled in the click.easy[®] reconstitution device should be stored in the original package at room temperature (15°-30°C / 59°-86°F).

Serostim[®] 8 mg click.easy[®] reconstituted solution should be stored in the refrigerator (2°-8°C / 36°-46°F) in the cartridge and should be used within 21 days.

Do not freeze.

HOW SUPPLIED

Serostim[®] 8 mg click.easy[®] is available in the following pack sizes:

- 1 vial of Serostim[®] 8 mg product and 1 cartridge of bacteriostatic solvent pre-assembled in 1 reconstitution device (click.easy[®]) comprising 1 device housing and 1 sterile transfer cannula.
- 5 vials of Serostim[®] 8 mg product and 5 cartridges of bacteriostatic solvent pre-assembled in 5 reconstitution devices (click.easy[®]) comprising each 1 device housing and 1 sterile transfer cannula.

Manufactured for: Serono Inc., Rockland, MA 02370

Rx Only

BX Rated

August 2003

AA0000-08/03

C. One.click Auto-injector Instructions for Use

one.click[®] Auto-injector Pen

for use with Serostim[®] [somatropin (rDNA origin) for injection] 8mg click.easy[®]

INSTRUCTIONS FOR USE

FOR COMPLETE DOSING AND SAFETY INFORMATION, PLEASE REFER TO THE SEROSTIM[®] [SOMATROPIN (RDNA ORIGIN) FOR INJECTION] PACKAGE INSERT.

IMPORTANT INFORMATION

- Serono's one.click[®] auto-injector pen is to be used exclusively with Serostim[®] [somatropin (rDNA origin) for injection] 8mg click.easy[®] in accordance with your medical practitioner's prescription.

- The one.click[®] inserts the needle automatically and accurately to the desired depth in the fatty tissue under the skin and administers a pre-selected dose of Serostim[®] 8mg click.easy[®] with just one click.
- Single use disposable sterile needles for the one.click[®] are supplied separately. Use only the one.click[®] needle 0.33 x 12mm - (29G x ½ “) distributed by Serono.
- The one.click[®] auto-injector pen containing the cartridge of reconstituted Serostim[®] placed in its storage box should be stored at 2-8°C/ 36-46°F in a refrigerator.

I. DESCRIPTION

one.click[®] AUTO-INJECTOR PEN COMPONENTS

Please refer to drawings at the end of these instructions

1. Blue activation cap
2. Depth adjuster
3. Cartridge cover
4. Cartridge holder (transparent plastic)
5. Plunger rod
6. Main body
7. Yellow one.click[®] button
8. Dose indicator
9. Green dose dial

CARTRIDGE AND NEEDLE

Please refer to drawings at the end of these instructions

10. Outer Needle cover
11. Blue inner needle cover
12. Needle
13. Sterility seal
14. Cartridge

DOSE ACCURACY TABLE

Clicks	1	2	3	4	5	6	7	8	9	10
micro litre (µl)	20	40	60	80	100	120	140	160	180	200
milligram (mg) Serostim [®]	0.12	0.23	0.35	0.46	0.58	0.70	0.82	0.93	1.05	1.16

Clicks	11	12	13	14	15	16	17	18	19	20
micro litre (µl)	220	240	260	280	300	320	340	360	380	400
milligram (mg) Serostim [®]	1.28	1.40	1.51	1.63	1.75	1.86	1.98	2.10	2.21	2.33

Clicks	21	22	23	24	25	26	27	28	29
micro litre (µl)	420	440	460	480	500	520	540	560	580
milligram (mg) Serostim [®]	2.45	2.56	2.68	2.80	2.91	3.03	3.15	3.26	3.38

Dose accuracy in accordance with ISO 11608.1: Pen-injectors for medical use, Part 1: Requirements and test methods

II. INSTALLING / CHANGING THE CARTRIDGE

1. Unlock and remove the blue activation cap. (Picture 1)
2. Unscrew the cartridge cover and then the cartridge holder. (Picture 2). Ensure that the piston rod comes back to baseline position.
3. Remove the empty cartridge from the cartridge holder (Picture 3), if any.
NOTE: Clean the empty cartridge holder as recommended in the “CARE OF YOUR one.click[®]” Section VI of this manual.
4. Insert a new cartridge containing the reconstituted Serostim[®] 8mg click.easy[®] into the clean cartridge holder.
5. Screw the cartridge holder with the cartridge back onto the one.click[®] main body.
6. Turn the cartridge holder until the disc on the plunger rod is against the cartridge - a slight ratchet sound is heard.
NOTE: For an accurate injection it is very important that the disc on the plunger rod is properly positioned against the cartridge plunger.
7. Screw the cartridge cover back onto the one.click[®] main body tightly.

III. SETTING THE INJECTION DEPTH

Turn the depth adjuster to the position recommended by your medical practitioner. The exposed needle length is approximately as follows: (Picture 4)

Setting	A	B	C
Exposed needle length	6 mm	4 mm	2 mm

IV. INJECTION WITH ONE.CLICK[®]:

You are now ready to carry out your injection by following the simple steps below:

1. Take a new needle and remove the protective sterility seal.
CAUTION: Do not use the needle if the sterility seal is damaged or unstuck.
2. Screw the new needle onto the cartridge holder and remove the outer needle cover. Do not remove the inner needle cover. (Picture 5)
3. Place the color end of the blue activation cap on a flat, non-slip surface.
4. Grip the one.click[®] on the cartridge cover and press down until a click is heard. (Picture 6)

5. Remove the blue activation cap. It will automatically remove the inner needle shield.
CAUTION: Do not press the yellow one.click[®] button while activating.
6. Remove the inner needle shield from the blue activation cap by placing the clear end on a flat surface. Press down and the inner needle shield pops out. (Picture 7)
7. Turn the green dose dial slowly until the required dose appears in the dose indicator window. (Picture 8)

When setting the dose, each “click” represents 20 µl. The minimum dose for injection is 1 “click” which is equivalent to 20 µl or 0.12 mg of Serostim[®]. The maximum dose is 29 “clicks” which is equivalent to 580 µl or 3.38 mg of Serostim[®].

NOTE: Please refer to DOSE ACCURACY TABLE above (clicks / µl / mg) for other dose settings.

NOTE: Do not hold the windows on the cartridge cover while adjusting the dose.

CAUTION: Never use force when adjusting the dose. If you have any problems setting the dose on your one.click[®], see “Additional Information” in Section V of this manual.

8. Prepare the injection site according to the instructions given by your medical practitioner. There is no need to pinch the skin at the injection site.
9. Hold the one.click[®] directly (right angle) against the skin. (Picture 9)
10. Press the yellow one.click[®] button for the injection to start. Keep the one.click[®] during approximately 10 seconds in this position until the injection is completed. (Picture 9). Ensure that the green dose dial rewinds to zero.
11. Withdraw the one.click[®] from the skin. After the injection, if a drop of blood appears, simply press for a few seconds with a medical wipe.
12. Cover the needle with the outer needle cover and unscrew it. (Picture 10)
CAUTION: Remember to discard the used needle safely, in a suitable container as recommended by your medical practitioner.
13. Push and screw the blue activation cap back into the cartridge cover.
14. Place your one.click[®] with cartridge containing the remaining reconstituted solution of Serostim[®] in its storage box and immediately place the box back into the refrigerator (2-8°C/ 36-46°F) (not into the freezer).

V. TROUBLESHOOTING GUIDE

<p>What if I cannot dial my complete dosage?</p>	<p>IF YOU CAN NOT DIAL YOUR DOSE, YOU SHOULD INJECT THE INDICATED DOSE AND THEN COMPLETE THE INJECTION WITH A NEW CARTRIDGE. FOR EXAMPLE: IF YOU REACH A DOSE VALUE OF 14 CLICKS IN THE WINDOW INSTEAD OF THE DESIRED 20 CLICKS. YOU SHOULD INJECT THE 14 CLICKS. THEN YOU SHOULD CHANGE THE CARTRIDGE, NOT FORGETTING TO CHANGE THE NEEDLE, AND SET YOUR NEXT DOSE TO 6 CLICKS (20 MINUS 14) AND INJECT THIS AMOUNT. THIS WILL ALLOW YOU TO HAVE THE CORRECT DOSE AND NOT WASTE ANY PRODUCT. CAUTION: Never force the dose dial if you do not obtain the required dosing amount.</p>
<p>What if I cannot set a dose?</p>	<p>Verify if the cartridge is empty. If so, follow instruction of</p>

	section II “Installing/Changing the cartridge” of this manual.
What if I have gone too far in dialing the dose?	Turn the green dose dial backward to correct the dose.
What if the green dose button turns freely?	If the green dose dial turns freely with no clicking, the one.click [®] is probably not activated. Repeat the activation step (point 3,4,5 of Section IV) ensuring that the blue activation cap is pushed down far enough into the one.click [®] or that the cartridge cover is screwed on completely.
What if the needle is stuck in the one.click [®] and I can not remove it?	When the one.click [®] is activated, the needle is hidden. To remove a stuck needle, you need to remove the cartridge cover. Once the cartridge cover is removed you can safely remove the needle by putting the outer cover on and unscrewing it.
What if I can not place the blue activation cap to activate the one.click [®] ?	You should check if an old inner needle shield has not been left in the blue activation cap.
What if I forget to insert the needle?	You will not be able to activate the one.click [®] nor to dial a dose.
What if the disc on the plunger rod is not properly positioned against the cartridge plunger?	Verify that the cartridge holder is properly screwed up into the main body. Turn until a slight ratchet sound is heard.
What if the green dose dial does not come back to zero?	Replace the cartridge in the one.click [®] with a new cartridge and notify your medical practitioner, nurse or pharmacist. If the issue is persistent, please send back the one.click [®] and the cartridge to your medical practitioner, nurse or pharmacist for replacement.
What if the piston rod does not move back into the main body when unscrewing the cartridge container?	Push the piston rod against a flat surface and it will move back inside the main body.
How do I remove the inner needle shield from the activation cap?	According to the one.click [®] instruction for use (Chapter IV. Picture 6 and Picture 7), the removal of the inner needle shield is shown by pressing down the blue activation cap against a table. You should not hold on the side of the activation cap when pressing, but: Press on the top cover to expel the activation cap, (the clear end being on a flat surface).

VI. GENERAL INSTRUCTIONS

CARE OF YOUR one.click[®]:

1. Clean the cartridge holder of your one.click[®] each time you change cartridges. Simply soak the empty cartridge holder in warm water for 10 minutes and let it dry in a vertical position.
2. If your one.click[®] contains a cartridge of reconstituted Serostim[®], it should not be exposed to light or freezing temperatures.

TRANSPORTING YOUR one.click[®]

Even for short travel distances, your one.click[®] auto-injector pen containing a cartridge of reconstituted Serostim[®] placed in its storage box should be transported in a cooling bag in order to maintain a temperature of 2-8°C/ 36-46°F. You should consult your medical practitioner before traveling long distances.

VII.GUARANTEE

Every effort has been made to ensure that the one.click[®] will function correctly for at least two years. After two years of operation your one.click[®] should be replaced. A new one.click[®] auto-injector pen can be obtained through your medical practitioner, nurse or pharmacist.

Date I received my one.click[®]:

_____/_____/_____
Day Month Year

Detailed information on Serono's Serostim[®] is provided in the respective package insert of the drug product.

If you are experiencing any problems with your one.click[®], please contact your medical practitioner, nurse or pharmacist.



Rx only

Manufactured for: Serono Inc., Rockland, MA 02370

August 2003

AA0000-08/03

NDA 19-764/S-025

NDA 20-604/S-030

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D. Cartridge label

Lot No:

Exp. Date:

DO NOT STORE ABOVE 25°C/70°F. STORE IN ORIGINAL PACKAGE AT ROOM TEMPERATURE.

RECONSTITUTE BEFORE USE WITH ENCLOSED SOLVENT USING THE CLICK.EASY® RECONSTITUTION DEVICE. SEE ENCLOSED INSTRUCTIONS FOR USE.

Approximately 10% mechanical loss can be associated with reconstitution and multi-dose administration.

Once reconstituted, store the cartridge in the refrigerator 2°-8°C/36°-46°F and use within 21 days. Do not freeze.

Usual dose: See package insert

Multiple dose cartridge

S.C.

NDC 44087-0080-1

Serostim® 8 mg click.easy

[SOMATROPIN (RDNA ORIGIN) FOR INJECTION]

8.8 MG (APPROXIMATELY 26.4IU)

Rx Only

- 1 vial somatropin (rDNA origin) for injection
- 1 cartridge bacteriostatic solvent pre-assembled in 1 reconstitution device (click.easy™) including 1 device housing and 1 sterile transfer cannula
- For subcutaneous injection

Bar code area

Contents:

ONE VIAL SEROSTIM® CONTAINING 8.8MG SOMATROPIN (APPROXIMATELY 26.4IU), 60.2 MG SUCROSE, 2.05 MG O-PHOSPHORIC ACID AND SODIUM HYDROXIDE OR O-PHOSPHORIC TO ADJUST PH.

ONE CARTRIDGE BACTERIOSTATIC SOLVENT CONTAINING 1.37 ML 0.3% (W/V) METACRESOL IN WATER FOR INJECTION.

MANUFACTURED FOR:

SERONO INC.

Rockland, MA 02370, USA

Serono holo

Serono Logo

DRAFT Serostim[®] 8 mg click.easy Solvent Cartridge Label

SEROSTIM[®] 8 MG CLICK.EASY [SOMATROPIN (RDNA ORIGIN) FOR INJECTION] Reconstituted solution for use only with the one.click[®] auto injector pen. This cartridge contains 5.83 mg/ml of Serostim [®]		
<div style="border: 1px solid black; padding: 5px; width: fit-content; margin: 0 auto;">Date of reconstitution: <i>to be filled in by the patient</i></div>		
ONCE RECONSTITUTED STORE AT 2°-8°C/36°-46°F IN THE CARTRIDGE AND USE WITHIN 21 DAYS AFTER RECONSTITUTION.		
<div style="border: 1px solid black; padding: 5px; width: fit-content; margin: 0 auto;"><i>Serono Logo area</i></div>	Lot No.	Solvent Lot No.
Lot No: EXP. DATE:		
BACTERIOSTATIC SOLVENT 1.37 ML (0.3% (W/V) METACRESOL IN WATER FOR INJECTION) FOR RECONSTITUTION OF SEROSTIM[®] 8 MG CLICK.EASY		
CODE: LC01XXXX		
<div style="border: 1px solid black; padding: 5px; width: fit-content; margin: 0 auto;"><i>Serono Logo area</i></div>		

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NDA 20-604/S-030

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DRAFT Serostim[®] 8 mg click.easy Vial Label

NDC 44087-0080-1	<i>Serono Logo area</i>
Serostim[®] 8 mg click.easy	
[SOMATROPIN (RDNA ORIGIN) FOR INJECTION]	
8.8 mg (approximately 26.4IU)	
S.C.	
MANUFACTURED FOR: SERONO INC. ROCKLAND, MA 02370, USA	
Lot No:	
Exp. Date:	