

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-640/S022

Trade Name: Humatrope

Generic Name: (somatropin [rDNA origin] injection)

Sponsor: Eli Lilly and Company

Approval Date: February 4, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-640/S022

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

19-640/S022

APPROVAL LETTER

NDA 19-640/S-022

Eli Lilly and Company
Attention: Gregory G. Enas, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Enas:

Please refer to your supplemental new drug application dated March 3, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Humatrope [somatropin (rDNA origin) for injection].

We acknowledge receipt of your submission dated September 26, 1998, received September 29, 1998, in response to our approvable letter dated September 4, 1998. We also refer to your submission of January 27, 1999.

This supplemental new drug application provides for an additional drug substance manufacturing facility in Speke, UK, as well as a new drug product formulation/presentation in 6, 12, and 24 mg multiple-use cartridges, each to be supplied with a separate diluent syringe and dosed via a re-useable "pen" device.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated January 27, 1999. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to draft labeling (package insert submitted January 27, 1999; patient package insert submitted March 3, 1998; immediate container and carton labels for the cartridges submitted August 17, 1998). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 19-640/S-022." Approval of this submission by FDA is not required before the labeling is used.

NDA 19-640/S-022

Page 2

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Crystal King, P.D., M.G.A., Regulatory Project Manager, at 301-827-6423.

Sincerely yours,

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 19-640/S-022

Page 3

cc:

Archival NDA 19-640

HFD-510/Div. Files

HFD-510/CKing/WBerlin/SMoore/SMalozowski

HF-2/MedWatch (with labeling + labeling review + attachment)

HFD-002/ORM (with labeling)

HFD-102/ADRA (with labeling)

HFD-40/DDMAC (with labeling)

HFD-613/OGD (with labeling)

HFD-95/DDMS (with labeling)

HFD-820/DNDC Division Director

DISTRICT OFFICE

Drafted by: CKing/012299

Initialed by:

final:

filename: mydoc/NDA/19640/19640/s22AP

APPROVAL (AP)

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
19-640/S022

APPROVABLE LETTER

NDA 19-640/S-022

Eli Lilly and Company
Attention: Tobias Massa, Ph.D.
Director, Regulatory Affairs (CM&C)
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Massa:

Please refer to your supplemental new drug application dated March 3, 1998, received March 5, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Humatrope (Somatotropin [rDNA origin] for Injection).

We acknowledge receipt of your submissions dated May 4, July 7 (two), July 31, and August 7, 1998. We also refer to your submission dated August 17, 1998. The review for this submission has not been completed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter. The user fee goal date for this application is September 5, 1998.

This supplement provide for an additional drug substance manufacturing facility in Speke, UK, as well as a new drug product formulation/presentation in 6, 12, and 24 mg multiple-use cartridges, each to be supplied with a separate diluent syringe, and dosed via a new re-useable pen device.

We have completed the review of this application, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. The stability protocol for routine lots (at least one lot per year) of Diluent Syringes includes sterility, bacterial endotoxin, and Metacresol (HPLC assay) testing. However, the stability protocol for the first three diluent syringe production lots does not include antimicrobial preservative effectiveness testing. Stability preservative effectiveness should be performed using the reconstituted Humatrope drug product. For testing the stability of preservative systems in the reconstituted drug product, the first three production lots should be tested with a microbial challenge assay at the start and at the end of the stability period, and at one point in the middle of the stability test period if the test period equals or exceeds two years. The first three batches of the diluent should be assayed for the chemical content of the preservatives at all appropriate test points. Upon demonstration of chemical content commensurate with microbial effectiveness in the first three production batches, chemical assays may be adequate to demonstrate the maintenance of the specified concentrations of preservatives for subsequent

lots placed into stability testing.

2. Bacterial endotoxin testing validation of the three new cartridge presentations (6 mg, 12 mg, and 24 mg) was not included in the submission. Please submit a validation report including methodology and data supporting bacterial endotoxin testing validation for the proposed cartridges.
3. As the diluent preservative is intended to preserve the reconstituted product, preservative effectiveness validation of the reconstituted (using the diluent syringe) lyophilized Humatrope / / should be performed. Please submit the methodology and data supporting the preservative effectiveness of the reconstituted Humatrope/diluent (6, 12, and 24 mg) products.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, contact Crystal Anne King, P.D., M.G.A., Project Manager, at 301-827-6423.

Sincerely,

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 19-640/S-022

Page 3

cc:

Archival NDA 19640

HFD-510/Division File

HFD-510/SSobel/SMalozowski/SMoore/WBerlin/CKing

HFD-160/PCooney/NSweeney

HFD-805/HAhn/RShore

HFD-95/DDMS

DISTRICT OFFICE

Drafted by: CKing 08.31.98

Initialed by: EGalliers 09.02.98

final: CKing 09.02.98

filename: NDA 19640/S022/AEltr

APPROVABLE (AE)

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

19-640/S022

LABELING

LILLY FRANCE

Größe 75 x 40 x 194
 Varnish number: 7540194 01-02
 Marbach-Nr. 1031125058
 Date of creation: 04.12.2008

To open, lift here and pull

6 mg Combination Package

6 mg Combination Package

6 mg Combination Package

SH 9000 FSAMS

CARTON HAS BEEN OPENED

Humatrope® somatotropin (rDNA origin) for Injection

6 mg Cartridge Kit

for use only with the Humatrope® (somatotropin [rDNA origin] for injection) pen injection device

Rx only

Refrigerate
Do Not Freeze
Do Not Shake

Kit contains:

One Humatrope Cartridge 6 mg
 One Prefilled Diluent Syringe

www.humatrope.com

Humatrope® somatotropin (rDNA origin) for Injection

6 mg

For Parenteral Use Only

Cartridge VL 7554 contains:

- Humatrope (somatotropin [rDNA origin] for injection), 6 mg
- Mannitol, 18 mg
- Glycine, 6 mg
- Dibasic Sodium Phosphate, 1.36 mg
- Phosphoric Acid and/or Sodium Hydroxide may have been added to adjust pH
- Nitrogen Overlay

Diluent Syringe VL 7618 contains:

- Water for Injection with 0.3% Metacresol as a preservative
- 1.7% Glycerin

For Dosage and Administration, see accompanying package insert.

Refrigerate • Do Not Freeze • Do Not Shake

Before Reconstitution:
 Store in a refrigerator 2° to 8°C (36° to 46°F).

To Reconstitute:
 See accompanying package insert.
 Reconstitute only with diluent provided.

After Reconstitution:
 Store reconstituted solution in a refrigerator 2° to 8°C (36° to 46°F) and use within 28 days.

This container is not child resistant.

Manufactured by Lilly France S.A.
 24110 Zaventem Belgium
 Lilly, the Lilly logo and Humatrope are trademarks of Eli Lilly and Company
 Indianapolis, IN 46285, USA

Lilly

Lilly

Lilly

3 00028 14701 6

Humatrope® somatotropin (rDNA origin) for Injection

6 mg

LILLY FRANCE - Feggenheim PRINTED PACKAGING DEVELOPMENT	ITEM CODE SH9000FSAMS	PREVIOUS ITEM CODE SH9000FSAMS	1/4 BLACK	FINISHED PRODUCT CODE MSS147	Approved by: NAME: _____ DATE: _____	Signature: _____	Created for: _____
RESPONSIBLE <i>Lilly</i>	SIZE (mm) 75 x 40 x 194	SICK CODE FILE N° 3821 03C001	2/4 CYAN	<input checked="" type="checkbox"/> Trade <u>00TAM</u>	Approved by: NAME: _____ DATE: _____	Signature: _____	Used case by: _____
	NB OF PAGES 1/1	PROOF N°: 2 DATE: 17 February 2005	2/4 MAGENTA	<input type="checkbox"/> Hospital			Date: _____
				<input type="checkbox"/> Sample			

LILLY FRANCE

Größe 75 x 40 x 194
 Varnish number: 7540194-01-02
 Mainbach-Nr. 1031125058
 Date of creation: 04.12.2008

To open, lift here and pull

Control No. / Exp. Date

12 mg
Combination Package

NDC 0002-B148-01
MS B148



Humatrope®
somatotropin (rDNA origin)
for injection

12 mg
Cartridge Kit
for use only with the
Humatrope®
(somatotropin [rDNA origin] for injection)
pen injection device

Rx only
Refrigerate
Do Not Freeze
Do Not Shake

Kit contains:
One Humatrope Cartridge 12 mg
One Prefilled Diluent Syringe

www.humatrope.com

Lilly



12 mg

12 mg
Combination Package

SH 9010 FSAMS

CARTON HAS BEEN OPENED

For Parenteral Use Only

Cartridge VL 7555 contains:

- Humatrope (somatotropin [rDNA origin] for injection), 12 mg
- Mannitol, 36 mg
- Glycine, 12 mg
- Dibasic Sodium Phosphate, 2.72 mg
- Phosphoric Acid and/or Sodium Hydroxide may have been added to adjust pH
- Nitrogen Overlay

Diluent Syringe VL 7619 contains:

- Water for Injection with 0.3% Metacresol as a preservative
- 0.29% Glycerin

For Dosage and Administration, see accompanying package insert.

Refrigerate • Do Not Freeze • Do Not Shake

Before Reconstitution:
Store in a refrigerator 2° to 8°C (36° to 46°F).

To Reconstitute:
See accompanying package insert.
Reconstitute only with diluent provided.

After Reconstitution:
Store reconstituted solution in a refrigerator 2° to 8°C (36° to 46°F) and use within 28 days.

This container is not child resistant.

Manufactured by Lilly France S.A.S.
F-67640 Fegersheim, France
for Eli Lilly and Company
Indianapolis, IN 46285, USA



3 00028 14801 3



12 mg
Combination Package

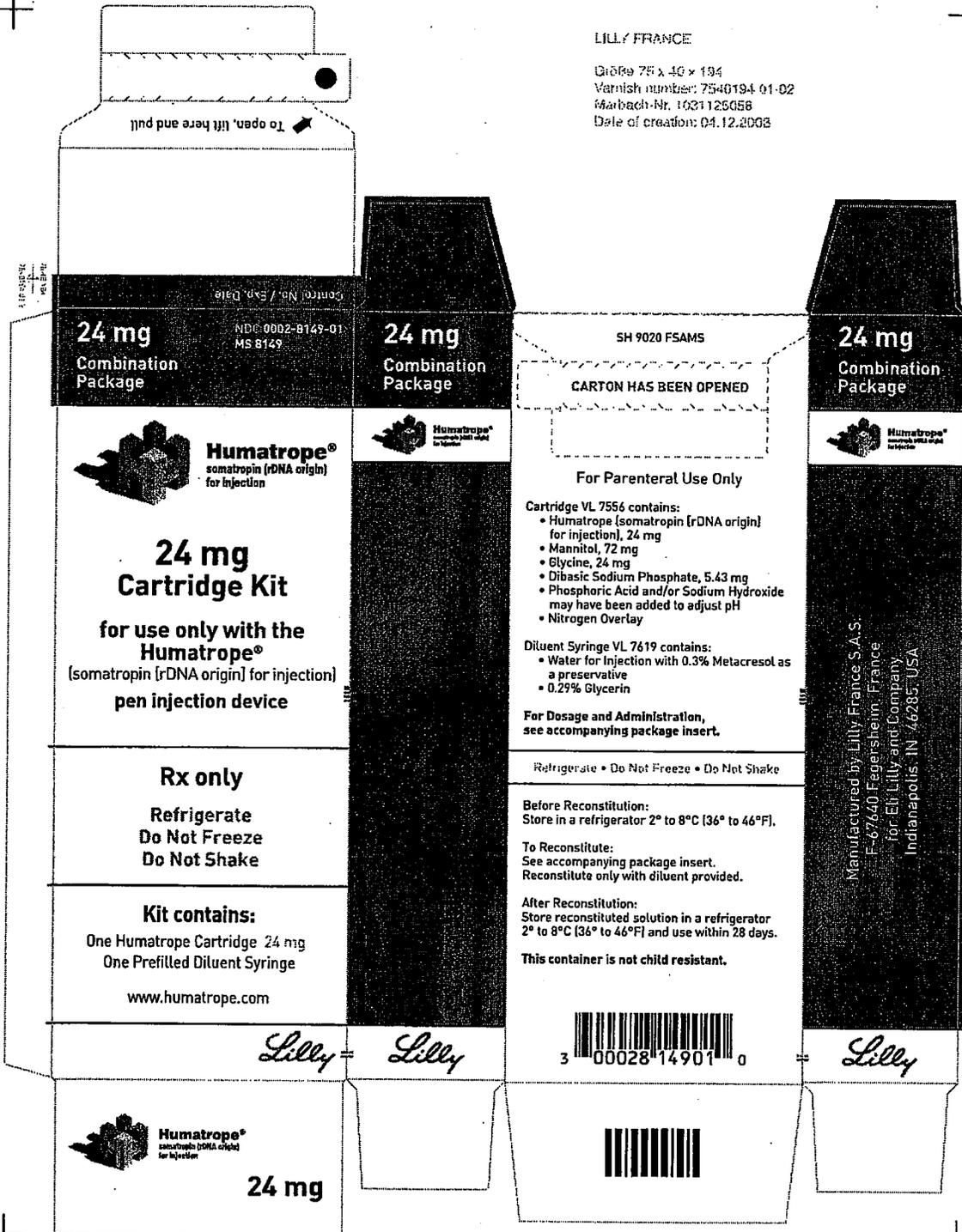


Humatrope®
somatotropin (rDNA origin)
for injection

LILLY FRANCE - Fegersheim PRINTED PACKAGING DEVELOPMENT	ITEM CODE SH9010FSAMS	PREVIOUS ITEM CODE (to be described)	1/4 BLACK	FINISHED PRODUCT CODE MSB148	Approved by: NAME: _____ DATE: _____	Created by: /
	RESPONSIBLE <i>Lilly</i>	SIZE (mm) 75 x 40 x 194	SICK CODE 3826	2.5 CVN	Approved by: NAME: _____ DATE: _____	Checked by: _____
	NB OF PAGES 1/1	PROOF N°: 1 DATE: 17 February 2005	3/4 MAGENTA	<input checked="" type="checkbox"/> Trade 001AM <input type="checkbox"/> Hospital <input type="checkbox"/> Sample	Signature: _____	Date: _____

LILLY FRANCE

Größe 75 x 40 x 194
Varnish number: 7540194-01-02
Marbach-Nr. 1031125058
Date of creation: 04.12.2003



LILLY FRANCE - Febrichem PRINTED PACKAGING DEVELOPMENT	ITEM CODE SH9020FSAMS	PREVIOUS ITEM CODE (to be registered)	1/4 BLACK	FINISHED PRODUCT CODE MS8149	Approved by: NAME: _____ DATE: _____	Created by: Signature: _____
RESPONSIBLE 	SIZE (mm) 75 x 40 x 194	SICK CODE FILE N° 3828 OSC001	2/4 CYAN 3/4 MAGENTA	<input checked="" type="checkbox"/> Trade 001AM <input type="checkbox"/> Hospital <input type="checkbox"/> Sample	Approved by: NAME: _____ DATE: _____	Checked by: Signature: _____ Date: _____
	NR OF PAGES 1/1	PROOF N°: 1 DATE: 17 February 2005				

For use with
6 mg
cartridge only

NDC 0002-7618-01
VL 7618

Sterile Diluent
for
Humatrope®
somatropin (rDNA origin)
for Injection

MAY REFRIGERATE OR
STORE AT ROOM TEMPERATURE
Do Not Freeze

• For injection with the Humatrope® (somatropin [rDNA origin] for injection) pen injection device.
• Contains: Water for Injection with 0.3% Metacresol as a preservative and 1.7% Glycerin.

Mfg. by Baxter Pharmaceutical Solutions LLC
Bloomington, IN 47403, USA for
Eli Lilly and Company, Indianapolis, IN 46285, USA *Lilly*
WG 4140 AMX Exp. Date/Control No.

(b) (4)	
DIE ID	Die No.: D-1290 KC Drawing No: N/A View: Printed Side Up
BKGD ID	D-1290-LB02 Approved by: Roger W. Wetzel Date: 3-7-05
LILLY APPROVALS	Graphics Operator: _____ Date: _____
	Proofreader: _____ Date: _____
	Label Editor or Label Editor Asst: _____ Date: _____
	Printing Quality Control: _____ Date: _____
(b) (4)	
VENDOR APPROVALS	Production Order Number: _____
	Item Number: _____ Scanner Code: _____
	OK FOR PRODUCTION (copy only) Client Services: _____ Date: _____
FINAL OK Production Engineering: _____ Date: _____	
(b) (4)	
COLOR ID	Item Code: WG 4140 AMX Colors: BLACK WG 4140 AMX 100% WHITE D-1290-LB02 COATING D-1290-LE02
	ENGINEER'S APPROVAL
	D-1290-LE02 Finishing Line No.: Baxter Pharmaceuticals Approved by: Tonjalee Miller Date: 09-05-03

	For use with 12 mg and 24 mg cartridges only	NDC 0002-7619-01 VL 7619
	Sterile Diluent for Humatrope® <small>somatropin (rDNA origin)</small> for Injection Rx only	 <small>(01)10300027619016</small>
<ul style="list-style-type: none"> • For Injection with the Humatrope® (somatropin [rDNA origin] for injection) pen injection device. • Contains Water for Injection with 0.3% Metacresol as a preservative and 0.29% Glycerin. 		
<small>Mfg. by Baxter Pharmaceutical Solutions LLC Bloomington, IN 47403, USA for Eli Lilly and Company, Indianapolis, IN 46285, USA</small>		
WG 4150 AMX	Exp. Date/Control No.	

DIE ID	Die No.: D-1290
	KC Drawing No: N/A View: Printed Side Up

BKGD ID	D-1290-LB02
	Approved by: _____
	Date: 3-7-05

LILLY APPROVALS	Graphics Operator: _____	Date: _____
	Proofreader: _____	Date: _____
	Label Editor or Label Editor Asst: _____	Date: _____
	Printing Quality Control: _____	Date: _____

VENDOR APPROVALS	Production Order Number: _____	
	Item Number: _____	Scanner Code: _____
	OK FOR PRODUCTION (copy only)	Client Services: _____ Date: _____
	FINAL OK	Production Engineering: _____ Date: _____

COLOR ID	Item Code: WG 4150 AMX
	Colors:
	BLACK WG 4150 AMX
	COATING D-1290-LE02

ENGINEER'S APPROVAL	D-1290-LE02
	Finishing Line No.: Baxter Pharmaceuticals
	Approved by: _____
	Date: 09-05-03

PA 9330 FSAMP

INFORMATION AND PATIENT INSTRUCTIONS

HUMATROPE®

Somatropin (rDNA origin) for Injection
CARTRIDGES



HUMATROPE CARTRIDGES ARE ONLY TO BE USED WITH HUMATROPEN® OR HUMATROPEN® 3 INJECTION DEVICES.

Important Things to Know

It is important to learn the names of the parts of the Humatrope Cartridge Kit and how these parts work before injecting yourself or your child. Make sure you have been properly trained by your nurse, pharmacist or doctor before you mix the drug (add the diluent liquid to the dry Humatrope powder) or inject it. Wash your hands and be careful to follow the instructions given to you by your nurse, pharmacist or doctor. After mixing, throw away the diluent syringe in a puncture-resistant container such as the type your nurse, pharmacist or doctor has told you to use.

Storage

Humatrope must be kept refrigerated (36° to 46°F [2° to 8°C]) before and after it is mixed. Do not freeze. Once Humatrope has been mixed and is in liquid form, it must be used within 28 days. Throw away any mixed Humatrope left over after 28 days. Before giving an injection, check the date on the cartridge. Do not use the cartridge if it has expired.

WARNING

HUMATROPE CARTRIDGES SHOULD NOT BE USED IF THE PATIENT IS ALLERGIC TO METACRESOL OR GLYCERIN.

Contents

- one cartridge with 6, 12, or 24 mg of dried Humatrope
- one prefilled syringe with diluent (the liquid used to mix the dried Humatrope)

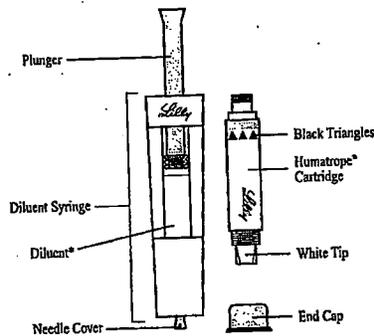
NOTE: There are three kinds of Humatrope cartridges that have different amounts of Humatrope (6, 12, or 24 mg). Make sure that you have the cartridge that your doctor prescribed.

Mixing the Humatrope in the Cartridge

Use only the prefilled diluent syringe to mix the Humatrope in the cartridge. DO NOT use the diluent that comes in the Humatrope vial box, or any other liquid.

Reconstitution Instructions

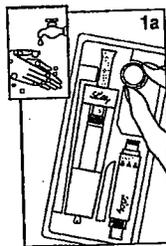
Parts



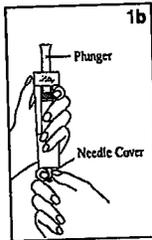
Use only this kit to prepare the Humatrope cartridge.

*Note: The liquid is colorless. It is shown here as blue for illustration purposes only.

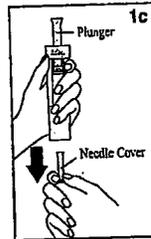
Preparing Your New Cartridge



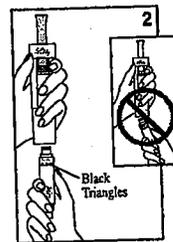
Remove ALL contents from the tray.
Note: This product is designed for left or right handed use so you may use whichever hand is most comfortable for you.



Grasp the gray Needle Cover, at the bottom of the Diluent Syringe.

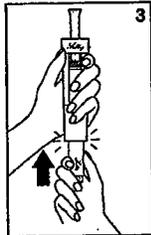


Remove the Needle Cover and discard. DO NOT depress the Plunger yet. It is okay if a drop of fluid is lost. It is not necessary to release air from the Diluent Syringe.

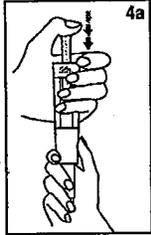


Hold the cartridge, with the Black Triangles up toward the Diluent Syringe. Align the cartridge and Diluent Syringe in a straight line. DO NOT insert the cartridge at an angle.

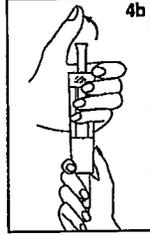
LILLY FRANCE - Fegersheim PRINTED PACKAGING DEVELOPMENT	ITEM CODE PA8330FSAMP	PREVIOUS ITEM CODE	1/3 BLACK 2-3 CYAN 3/3 PMS 485	FINISHED PRODUCT CODE MS8147 / MS8148 / MS8149	Approved by: NAME: _____ Signature: _____ DATE: _____	Created by: /
	RESPONSIBLE	SIZE (mm) 176 x 250		SICK CODE 629	FILE N° 05C082	
Lilly	NB OF PAGES 1/2	PROOF N°: 2	DATE: 06 December 2005	<input checked="" type="checkbox"/> Trade <input type="checkbox"/> Hospital <input type="checkbox"/> Sample		Date: _____



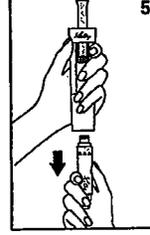
3
PUSH the cartridge **STRAIGHT** in until it stops **AND** the **Black Triangles ARE COVERED**. You may hear or feel a click. **DO NOT** twist the cartridge.



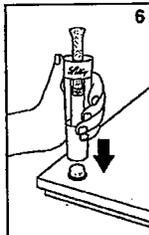
4a
 Hold the Diluent Syringe and the cartridge together with **TWO HANDS**. Push and release the Plunger 2 or 3 times until the Diluent is in the cartridge.



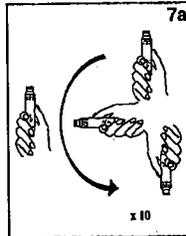
4b
 Remove your thumb from the Plunger and check that the Diluent Syringe is empty (it is normal for small drops of Diluent to remain in the Diluent Syringe).



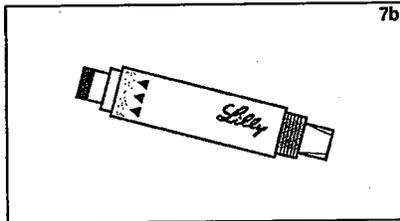
5
 With your thumb **OFF** the plunger, pull the cartridge away from the Diluent Syringe.



6
 Place the End Cap on a hard, flat surface. Push the Diluent Syringe onto the End Cap and immediately discard the Diluent Syringe as instructed by your healthcare professional.



7a
 Mix the cartridge by gently inverting 10 times and let it sit for 3 minutes, **DO NOT SHAKE**.



7b
 Inspect the solution. The Humatrope solution should be clear. If the solution is clear, your cartridge is now prepared and ready to be attached to your pen injection device (see the User Manual for your pen injection device).
 If the solution is cloudy or contains particles, gently invert the cartridge 10 additional times. Let the cartridge sit for 5 more minutes. If the solution remains cloudy or contains particles, **DO NOT USE THE CARTRIDGE**.
 Contact your healthcare professional or Lilly.
 If you have questions about preparing your Humatrope cartridge, you should contact your Humatrope provider or your healthcare professional.

Injections can be given in the following areas:

- Abdomen (above, below, or either side of the navel)
- Front of the upper thighs
- Upper, outer buttocks
- Back of the arms above the elbow and below the shoulder

Discuss use of the pen injection device, the right places to inject, and site rotation with your nurse or doctor.

Literature revised August 1, 2005

Manufactured by Lilly France S.A.S.
 F-67640 Fegersheim, France
 for Eli Lilly and Company
 Indianapolis, IN 46285, USA

www.humatrope.com

PA 9330 FSAMP

LILLY FRANCE - Fegersheim PRINTED PACKAGING DEVELOPMENT	ITEM CODE PA9330FSAMP	PREMISE/STATION CODE —	FINISHED PRODUCT CODE MS8147 / MS8148 / MS8149	Approved by: NAME: _____ DATE: _____	Signature: _____	Created by: _____
RESPONSIBLE →	SIZE (mm) 176 x 250	SICK CODE 629	FILE N° 05C062	<input checked="" type="checkbox"/> Trade 001AM	Approved by: NAME: _____ DATE: _____	Checked by: _____
<i>Lilly</i>	NB OF PAGES 2/2	PROOF N°: 2	1/3 BLACK OF 3 3/3 PMS 485	<input type="checkbox"/> Hospital	Signature: _____	Date: _____
	DATE: 06 December 2005		<input type="checkbox"/> sample			

Humatrope®
somatropin (rDNA origin)
for injection

Model MS8050

HumatroPen®
Injection Device For Use With Humatrope® Cartridges



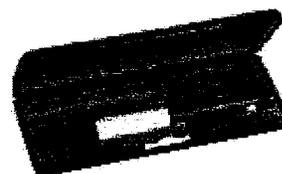
If you have questions, call 1-800-847-6988

Lilly

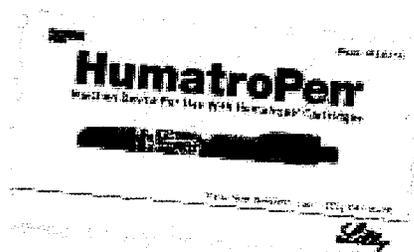
HumatroPen® Package
(When first opened)



Blue protective storage case



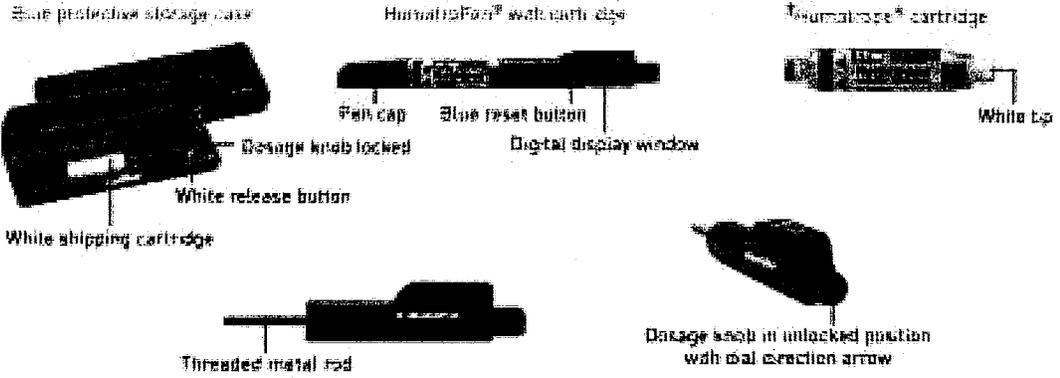
HumatroPen® Injection Device and storage case



HumatroPen® User Guide

- a** Please fold out to reference the diagrams for the **HumatroPen®** Injection Device.

HumatroPen® and Cartridge Elements

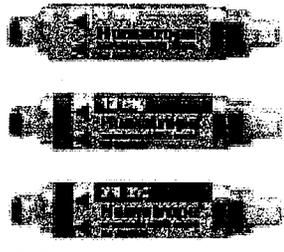


b † Sold separately by prescription as part of the Humatrope® Cartridge Kit.

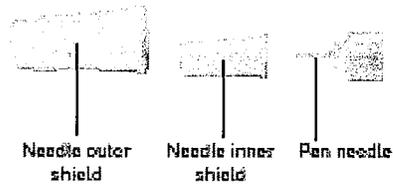
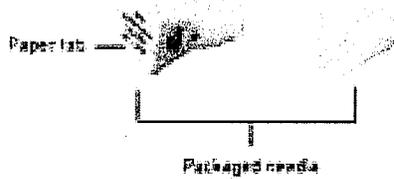
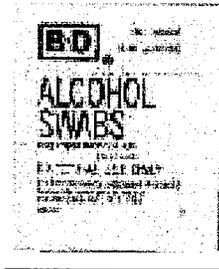
Accessories Sold Separately

Additional supplies you will need before using the HumatroPen® (all sold separately) are:

Humatrope® Cartridge Kit
(6, 12, or 24 mg quantity) as
prescribed by your healthcare
professional.



Alcohol swab



- c** Becton, Dickinson and Company pen needles are suitable for use with the HumatroPen®.

If you have questions, call 1-800-847-6988

Contents

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Humatrope®
somatropin (rDNA origin)
for injection

Introducing the HumatroPen®
Injection Device



If you have questions, call 1-800-847-6988

Introduction

This booklet is the User Guide for the HumatroPen[®] Injection Device. **Before using the HumatroPen, please read this User Guide thoroughly.** Keep this important guide for future reference. Your healthcare professional has told you the Humatrope[®] dose that you or your child should receive. **DO NOT change this dose unless directed by your healthcare professional.** If you have any questions about the HumatroPen Injection Device, please call Eli Lilly and Company at 1-800-847-6988 or visit www.humatrope.com.

WARNING: DO NOT USE THE HUMATROPEN INJECTION DEVICE AND HUMATROPE CARTRIDGES IF YOU ARE ALLERGIC TO METACRESOL OR GLYCERIN.

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for injection**

Important Notes

The HumatroPen is not recommended for use by blind or visually impaired individuals without the assistance of a sighted individual trained in its use.

Maintenance and Care of the HumatroPen

- The pen requires no maintenance.
- Soiled parts can be cleaned with a damp cloth. Do not use alcohol or other cleaning agents.
- Protect the pen and case from moisture especially when transporting in a cooler.
- For the cleaning of the HumatroPen Injection Device, the body of the HumatroPen may be wiped with a cloth slightly dampened with water. **DO NOT IMMERSE THE HUMATROPEN IN WATER.**
- The case is not watertight and will not protect the pen if immersed.
- Do not soak or immerse the pen in liquid.
- Do not apply oil or other lubricant.

If you have questions, call 1-800-847-6988

Storage of the HumatroPen

- All Humatrope cartridges and diluent must be refrigerated at temperatures between +2° and +8°C (36° and 46°F). DO NOT FREEZE. A prepared cartridge can be left on a pen for 28 days in the refrigerator. If any reconstituted product remains after 28 days, it should be discarded.
- While traveling, daily room temperature exposure should not exceed 30 minutes.
- Use a new needle for each injection. Do not store the pen with needle attached. This could cause liquid to leak, air bubbles to form, or growth hormone crystals to clog the needle.
- Pen should be stored with dosage knob in locked position.
- Discomfort may be noticed at the injection site if Humatrope is given cold. Let Humatrope stand at room temperature for 10 minutes before injecting.

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Terms and Definitions

It may be helpful to refer to the fold-out diagrams on the inside front cover of this booklet, page X, as you review these terms.

Dosage knob - The cylindrical knob extending from the end of the HumatroPen that turns to dial the dosage setting of Humatrope. The arrow marked on the flat end of the dosage knob indicates the direction in which the knob is turned to dial the dose.

Dosage knob click - The slight sharp noise that is heard and the snap felt when the dosage knob is turned.

Dosage setting - The numbers that appear in the digital display window and correspond to the number of dosage knob clicks. The dosage setting you dial should be calculated by your healthcare professional to correspond to the prescribed Humatrope dose. The chart on page XX illustrates the relationship between the Humatrope dose and the HumatroPen dosage setting.

If you have questions, call 1-800-847-6988

Humatrope cartridge - A sealed container of Humatrope powder that attaches to the HumatroPen. Humatrope is mixed directly in the cartridge and stored there. Cartridges are available in three (3) Humatrope quantities: 6 mg, 12 mg, and 24 mg.

Reconstitution - The mixing of diluent (liquid) with the Humatrope powder in order to make it injectable. Reconstituted Humatrope must be refrigerated and used within 28 days.

Release button - The white button on the opposite side of the HumatroPen from the digital display window. Pressing the white release button unlocks the dosage knob.

Reset button - The blue ridged button on the slanted area near the digital display window. The blue reset button allows you to dial the dosage knob backward. Note that when the dosage knob is turned backward, no clicking sound is heard.

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for injection



† *Humatrope Cartridges sold separately by prescription as part of the Humatrope Cartridge Kit.*

If you have questions, call 1-800-847-6988

Features

The HumatroPen Injection Device system is:

- **Convenient** - One (1) injection device that can be used with any one of three (3) Humatrope cartridges (6 mg, 12 mg, and 24 mg).
- **Versatile** - Your healthcare professional can adjust the dose in either 0.1, 0.2, or 0.4 mg increments depending on the strength of reconstituted Humatrope in the cartridge.
- **Stable** - Once reconstituted, refrigerated Humatrope in cartridges can be used for up to 28 days.
- **“Sense”-able** - *See, Hear, and Feel*, as you dial the dosage setting that corresponds to the prescribed Humatrope dose.

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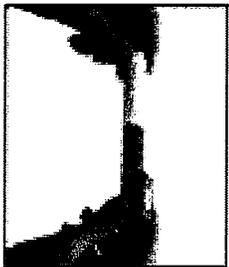


Steps for Using the HumatroPen Injection Device

Follow these steps for using the HumatroPen. Refer to the fold-out diagrams on the inside front cover, page X, as you go through these steps.

1. Getting Started

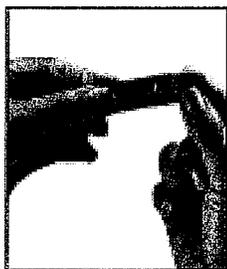
- Wash your hands before you start.
-
- Before first-time use, remove the pen cap and unscrew the white shipping cartridge from the HumatroPen. Dispose of the white shipping cartridge.



If you have questions, call 1-800-847-6988



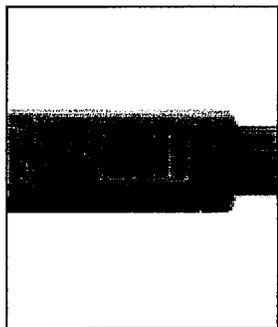
- Firmly press the white release button on the HumatroPen to unlock the dosage knob. The numbers "00" will appear in the digital display window.



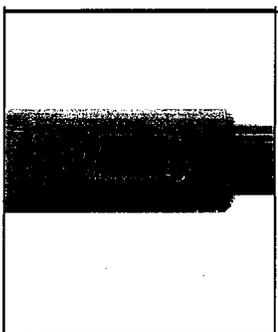
- Press and hold in the blue reset button and turn the dosage knob counterclockwise (in the direction opposite to the arrow on the end of the dosage knob) until the metal rod is fully retracted and stops.

NOTE: Do not use excessive force while turning the dosage knob. If the dosage knob does not turn, it is already in the correct position.

Humatrope[®]
somatropin (rDNA origin)
for injection



- You will see either "00" or "--" in the digital display window.
- If the display shows "00" in the digital display window, then proceed to the next page.

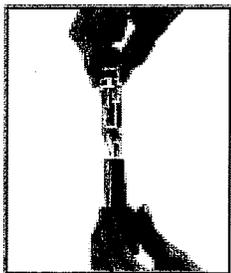


- If the display shows "--" in the digital display window, then press down the dosage knob until it locks in place. Press the white release button. The dosage knob will unlock, and the numbers "00" will reappear in the digital display window.

NOTE: The digital display will automatically shut off in two (2) minutes. The display can be reactivated by pressing down the dosage knob until it locks in place. Then press the white release button, and "00" will reappear.

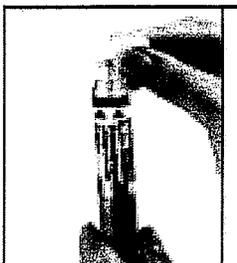
If you have questions, call 1-800-847-6988

Follow the mixing (reconstitution) directions as described in your Humatrope Cartridge Kit.



- If a cartridge is already attached to your pen: go to “Attaching the Pen Needle” on page X.
- OR**
- If a cartridge is **not** already attached to your pen: place a **reconstituted** cartridge on the pen by screwing the cartridge counterclockwise (in the direction opposite the arrow on the end of the dose knob) into the pen. Go to “Attaching the Pen Needle” on page X.

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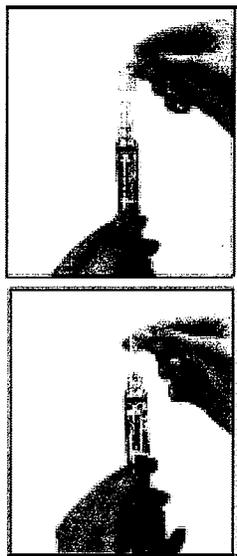
2. Attaching the Pen Needle

- Wipe the rubber seal on the Humatrope cartridge with an alcohol swab.



- Remove the tab from the needle outer shield but do not remove the needle. Holding the HumatroPen upright and away from your face, screw the needle shield onto the Humatrope cartridge until snug.
- Remove the needle outer shield but do not discard.

If you have questions, call 1-800-847-6988

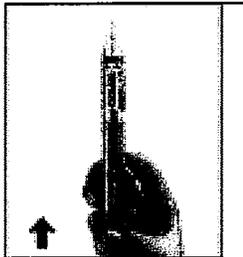


3. Priming the HumatroPen Injection Device

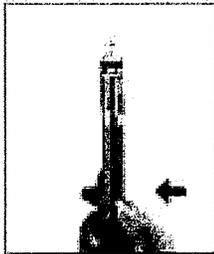
The HumatroPen must be primed before setting or injecting **the first dose** from each **new** cartridge. After priming the HumatroPen with a new cartridge, it is **not** necessary to prime the HumatroPen again between doses. This is only necessary when you remove or replace the cartridge.

- Hold the HumatroPen with the pen needle pointing upright and away from your face. Pull off and discard the needle inner shield.

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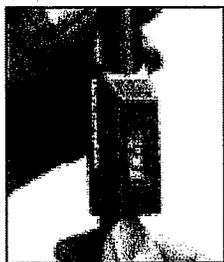


- Push in the dosage knob at the end of the HumatroPen until it locks in place. A small stream of solution and air bubbles may come out of the tip of the pen needle.



- Continuing to hold the HumatroPen with the pen needle upright, unlock the dosage knob by firmly pressing the white release button. You should see, hear, and feel the dosage knob unlock.

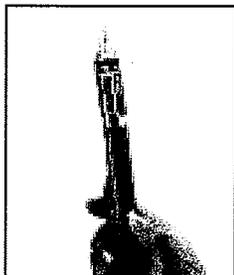
If you have questions, call 1-800-847-6988



- Turn the dosage knob clockwise, in the direction of the arrow marked on its end, until "01" appears in the digital display window and a click is heard as the number locks in place. Holding the HumatroPen upright, push the dosage knob in until it locks in place. "01" will remain in the digital display window until the white release button is pressed. Then press the white release button. Repeat this procedure until Humatrope solution appears at the pen needle tip. Once the solution appears at the pen needle tip—the injection device is primed.

NOTE: It is normal for a small air bubble to remain in the cartridge.

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4. Dialing the Prescribed Dose

- With your healthcare professional, determine the HumatroPen dosage setting (number of dosage knob clicks) that corresponds to the prescribed dose of Humatrope.
- To dial the dose, press the white release button. The numbers "00" should reappear in the digital display window. The dosage knob is now unlocked. Do not depress the dosage knob while setting the dose. This will cause the solution to be released from the HumatroPen prior to injection, making the dose inaccurate.

If you have questions, call 1-800-847-6988



- Turn the dosage knob in the direction of the arrow until the dosage setting corresponding to the prescribed dose appears in the digital display window. You will hear and feel a click as the numbers are dialed.

NOTE: The HumatroPen will dial to a maximum dosage setting of 12 (twelve clicks of the dosage knob).

- If the dosage knob will not dial the prescribed dosage setting, the cartridge may be nearly empty and may not contain enough Humatrope solution for a complete dose. Talk with your healthcare professional at the start of therapy about how to deal with this.

NOTE: If you turn the dosage knob past the correct number of clicks, press and hold in the blue reset button and dial the dosage knob counterclockwise (in the direction opposite to the arrow) until the correct number appears in the digital display window. If you dial back past "00", refer to Troubleshooting Tip #7.

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5. Preparing the Injection Site

- Choose an appropriate site for injection as instructed by your healthcare professional. Using an alcohol swab, apply firm pressure to the injection site and rub outward in increasingly larger circles. Do not retrace your steps. Let the alcohol dry a few seconds before injecting.

NOTE: Humatrope should be injected subcutaneously (under the skin). Rotate injection sites daily. See the Injection Site Chart on pages XX-XX and talk to your healthcare professional about injection site rotation.

If you have questions, call 1-800-847-6988

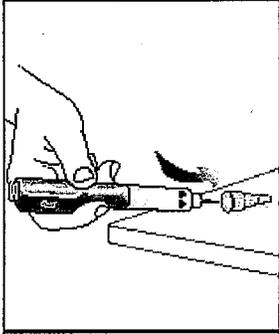


6. Injecting the Humatrope Dose

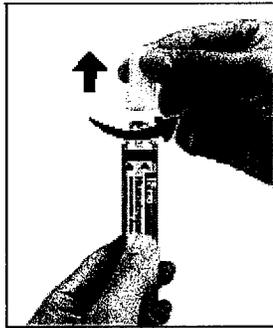
- Gently pinch up a large area of skin. Quickly push the pen needle into the skin, as instructed by your healthcare professional.
- Inject the dose of Humatrope by slowly pushing the dosage knob in until it locks in place, then slowly count to five (5). Let go of the pinched-up area of skin. Then pull the pen needle straight out.
- After injection, the dosage setting will stay in the digital display window. The display will turn off after two (2) minutes.

NOTE: It is normal for a small drop of Humatrope solution to form on the pen needle tip after removing it from the skin. It is also quite common to see a small drop of Humatrope solution or blood on the skin at the injection site. Simply apply pressure to the site.

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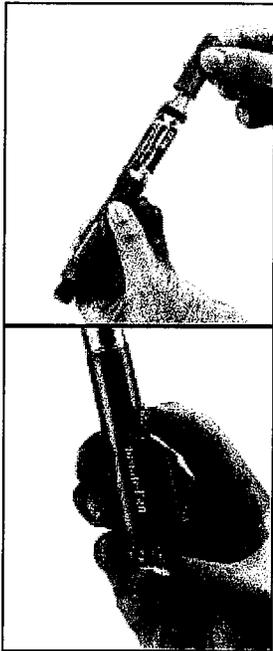


- Carefully replace the needle outer shield as instructed by your healthcare professional.



- Remove the capped needle by turning counterclockwise and throw it away as instructed by your healthcare professional.

If you have questions, call 1-800-847-6988



- Recap the HumatroPen, leaving the cartridge in place. Make sure the dosage knob is locked in place. If it is not, push the dosage knob in until you feel it lock in place.

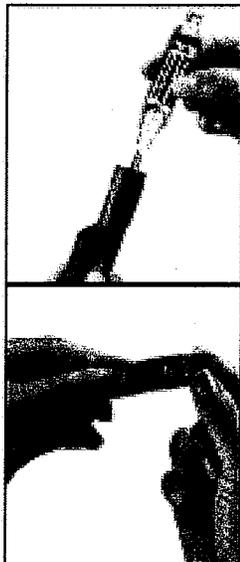
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for injection**



- Store the HumatroPen with attached Humatrope cartridge in the blue protective storage case in the refrigerator until the time of the next injection. **DO NOT FREEZE.**
- At the time of the next injection from the same cartridge, reinspect the solution for clarity as described in your Humatrope Cartridge Kit. Making sure the cartridge remains snug, attach a new (sterile) pen needle as described in Step 2, on page XX. To dial and inject the dose, proceed from Step 4, on page XX.

If you have questions, call 1-800-847-6988

Replacing a Cartridge



When a Humatrope cartridge needs to be replaced:

- Wash your hands.
- Remove the pen cap.
- Unscrew the empty cartridge from the HumatroPen.
- Dispose of the cartridge as directed by your healthcare professional.
- Check that the threaded metal rod is completely wound back into the HumatroPen. To rewind the threaded metal rod, press and hold in the blue reset button, and turn the dosage knob counterclockwise (in the direction opposite to the arrow on the end of the dosage knob) until it stops.

NOTE: Do not use excessive force when turning the dosage knob. If the dosage knob does not turn, it is already in the correct position.

- Return to the top of page XX, and follow all of the remaining *Steps for Using the HumatroPen Injection Device*.

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Cleaning the HumatroPen Injection Device

The body of the HumatroPen may be wiped with a cloth slightly dampened with water only. **DO NOT IMMERSE THE HUMATROPEN IN WATER.**

Injection Site Chart

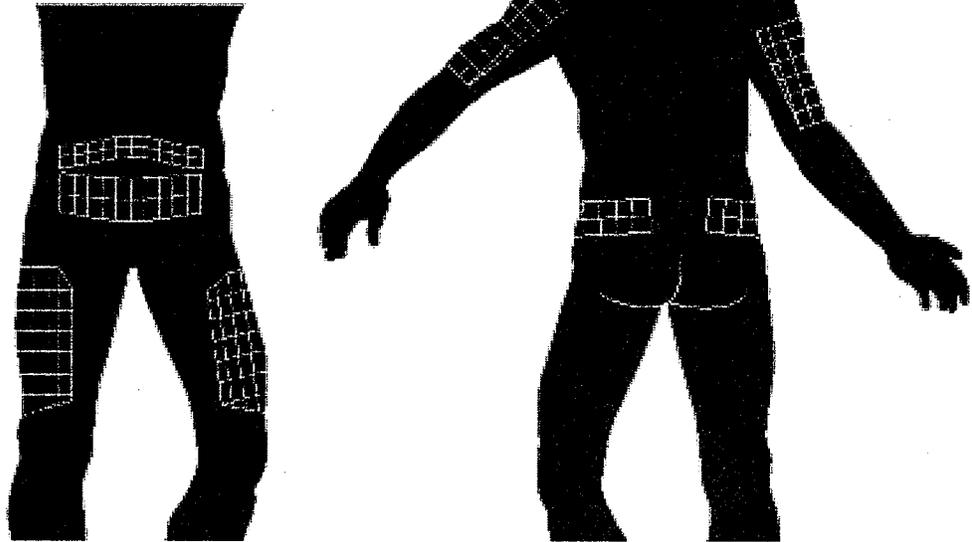
Injections can be given in the following areas:

- Abdomen (above, below, or either side of the navel)
- Front of the upper thighs
- Upper, outer buttocks
- Back of the arms above the elbow and below the shoulder

Discuss the appropriate injection sites and site rotation with your healthcare professional.

If you have questions, call 1-800-847-6988

Discuss the appropriate injection sites and site rotation with your healthcare professional.



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for injection**

Determining the Humatrope Dose

Your healthcare professional should discuss the prescribed dose and the appropriate dosage setting with you. The following conversion chart illustrates the relationship between the prescribed dose and the dosage setting (number of clicks) on your HumatroPen. If you have any questions, ask your healthcare professional.

If you have questions, call 1-800-847-6988

Conversion Chart

After Reconstitution

Clicks	Volume (mL)	6 mg Cartridge Dose (mg)	12 mg Cartridge Dose (mg)	24 mg Cartridge Dose (mg)
1	0.05	0.1	0.2	0.4
2	0.10	0.2	0.4	0.8
3	0.15	0.3	0.6	1.2
4	0.20	0.4	0.8	1.6
5	0.25	0.5	1.0	2.0
6	0.30	0.6	1.2	2.4
7	0.35	0.7	1.4	2.8
8	0.40	0.8	1.6	3.2
9	0.45	0.9	1.8	3.6
10	0.50	1.0	2.0	4.0
11	0.55	1.1	2.2	4.4
12	0.60	1.2	2.4	4.8

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Commonly Asked Questions

How should I store the Humatrope cartridges and the HumatroPen?

Cartridges-Humatrope must be kept refrigerated (36° to 46°F or 2° to 8°C) before and after reconstitution. **DO NOT FREEZE.** Store the HumatroPen with the Humatrope cartridge attached in the refrigerator until time of the next injection. Reconstituted Humatrope must be used within 28 days. Discard any remaining Humatrope after 28 days. Check the date on the cartridge. **Do not** use the cartridge if it has expired.

HumatroPen-Store the HumatroPen with the dosage knob locked in the depressed position. Store the HumatroPen with the Humatrope cartridge attached in the blue protective storage case in the refrigerator until the time of the next injection. **Do not store the HumatroPen with the pen needle attached because this could cause a safety hazard. DO NOT FREEZE.**

If you have questions, call 1-800-847-6988

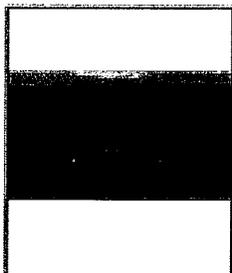
When should I attach a new pen needle to the HumatroPen?

Use a new pen needle for each injection. Do not attach a pen needle until you are ready to use the HumatroPen. **Pen needles are to be used one (1) time only and then discarded properly.**

What is the lifetime of the HumatroPen?

The HumatroPen should last approximately two (2) years from the first use. However, the lifetime may vary by a few months. When the pen is about to expire, "≡" will appear in the digital display window. Please call Eli Lilly and Company at 1-800-847-6988 for assistance. The digital display window will show "≡≡" when the pen has expired and should no longer be used.

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for injection**



How will I know if my HumatroPen battery is low?

When "bt" (see adjacent photo) appears in the digital display window, this indicates that the HumatroPen has a low battery. It is time to replace the injection device immediately. Call Eli Lilly and Company at 1-800-847-6988 for assistance.

If you have questions, call 1-800-847-6988

Troubleshooting Tips

It may be helpful to refer to the fold-out diagrams on the inside front cover, page X, as you review these tips.

1. Problem: The Humatrope cartridge and HumatroPen injection device will not screw together.

Action: The threaded metal rod in the injection device may not be completely wound back.

- Check to make sure the dosage knob is unlocked by pressing the white release button.
- Turn the injection device so the dosage knob on the end is facing you.
- Press and hold down the blue reset button and turn the dosage knob counterclockwise (in the direction opposite the arrow on the end of the dosage knob).
- **Make sure you turn the dosage knob until it stops.** This will retract the threaded metal rod in the injection device.
- Screw the white-tipped end of the cartridge onto the HumatroPen, as described on page XX.

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2. Problem: Humatrope solution is not clear after mixing.

Action: Gently invert the HumatroPen up and down ten (10) times. **DO NOT SHAKE.** Then let the HumatroPen sit for at least three (3) minutes. If the Humatrope solution remains cloudy or contains particles, then gently invert the HumatroPen up and down ten (10) more times. Let the HumatroPen sit for five (5) more minutes. **The Humatrope solution should then be clear. If the solution remains cloudy or contains particles, the contents MUST NOT be injected.** Call your healthcare professional or Humatrope provider.

3. Problem: The small white plastic piece in the end of the cartridge moves when the dosage knob is unlocked.

Action: This is normal. The white plastic piece may move freely inside the cartridge.

If you have questions, call 1-800-847-6988

4. Problem: Dosage knob is unlocked and display turns off **before** dose is dialed.

Action: The display will turn off after two (2) minutes to save battery life. The display can be reactivated by pressing down the dosage knob until it locks in place. Press the white release button. The dosage knob will be unlocked, and the numbers "00" will appear in the digital display window.

5. Problem: Dosage knob is unlocked and display turns off **after** dose is dialed.

Action: The display will turn off after two (2) minutes to save battery life. If you are unsure of the dosage setting, press and hold in the blue reset button and slowly turn the dosage knob counterclockwise (in the direction opposite to the arrow on the end of the dosage knob) until the digital display turns back on. Then release the reset button and turn the dosage knob clockwise, in the same direction of the arrow, until you reach the prescribed dose. Proceed with the injection.

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6. Problem: You have over-dialed the dose.

Action: Press and hold in the blue reset button and turn the dosage knob counterclockwise (in the direction opposite to the arrow on the end of the dosage knob) until the correct dosage setting appears in the digital display window.

7. Problem: You have dialed back past "00".

Action: DO NOT PUSH IN THE DOSAGE KNOB. Two dashes "--" will appear in the digital display window. Dial the dosage knob forward again in the direction of the arrow. The "00" should reappear in the digital display window. Follow the steps to dial the number of dosage knob clicks that corresponds to the prescribed dose as described on pages XX-XX.

If you have questions, call 1-800-847-6988

8. Problem: Full dose cannot be dialed.

Action: The Humatrope cartridge does not contain a full dose. Follow the procedure recommended by your healthcare professional at the start of therapy.

9. Problem: After the Humatrope cartridge is changed, the dosage knob is stuck and will not turn.

Action: Please call Eli Lilly and Company at 1-800-847-6988 for instructions on replacing the HumatroPen.

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10. Problem: Dosage knob is dialed beyond the maximum dose — dosage setting of 12 (twelve).

Action: The dose is still accurate up to the dosage setting of 12. However, the additional drug dose beyond the maximum dose of 12 will be wasted. (Humatrope solution will flow out from the pen needle tip as you dial past 12.) To dial back, see Troubleshooting Tip #6, on page XX.

11. Problem: After insertion of the needle through the skin, the dosage knob will not depress.

Action: First withdraw the needle from the skin. Check to make sure the pen needle is screwed on tightly. If the needle is tight, then the problem could be a clogged pen needle. Replace the pen needle.

If you have questions, call 1-800-847-6988

12. Problem: Following an injection, Humatrope solution continues to drip out of the pen needle.

Action: Air bubbles may be present in the cartridge. Before dialing the next dose, follow Step 3, *Priming the HumatroPen Injection Device*, on pages XX-XX. See also Step 6, *Injecting the Humatrope Dose*, on page XX.

13. Problem: A click sound is not heard when the dosage knob is depressed.

Action: The sound level of the HumatroPen dosage knob varies depending on dose size, speed of pressing dosage knob, and the injection device itself. As long as the knob locks in place, the HumatroPen is working properly.

**Humatrope®
somatotropin (rDNA origin)
for injection**

14. Problem: Display shows "≡" instead of "00".

Action: The expected life of the HumatroPen is about to expire. The display will work for approximately another four (4) weeks before it shuts off automatically. The mechanical parts of the pen will remain functional. Please call Eli Lilly and Company at 1-800-847-6988 for instructions on replacing the HumatroPen.

15. Problem: Flashing "--" or "00" appears in the digital display window.

Action: You may have dialed too quickly or slowly. A flashing "--" or "00" indicates that a counting error may have occurred. **DO NOT INJECT.** Point the pen away from your face, depress the dosage knob until a click is heard as the number locks in place, and continue preparing your dose by following Step 4, *Dialing the Prescribed Dose*, on pages XX-XX.

If you have questions, call 1-800-847-6988

16. Problem: With a Humatrope cartridge attached to the HumatroPen, the dosage knob does not fully extend when the white release button is pressed.

Action: Loosen the cartridge by turning the cartridge $\frac{1}{4}$ turn in a clockwise direction (in the same direction as the arrow on the end of the dosage knob). The dosage knob should now fully extend. Retighten the cartridge. Turn the dosage knob in the direction of the arrow marked on its end until "01" appears in the digital display window. Push in the dosage knob until it locks in place. Press the white release button. Before dialing the next dose, follow Step 3, *Priming the HumatroPen Injection Device*, on pages XX-XX. If the dosage knob still does not fully extend, please call Eli Lilly and Company at 1-800-847-6988 for instructions on replacing the HumatroPen.

Humatrope®
somatropin (rDNA origin)
for injection

17. Problem: How can I check that the medication comes out of my pen when I push the dosage knob?

Action: If you suspect that your pen may have been damaged, you can check that your pen is delivering the medication by performing the steps below.

1. Hold pen with needle pointing upright and away from your face.
2. Remove needle container and needle cap.
3. Depress the dosage knob until it locks in place.
4. You should hear or feel a click when the dosage knob is fully depressed.
5. A drop of liquid may appear at the tip of the needle.
6. Unlock the dosage knob by pressing the white release button.
7. Turn the dosage knob as indicated by direction of the arrow on the end of the dosage knob until "01" appears in the digital display window and a click is heard or felt.
8. Depress the dosage knob until it locks in place.
9. The check is complete when liquid is seen at the tip of the needle.
10. If liquid does not appear repeat Steps 6, 7, and 8 above until at least a drop of liquid is seen.
11. If liquid does not appear after repeating the procedure several times, please call Eli Lilly and Company at 1-800-847-6988 for instructions on replacing the HumatroPen.

If you have questions, call 1-800-847-6988

Replacement of the HumatroPen

Eli Lilly and Company ("Lilly") will replace this HumatroPen for the HumatroPen user without charge at any time, if the pen is damaged or stops working properly, or if the low battery indicator ("bt") or the expiration indicator ("≡") is displayed in the digital display window of the pen.

To return the HumatroPen for replacement, please call 1-800-847-6988 toll-free for instructions.

If you are concerned that the HumatroPen may not be working properly, please call 1-800-847-6988 toll-free for assistance.

Lilly's replacement of the HumatroPen for the HumatroPen user without charge is the user's only remedy for any claim relating to the HumatroPen. Lilly is not liable for incidental or consequential damages.

Humatrope®
somatropin (rDNA origin)
for injection

Manufactured for Eli Lilly and Company
Pharmaceutical Delivery Systems
Indianapolis, IN 46285, USA

Packaged by Lilly France S.A.S.
F-67640 Fegersheim, France

Made in Switzerland

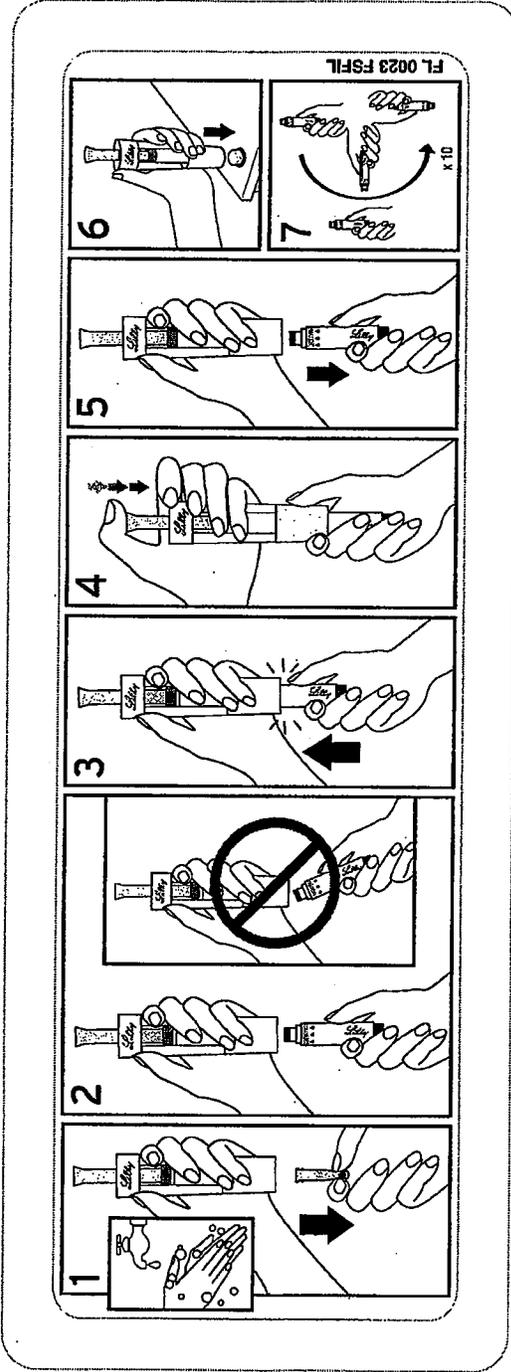
www.lilly.com
1-800-847-6988
www.humatrope.com

June 2005

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US Patent Nos. 5,334,162; 5,383,865; and 5,454,786.

PA 9184 FSAMP

Lilly



FL 0023 FSFIL

LILLY FRANCE - Egersheim PRINTED PACKAGING DEVELOPMENT RESPONSIBLE	ITEM CODE F0023FSFIL	PREVIOUS ITEM CODE N/A	FINISHED PRODUCT CODE MSS551	Approved by: NAME: _____ DATE: _____	Created by: 
	SIZE (mm) 100 x 210	SICK CODE FILE N° 04R098	<input checked="" type="checkbox"/> Trade <input type="checkbox"/> Hospital <input type="checkbox"/> Sample	Approved by: NAME: _____ DATE: _____	Checked by: Signature: _____ Date: _____
NB OF PAGES 1/1	1/3 BLACK 2/3 PMS 486 3/5 CYAN	PROOF N°: 4 DATE: 06 July 2004			
					



(01)10300027554010

6 mg

NDC 0012-7564-0
YL7555

Humatrope®
somatropin (rDNA origin)
for injection

Rx only

Refrigerate • Do Not Freeze • Do Not Shake

6 mg cartridge

for use with the Humatrope®

Isomatropin (rDNA origin) for injection

pen injection device.

Manufactured by Lillyfranca S.A.S., F-03140 Fegagnano, France
for Eli Lilly and Company, Indianapolis, IN 46165, USA

YL 0630 FSAMX

Control No. / Exp. Date





(01)10300027556017

12 mg NDC 0002-7555-01
VL7555

Humatrope®
somatropin (rDNA origin)
for injection
Rx only

Refrigerate • Do Not Freeze • Do Not Shake
12 mg cartridge

for use with the Humatrope®
(somatropin rDNA origin) for injection
pen injection device

Manufactured by Lilly France S.A.S., F-91940 Evry-Courcouronnes, France
for Eli Lilly and Company, Indianapolis, IN 46168, USA

YL 0540 FSAMX

Control No. / Exp. Date





(01)10300027556014

24 mg

HBC 0002-7556-01
VL7556

Humatrope®
somatropin (rDNA origin)
for injection

Rx only

Refrigerate • Do Not Freeze • Do Not Shake

24 mg cartridge

for use with the Humatrope®

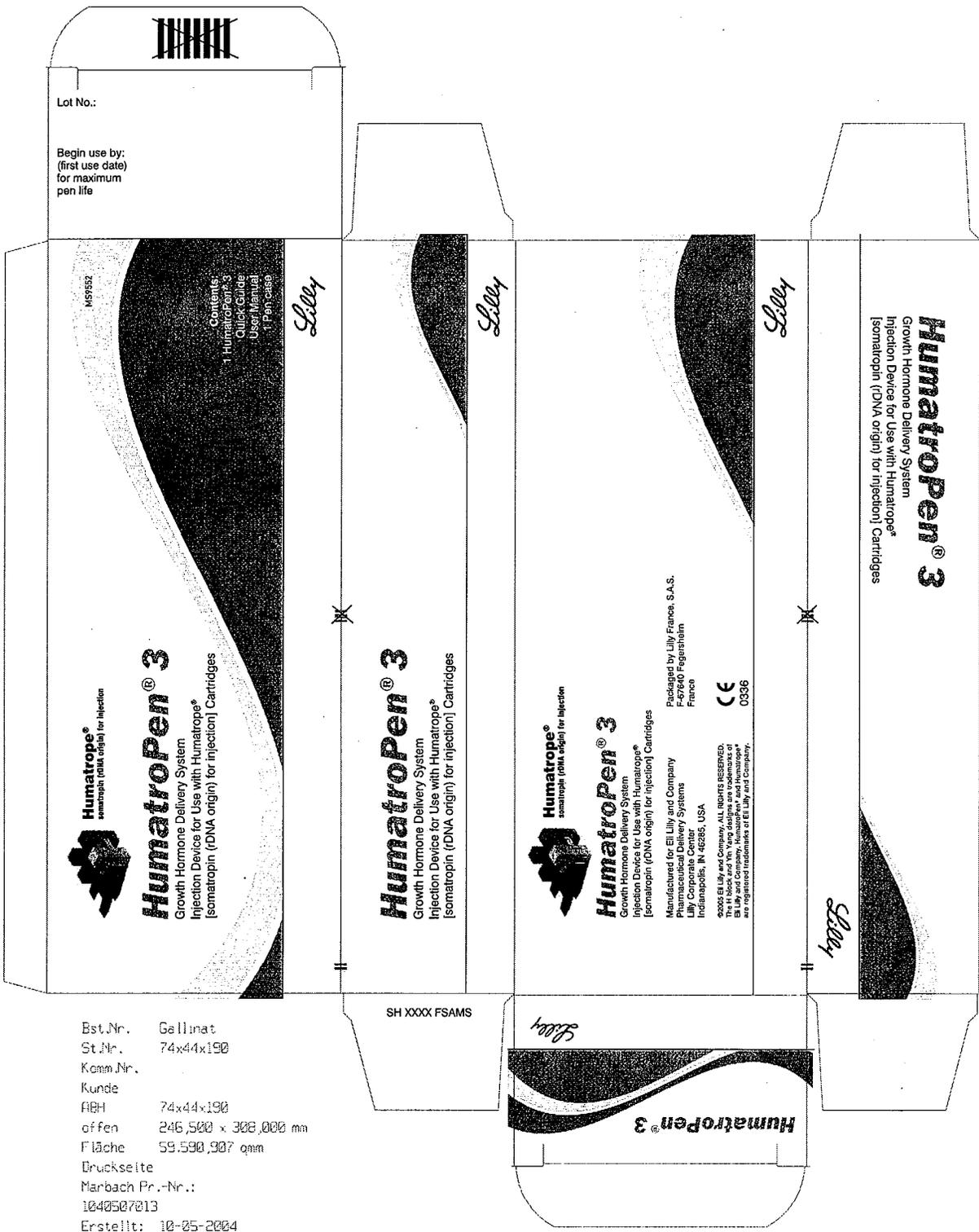
Isomatropen (rDNA origin) for injection
pen injection device

Manufactured by Lilly France S.A.S., F-93560 Fresnes en France
for Eli Lilly and Company, Indianapolis, IN 46285, USA

VL 0550 FSAMX

Control No. / Exp. Date





Lot No.:
Begin use by:
(first use date)
for maximum
pen life

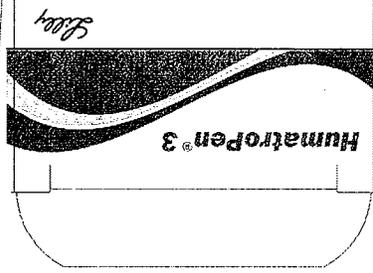
MS9552
Contents:
1 Humatrope® 3
Quick Guide
User Manual
1 Pen case
Humatrope®
[somatotropin (DNA origin) for injection]
Humatrope® 3
Growth Hormone Delivery System
Injection Device for Use with Humatrope®
[somatotropin (DNA origin) for injection] Cartridges

Humatrope® 3
Growth Hormone Delivery System
Injection Device for Use with Humatrope®
[somatotropin (DNA origin) for injection] Cartridges

Humatrope®
[somatotropin (DNA origin) for injection]
Humatrope® 3
Growth Hormone Delivery System
Injection Device for Use with Humatrope®
[somatotropin (DNA origin) for injection] Cartridges
Manufactured for Eli Lilly and Company
Pharmaceutical Delivery Systems
Lilly Corporate Center
Indianapolis, IN 46285, USA
Packaged by Lilly France, S.A.S.
F-67610 Fegersheim
France
CE 0336
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Eli Lilly and Company, Humatrope® and Humatrope®
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Bst.Nr. Gallinat
St.Nr. 74x44x190
Komm.Nr.
Kunde
AGH 74x44x190
offen 246,505 x 300,000 mm
Fläche 59.590,907 mm²
Druckseite
Marbach Pr.-Nr.:
1040507013
Erstellt: 10-25-2004

SH XXXX FSAMS



LILLY FRANCE - Fegersheim PRINTED PACKAGING DEVELOPMENT	ITEM CODE SHMAD016AM	PREVIOUS ITEM CODE (TO BE DESTROYED)	1/4 BLACK	FINISHED PRODUCT CODE MS9552	Approved by: NAME: _____ DATE: _____ Signature: _____	Created by:
RESPONSIBLE Nathalie Claude	SIZE (mm) 74 x 44 x 190	SICK CODE FILE N° MAQUETTE	2/4 CYAN	<input checked="" type="checkbox"/> Trade 001AM <input type="checkbox"/> Hospital <input type="checkbox"/> Sample	Approved by: NAME: _____ DATE: _____ Signature: _____	Checked by:
	NB OF PAGES 1/1	PROOF N°: 2 DATE: 28 January 2005	3/4 MAGENTA			Checked by: DATE: _____

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

19-640 /S022

CHEMISTRY REVIEW(S)

CHEMISTS REVIEW		1. ORGANIZATION DMEDP II, HFD-510	2. NDA NUMBER 19-640
3. NAME AND ADDRESS OF APPLICANT Eli Lilly and Co. Lilly Technology Center Indianapolis IN 46285		4. SUPPLEMENT NUMBER, DATE SCF-022 3-3-98	
5. PROPRIETARY NAME Humatrope	6. NAME OF THE DRUG Somatropin (rdna origin) for injection	7. AMENDMENTS, REPORT, DATE 8-17-98	
8. SUPPLEMENT PROVIDES FOR A additional drug substance manufacturing facility in Speke UK as well as a new drug product formulation/presentation in 6, 12, and 24 mg multiple-use cartridges, each to be supplied with a separate diluent syringe, and dosed via a re-useable "pen" device.			
9. PHARMACOLOGICAL CATEGORY Growth hormone	10. HOW DISPENSED RX	11. RELATED IND, NDA, DMF	
12. DOSAGE FORM injection	13. POTENCY 5 mg vials and, 6, 12, and 24 mg cartridges		
14. CHEMICAL NAME AND STRUCTURE See Chemistry Review #1			
15. COMMENTS Chemistry Review #2. An approvable letter was sent to the sponsor after review of the original application and three amendments (see original chemistry review dated 8-7-98). Primarily, there were several deficiencies in the microbiology section of the application, which the sponsor has subsequently addressed in the amendment of 8-17-98. The microbiology reviewer has reviewed this amendment and recommended the application be approved on the basis of sterility assurance (see microbiologist's review #2 dated 10-16-98). Also, the sponsor provided some labeling changes, at the request of the Agency, in the 8-17-98 amendment. These included primarily, inclusion of the generic name with the trade name on all images of the pen device throughout all labeling presentations, _____ the cartridges are supplied separately. No further CMC issues exist for this application. An amendment containing minor biopharm information was submitted on 8-7-98.			
16. CONCLUSION AND RECOMMENDATION The revised labeling provided in the 8-17-98 amendment is acceptable. The sponsor's responses to the microbiology deficiencies have been reviewed, and the application has been recommended for approval on the basis of assurance of sterility. The Biopharmaceutics review of the original application and the 8-7-98 amendment should be consulted concerning the approvability of the application. No further CMC issues exist for this application, and it may be approved based on chemistry review.			
17. NAME WILLIAM K. BERLIN	18. REVIEWERS SIGNATURE	19. DATE COMPLETED 10-20-98	
DISTRIBUTION: ORIGINAL JACKET		CSO	REVIEWER DIVISION FILE

AP

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
19-640/S022

MICROBIOLOGY REVIEW(S)

D. CONCLUSIONS:

The submission is recommended for approval for microbiology issues concerning sterility assurance. Specific comments are provided in section "E. Review Notes".

Neal Sweeney, Ph.D.

cc: NDA 19-640/SCF-022
HFD-510/C.King/W.Berlin
HFD-805/Consult File/N. Sweeney

Drafted by: N. Sweeney, October 16, 1998
R/D initialed by P. Cooney, October 16, 1998

2 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process

Withheld Track Number: Microbiology-19640
5022
MICROA 2

REVIEW FOR HFD-510

OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805
Microbiologist's Review #1 of NDA 19-640 SCF-022
July 30, 1998

- A. 1. **APPLICATION NUMBER:** NDA 19-640 SCF-022
- APPLICANT:** Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
(317) 276-2000
2. **PRODUCT NAME:** Humatrope® (Somatropin, rDNA origin)
3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** Somatropin (rDNA origin) Injection, 5 mg, 6 mg, 12 mg, and 24 mg cartridges. For subcutaneous or intramuscular injection.
4. **METHODS OF STERILIZATION:** Cartridge: / ~~_____~~
Diluent Syringe: / ~~_____~~ /
5. **PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:** Polypeptide hormone which has an amino acid sequence identical to that of human growth hormone. The drug product is indicated for pediatric and adult growth hormone deficiencies and Turner Syndrome.
- B. 1. **DATE OF INITIAL SUBMISSION:** March 3, 1998
2. **RELATED DOCUMENTS:** (none)
3. **DATE OF CONSULT:** March 16, 1998
4. **ASSIGNED FOR REVIEW:** April 8, 1998
5. **SUPPLEMENT PROVIDES FOR:** (1) Three additional (6 mg, 12 mg, and 24 mg) product presentations, (2) Eli Lilly (Liverpool, UK) as a second manufacturing site for the drug substance, and (3) updated method of drug substance manufacture.
- C. **REMARKS:** Humatrope cartridges are intended for use exclusively with the HumatroPen (a.k.a. Insulin Pen Injector) delivery device. As agreed during the 3/6/97 pre-NDA supplement meeting, HumatroPen is part of a drug-device combination product, and CDER will be the lead center for review of the

submission. A 5mg Humatrope vial and diluent vial drug product are currently marketed in the U.S.

D. CONCLUSIONS:

The submission is approvable pending resolution of microbiology issues. Specific comments are provided in section "E. Review Notes" and "List of Microbiology Comments and Deficiencies".

Neal Sweeney, Ph.D.

cc: NDA 19-640 SCF-022
HFD-510/C.King/W.Berlin
HFD-805/Consult File/N. Sweeney.

Drafted by: N. Sweeney, July 30, 1998
R/D initialed by P. Cooney, July 30, 1998

13 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
19-640/S022

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 19-640/SCF-022	SUBMISSION DATE:	07-AUG-98
BRAND NAME:	Humatrope®	
GENERIC NAME:	somatropin, rDNA, for injection	
REVIEWER:	Robert M. Shore, Pharm.D.	
SPONSOR:	Eli Lilly and Co., Indianapolis, IN	
TYPE OF SUBMISSION:	BB: Supplemental information	

SUBMISSION:

The sponsor submitted results of a 4-period, 4-treatment crossover bioequivalence study between their marketed 5 mg vial and three test treatments – two new cartridges of Humatrope (6 and 24 mg) and the vial formulation administered / ~~_____~~ / It should be noted that the sponsor is seeking approval of a third cartridge – 12 mg – but since the 12 and 24 mg cartridges are proportional in their ingredients, the bioequivalence study included only the higher strength formulation. These data were actually reviewed under IND 27,032 in 1993-1995. The conclusion from the 4-way ANOVA was that the two new cartridges failed to demonstrate bioequivalence with the marketed vial formulation. After these conclusions were conveyed to the sponsor under the NDA, the Agency received a response which included a re-analysis of the data with exclusion of the /~~---~~/ arm of the study due to higher variability in that arm as compared to the other three arms. This re-analysis would have allowed for the conclusion of bioequivalence between the two cartridges and the marketed formulation. The Office of Epidemiology and Biostatistics / Quantitative Methods and Research Staff (QMRS) was consulted as to whether or not such a *post hoc* re-analysis was acceptable. The statistical consult can be found in Appendix 1.

DISCUSSION:

The results of the re-analysis were found to be acceptable by QMRS. Therefore, OCPB is revising the 'Not Approvable' recommendation from the original review of NDA 19-640/SCF-022 in accordance with the statistical consult. The re-analysis of the bioequivalence study indicated that the 90% confidence interval (90%CI) for C_{max} and AUC_{inf} for the 6 mg cartridge was within the acceptable interval of (80%-125%). For the 24 mg cartridge, the 90% CI for AUC_{inf} was acceptable but C_{max} failed – the upper bound of the 90%CI was 126%. In discussion with the Medical Division it was decided that C_{max} was inherently more variable and less clinically relevant than AUC_{inf}, thus the Medical Division was willing to approve the 24 mg cartridge.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 19-640/SCF-022 BB submitted 07-AUG-98 and finds that the re-analysis of the bioequivalence study is acceptable. As such, OCPB recommends approval of the new cartridge strengths (6, 12, and 24 mg) based on this re-analysis. This recommendation should be conveyed to the sponsor.

Robert M. Shore, Pharm.D.
Division of Pharmaceutical Evaluation II (DPE-2)
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 28-AUG-98
RD initialed by Mei-Ling Chen, Ph.D., DPE-2 Division Director 01-SEP-98

FT initialed by Hae-Young Ahn, Ph.D., Team Leader _____

CC: NDA 19-640/SCF-022 (orig.,1 copy), HFD-510(King, Malozowski), HFD-870(Ahn, ChenME), HFD-850(Lesko), HFD-705(HigginsKar), CDR (Barbara Murphy).

Code: AP

Appendix 1. Statistical Consult

August 20, 1998

The problem

A company proposed to do a bioequivalence study with a reference growth hormone (treatment D). There were two objectives: 1) was the reference bioequivalent to two new preparations (treatments B and C) and 2) was the reference bioequivalent to ~~injection~~ injection (treatment A). The study was a 4 period, 4 treatment study and all 3 comparisons were going to be made in the analysis. When the analysis was conducted it was found that treatments D and A were very different and did not pass the test for bioequivalence. Treatment A had a higher variability than the rest of the treatments. The other two treatments also failed the test for bioequivalence though the 90% confidence intervals were much closer to being within the 80 to 125% boundaries. The company decided to abandon treatment A and they reanalyzed the data without treatment A. The confidence intervals of treatments B and C based on this reduced data set were contained within the 80 to 125% boundaries.

From a regulatory perspective, the company stated that they would analyze all three treatments with the reference and it is not clear if they should be able to change their analysis based on negative results. If treatment A was decreasing the overall variability and thereby helping B and C pass, they would certainly not choose to remove it based on statistical issues. However, statistically, this is a valid argument. The statistical analysis used does assume that the 4 treatments have equal variability and, if one of the treatments has very different variability, it should be removed from the analysis. Also, the removal of one or more treatments from the analysis of a bioequivalence study has been done in the past, especially for cases where the treatment removed was somehow different from the remaining treatments. This does seem to be the case in this study. Treatment A ~~is obtaining lower blood levels than the other treatments~~ and it is obtaining lower blood levels than the other treatments.

In reviewing the data we found that treatment A does have the largest variability among the four treatments and with its removal from the data set, the confidence intervals for treatments B and C become more narrow. In fact, treatment B will pass the test for bioequivalence for all three parameters and treatment C will pass for the two AUC parameters and will fail for C_{max} with an upper bound of only 1.26.

There is another possible argument for the analysis of this data. It could be argued that each comparison made from this study should be made with the other treatments removed from the data set. For example, when doing the analysis comparing B and D, A and C would be removed from the data set. In these case where all the treatments except for the two being compared are removed from the analysis, B will still pass the test for bioequivalence, though C will fail on all parameters. This is happening because just as A increases the variability when it is present, B decreases the variability. When only treatments C and D are included in the data set the variability is large enough to cause that upper bounds of the confidence intervals to be greater than 125%.

Additional Information

The treatment labeling is as follows:

- A = HumatropeR
- B = HumatropeR Pen formulation 18 IU
- C = HumatropeR Pen formulation 72 IU
- D = HumatropeR Standard syringe

The Variability

The following table gives some non model based summary statistics for the raw values of the parameters, i.e., not dose-normalized. Formulation A does have the largest CV. Formulation B, C, and D are more comparable with B having the smallest variability and C the largest of the three.

Parameter		A	B	C	D
Cmax	Mean	13.0	52.1	56.7	52
	std. dev.	5.4	9.36	21.4	15.2
	CV%	41%	18%	38%	29%
	mean of ln values	2.46	3.94	3.98	3.91
	std. dev ln values	.52	.18	.35	.29
AUCt	Mean	115.6	467.9	507.5	436.9
	std. dev.	49.4	73.5	122.8	99.8
	CV%	43%	16%	24%	23%
	mean of ln values	4.63	6.14	6.16	6.05
	std. dev ln values	.56	.15	.28	.24
AUCinf	Mean	123.7	487.8	507.5	448.4
	std. dev.	49.5	81.5	122.8	98.4
	CV%	40%	17%	24%	22%
	mean of ln values	4.72	6.18	6.20	6.08
	std. dev ln values	.49	.16	.28	.23

We constructed a table similar to one constructed by the sponsor that contains the within subject variability on the log scale and the corresponding CV for Cmax, AUCt, and AUCinf based on the model used in the analysis. The raw data was used with five data sets corresponding with different formulations removed. As you can see, the largest variability is seen with A and D only, since A has the largest variability. The full data set has a high CV but once A is removed (B, C, and D) the variability decreases substantially. The smallest variability is seen with B and D only.

PK Parameter	Data Set	Within-subj. var. on log scale	CV on Natural Scale ¹
C _{max}	A and D only	0.165	42.4 %
	B and D only	0.034	18.6 %
	C and D only	0.079	28.7 %
	B, C, and D	0.063	25.5 %
	Full	0.109	33.9 %
AUC _t	A and D only	0.148	39.9 %
	B and D only	0.008	9.0 %
	C and D only	0.039	19.9 %
	B, C, and D	0.026	16.2 %
	Full	0.086	30.0 %
AUC _{inf}	A and D only	0.114	34.7 %
	B and D only	0.007	8.4 %
	C and D only	0.033	18.3 %
	B, C, and D	0.024	15.6 %
	Full	0.066	26.1 %

¹ sqrt(exp(variance)-1)

The Equivalence Analysis

The sponsor conducted their analysis on their dose-normalized C_{max}, AUC_t and AUC_{inf}, though it was not clear how the sponsor conducted their dose-normalizing. We conducted the equivalence analysis using the raw values of the pharmacokinetic parameters, the sponsor's dose-normalized parameters, and our calculated dose-adjusted parameters. We calculated the dose-adjusted parameters by dividing the raw pharmacokinetic parameters by the dose. The following table contains the 90% confidence intervals of the ratio for all three types of parameters. Note that the sponsor's dose-normalized C_{max} is identical to our dose-adjusted C_{max}, the sponsor's dose-normalized AUC_t is almost identical to the raw AUC_t, and that the sponsor's dose-normalized AUC_{inf} is almost identical to our dose-adjusted AUC_t.

Parameter	Data set	Raw Values	Sponsor's Normalized	Adjusted (Raw/Dose)	Pass or Fail
B vs. D					
Cmax	Full	(85, 128)	(85, 128)	(85, 128)	Fail
	Reduced	(89, 122)	(89, 121)	(89, 121)	Pass
	Only B and D	(92, 117)	(92, 117)	(92, 117)	Pass
AUCt	Full	(92, 133)	(93, 133)	(92, 132)	Fail
	Reduced	(100, 122)	(100, 122)	(100, 122)	Pass
	Only B and D	(104, 118)	(104, 118)	(104, 118)	Pass
AUCinf	Full	(96, 131)	(92, 132)	(96, 131)	Fail
	Reduced	(102, 123)	(100, 122)	(102, 123)	Pass
	Only B and D	(106, 118)	(104, 118)	(106, 118)	Pass
C vs. D					
Cmax	Full	(89, 133)	(88, 133)	(88, 133)	Fail
	Reduced	(93, 127)	(93, 126)	(93, 126)	Fail
	Only C and D	(92, 133)	(92, 132)	(92, 132)	Fail
AUCt	Full	(94, 135)	(94, 135)	(94, 135)	Fail
	Reduced	(102, 124)	(102, 124)	(102, 124)	Pass
	Only C and D	(99, 129)	(99, 129)	(100, 128)	Fail
AUCinf	Full	(97, 134)	(94, 135)	(97, 133)	Fail
	Reduced	(103, 125)	(102, 124)	(103, 125)	Pass
	Only C and D	(101, 129)	(100, 128)	(102, 128)	Fail

Conclusion

Since removal of a treatment in a bioequivalence study has been done previously, it seems reasonable to remove treatment A in this situation. It is a clearly different type of treatment, obtains much lower mean values, and has increased variability. The issue of whether or not to further reduce the data set is less clear.

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 19-640/SCF-022 SUBMISSION DATE: 03-MAR-98, 07-JUL-98

BRAND NAME: Humatrope®

GENERIC NAME: somatotropin, rDNA, for injection

REVIEWER: Robert M. Shore, Pharm.D.

SPONSOR: Eli Lilly and Co.,
Indianapolis, IN

TYPE OF SUBMISSION: Formulation revision: new cartridge strengths

SUBMISSION:

Humatrope is a drug product manufactured by Eli Lilly which contains recombinant human growth hormone (GH). It is currently indicated for: 1) Pediatric patients who have growth failure due to inadequate secretion of normal endogenous GH (starting dosage of 0.18 mg/kg/week divided in three, six, or seven injections per week; maximum dose of 0.3 mg/kg/week), 2) pediatric patients with Turner's Syndrome (weekly dosage of up to 0.375 mg/kg in three injections per week), and 3) Adults with GH deficiency (starting dose of mg/kg/week in daily injections; maximum dose of mg/kg/week). Labeling indicates that doses should be individualized for each patient.

Currently only one formulation is available - a vial containing 5 mg lyophilized somatotropin which is injected, with a regular syringe SC or IM after reconstitution with the supplied diluent. This supplement seeks approval of three new product presentations: 6, 12, and 24 mg cartridges for use with the HumatroPen delivery device. The lyophilized powder is compositionally and proportionally similar across all three cartridge formulations; however, the diluent for the 6 mg cartridge differs from the 12 and 24 mg cartridges in the glycerin content. The formulations for the cartridges are listed in Table 1. The marketed formulation is: 5 mg somatotropin (15 IU or 225 nanomoles); 25 mg mannitol; 5 mg glycine; and 1.13 mg dibasic sodium phosphate. and/or may have been added at the to adjust the pH. The diluent for the 5 mg vial contains water for injection with 0.3% M-cresol as a preservative and 1.7% glycerin

A single blind, four-way cross-over study (N=15) involving normal, male adults was conducted to study the relative bioavailability of 1) the 6 mg cartridge, 2) the 24 mg cartridge, and 3) the currently marketed formulation administered // not relevant to this supplement). Although the 12 mg formulation was not studied, it falls between the 6 and 24 mg formulations and is similar to the 24 mg formulation; therefore, it is possible to interpolate the results for the 12 mg cartridge. The study report, along with follow-up analyses requested by the Agency, was submitted under IND 27,032 on 28-JUL-93, 09-JUN-95, and 08-DEC-95 and was reviewed by Dr. TM Chen (no new information has been submitted in the current submission). A final review by Dr. Chen on 08-DEC-95 indicated that each of the cartridge formulations tested, as well as the marketed formulation injected // was 'bioinequivalent to [the marketed formulation], based on log-transformed data for mean hGH Cmax and AUC values. There were only 2 occasions out of 60 separate data sets (for 15 subjects) where detectable but relatively low baseline serum levels of GH occurred. Therefore, no correction for baseline was employed in the PK data calculation.' The 90% confidence intervals are listed in Table 2.

Table 2. 90% Confidence Intervals for Humatrope Formulations

Parameter	Comparison	Lower Limit	Point Estimate	Upper Limit
C _{max}	6 mg vs. 5 mg	0.84	1.04	1.29
	24 mg vs. 5 mg	0.89	1.10	1.36
AUC _{0-t}	6 mg vs. 5 mg	0.91	1.10	1.34
	24 mg vs. 5 mg	0.94	1.13	1.37
AUC _{0-inf}	6 mg vs. 5 mg	0.91	1.10	1.34
	24 mg vs. 5 mg	0.93	1.13	1.37

DISCUSSION:

The proposed cartridges lack bioequivalence with the marketed formulation (i.e., the 90% CI exceeds 80-125). On average the new formulations appear to be about 5-15% more bioavailable than the current marketed formulation. On 08-JUL-98 a number of clinical issues were discussed with Dr. Malozowski (Medical Officer), including:

1. The bioequivalence study used healthy males. Endogenous GH production variability may have contributed to the intra-subject variability in GH and therefore these results may be the 'worst case' scenario. GH Deficient patients would probably show no greater, and possibly less, variability in their GH levels and therefore the results in the population of interest may be different (i.e., bioequivalence).
2. Humatrope is indicated for use in both Pediatric and Adult populations; it is used at much lower doses in Adults than in Pediatrics. Generally, the Adult population tends to show adverse effects more readily than the pediatric population. Thus, the increased bioavailability of the cartridges as compared to the marketed formulation may be a safety issue, especially in the Adult population.
3. There is more concern about starting a patient on the new formulation than in switching from the marketed formulation. Once a patient is started, he/she may become 'tolerant' to adverse effects and slight changes in systemic exposure may not have a negative impact. However, if a patient is started on a cartridge formulation which has an average greater systemic exposure from the start, there could be adverse effects.

RECOMMENDATION:

The results from a pharmacokinetic study between two of three new cartridge formulations and the current marketed 5 mg vial formulation of Humatrope indicated a lack of bioequivalence. There are a number of clinical issues regarding these results that should be addressed by the Medical Officer who should make an assessment of therapeutic equivalence for these new cartridges. However, OCPB finds that this submissions supports a recommendation of 'Not Approvable' because the new cartridges are, on average, about 5-15% more bioavailable than the marketed 5 mg vial and the 90% confidence intervals are too wide.

COMMENTS TO BE SENT TO SPONSOR:

1. Results from the pharmacokinetic study between two of three new cartridge formulations and the current marketed 5 mg vial formulation of Humatrope indicated a lack of bioequivalence. Using the two 1-sided 90% confidence interval analysis, the new cartridges were, on average, about 5-15% more bioavailable than the marketed 5 mg vial and the 90% confidence intervals exceeded the acceptable 0.8-1.25 limits. However, a final decision regarding the clinical impact of these results will be made by the Medical Officer.
-

Robert M. Shore, Pharm.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 13-JUL-98

FT initialed by Hae-Young Ahn, Ph.D., Team Leader _____

CC: NDA 19-640/SCF-022 (orig., 1 copy), HFD-510(King, Malozowski), HFD-870(Shore, Ahn, ChenME), CDR (Barbara Murphy).

Code: NA

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

19-640/S022

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Division of Metabolic and Endocrine Drug Products
CONSUMER SAFETY OFFICER REVIEW

Application Number and Submission Date:

NDA 19-640/S-022-submitted March 3, 1998
NDA 19-640/S-023-submitted March 16, 1999
NDA 19-640/S-025-submitted June 30, 1999

Name of Drug: Humatrope [Somatropin, (rDNA origin) for injection]

Sponsor: Lilly Research Laboratories

Material Reviewed:

Supplemental application S-022-FA (FPL) submitted June 30, 1999
Supplemental application S-023- FPL submitted March 16, 1999
Supplemental application S-025-FPL submitted June 30, 1999

Background and Summary

S-023 was submitted under 314.70(c) as a "Special supplement-Changes Being Effected" and provided for revisions to the CONTRAINDICATIONS and WARNINGS section of the package insert in response to our January 4, 1999 letter.

S-025 was submitted under 314.70(c) as a "Special supplement-Changes Being Effected" and contained the FPL for S-022 with some revisions to both the package insert and device labeling.

Review

S-023

The **package insert** contained in S-023 was compared to the currently approved package insert (**PA 1640 AMP, Literature revised February 12, 2001**, approved with S-026 on February 12, 2001 and FPL acknowledge and retained on August 15, 2001). All the revisions proposed in S-023 are contained in the currently approved labeling. **Therefore S-023 can be administratively closed.**

S-025

The labeling contained in S-025 contained the FPL for the approved S-022 (which provided for, among other things, a new presentation in a 6, 12, and 24 mg multiple-use cartridges, each to be supplied with a separate diluent syringe and dosed via a reuseable "pen" device) and other revisions. The supplement contained the following pieces of labeling:

Package insert.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-640\S-022

Eli Lilly & Co.
Attention: Gregory Enas, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Enas:

We acknowledge receipt of your JUNE 30, 1999 submission containing final printed labeling in response to our FEBRUARY 4, 1999 letter approving your supplemental new drug application for HUMATROPE (SOMATROPIN [RDNA ORIGIN] FOR INJECTION).

We have reviewed the labeling that you submitted in accordance with our FEBRUARY 4, 1999 letter and we find it acceptable. The package insert contained in this submission has been superceded by that approved with supplement -026.

If you have any questions, call Monika Johnson, Regulatory Project Manager, at 301-827-6370.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Kati Johnson
6/7/02 12:57:39 PM
signing for David Orloff, MD

The package insert contained in both S-022 and S-025 have been superceded by the package insert approved with supplement -026.

Patient package insert

The FPL for the package insert contained S-025 (**PA 9171 FSAMP, Literature issued March 1999**) was compared to the draft patient package insert labeling submitted March 3, 1998. The only revision made to the labeling was the addition of the statement, "Do not use excessive force while turning the dosage knob / ~~_____~~ / In Step 1. This is an acceptable editorial revision.

NOTE: In S-025, the packager insert and the patient package insert were attached via a perforation. In the FPL submitted for S-026, the PI was a freestanding document (did not contain an attached patient package insert).

Cartridge Kit Packaging

The FPL for the 6, 12, and 24 mg cartridge kits were compared to the draft labeling submitted August 17, 1998. Although the firm has revised the design of the carton, the only revisions to the text are as follows:

1. The firm has added the statement; "This container is not child resistant." To the back of the carton. The revision was mentioned in the cover letter for S-025.
2. The side of the carton has been revised from / ~~_____~~ /
/ ~~_____~~ / Manufactured by Lilly France S.A. F-67640 Fegersheim, 'France for Eli Lilly and Company, Indianapolis, IN 46285, USA"

These are acceptable editorial revisions.

The FPL for the different strength products are as follows:

6 mg cartridge kit-**SH 8740 FSAMS**

12 mg cartridge kit- **SH 8750 FSAMS**

24 mg cartridge kit- **SH 8760 FSAMS**

HumatroPen Kit Packaging

The FPL (**MS8050**) was compared to the draft labeling submitted August 17, 1998. Minor formatting changes have been made (i.e., the changing of page numbers in the Table of Contents, the statement about the use of excessive force described above in the PI labeling revisions) The firm has also included two additional "troubleshooting tips" (#15 and #16), which do not effect the safety and efficacy of the device.

Sterile Diluent for HumatroPen Injection Device

The FPL for the diluent to be used with the 6 mg cartridge (**DV3292 DVX**) and with either the 12 or 24 mg cartridges (**DV 3293 DVX**) were compared to the draft labeling submitted March 3, 1998. Other than revising the identifier numbers, they are identical

This is an acceptable editorial revision.

Conclusions

S-023 should be administratively closed.

An approval letter for S-025 should be drafted.

The currently approved labeling for Humatrope Cartridges for used with the HumatroPen injection Device are as follows:

Package Insert: **PA 1640 AMP, Literature revised February 12, 2001**

Patient Package Insert: **PA 9171 FSAMP, Literature issued March 1999**

Cartridge Kit Packaging:

6 mg cartridge kit-**SH 8740 FSAMS**

12 mg cartridge kit- **SH 8750 FSAMS**

24 mg cartridge kit- **SH 8760 FSAMS**

HumatroPen Kit Packaging: **MS8050**

HumatroPen Sterile Diluent:

For use with 6 mg cartridge-**DV 3292 DVX**

For use with 12 or 24 mg cartridge-**DV 3293 DVX**

NOTE: Although not part of these supplemental applications, in doing the labeling history of this application, it was determined that the currently approved labeling for the **VIAL** presentation is as follows:

Humatrope 5 mg (Vial No. 7335)-**YD 7772 AMX**

Sterile Diluent 5 mL (Vial No. 7336)-**YD 7782 AMX**

Carton Label (for container containing 1 vial Humatrope and 1 vial diluent)-**SF 2472 AMS**

This labeling was approved with the initial NDA (FPL submitted 2/19/87)

Kati Johnson

Chief, Project Management Staff, HFD-510

Drafted: Revised/Initialed:

Finalized:KJ 6/6/02

Filename:

PM LABELING REVIEW

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Kati Johnson
6/7/02 11:57:05 AM
CSO

FAX MEMO

DATE: August 5, 1998

APP. #: NDA 19-640/SCF-022
 Humatrope

TO: Dr. Tobias Massa
 Director, Regulatory Affairs (CM&C)

FROM: Crystal A. King, P.D., M.G.A., Project Manager
 Division of Metabolic and Endocrine Drug Products, HFD-510

RE: MICROBIOLOGY REVIEW COMMENTS
 Formulation revision: new cartridge strengths

Our microbiology reviewer, Dr. Neal Sweeney, has completed his review of your March 3, 1998, submission. Following are his comments.

1. The stability protocol for routine lots (at least one lot per year) of Diluent Syringes includes sterility, bacterial endotoxin, and Metacresol (HPLC assay) testing. However, the stability protocol for the first three diluent syringe production lots does not include antimicrobial preservative effectiveness testing. Stability preservative effectiveness should be performed using the reconstituted Humatrope drug product. For testing the stability of preservative systems in the reconstituted drug product, the first three production lots should be tested with a microbial challenge assay at the start and at the end of the stability period, and at one point in the middle of the stability test period if the test period equals or exceeds two years. The first three batches of the diluent should be assayed for the chemical content of the preservatives at all appropriate test points. Upon demonstration of chemical content commensurate with microbial effectiveness in the first three production batches, chemical assays may be adequate to demonstrate the maintenance of the specified concentrations of preservatives for subsequent lots placed into stability testing.
2. Bacterial endotoxin testing validation of the three new cartridge presentations (6 mg, 12 mg, and 24 mg) was not

included in the submission. Please submit a validation report including methodology and data supporting bacterial endotoxin testing validation for the proposed cartridges.

3. As the diluent preservative is intended to preserve the reconstituted product, preservative effectiveness validation of the reconstituted (using the diluent syringe) lyophilized Humatrope plugs should be performed. Please submit the methodology and data supporting the preservative effectiveness of the reconstituted Humatrope/diluent (6, 12, and 24 mg) products.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

Should you have any questions, please do not hesitate to contact me at 301-827-6423.

Crystal Anne King, P.D., M.G.A.
Project Manager

Cleared for Faxing:

Stephen K. Moore, Ph.D.
Chemistry Team Leader

cc: Original NDA 19-640/SCF-022
HFD-510/Div. File
HFD-510/CKing/SMoore/WBerlin
HFD-160/NSweeney/PCooney

MICROBIOLOGY REVIEW

FAX MEMO

DATE: July 22, 1998

APP. #: NDA 19-640/SCF-022
 Humatrope

TO: Dr. Tobias Massa
 Director, Regulatory Affairs (CM&C)

FROM: Crystal A. King, P.D., M.G.A., Project Manager
 Division of Metabolic and Endocrine Drug Products, HFD-510

RE: BIOPHARMACEUTICS REVIEW COMMENTS
 Formulation revision: new cartridge strengths

Our biopharmaceutics reviewer, Dr. Robert Shore, has completed his review of your March 3, 1998, submission. Following are his comments.

“Results from the pharmacokinetic study between two of three new cartridge formulations and the current marketed 5 mg vial formulation of Humatrope indicated a lack of bioequivalence. Using the two 1-sided 90% confidence interval analysis, the new cartridges were, on average, about 5-15% more bioavailable than the marketed 5 mg vial and the 90% confidence intervals exceeded the acceptable 0.8-1.25 limits. However, a final decision regarding the clinical impact of these results will be made by the Medical Officer.”

Should you have any questions, please do not hesitate to contact me at 301-827-6423.

Crystal Anne King, P.D., M.G.A.
Project Manager

cc: Original NDA 19-640/SCF-022

HFD-510/Div. File

HFD-510/CKing

HFD-510/RShore

Note: copy telefaxed to David Staehler (receipt confirmed)

BIOPHARMACEUTICS REVIEW