FOLLISTIM® AQ Cartridge (follitropin beta injection) 使用说明

Follistim® AQ Cartridge
(follitropin beta injection) 300 IU, 600 IU, 900 IU
For use only with Follistim Pen®

非实际尺寸。

使用前须知

收集用品之前，请用肥皂和水洗手并擦干。若要给自己进行注射，您需要：

- FOLLISTIM AQ Cartridge、FOLLISTIM Pen®，以及新的随药液管一起提供的 BD Micro-Fine™ Pen Needle。
- 干净的表面、酒精和棉球或酒精棉片、消毒纱布、抗菌肥皂以及用于丢弃使用过的物品的防穿刺容器。

FOLLISTIM AQ Cartridge 仅用于 FOLLISTIM Pen。将 FOLLISTIM AQ Cartridge 用于 FOLLISTIM Pen 之前，请仔细阅读所有说明。否则，可能会导致给予的剂量不正确。

此处提供的指南为简要指南。仅应在收到医疗服务人员的完整说明后才能使用。

如何使用 FOLLISTIM AQ Cartridge

1.准备　　准备 FOLLISTIM Pen®


图 1A

组装 FOLLISTIM Pen

- 拔掉套在笔身上的保护帽（**图 1A**），将其置于干净、干燥的表面上。
- 从药液管架中旋出整个笔身。将笔身和药液管架置于干净、干燥的表面上。


图 1B

- 将 FOLLISTIM AQ Cartridge 从其包装中取出，使用酒精棉片清洁药液管的橡胶密封条。
- 将药液管插入带金属边缘盖的药液管架（**图 1B**）。


图 1C

- 将笔身完全旋入内含已插入药液管的药液管架（**图 1C**），确保不留有空隙。
- 将箭头（▲）对准黄色对准标记（▬）的中间。


图 1D

装针

- 使用酒精棉片清洁药液管架的开口端。
- 撕掉外部针罩中 BD Micro-Fine™ Pen Needle 的保护性纸封条。
- 确保 FOLLISTIM Pen 中存在 FOLLISTIM AQ Cartridge 以后，装上新的 BD Micro-Fine Pen Needle。
- 将药液管架的一端推入外部针罩。
- 拧紧在一起（**图 1D**）。

您的 FOLLISTIM Pen 现已组装并填充完毕。请记住：

1. 请勿触碰针头，且勿将未套护帽的针头置于任何表面上。
2. 每次注射必须使用新的 BD Micro-Fine Pen Needle。

请阅读 FOLLISTIM AQ Cartridge 随附的患者信息 or Patient Information，并与您的医生进行讨论。也可查看医生处方信息 or Prescribing Information。

2.设置 准备注射并设置剂量

图 2A

准备好进行注射

- 使用酒精棉片在皮肤上清洁出大约 2 英寸的用于扎针的区域。最佳注射部位为肚脐正下方或大腿上部外侧。
- 轻轻拿掉外部针罩，内部针罩原封不动（**图 2A**），然后置于一旁。不要丢弃外部针罩。
- 小心去掉内部针罩（**图 2B**）并丢弃。去掉笔帽后请勿触摸笔针或让其接触任何表面。

图 2B

- 手持 FOLLISTIM Pen，笔针向上。使用手指轻弹药液管架，使气泡集中到针尖。

调整剂量

图 2C

- 转动用量旋钮，直至听到咔嗒一声。笔针向上，推动注射按钮。
- 此时会在针尖处出现一小滴药液（**图 2C**）。如果您没有看到药液滴，请重复前面的步骤；否则您可能无法获得正确的剂量。
- 如果您已经使用过 FOLLISTIM AQ Cartridge 但需要再注射一剂，则请装上新的 BD Micro-Fine Pen Needle，注意针尖是否会出现一小滴药液。如果没有看到药液滴，请重复前 2 个步骤。

图 2D

- 如果所需剂量为 50 国际单位 (IU) 到 450 IU，请转动剂量旋钮，使正确的剂量对准剂量窗口每一侧的剂量标记（**图 2D**）。
- 如果转过了所需的剂量，请勿将剂量旋钮往回转（往回转不会损坏笔，但会丢失药液）。此时应继续转动，直至转过了 450 IU 标记，只要能够转得动。剂量旋钮必须能够自由转动。
- 将注射按钮一推到底。从“0”开始转到正确的剂量。

您现在可以完成注射操作了。请记住：

1. 在笔针已扎到皮肤里面时，请勿尝试纠正剂量旋钮转动调整过程中的错误。这样来纠正错误可能会导致剂量不正确。
2. 如果您的处方剂量超出 FOLLISTIM Pen 能够输送的剂量，或者超出药液管中剩余的药量，则需自行进行多次注射。

3.注射 注射 FOLLISTIM AQ Cartridge

图 3A

- 用 2 个手指捏紧清洁过的皮肤区域。
- 用另一只手将整个笔针以 90 度角垂直插入皮肤（**图 3A**）。
- 将注射按钮按到底。等 5 秒钟。剂量窗口的中间应该在“0”旁边显示一个点。如果您在剂量窗口中没有看到“0”，请按照以下说明操作。*
- 快速将笔针拔出，然后使用酒精棉片压住注射部位。
- 按压注射部位的同时轻轻按摩几下。

*如果剂量窗口中的数字没有显示为“0”，而您无法将注射按钮一推到底，请勿尝试将按钮硬推下去。您的 FOLLISTIM AQ Cartridge 可能已经空了。这意味着您没有接受完整的剂量。请勿调整剂量刻度的设置。剂量窗口中的数字是完成处方剂量所需的药液量。写下该数字。去掉笔针，对其进行适当处置。将剂量旋钮转过 450 IU 标记，直到不能再转，然后将注射按钮完全推入，将刻度窗口重置为“0”。要完成 FOLLISTIM AQ Cartridge 的剂量，请选择新的注射部位并重复此步骤之前的所有说明。

注射完成！

存放和处置：每个笔针只能进行一次注射。注射完成后，立即取下使用过的笔针并对其进行处置。存放注射笔前，必须先将笔针从 FOLLISTIM Pen® 中取出。

请阅读 FOLLISTIM AQ Cartridge 随附的患者信息 or Patient Information，并与您的医生进行讨论。也可查看医生处方信息 or Prescribing Information。

ORGANON

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PATIENT INFORMATION

Follistim® (Fol'-lis-tim) AQ Cartridge
(follitropin beta) injection
for subcutaneous use

Read this Patient Information before you start using Follistim® AQ Cartridge and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is Follistim AQ Cartridge?

Follistim AQ is a prescription medicine that contains follicle-stimulating hormone (FSH). The medicine is taken with the Follistim Pen®.

Follistim AQ Cartridge is used:

In women:
- to help healthy ovaries to develop (mature) and release eggs
- as part of treatment programs that use special techniques (skills) to help women get pregnant by causing their ovaries to produce more mature eggs

In men:
- to help bring about the production and development of sperm

Who should not use Follistim AQ Cartridge?

Do not start using Follistim AQ Cartridge if you are a Woman or Man who:
- is allergic to recombinant human FSH products
- has a high level of FSH in your blood indicating that your ovaries (women only) or testes (men only) may be permanently damaged and do not work at all
- has uncontrolled thyroid, pituitary, or adrenal gland problems
- is allergic to streptomycin or neomycin (types of antibiotics)
- has a tumor of the hypothalamus, pituitary gland, breast, uterus (women only), ovary (women only), or testis (men only)

Do not start using Follistim AQ Cartridge if you are a Woman who:
- is pregnant or think you may be pregnant
- has heavy or irregular vaginal bleeding and the cause is not known
- has ovarian cysts or enlarged ovaries, not due to polycystic ovary syndrome (PCOS)

Talk to your healthcare provider before taking this medicine if you have any of the conditions listed above.

Before you use Follistim AQ, tell your healthcare provider about all of your medical conditions, including if you:
- have an increased risk of blood clots (thrombosis)
- have ever had a blood clot (thrombosis), or anyone in your immediate family has ever had a blood clot (thrombosis)
- had stomach (abdominal) surgery
- had twisting of your ovary (ovarian torsion)
- had or have a cyst in your ovary
- have polycystic ovary disease
- have any other medical conditions
- are breastfeeding or plan to breastfeed. It is not known if the medicine in Follistim AQ Cartridge passes into your breast milk. You and your healthcare provider should decide if you will take Follistim AQ Cartridge or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may affect how Follistim AQ Cartridge works. Follistim AQ Cartridge may also affect how your other medicines work. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I use Follistim AQ Cartridge?

- Be sure that you read, understand, and follow the "Patient Instructions for Use" that come with Follistim AQ Cartridge.
- Use Follistim AQ Cartridge exactly as your healthcare provider tells you to.
- Your healthcare provider will tell you how much Follistim AQ Cartridge to use, how to inject it, and how often it should be injected.
- Do not inject Follistim AQ Cartridge at home until your healthcare provider has taught you the right way to put the cartridge and pen device together and to inject yourself.
- Do not mix any other medicines into the cartridge.
- Do not change your dose of Follistim AQ Cartridge unless your healthcare provider tells you to.
- Call your healthcare provider immediately if you use too much Follistim AQ Cartridge.
- If you miss or forget to take a dose, do not double your next dose. Ask your healthcare provider for instructions.
- Use Follistim AQ Cartridge only with the Follistim Pen.
- Do not use the Follistim Pen if you are blind or visually impaired unless you have assistance from an individual with good vision who is trained in the right way to use the pen.
- Do not re-use the BD Micro-Fine™ Pen Needle.
- Your healthcare provider will do blood and urine hormone tests while you are taking Follistim AQ Cartridge. Make sure you follow-up with your healthcare provider to have your blood and urine tested when told to do so.

Women:

- Your healthcare provider may do ultrasound scans of your ovaries. Make sure you follow-up with your healthcare provider to have your ultrasound scans.

Men:

- Your healthcare provider may test your semen while you are taking Follistim AQ Cartridge. Make sure you follow-up with your healthcare provider to give a semen sample for testing.

What are the possible side effects of Follistim AQ Cartridge?

Side effects are grouped by how serious they are and how often they may happen.

Serious side effects include:

In women:

- Ovarian enlargement
- Ovarian hyperstimulation syndrome (OHSS). OHSS is a serious medical problem that can happen when the ovaries are over stimulated. In rare cases it has caused death. OHSS causes fluid to build up suddenly in your stomach and chest areas and can cause blood clots to form.
- Lung problems. Follistim AQ Cartridge can cause you to have fluid in your lungs (atelectasis) and trouble breathing (acute respiratory distress syndrome).
- Blood clots. Follistim AQ Cartridge may increase your chance of having blood clots in your blood vessels. Blood clots can cause:
  - blood vessel problems (thrombophlebitis)
  - stroke
  - loss of your arm or leg
  - blood clot in your lungs (pulmonary embolus)
  - heart attack
- Ovarian torsion. Follistim AQ Cartridge may increase the chance of twisting of the ovaries in women with certain conditions such as OHSS, pregnancy and previous abdominal surgery. Twisting of the ovary could cause the blood flow to the ovary to be cut off.
- Pregnancy and birth of multiple babies. Having a pregnancy with more than one baby at a time increases the health risk for you and your babies. Discuss your chances of multiple births with your healthcare provider.
- Birth defects. A woman's age, certain sperm problems, genetic background of both parents and a pregnancy with multiple babies can increase the chance that your baby might have birth defects.
- Ectopic pregnancy (pregnancy outside of the womb). The chance of a pregnancy outside of the womb is increased in women with damaged fallopian tubes.
- Miscarriage. The chance of loss of an early pregnancy may be increased in women who have difficulty with becoming pregnant at all.

Call your healthcare provider right away if you develop any of the following:

- pain in your lower stomach area
- nausea
- vomiting
- weight gain
- diarrhea
- decreased urine output
- trouble breathing
- any other unusual symptoms that concern you

The most common side effects of Follistim AQ Cartridge include:

In women:

- headache
- nausea
- stomach pain
- discomfort or pain in the lower stomach area
- cyst (closed sac) in the ovary
- feeling tired

In men:

- headache
- pain at the injection site
- bruising, swelling or redness at the injection site
- breast enlargement
- acne
- testicular cyst

These are not all the possible side effects of Follistim AQ Cartridge. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider immediately if you get worsening or strong pain in the lower stomach area (abdomen). Also, call your healthcare provider immediately if this happens some days after the last injection has been given.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Follistim AQ Cartridge?

- Store Follistim AQ Cartridge in the refrigerator between 2°C to 8°C (36°F to 46°F) until the expiration date.
- Follistim AQ can be stored at or below 25°C (77°F) for 3 months or until the expiration date, whichever comes first. Once the rubber inlay of the Follistim AQ Cartridge has been pierced by a needle, the product may be stored only for a maximum of 28 days at 2°C to 25°C (36°F to 77°F).
- Keep Follistim AQ Cartridge away from light.
- Do not freeze.

Keep Follistim AQ Cartridge and all medicines out of the reach of children.

General information about Follistim AQ Cartridge

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information leaflet. Do not use Follistim AQ for a condition for which it was not prescribed. Do not give Follistim AQ Cartridge to other people, even if they have the same condition that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about Follistim AQ Cartridge. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for more information about Follistim AQ Cartridge that is written for healthcare professionals.

For more information, go to **www.follistim.com** or call 1-844-674-3200.

What are the ingredients in Follistim AQ Cartridge?

Active ingredient: follitropin beta

Inactive ingredients: benzyl alcohol NF-10 mg/mL (preservative), methionine, polysorbate 20, sodium citrate, sucrose, Water for Injection. Hydrochloric acid and/or sodium hydroxide are used to adjust the pH.

Manufactured by: Organon USA LLC, a subsidiary of
ORGANON & Co.,
Jersey City, NJ 07302, USA
U.S. License No. 2331

For patent information: www.organon.com/our-solutions/patent/

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患者信息

Follistim® (Fol'-lis-tim) AQ Cartridge
(follitropin beta) injection
for subcutaneous use

在您开始使用 Follistim® AQ Cartridge 之前以及每次续药时，请阅读此患者信息。本说明书可能包含新增信息。此信息不能代替与医疗保健提供者讨论您的医疗状况或治疗。

什么是 Follistim AQ Cartridge？

Follistim AQ 是一种处方药，其中含有促卵泡激素 (FSH) 成份。该药与 Follistim Pen® 一起使用。

Follistim AQ Cartridge 用于：

女性：
- 帮助健康的卵巢发育（成熟）并释放卵子
- 作为治疗计划的一部分，通过特殊技术（技巧）促使女性卵巢产生更多成熟的卵子，从而帮助女性受孕

男性：
- 帮助促进精子生成和发育

哪些人群不适合使用 Follistim AQ Cartridge？

具有以下情况的女性或男性不能使用 Follistim AQ Cartridge：
- 对重组人 FSH 药物过敏
- 血液中的 FSH 浓度高，表明卵巢（女性）或睾丸（男性）已永久损坏，不再起到任何作用
- 有异常甲状腺、脑垂体或肾上腺问题
- 对链霉素或新霉素（抗生素类药物）过敏
- 下丘脑、脑下垂体、胸部、子宫（女性）、卵巢（女性）或睾丸（男性）肿瘤

具有以下情况的女性不能使用 Follistim AQ Cartridge：
- 妊娠或可能妊娠
- 严重或不规律阴道出血且原因不明
- 非多囊卵巢综合征 (PCOS) 导致的卵巢囊肿或肥大

如果您有以上任何一种症状，请在使用此药物之前咨询您的医疗保健提供者。

在使用 Follistim AQ 之前，请告知您的医疗保健提供者有关您的所有医疗状况，包括如果您：
- 有较高的血凝块（血栓）风险
- 曾有过血凝块（血栓），或您的某位直系亲属曾有过血凝块（血栓）
- 曾做过胃部（腹部）手术
- 曾有过卵巢扭转症状（卵巢扭转）
- 曾患有或目前患有卵巢囊肿病症
- 患有多囊卵巢疾病
- 存在任何其他疾病状况
- 正在哺乳期或即将哺乳。尚不清楚 Follistim AQ Cartridge 中的药物是否会渗入乳汁。您和您的医疗保健提供者应当一起决定是否使用 Follistim AQ Cartridge 或是否哺乳。您不应该两者兼顾，只能选择其一。

将使用的所有药物告诉您的医疗保健提供者，包括所有的处方药和非处方药、维生素和中草药补品。某些药物可能会影响 Follistim AQ Cartridge 的效果。Follistim AQ Cartridge 也可能会影响其他药物的药效。在使用新药物的时候，将您使用的药物列出并向医护人员和药剂师出示。

我应该如何使用 Follistim AQ Cartridge？

- 确保您已经仔细阅读、理解并遵守 Follistim AQ Cartridge 随附的"患者使用说明"。
- 谨遵医嘱使用 Follistim AQ Cartridge。
- 医疗保健提供者将告知您 Follistim AQ Cartridge 的使用剂量、注射方法以及注射频率。
- 请勿在家注射 Follistim AQ Cartridge，除非您的医疗保健提供者已经教会您如何正确地将药液管安装在笔中，以及如何自行注射。
- 请勿将任何其他药物混入药液管中。
- 除非医疗保健提供者有要求，否则不要改变您使用 Follistim AQ Cartridge 的剂量。
- 如果 Follistim AQ Cartridge 使用过量，请立即致电给您的医疗保健提供者。
- 如果您错过了或忘记了服药，请不要在下一次加倍剂量来补偿。请咨询您的医疗保健提供者，获得解决办法。
- Follistim AQ Cartridge 只能配合 Follistim Pen 使用。
- 如果您是盲人或视力受损人员，请勿使用 Follistim Pen，除非您有具有良好视力且经过注射笔正规使用培训的人员帮助。
- 请勿反复使用 BD Micro-Fine™ Pen Needle。
- 使用 Follistim AQ Cartridge 期间，医疗保健提供者将对您的血液和尿液激素进行检测。请确保随访医疗保健提供者，在规定时间进行血液和尿液激素试验。

女性：

- 医疗保健提供者可能会对您的卵巢进行超声波扫描。请确保随访医疗保健提供者，进行超声波扫描。

男性：

- 在您使用 Follistim AQ Cartridge 期间，医疗保健提供者可能会对您进行精液测试。请确保随访医疗保健提供者，提供精液测试样本。

Follistim AQ Cartridge 可能有哪些副作用？

副作用根据其严重程度和发生频率进行分组。

严重副作用包括：

女性：

- 卵巢肿大
- 卵巢过激综合征 (OHSS)。OHSS 是一种严重的医学问题，当卵巢过度受到刺激时就会引起这一症状。在罕见情况下，可能导致死亡。OHSS 导致突发性腹部和胸腔积液，可能引起血凝块形成。
- 肺部问题。Follistim AQ Cartridge 可能导致肺部积液（肺不张）和呼吸困难（急性呼吸窘迫综合征）。
- 血栓。Follistim AQ Cartridge 可能导致血管中的血栓形成风险增加。血凝块会导致：
  - 血管问题（血栓性静脉炎）
  - 卒中
  - 截肢
  - 肺部血凝块（肺栓塞）
  - 心脏病发作
- 卵巢扭转。在特定条件下，如 OHSS、妊娠和曾做过腹部手术，Follistim AQ Cartridge 可能导致女性卵巢扭转的几率增加。卵巢扭转可能导致血液无法正常流入卵巢。
- 多胎的妊娠和出生。一次性多胎妊娠给孕妇和婴儿都会造成健康危险。请向医疗保健提供者咨询多胞胎的可能性。
- 出生缺陷。孕妇年龄、精子异常、双方父母的遗传背景以及多胞胎妊娠可能导致婴儿的出生缺陷风险加大。
- 异位妊娠（子宫外孕）。女性在输卵管功能受损的情况下，患有子宫外孕的几率也会加大。
- 流产。对于很难怀孕的女性，怀孕早期的流产几率可能更大。

如果您出现以下任何症状，请立即致电医疗保健提供者：

- 小腹部位疼痛
- 恶心
- 呕吐
- 体重增加
- 腹泻
- 尿量减少
- 呼吸困难
- 令您担心的任何其他异常症状

Follistim AQ Cartridge 最常见的副作用包括：

女性：

- 头痛
- 恶心
- 胃痛
- 小腹部位不适或疼痛
- 卵巢囊肿（闭囊）
- 感觉疲劳

男性：

- 头痛
- 注射部位疼痛
- 注射部位青肿、肿胀或发红
- 乳房变大
- 痤疮
- 睾丸囊肿

这些并非 Follistim AQ Cartridge 可能引起的全部不良反应。欲了解更多信息，请咨询医疗保健提供者或药剂师。

如果胃下部（腹部）疼痛加重或非常严重，请立即致电您的医疗保健提供者。此外，如果在进行最后一次注射几天时间后出现上述症状，也请立即致电您的医疗保健提供者。

如果有任何困扰您的副作用，或经过一段时间仍不消失，请告知医疗保健提供者。

给您的医生打电话询问有关副作用的医学建议。您可以致电 1-800-FDA-1088，向 FDA 报告副作用。

我应该如何贮存 Follistim AQ Cartridge？

- 在过期之前，请将 Follistim AQ Cartridge 贮存在 2°C 至 8°C（36°F 至 46°F）的冰箱中。
- 也可将 Follistim AQ 在 25°C (77°F) 或更低温度的环境中存放 3 个月或直到过期，以较早时间为准。如果 Follistim AQ Cartridge 的橡胶密封条已被笔针刺穿过，则最多只能将该产品贮存在 2°C 至 25°C（36°F 至 77°F）环境中 28 天。
- 请避光保存 Follistim AQ Cartridge。
- 请勿冷冻。

请将 Follistim AQ Cartridge 和所有药物放在儿童触及不到的地方。

Follistim AQ Cartridge 基本信息

有时处方规定将药物用于《患者信息》宣传册未列明的用途。请勿将 Follistim AQ 用于处方以外的用途。不要将 Follistim AQ Cartridge 给其他人使用，即使他人和您有相同的症状。这可能会伤害他人。

《患者信息》宣传册总结了与 Follistim AQ Cartridge 有关的最为重要的信息。如果您想了解更多信息，请咨询您的医疗服务提供者。您可以询问药剂师或医疗保健提供者，以获取专门为医疗保健提供者提供的有关 Follistim AQ Cartridge 的信息。

如需了解更多信息，请访问 **www.follistim.com** 网站，或致电 1-844-674-3200。

Follistim AQ Cartridge 包含哪些成分？

活性成分：促滤泡素 β

非活性成分：苯甲醇 NF-10 mg/mL（防腐剂）、蛋氨酸、聚山梨酯 20、柠檬酸钠、蔗糖、注射用水。使用盐酸和/或氢氧化钠来调节 pH 值。

委托制造商：Organon & Co.，的子公司
Organon USA LLC
Jersey City, NJ 07302, USA（美国）

美国执照编号 2331

专利信息：www.organon.com/our-solutions/patent/

修订日期：2024 年 2 月

usppi-og8328-SOi-2402r001

INSTRUCTIONS FOR USE
FOLLISTIM® (Fol´-lis-tim) AQ Cartridge
(follitropin beta)
injection, for subcutaneous use

Read this Instructions for Use before you start using FOLLISTIM® AQ Cartridge and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

Important Information

- FOLLISTIM AQ Cartridge is injected subcutaneously (beneath the skin) only.
- FOLLISTIM AQ Cartridge is for single-patient-use only.
- FOLLISTIM AQ Cartridge is used with FOLLISTIM Pen (supplied separately).
- FOLLISTIM Pen is not recommended for use by the blind or visually impaired without the help of a person trained to use the injection device.
- Learn about all of the parts of the FOLLISTIM Pen (See Figure 1), FOLLISTIM AQ Cartridge (See Figure 2) and the BD Micro-Fine™ Pen Needle (See Figure 3).
- The BD Micro-Fine™ Pen Needle is for use only with the FOLLISTIM AQ Cartridge. Each needle is for 1 injection only.
- Do not add any other medicine to the FOLLISTIM AQ Cartridge.
- Be very careful when handling the needle. If you are giving an injection to another person, accidental needle sticks with used needles can cause serious infections or infections that may lead to death.

Storing FOLLISTIM AQ Cartridge

- Store unused FOLLISTIM AQ Cartridge in the refrigerator between 36°F to 46°F (2°C to 8°C) until the expiration date.
- If needed, FOLLISTIM AQ Cartridge can be stored at room temperature up to 77°F (25°C) for 3 months or until the expiration date, whichever comes first.
- After first use, store FOLLISTIM AQ Cartridge either in the refrigerator or at room temperature between 36°F to 77°F (2°C to 25°C). Throw away after 28 days, even if there is still medicine in the FOLLISTIM AQ Cartridge.
- Keep FOLLISTIM AQ Cartridge in the original carton to protect from light.
- Do not freeze.

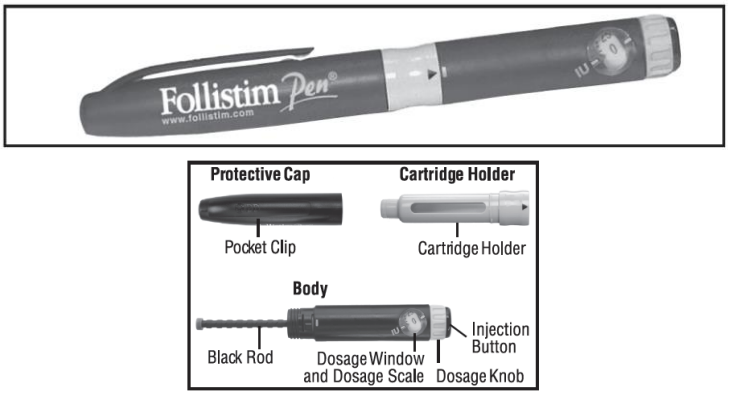

Figure 1. FOLLISTIM Pen and its Parts

Figure 2. Parts of FOLLISTIM AQ Cartridge

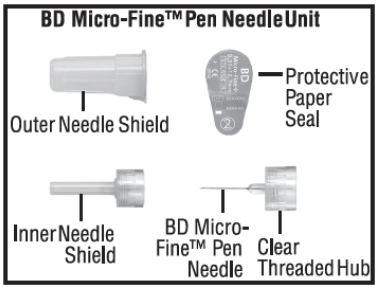

Figure 3. Parts of BD Micro-Fine Pen Needle Unit

A. Getting Ready

- Remove the FOLLISTIM AQ Cartridge out of the refrigerator.
- Injecting cold medicine can cause discomfort at the injection site. Allow the FOLLISTIM AQ Cartridge to reach room temperature before injecting.
- Check the liquid in the cartridge to make sure it is clear and colorless. **Do not use**, if the liquid is not clear and colorless or has particles in it**.**
- **Gather the supplies you will need for your injection. You will need:**
  - a clean dry surface
  - FOLLISTIM Pen
  - FOLLISTIM AQ Cartridge
  - BD Micro-Fine Pen Needle
  - alcohol pads
  - cotton balls or sterile gauze
  - a puncture-proof container to throw away the used cartridge and needle
- Wash your hands with soap and water and dry them before you use FOLLISTIM Pen and when you replace the cartridge.

B. Loading the FOLLISTIM Pen with the FOLLISTIM AQ Cartridge

- Hold the FOLLISTIM Pen Body firmly with one hand. With the other hand, pull the Protective Cap straight off with your other hand (See Figure 4). Put the cap aside on a clean, dry surface.

Figure 4

- Unscrew the Pen Body from the Cartridge Holder (See Figure 5). Place the Cartridge Holder and the Pen Body aside.

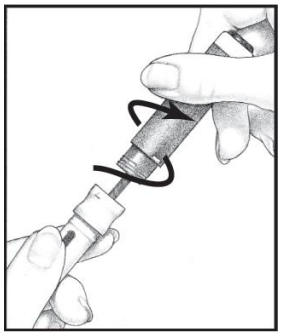

Figure 5

- Take the FOLLISTIM AQ Cartridge out of the package. Clean the rubber inlay on the cartridge with an alcohol pad. Put the FOLLISTIM AQ Cartridge into the Cartridge Holder (See Figure 6). The metal rimmed cap goes in first.

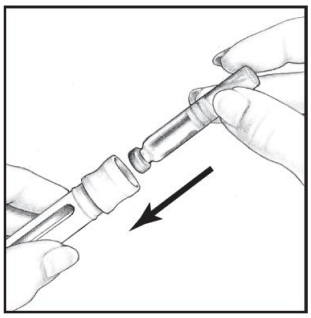

Figure 6

- Insert the Pen Body into the Cartridge Holder. The black rod must press against the Rubber Piston on the cartridge. Screw the Pen Body fully onto the Cartridge Holder (See Figure 7). Make sure there is no gap between the Pen Body and the Cartridge Holder. The arrow (▲) on the Cartridge Holder should point to the middle of the yellow alignment mark (▬) on the Pen Body.

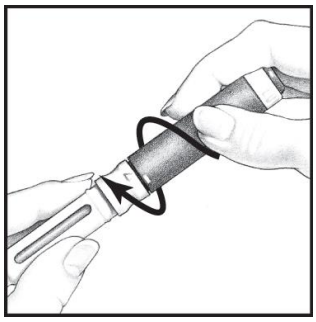

Figure 7

- Clean the open end of the Cartridge Holder with an alcohol pad (See Figure 8).

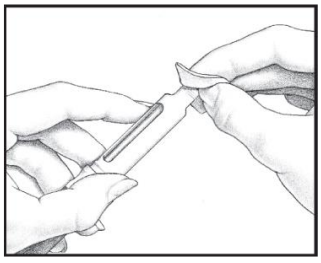

Figure 8

- Pick up a new BD Micro-Fine Pen Needle that is in its Outer Needle Shield. Peel off the protective paper seal (See Figure 9). **Do not** touch the needle. **Do not** place the open needle on any surface. **Use only the BD Micro-Fine 0.33 mm × 12.7 mm (29G) Pen Needles as supplied with the FOLLISTIM AQ Cartridge.**
- Use a new BD Micro-Fine Pen Needle with each injection. Never reuse a needle. Attach a new BD Micro-Fine Pen Needle after you make sure there is a FOLLISTIM AQ Cartridge in the Cartridge Holder.

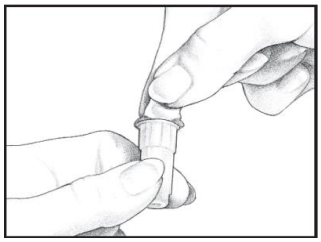

Figure 9

- Hold the Outer Needle Shield firmly in one hand while holding the Cartridge Holder firmly in the other hand. Push the end of the Cartridge Holder into the Outer Needle Shield. Screw them tightly together (See Figure 10). Place your FOLLISTIM Pen aside.

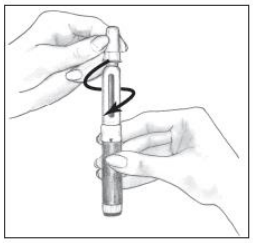

Figure 10

C. Preparing the Injection Site

- When giving a subcutaneous injection, follow your healthcare provider's instructions about changing the site for each injection. This will help lower your chances of having a skin reaction.
- **Do not** inject FOLLISTIM AQ Cartridge into an area that is tender, red, bruised, or hard.
- The recommended sites for injecting FOLLISTIM AQ Cartridge are:
  - just below your belly button (navel) (See Figure 11)

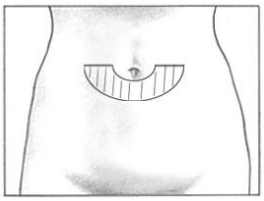

Figure 11

  - the upper outer area of your thigh (See Figure 12)

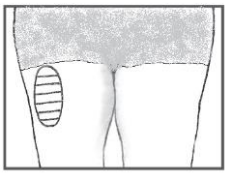

Figure 12

- Choose an injection site. Clean the skin at the injection site with an alcohol wipe. Clean about two inches around the injection site where the needle will be inserted. Do not touch the cleaned area of skin.

D. Dialing the Dose Before You Give the Injection

- Your healthcare provider will decide on the dose of FOLLISTIM AQ Cartridge to be given. This dose may be increased or decreased as your treatment progresses depending on your individual type of treatment.

- FOLLISTIM AQ Cartridge using FOLLISTIM Pen can be injected subcutaneously (beneath the skin) in prescribed doses from 50 International Units (IU) up to 450 IU, in marked 25 IU increments. The Dosage Scale on the Pen has numbers and audible clicks to help you set the correct dose.
- Hold the FOLLISTIM Pen and pull off the outer needle shield. Leave the Inner Needle Shield in place over the needle attached to the Pen (See Figure 13). Do not throw away the Outer Needle Shield, you will need it later when you throw away the needle.

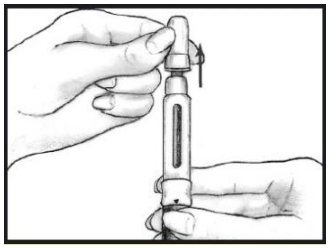

Figure 13

- Carefully remove the Inner Needle Shield and throw it away (discard) (See Figure 14). **Do not** touch the needle or let the needle touch any surface while uncapped.

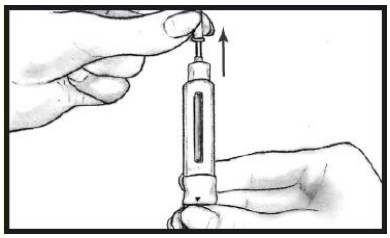

Figure 14

- Hold the FOLLISTIM Pen with the needle pointing upwards. Tap the Cartridge Holder gently with your finger to help air bubbles rise to the top of the needle. The small amount of air bubbles will not affect the amount of medicine you receive.
- With an unused cartridge loaded:
  1. Dial the Dosage Knob until you hear 1 click. With the needle pointing upwards, push in the Injection Button.
  2. Look for a droplet of medicine at the tip of the needle (See Figure 15). If you see the droplet, then you can dial in your dose.
  3. If you do **not** see a droplet, repeat number 1 (above) until you see droplet.

     You must **make sure you see a droplet** of medicine (**check the flow of medicine**) or you may **not** inject the correct dose amount.

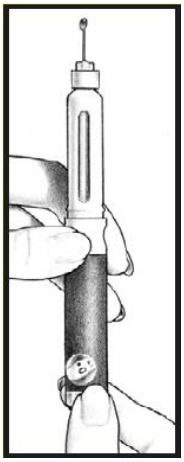

Figure 15

- With a partially used cartridge, to give yourself another dose of medicine you will need to attach a new BD Micro-Fine Pen Needle and look for a droplet forming at the tip of the needle (See Figure 15). If you see a droplet, then you can dial in your dose.
  If **no** droplet:
  1. Dial the Dosage Knob until you hear one click. With the needle pointing upwards, push in the Injection Button.
  2. Look for a droplet at the tip of the needle. If you see the droplet, then you can dial in your dose.
- Your FOLLISTIM AQ Cartridge should be one of the following:
  - Silver Metal Cap – 300 international units
  - Gold Metal Cap – 600 international units
  - Blue Metal Cap – 900 international units

  If you do **not** have one of the cartridges above, please contact your healthcare provider.
- For doses of 50 IU up to 450 IU, turn the Dosage Knob until the correct dosage aligns with the dosage markers on each side of the Dosage Window (See Figure 16).

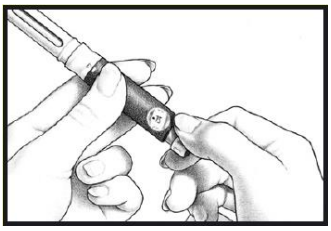

Figure 16

- If by mistake you dial past the correct dose number, **do not** try to turn the Dosage Knob backward to fix the mistake. Continue to turn the Dosage Knob in the same direction past the 450 IU mark, as far as it will turn. The Dosage Scale must move freely. Push the Injection Button in all the way (See Figure 17). Start to dial again starting from "0" upwards. By following these directions, you will not lose any medicine from the FOLLISTIM AQ Cartridge (See “Checking the Medicine Level Remaining”).

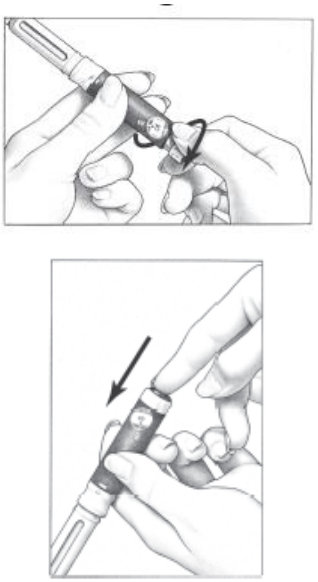

Figure 17

  - **If you turn the Dosage Knob backward to correct the mistake, it will not damage the FOLLISTIM Pen, but you will lose some medicine from the FOLLISTIM AQ Cartridge.**
  - **Never dial your dose or try to correct a dialing mistake when the needle is still in your skin. You may receive an incorrect dose.**
  - **If your prescribed dose is more than the deliverable dose of FOLLISTIM Pen or more than the amount remaining in the cartridge, you will need to give yourself more than 1 injection.**

E. Giving Yourself an Injection

- Pinch a fold of skin at the cleaned injection site with one hand. **Do not** touch the cleaned area of skin.
- With the other hand hold the FOLLISTIM Pen with FOLLISTIM AQ Cartridge loaded and BD Micro-Fine Needle. Use a quick “dart-like” motion to insert the needle straight up and down (90° angle).
- Press the injection button all the way in to make sure you give yourself a full injection (See Figure 18). Wait for 5 seconds before pulling the needle out of the skin. The middle of the Dosage Window should display a dot next to the "0".

Figure 18

If the injection button does **not** push in all the way, and the number in the Dosage Window does not read "0", it means there is not enough medicine left in the cartridge to complete your prescribed dose. The number in the Dosage Window will give you the amount of medicine needed to complete your dose. Write this number down. This will be the number you dial for the completion of your dose. **Start over** with a new FOLLISTIM AQ Cartridge and a new needle and follow all the instructions up to this step (See “Giving Yourself an Injection”). Make sure you choose a different injection site to complete your prescribed dose of medicine FOLLISTIM AQ Cartridge.

- Remove the BD Micro-Fine Needle from your skin and firmly press down on the injection site with an alcohol swab. Be very careful when handling the needle. If you are giving an injection to another person, accidental needle sticks with used needles can cause serious infections or infections that may lead to death.

- Carefully follow these instructions. Place the Outer Needle Shield on a flat table surface with the opening pointing up. The opening of the Outer Needle Shield is the wider end with the rim. Without holding on to the Outer Needle Shield, carefully insert the needle (attached to the FOLLISTIM Pen) straight into the center of the opening of the Outer Needle Shield and push down firmly (See Figure 19). Be sure the Outer Needle Shield is completely covering the entire needle.

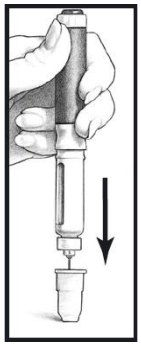

Figure 19

- Grip the Outer Needle Shield carefully and use it to unscrew the needle from the Cartridge Holder (See Figure 20).

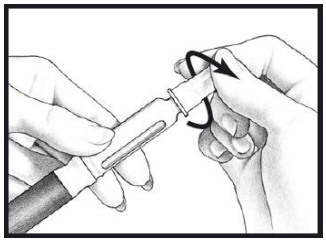

Figure 20

- Throw away the Outer Needle Shield with the used needle right away. Do not throw away in a trash can. (See “How Do I Throw Away Used Cartridges and Needles?”)
- If there is medicine left in the FOLLISTIM AQ Cartridge for more injections, put the Pen Cap back on the Pen Body and store your FOLLISTIM Pen in a safe place in the refrigerator (not in the freezer) or at room temperature. Never store the FOLLISTIM Pen with a needle attached to it.
- Unscrew the Pen Body from the Cartridge Holder with the **empty** FOLLISTIM AQ Cartridge (See Figure 21).

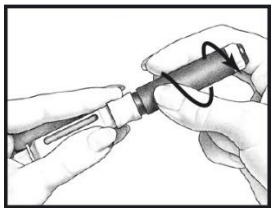

Figure 21

- Remove the empty FOLLISTIM AQ Cartridge from the Cartridge Holder (See Figure 22). Safely, throw away (dispose of) the empty FOLLISTIM AQ Cartridge right away. **Do not** put the cartridge in your household trash. (See “How Do I Throw Away Used Cartridges and Needles?”)

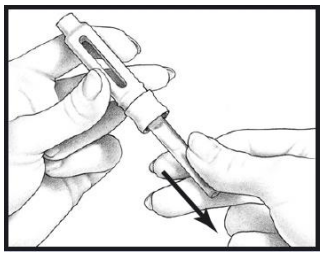

Figure 22

F. Checking the Medicine Level Remaining
For women and men:

Have your healthcare provider advise you of the number of prescribed doses that are in the full unused FOLLISTIM AQ Cartridge.

- **Do not** use the cartridge beyond the advised number of doses. Otherwise, there may not be enough medicine for your prescribed dose.

For women only:

- Keep a FOLLISTIM Pen Treatment Diary as follows:
  1. Record the FOLLISTIM AQ Cartridge content on Day 1. This will either be 300, 600 or 900 international units depending on what your healthcare provider has prescribed for you.
  2. Record the dose you have been prescribed for your injection.
  3. Subtract your Day 1 dose from the FOLLISTIM AQ Cartridge content (300, 600 or 900 international units). (See Figure 23.) This will give you the **remaining** FOLLISTIM AQ Cartridge content after the Day 1 dose is taken.

4. Place the number determined as the content after Day 1 (See number 3) in the box as the FOLLISTIM AQ Cartridge content **available** for Day 2. (See Figure 23.)
5. Subtract your Day 2 dose from the FOLLISTIM AQ Cartridge content you recorded in Step 4. This will give you the **remaining** FOLLISTIM AQ Cartridge content after Day 2. Record this number of units. (See Figure 23.)
6. Repeat the steps to determine the FOLLISTIM AQ Cartridge content **available** and FOLLISTIM AQ Cartridge **remaining** for each day of use.

Day	Date	Dose Prescribed	FOLLISTIM AQ Cartridge Content **Available**	FOLLISTIM AQ Cartridge Content **Remaining**
1	month/day/year	150	600	450
2	month/day/year	150	450	300
3	month/day/year	150	300	150
4	month/day/year	150	150	0

Figure 23. Example of Treatment Diary Starting with a 600 International Unit Cartridge

If you do not know if there is not enough medicine left in the FOLLISTIM AQ Cartridge for your next prescribed dose, see section “If There is Not Enough FOLLISTIM AQ in the Cartridge”.

G. If There is Not Enough FOLLISTIM AQ in the Cartridge

1. If you realize **before** you inject that you do not have enough medicine remaining in your FOLLISTIM AQ Cartridge for your complete dose, follow either Option 1 or Option 2. **Do not** follow both.
   - Option 1:
     - Dial your dose and inject the remaining medicine in the FOLLISTIM AQ Cartridge. The Dosage Knob Injection Button will not push in all the way (do not try to force down the button) and the Dosage Window number will not read "0" but will read the number of units you will need to complete your prescribed dose.
     - Write down the number of units needed to complete your dose.
     - Remove the needle and throw it away (dispose of it) properly (see “How Do I Throw Away Used Cartridges and Needles?”).
     - Using the Dosage Knob, reset the Dial Window to "0" by turning the Dosage Knob past the 450 IU mark as far as it will turn and push the Injection Button in all the way.
     - Before you replace a FOLLISTIM AQ Cartridge, be sure that a BD Micro-Fine Pen Needle is not attached to the FOLLISTIM Pen.
     - Insert a new cartridge into the FOLLISTIM Pen and attach a new BD Micro-Fine needle.
     - Dial to the number of units you have written down to complete your prescribed dose.
     - Prepare a different injection site and inject the remaining medicine to complete your dose (See “Giving Yourself an Injection”).
   - Option 2:
     - Remove the FOLLISTIM AQ Cartridge.
     - **Start over** with a new FOLLISTIM AQ Cartridge and Insert into the FOLLISTIM Pen.
     - Follow the instructions for “Dialing the Dose” and “Giving Yourself an Injection.”
2. If you realize **after** you have inserted the needle at the injection site that you do not have enough medicine remaining in your FOLLISTIM AQ Cartridge for your complete dose:
   - Inject the remaining content in the FOLLISTIM AQ Cartridge. The Injection Button will not push in all the way and the number in the Dosage Window will not read "0" but will read the number of units you will need to complete your prescribed dose.
   - Wait 5 seconds before removing the needle from your skin and gently apply pressure to the injection site with an alcohol pad.

- Throw away (dispose of) the used needle (See “How Do I Throw Away Used Cartridges and Needles?”).
- Write down the number of units needed to complete your dose.
- Using the Dosage Knob, reset the Dial Window to "0" by turning the Dosage Knob past the 450 IU mark as far as it will turn and push the Injection Button in all the way.
- Insert a new cartridge into the FOLLISTIM Pen and attach a new BD Micro-Fine needle.
- Dial to the number you have recorded to complete your prescribed dose.
- Prepare a different injection site and inject the remaining medicine to complete your dose (See “Giving Yourself an Injection”).

H. How to Solve Problems with FOLLISTIM AQ Cartridge and FOLLISTIM Pen

If you have problems with using the FOLLISTIM AQ Cartridge and the FOLLISTIM Pen, see the following chart. If you still have problems after following the chart or if your problem is not on the chart, contact your healthcare provider.

PROBLEM	POSSIBLE CAUSES	WHAT TO DO
The Pen Body will not screw tightly into the Cartridge Holder.	Is something in the way?	Take out the FOLLISTIM Cartridge and check the Cartridge Holder to see if anything is in the way. Follow the instructions in this pamphlet to Screw the Pen Body fully onto the Cartridge Holder.
No medicine is coming out while checking the flow.	The Cartridge Holder and the Pen Body are not properly screwed together.	Remove the current needle. Carefully follow instructions (Fig. 19 and Fig. 20) to prevent accidental needle sticks. Tighten the Pen Body to the Cartridge Holder ensuring the arrow on the Cartridge Holder is pointing to the middle of the yellow alignment mark on the Pen Body. Attach a new needle to the Pen. Recheck the flow as follows: a. Dial the Dosage Knob until you hear one click. With needle pointing upwards, push in the Injection Button. b. Look for a droplet at the tip of the needle.
	Is the FOLLISTIM Cartridge empty?	Change to a new cartridge.
	Has the needle been properly attached to the FOLLISTIM Pen?	Remove needle and replace with a new one, ensuring that the needle is screwed on tightly to the Pen. Recheck the flow as follows: a. Dial the Dosage Knob until you hear one click. With needle pointing upwards, push in the Injection Button. b. Look for a droplet at the tip of the needle.

PROBLEM	POSSIBLE CAUSES	WHAT TO DO
You are concerned that you can turn the Dosage Knob to the next number without clicking and the Injection Button spins freely.	This is not a problem.	The system is in the reset mode. The Injection Button and Dosage Knob must be pushed all the way down to '0' to re-engage the mechanism and the correct dose can now be set. A click will be heard for each setting in the viewing window.
The Dosage Knob does not go back to '0' while you are injecting.	Is the FOLLISTIM Cartridge empty?	Change to a new cartridge.
	Is the needle blocked?	a. Remove the needle from the skin and dispose of safely. b. Check the Dosage Window and note how much remaining medicine to inject. c. Attach a new needle. Recheck the flow as follows: a. Dial the Dosage Knob until you hear one click. With needle pointing upwards, push in the Injection Button. b. Look for a droplet at the tip of the needle. c. Dial remaining dose.
Some of the medicine is dripping out of the needle when you withdraw it from your skin.	Did you take the needle out of your skin before waiting 5 seconds as directed in Step 15?	If this happens you should inform your doctor. To avoid this problem again, you should always wait 5 seconds after you push the Injection Button before you withdraw the needle from your skin.
The needle is left on the FOLLISTIM Pen.	Have you missed any of the instructions?	Dispose of the needle in a properly secured container as instructed by your doctor. Carefully follow instructions (Fig. 19 and Fig. 20) to prevent accidental needle sticks. Change to a new FOLLISTIM Cartridge and a new needle.
After your last injection, a remaining volume may be left in the cartridge in addition to the normal quantity of medicine dispensed.	The cartridge contains extra volume for checking the medicine flow.	This is not a problem.
You cannot get the cartridge out of the FOLLISTIM Pen.	Is the needle attached?	Remove the needle from the FOLLISTIM Pen and dispose of properly. (Unscrew the Cartridge Holder from the Pen Body and take out the cartridge.)

PROBLEM	POSSIBLE CAUSES	WHAT TO DO
You are not sure how much medicine is left in the cartridge, and you do not want to start an injection and then find out that there is not enough medicine.	Have you kept good records of your doses?	In case of any doubt, you should load a new, unused FOLLISTIM Cartridge into the FOLLISTIM Pen. See **"If There is Not Enough FOLLISTIM AQ in the Cartridge."** To avoid this problem again, you should record your injections. (Women should use a treatment diary.)

Important: If you have a question, always mention the Lot number of your FOLLISTIM Pen as printed on the Pen Body. If you have a complaint, please do not discard any product or packaging.

For questions on information contained in this leaflet, call 1-844-674-3200.

www.follistim.com

How Do I Throw Away Used Cartridges and Needles?

- Put **your used cartridges and needles in** an FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) loose needles and cartridges in your household trash.
- If you do not have an FDA-cleared sharps container, you may use a household container that is:
  - made of heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used cartridges and needles. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.

How Do I Care for the FOLLISTIM Pen?

1. Clean all exposed parts of the FOLLISTIM Pen with a clean, damp cloth such as a paper towel. Never wash it in water, detergent, or strong medical cleaners.
2. Handle the FOLLISTIM Pen carefully to avoid causing damage. You could damage the FOLLISTIM Pen by dropping it or handling it roughly.
3. Keep the FOLLISTIM Pen away from dust and dirt.
4. Never store the FOLLISTIM Pen with a needle attached to it. If you store the FOLLISTIM Pen with the needle attached, the medicine could leak out and there is risk of contamination.
5. If the FOLLISTIM Pen breaks or is damaged, do not try to fix it yourself. Contact your healthcare provider.
6. Do not share your FOLLISTIM Pen with another person.

Keep FOLLISTIM Pen, FOLLISTIM AQ Cartridge, any other supplies and all medicines out of the reach of children.

Manufactured by: Organon USA LLC, a subsidiary of
ORGANON & Co.,
Jersey City, NJ 07302, USA
U.S. License No. 2331

For patent information: www.organon.com/our-solutions/patent/

This Instructions for Use was approved by the U.S. Food and Drug Administration

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usppi-og8328-SOi-2402r001

使用说明书
FOLLISTIM® (Fol´-lis-tim) AQ Cartridge
(follitropin beta)
注射剂，用于皮下注射

在开始使用 FOLLISTIM® AQ Cartridge 以及每次续药时，请阅读该使用说明。本说明书可能包含新增信息。此信息不能代替与医疗保健提供者讨论您的医疗状况或治疗。

重要信息

- FOLLISTIM AQ Cartridge 仅适用于皮下注射。
- FOLLISTIM AQ Cartridge 仅供单个患者使用。
- FOLLISTIM AQ Cartridge 与 FOLLISTIM Pen（单独提供）一起使用。
- 不建议盲人或视障人士在没有经过注射装置培训的人帮助的情况下使用 FOLLISTIM 注射笔。
- 了解 FOLLISTIM Pen（参见图 1）、FOLLISTIM AQ Cartridge（参见图 2）和 BD Micro-Fine™ Pen Needle（参见图 3）的所有部件。
- BD Micro-Fine™ Pen Needle 仅适用于 FOLLISTIM AQ Cartridge。每根笔针仅供注射一次。
- 请勿将任何其他药物加入 FOLLISTIM AQ Cartridge 中。
- 处理笔针时要非常小心。在为他人注射时，被使用过的笔针意外刺伤会导致严重感染或可能导致死亡的感染。

储存 FOLLISTIM AQ Cartridge

- 在过期之前，请将未使用过的 FOLLISTIM AQ Cartridge 贮存在 36°F 至 46°F（2°C 至 8°C）的冰箱中。
- 如果需要，FOLLISTIM AQ Cartridge 可以在室温 77°F (25°C) 以内的温度下保存 3 个月或直至到期日（以先到者为准）。
- 首次使用后，请将 FOLLISTIM AQ Cartridge 存放在冰箱中或 36°F 至 77°F（2°C 至 25°C）的室温下。28 天后应丢弃，即使 FOLLISTIM AQ Cartridge 中仍有药物也是如此。
- 将 FOLLISTIM AQ Cartridge 放在原装纸箱中避光保存。
- 请勿冷冻。

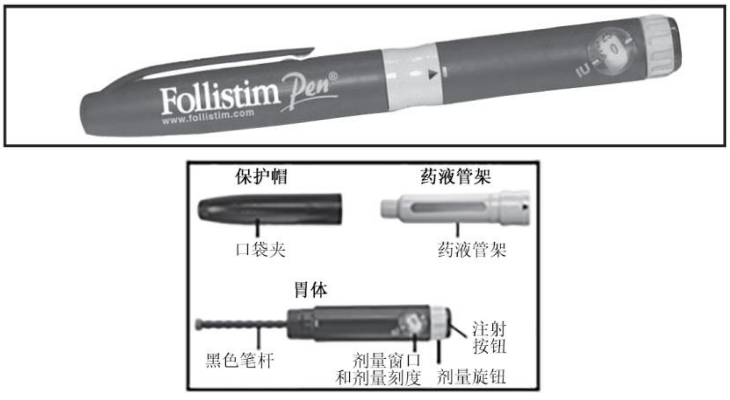


图 1. FOLLISTIM Pen 及其零件

图 2. FOLLISTIM AQ Cartridge 的部件

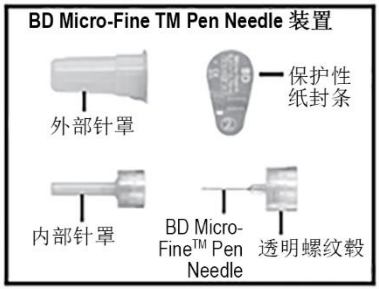


图 3. BD Micro-Fine Pen Needle 装置的部件

A. 准备工作

- 从冰箱中取出 FOLLISTIM AQ Cartridge。
- 注射凉的药物可能会导致注射部位不适。在注射前让 FOLLISTIM AQ Cartridge 达到室温。
- 检查药筒内的液体，确保其清澈无色。如果液体不清澈无色或者其中含有颗粒，**请勿使用。**
- **准备好注射需要的相关用品。您将需要使用：**
  - 干净的桌子
  - FOLLISTIM Pen
  - FOLLISTIM AQ Cartridge
  - BD Micro-Fine Pen Needle
  - 酒精片
  - 棉球或无菌纱布
  - 用于盛放使用过的药液管和笔针的防刺穿容器
- 在使用 FOLLISTIM Pen 和更换药液管之前，请使用肥皂和水对双手进行彻底清洗，然后晾干。

B. 将 FOLLISTIM AQ Cartridge 装入 FOLLISTIM Pen 中

- 用一只手牢牢握住 FOLLISTIM Pen 的笔身。用另一只手将保护盖直接拉下（见图 4）。将笔帽置于干净的干燥表面上。

图 4

- 从药液管架中旋出笔身（参见图 5）。将药液管架和笔身放在一边。

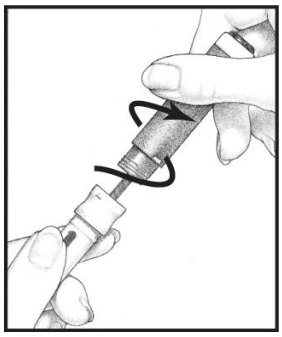


图 5

- 将 FOLLISTIM AQ Cartridge 从其包装中取出。使用酒精棉片清洁药液管的橡胶密封条。将 FOLLISTIM AQ Cartridge 放入药液管架（见图 6）。金属边帽端先入。

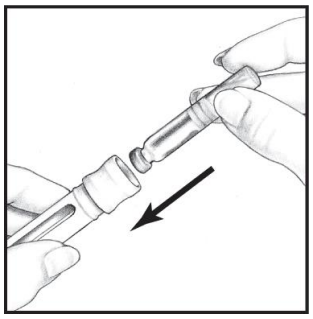


图 6

- 将笔身插入药液管架。黑色笔杆必须与药液管上的橡胶活塞相触。将笔身完整旋入药液管架中（参阅图 7）。确保笔身和药液管架之间没有空隙。药液管架上的箭头 (▲) 应对准蓝色笔身上黄色对准标记 (▬) 的中间。

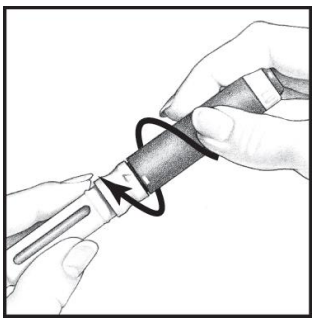


图 7

- 使用酒精棉片清洁药液管架的开口端（参阅图 8）。

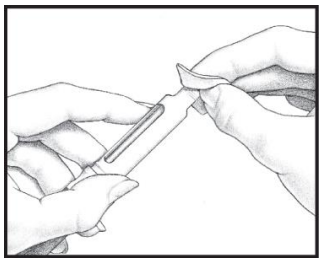


图 8

- 拿起一根新的仍在外部针罩中的 BD Micro-Fine Pen Needle。撕掉保护性纸封条（参阅图 9）。**请勿**触碰笔针。**请勿**将不带针罩的笔针置于任何表面上。**仅使用与 FOLLISTIM AQ Cartridge 一起提供的 BD Micro-Fine 0.33 mm x 12.7 mm (29G) Pen Needle 笔针。**
- 每次注射都使用新的 BD Micro-Fine Pen Needle。不要重复使用笔针。确保药液管架中存在 FOLLISTIM AQ Cartridge 后，再安装新的 BD Micro-Fine Pen Needle。

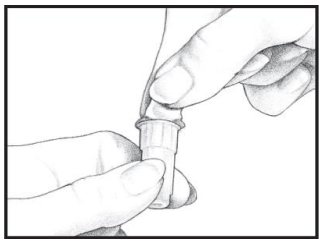


图 9

- 一只手紧握住外部针罩，另一只手紧握住药液管架。将药液管架的一端推入外部针罩。旋紧（参阅图 10）。将您的 FOLLISTIM Pen 放在一边。

图 10

C. 准备注射部位

- 进行皮下注射时，请按照医疗保健提供者的说明每次选择不同的注射部位。这将帮助您降低皮肤反应的风险。
- **请勿**选择脆弱、发红、青肿或坚硬的身体部位来注射 FOLLISTIM AQ Cartridge 药液。
- 适合进行皮下注射 FOLLISTIM AQ Cartridge 药液的推荐部位包括：
  - 肚脐眼（肚脐）正下方（参阅图 11）

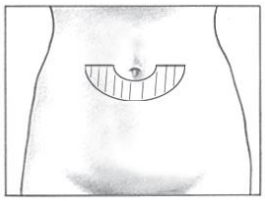


图 11

  - 大腿上部外侧（参阅图 12）

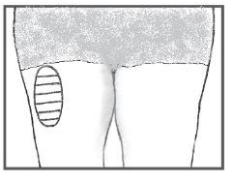


图 12

- 选择注射部位。用酒精湿巾清洁注射部位的皮肤。使用酒精棉擦拭，在注射部位周围清洁出大约 2 英寸的扎针用的皮肤区域。请勿触碰到已清洁的皮肤区域。

D. 在注射之前，先调好剂量

- FOLLISTIM AQ Cartridge 药液的注射剂量由您的医疗保健提供者决定。该剂量在治疗过程中可能会增加，也可能会减少，具体取决于您个人的治疗类型。
- 使用 FOLLISTIM Pen 的 FOLLISTIM AQ Cartridge 可以按处方剂量在皮下（皮肤下部）进行注射，剂量范围为 50 IU（国际单位）到 450 IU，增量为标记的 25 IU。笔身上有以数字显示的用量刻度，并会发出咔哒声，帮助您设定正确的剂量。
- 握住 FOLLISTIM Pen 并拉掉外针护罩。内部针罩原封不动地罩在连接到笔的笔针上（参阅图 13）。请勿丢弃外部针罩；您在稍后丢弃笔针时会需要用到它。

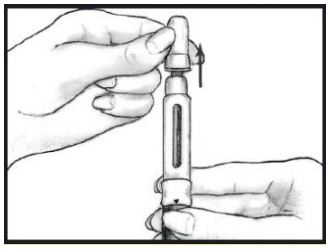


图 13

- 小心地取出内针护罩并将其扔掉（丢弃）（见图 14）。**请勿**在未盖帽的情况下触摸笔针或让笔针接触任何表面。

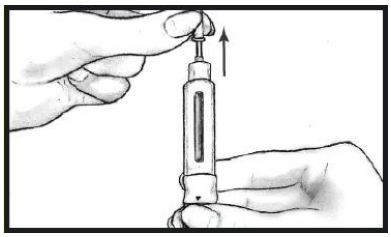


图 14

- 手持 FOLLISTIM Pen，笔针向上。使用手指轻弹药液管架，使气泡上升到针尖。这一点点气泡不会影响您所接受的药量。
- 在装载了未使用的药液管后：
  1. 转动剂量旋钮，直至听到咔嗒一声。笔针向上，推动注射按钮。
  2. 查看针尖处是否有一滴药液（见图 15）。如果看到了小液滴，则可转动剂量旋钮来调整剂量。
  3. 如果您**没有**看到液滴，请重复第 1 步（上文），直到看到液滴。

     您**必须确保看到一小滴**药液（**检查药液流动性**），否则，您注射的药量可能**不**正确。

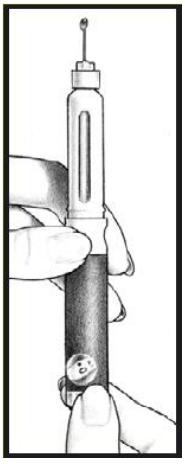


图 15

- 对于已经使用了一部分药液的药液管，如果您想要再注射一剂药物，则需安装一个新的 BD Micro-Fine Pen Needle，然后看针尖是否会形成一个小液滴（参见图 15）。如果看到了小液滴，则可转动剂量旋钮来调整剂量。

  如果**没有**小液滴，则请执行以下操作：

  1. 转动用量旋钮，直至听到咔嗒一声。笔针向上，推动注射按钮。
  2. 查看针尖是否有小液滴。如果看到了小液滴，则可转动剂量旋钮来调整剂量。
- 您的 FOLLISTIM AQ Cartridge 应该属于下列型号之一：
  - 银色金属帽 – 300 国际单位
  - 金色金属帽 – 600 国际单位
  - 蓝色金属帽 – 900 国际单位

  如果您**没有**上述任一型号的药液管，请联系您的医疗保健提供者 。
- 如果所需剂量为 50 IU 到 450 IU，请转动用量旋钮，使正确的用量对准用量窗口每一侧的用量标记（参见图 16）。

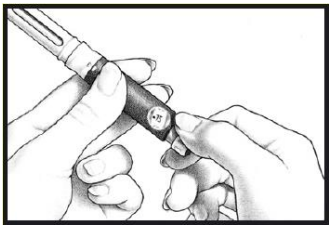
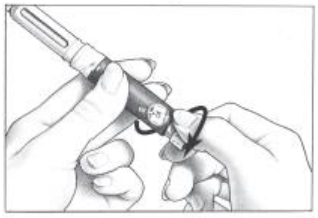


图 16

- 如果您错误地将旋钮转过了正确的剂量数字，**请勿**将剂量旋钮往回转来纠正错误。此时应往同一方向继续转动剂量旋钮，直至转过了 450 IU 标记，只要能够转得动就行。剂量刻度必须能够自由转动。将注射按钮按到底（参见图 17）。从“0”开始再次转动剂量旋钮。只要按照这些指示操作，您就不会丢失 FOLLISTIM AQ Cartridge 中的任何药液（参见“检查剩余药液容量”）。



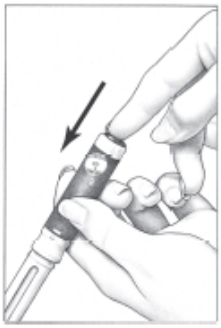


图 17

  - **如果您将剂量旋钮往回转来纠正错误，虽然不会损坏 FOLLISTIM Pen，但会损失 FOLLISTIM AQ Cartridge 中的部分药液。**
  - **当笔针仍在皮肤内时，切勿调节剂量或尝试纠正调节错误。您获得的剂量可能不正确。**
  - **如果 FOLLISTIM Pen 内的可用剂量或药液管中的剩余量多于您的处方剂量，您将需要进行多于 1 次的注射。**

E. 自行注射

- 用一只手在清洁的注射部位捏住一层皮肤。**请勿**触碰到已清洁的皮肤区域。
- 用另一只手握住 FOLLISTIM Pen，该笔应装有 FOLLISTIM AQ Cartridge 和 BD Micro-Fine Needle。以垂直向上或向下（90 °）的角度，迅速“投掷”式地扎入笔针。
- 将注射按钮按到底，确保自行注射完整的剂量（参见图 18）。等 5 秒钟，然后将笔针从皮肤拔出。用量窗口中间应显示“0”旁边有一个点。

图 18

如果注射按钮**没有**一推到底，而且剂量窗口中的数字没有显示为“0”，则表明药液管中的药物不够，无法完成您的处方剂量。剂量窗口中的数字就是完成处方剂量所需注射的药量。将这个数字写下来。这是完成您的处方剂量所需继续注射的剂量。**重新开始使用**新的 FOLLISTIM AQ Cartridge 和新的笔针，并按照这一步之前的指示进行操作 （参见“自行注射”）。确保选择不同的注射部位来完成处方规定剂量的 FOLLISTIM AQ Cartridge 的注射。

- 从皮肤上取下 BD Micro-Fine Needle，并用酒精棉签用力按压注射部位。处理笔针时要非常小心。在为他人注射时，被使用过的笔针意外刺伤会导致严重感染或可能导致死亡的感染。

- 请仔细遵循这些说明。将外部针罩置于平整的桌面上，开口端朝上。外部针罩的开口端是有边的较宽的一端。在未握住外针护罩的情况下，小心地将笔针（与 FOLLISTIM Pen 相连）直接插入外针护罩开口的中心，并用力向下推（见图 19）。确保外针护罩完全覆盖整个笔针。

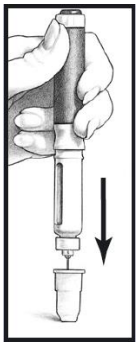


图 19

- 小心握住外部针罩，以便将笔针从药液管架中旋出（参见图 20）。

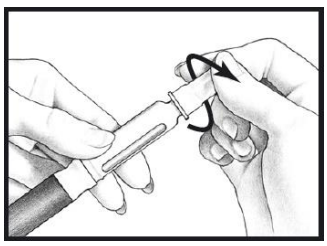


图 20

- 立即扔掉带有使用过的笔针的外部针罩。不要扔在垃圾桶中。（参见“如何扔掉使用过的药液管和笔针？”）
- 如果 FOLLISTIM AQ Cartridge 中剩余的药物还可以进行多次注射，请将笔帽重新套到笔身上，然后将 FOLLISTIM Pen 存放到冰箱中的安全位置（不要放在冷冻柜中），或者室温保存。不要没有取下笔针就存放 FOLLISTIM Pen。
- 将笔身从带有**空的** FOLLISTIM AQ Cartridge 的药液管架中旋出（参见图 21）。

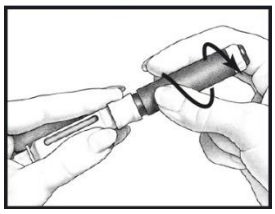


图 21

- 从药液管架中取出空的 FOLLISTIM AQ Cartridge（见图 22）。立即以安全的方式扔掉（处理 ）空的 FOLLISTIM AQ Cartridge 。**请勿**将药液管放入家用垃圾中。（参见“如何扔掉使用过的药液管和笔针？”）

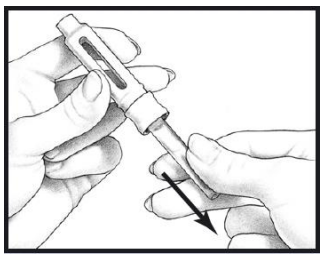


图 22

F. 检查剩余药液容量

女性和男性患者：

请您的医疗保健提供者告知您未使用的完整 FOLLISTIM AQ Cartridge 中所含处方剂量的数量。

- **不要**使用超出建议的剂量数的药液管。否则，可能没有足够的药物可满足处方剂量。

仅适用于女性患者：

- 请按如下方式记录 FOLLISTIM Pen 治疗日记：
  1. 记录第 1 天的 FOLLISTIM AQ Cartridge 药量。该药量可能是 300、600 或 900 国际单位，具体取决于您的医疗保健提供者为您开具的处方。
  2. 记录您进行注射的处方剂量。
  3. 从 FOLLISTIM AQ Cartridge 含量（300、600 或 900 国际单位）中减去第 1 天的剂量。（见图 23）这就会得出注射完第 1 天的剂量后**剩余的** FOLLISTIM AQ Cartridge 含量。
  4. 将得出的作为第 1 天注射后剩余含量的数字（参见第 3 步）填入相应的框中，作为**可供**第 2 天**使用的** FOLLISTIM AQ Cartridge 含量（参见 图 23）。
  5. 从您在步骤 4 中记录的 FOLLISTIM AQ Cartridge 含量中减去第 2 天的剂量。这将得出第 2 天之后**剩余的** FOLLISTIM AQ Cartridge 含量。记录该单位数。（请参见图 23。）
  6. 重复相关步骤，确定**可供使用的** FOLLISTIM AQ Cartridge 含量，以及每天使用后**剩余的** FOLLISTIM AQ Cartridge 药量。

天	日期	处方剂量	FOLLISTIM AQ Cartridge **可用**含量	FOLLISTIM AQ Cartridge **剩余**含量
1	年/月/日	150	600	450
2	年/月/日	150	450	300
3	年/月/日	150	300	150
4	年/月/日	150	150	0

图 23. 治疗日记示例，一开始使用 600 国际单位的药液管

如果您不知道 FOLLISTIM AQ Cartridge 中是否已经没有足够的用于下一次处方剂量的药物，请参阅“如果药液管中没有足够的 FOLLISTIM AQ”。

G. 如果药液管中没有足够的 FOLLISTIM AQ

1. 如果您在注射**之前**意识到 FOLLISTIM AQ Cartridge 中没有进行完整剂量注射所需的足够药物，请按下面的选项 1 或选项 2 进行操作。**请不要** 同时 进行这两个选项的操作。
   - 选项 1：
     - 通过转动剂量旋钮调节好剂量，然后注射 FOLLISTIM AQ Cartridge 中剩余的药物。剂量旋钮注射按钮不会一推到底（不要试着将按钮向下硬推），而剂量窗口的数字也不会显示为“0”，但会显示完成处方剂量所需的单位数。
     - 写下完成处方剂量所需的单位数。
     - 取出笔针并丢弃（处置）（请参阅“如何正确丢弃用过的药液管和笔针？”）。
     - 使用剂量旋钮将刻度窗口重置为“0”，方法是：将剂量旋钮转过 450 IU 标记（只要能够转得动），然后将注射按钮一按到底。
     - 在您更换 FOLLISTIM AQ Cartridge 之前，请确保 BD Micro-Fine Pen Needle 没有装在 FOLLISTIM Pen 上。
     - 将新的药液管插入 FOLLISTIM Pen，然后连接新的 BD Micro-Fine Pen Needle。
     - 将剂量旋钮转到您写下的单位数，以便完成需要注射的处方剂量。
     - 准备一个不同的注射部位，注射剩余的药物以完成您的处方剂量（参见“自行注射”）。
   - 选项 2：
     - 取出 FOLLISTIM AQ Cartridge。
     - 使用新的 FOLLISTIM AQ Cartridge **重新开始**，将其插入 FOLLISTIM Pen 中。
     - 遵循“调好剂量”和“自行注射”的说明。
2. 如果您在将笔针插入注射部位**之后**认识到 FOLLISTIM AQ Cartridge 中没有完成注射剂量所需的足够药物，请执行以下操作：
   - 注射 FOLLISTIM AQ Cartridge 中的剩余含量。注射按钮不会一推到底，剂量窗口中的数字不会显示为“0”，而会显示为完成处方剂量还需要的单位数。
   - 等 5 秒，将笔针从皮肤中取出，然后使用酒精棉片轻轻压住注射部位。
   - 扔掉（处理）使用过的笔针（参见“如何扔掉使用过的药液管和笔针？”）。
   - 写下完成处方剂量所需的单位数。
   - 使用剂量旋钮将刻度窗口重置为“0”，方法是：将剂量旋钮转过 450 IU 标记（只要能够转得动），然后将注射按钮一按到底。
   - 将新的药液管插入 FOLLISTIM Pen，然后连接新的 BD Micro-Fine Pen Needle。
   - 将剂量旋钮转到您记录下的数字，以便完成需要注射的处方剂量。
   - 准备一个不同的注射部位，注射剩余的药物以完成您的处方剂量（参见“自行注射”）。

H. 如何解决 FOLLISTIM AQ Cartridge 和 FOLLISTIM Pen 的问题

如果您有 FOLLISTIM AQ Cartridge 和 FOLLISTIM Pen 的使用问题，请参阅下表。如果您在参阅下页中的图表后仍有问题，或者您的问题不在该图表上，请与您的医疗保健提供者联系。

问题	可能原因	如何操作
笔身在药液管架中拧不紧。	是否有东西堵在里面？	取出 FOLLISTIM Cartridge，查看药液管架中是否有东西堵在里面。遵照这个小册子中的说明，将笔身完全旋入药液管架中。

问题	可能原因	如何操作
检查流量时没有药物流出。	药液管架和笔身没有拧紧。	取出当前使用的笔针。请仔细遵循说明（图 19 和图 20），以防止意外受到笔针的伤害。将笔身拧紧到药液管支架上，确保药液管支架上的箭头指向笔身上黄色对齐标记的中间。将新的笔针装到笔上面。 按如下方式重新检查药液流动性： a. 转动用量旋钮，直至听到咔嗒一声。当笔针指向上时，推动注射按钮。 b. 查看针尖是否有小液滴。
	FOLLISTIM Cartridge 是否空了？	更换新的药液管。
	笔针是否已正确安装到 FOLLISTIM Pen 上面？	取下笔针，换用新的笔针，确保笔针紧紧地拧在笔上面。 按如下方式重新检查药液流动性： a. 转动用量旋钮，直至听到咔嗒一声。当笔针指向上时，推动注射按钮。 b. 查看针尖是否有小液滴。
您担心的是，您将剂量旋钮转到下一个数字时没有咔嗒声，而注射按钮可以自由旋转。	这不是一个问题。	系统正处于重置模式。注射按钮和剂量旋钮必须一直向下推到‘0’才能重新启用相关机制，此时可以设置正确的剂量。在显示窗口中，每一次设定都会听到一声咔嗒。
在注射时剂量旋钮没有回到‘0’。	FOLLISTIM Cartridge 是否空了？	更换新的药液管。
	笔针是否堵塞？	a. 从皮肤中拔出笔针，安全地进行处置。 b. 检查剂量窗口，记下还剩多少药物要注射。 c. 安装新的笔针。 按如下方式重新检查药液流动性： a. 转动用量旋钮，直至听到咔嗒一声。当笔针指向上时，推动注射按钮。 b. 查看针尖是否有小液滴。 c. 通过转动剂量旋钮调好剩余的剂量。
将笔针从皮肤中抽出时，针尖有药液滴出。	您是否还没有等够步骤 15 中要求的 5 秒钟，就将笔针从皮肤中抽出？	如果出现这种情况，您应该告知医生。为了避免这个问题再次发生，您在按下注射按钮后应始终等待 5 秒钟，然后再将笔针从皮肤中抽出。
笔针留在了 FOLLISTIM Pen 上面。	您是否漏看了某些说明？	请遵守医嘱，将笔针放到有安全保障的容器中进行处置。请仔细遵循说明（图 19 和图 20），以防止意外受到笔针的伤害。改用新的 FOLLISTIM Cartridge 和新的笔针。
在最后一次注射后，您发现药液管中剩余的药量超出正常情况下剩余的药量。	药液管中有额外的剂量，用于检查药液流动性。	这不是一个问题。

问题	可能原因	如何操作
无法将药液管从 FOLLISTIM Pen 中取出。	笔针是否装在上面？	将笔针从 FOLLISTIM Pen 上面取下来，进行适当处置。（将药液管架从笔身拧下来，取出药液管。）
您无法确定药液管中留有多少药物，而且您也不想匆忙进行注射，半途中却发现没有足够的药物。	您是否一直对剂量进行详细的记录？	在不确定的情况下，应该将新的、未使用过的 FOLLISTIM Cartridge 装入 FOLLISTIM Pen 中。请参阅**“如果药液管中没有足够的 FOLLISTIM AQ”。** 为了避免此问题再次发生，您应该记录注射情况。（女性患者应记录治疗日记）。

重要事项：如果您有问题，请在提问时提及印在 FOLLISTIM Pen 笔身上的批号。如果您要投诉，请不要丢弃任何产品或包装。

如对本宣传册中的信息有疑问，请拨打 1-844-674-3200。

www.follistim.com

如何丢弃用过的药液管和笔针？

- 使用后，请立即**将使用过的药液管和笔针放入** FDA 批准的锐器处理容器中。**请勿**将松散的笔针和药液管扔进（处理）家用垃圾中。
- 如果您没有 FDA 批准的锐器容器，您可以使用满足以下条件的家用容器：
  - 由耐用塑料制成，
  - 可以用紧密贴合、防刺穿的盖子盖上，其中不会有尖锐物体掉出来，
  - 使用时直立且稳定，
  - 不会泄漏，
  - 正确标记以警告容器内有危险废品。
- 当您的锐器废弃物收集器接近满时，您需要按照当地的指导要求，以正确的方式处理锐器废弃物收集器。州内或地方可能有关于如何丢弃使用过的药液管和笔针的法律。有关安全处理锐器的更多信息，以及有关您所居住州的锐器处理的具体信息，请访问 FDA 网站：http://www.fda.gov/safesharpsdisposal。

请不要将使用过的锐器废弃物收集器扔进家庭垃圾中，除非您所在地区的规定允许这样做。**请勿**回收用过的锐器处理容器。

如何清理维护 FOLLISTIM Pen？

1. 使用干净、润湿的织物（如纸巾）清洁 FOLLISTIM Pen 的所有外露的部分。千万不要用水、洗涤剂或功能强大的医疗清洗机进行清洗。
2. 小心使用 FOLLISTIM Pen，避免造成损坏。将 FOLLISTIM Pen 掉落在地上或使用时过于粗鲁都可能造成笔的损坏。
3. 不要让 FOLLISTIM Pen 沾染上尘垢。
4. 不要没有取下笔针就存放 FOLLISTIM Pen。如果您在存放 FOLLISTIM Pen 时没有取下笔针，则可能造成药物漏出，形成污染。
5. 如果 FOLLISTIM Pen 破损，请勿自行修理。请与您的医疗保健提供者联系。
6. 请勿与他人共用 FOLLISTIM Pen。

请将 FOLLISTIM Pen、FOLLISTIM AQ Cartridge、任何其他用品和所有药物放置在儿童接触不到的地方。

委托制造商：Organon & Co.，的子公司
Organon USA LLC
Jersey City, NJ 07302, USA（美国）

美国执照编号 2331

专利信息：www.organon.com/our-solutions/patent/

本“使用说明”已获得美国食品药品监督管理局的批准　　修订日期：2024 年 2 月

usppi-og8328-SOi-2402r001

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

FOLLISTIM® AQ Cartridge (follitropin beta) injection, for subcutaneous use
Initial U.S. Approval: 1997

----------INDICATIONS AND USAGE----------

Follistim AQ Cartridge is a gonadotropin indicated:

In Women for:

- Induction of Ovulation and Pregnancy in Anovulatory Infertile Women in Whom the Cause of Infertility is Functional and Not Due to Primary Ovarian Failure (1.1)
- Pregnancy in Normal Ovulatory Women Undergoing Controlled Ovarian Stimulation as Part of an In Vitro Fertilization (IVF) or Intracytoplasmic Sperm Injection (ICSI) Cycle (1.2)

In Men for:

- Induction of Spermatogenesis in Men with Primary and Secondary Hypogonadotropic Hypogonadism (HH) in Whom the Cause of Infertility is Not Due to Primary Testicular Failure (1.3)

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

See Dose Conversion Table 1 for Follistim AQ Cartridge with Pen Injector (2.1)

In Anovulatory Women Undergoing Ovulation Induction (2.2):

- Starting daily dose of 50 international units of Follistim AQ Cartridge is administered subcutaneously for at least the first 7 days. The dose is increased by 25 or 50 international units at weekly intervals until follicular growth and/or serum estradiol levels indicate an adequate response.
  - When an acceptable pre-ovulatory state is achieved, final oocyte maturation is achieved with 5,000 to 10,000 international units of urinary human chorionic gonadotropin (hCG).
  - The woman and her partner should have intercourse daily, beginning on the day prior to the administration of hCG and until ovulation becomes apparent.

In Normal Ovulatory Women Undergoing Controlled Ovarian Stimulation as Part of an In Vitro Fertilization or Intracytoplasmic Sperm Injection Cycle (2.3):

- Starting dose of 200 international units (actual cartridge doses) of Follistim AQ Cartridge is administered subcutaneously for at least the first 7 days of treatment. Subsequent doses can be adjusted down or up based upon ovarian response as determined by ultrasound evaluation of follicular growth and serum estradiol levels. Dosage reduction in high responders can be considered from the 6th day of treatment onward according to individual response.
  - Final oocyte maturation is induced with a dose of 5,000-10,000 international units of urinary hCG.
  - Oocyte (egg) retrieval is performed 34 to 36 hours later.

Induction of Spermatogenesis in Men (2.4):

- Pretreatment with urinary hCG alone (1,500 international units twice weekly) is required. If serum testosterone levels have not normalized after 8 weeks of hCG treatment, the dose may be increased to 3,000 international units twice a week.
- After normalization of serum testosterone levels, administer 450 international units per week (225 international units twice weekly or 150 international units three times weekly) of Follistim AQ Cartridge subcutaneously with the same pre-treatment hCG dose used to normalize testosterone levels.

---------- DOSAGE FORMS AND STRENGTHS ----------

Injection: Follistim AQ Cartridge 300 International Units per 0.36 mL in a single-patient-use cartridge (3)
Injection: Follistim AQ Cartridge 600 International Units per 0.72 mL in a single-patient-use cartridge (3)
Injection: Follistim AQ Cartridge 900 International Units per 1.08 mL in a single-patient-use cartridge (3)

----------CONTRAINDICATIONS----------

Women and men who exhibit:

- Prior hypersensitivity to recombinant hFSH products (4)
- High levels of FSH indicating primary gonadal failure (4)
- Presence of uncontrolled non-gonadal endocrinopathies (4)
- Hypersensitivity reactions related to streptomycin or neomycin (4)
- Tumors of the ovary, breast, uterus, testis, hypothalamus or pituitary gland (4)

Women who exhibit:

- Pregnancy (4, 8.1)
- Heavy or irregular vaginal bleeding of undetermined origin (4)
- Ovarian cysts or enlargement not due to polycystic ovary syndrome (PCOS) (4)

---------- WARNINGS AND PRECAUTIONS ----------

Treatment with Follistim AQ may result in:

- Abnormal Ovarian Enlargement (5.1)
- Ovarian Hyperstimulation Syndrome (OHSS) (5.2)
- Pulmonary and Vascular Complications (5.3)
- Ovarian Torsion (5.4)
- Multi-fetal Gestation and Birth (5.5)
- Congenital Anomalies (5.6)
- Ectopic Pregnancy (5.7)
- Spontaneous Abortion (5.8)
- Ovarian Neoplasms (5.9)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions (≥2%) in women undergoing ovulation induction are ovarian hyperstimulation syndrome, ovarian cyst, abdominal discomfort, abdominal pain and lower abdominal pain. (6.1)

The most common adverse reactions (≥2%) in women undergoing controlled ovarian stimulation as part of an IVF or ICSI cycle are pelvic discomfort, headache, ovarian hyperstimulation syndrome, pelvic pain, nausea and fatigue. (6.1)

The most common (≥2%) adverse reactions in men undergoing induction of spermatogenesis are headache, acne, injection site reaction, injection site pain, gynecomastia, rash and dermoid cyst. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Organon USA LLC, a subsidiary of Organon & Co., at 1-844-674-3200 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------

Lactation: It is not known whether this drug is excreted in human milk. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 7/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Follistim® AQ Cartridge (follitropin beta) injection, is indicated:

In Women for:

1.1 Induction of Ovulation and Pregnancy in Anovulatory Infertile Women in Whom the Cause of Infertility is Functional and Not Due to Primary Ovarian Failure

Prior to initiation of treatment with Follistim AQ Cartridge:

- Women should have a complete gynecologic and endocrinologic evaluation.
- Primary ovarian failure should be excluded.
- The possibility of pregnancy should be excluded.
- Tubal patency should be demonstrated.
- The fertility status of the male partner should be evaluated.

1.2 Pregnancy in Normal Ovulatory Women Undergoing Controlled Ovarian Stimulation as Part of an In Vitro Fertilization (IVF) or Intracytoplasmic Sperm Injection (ICSI) Cycle

Prior to initiation of treatment with Follistim AQ Cartridge:

- Women should have a complete gynecologic and endocrinologic evaluation and diagnosis of cause of infertility.
- The possibility of pregnancy should be excluded.
- The fertility status of the male partner should be evaluated.

In Men for:

1.3 Induction of Spermatogenesis in Men with Primary and Secondary Hypogonadotropic Hypogonadism (HH) in Whom the Cause of Infertility is Not Due to Primary Testicular Failure

Prior to initiation of treatment with Follistim AQ Cartridge:

- Men should have a complete medical and endocrinologic evaluation.
- Hypogonadotropic hypogonadism should be confirmed and primary testicular failure should be excluded.
- Serum testosterone levels should be normalized with human chorionic gonadotropin (hCG) treatment.
- The fertility status of the female partner should be evaluated.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If the solution is not clear and colorless or has particles in it, the solution should not be used.
- Do not add any other medicines into the Follistim AQ Cartridge.
- Follistim AQ Cartridge with the pen injector device delivers on average an 18% higher amount of follitropin beta when compared to reconstituted Follistim delivered with a conventional syringe and needle. When administering Follistim AQ Cartridge, a lower starting dose and lower dose adjustments (as compared to reconstituted Follistim) should be considered. For that purpose the following Dose Conversion Table is provided:

Table 1: Follistim AQ Cartridge Administered Subcutaneously with the Follistim Pen Dose Conversion Table*

Lyophilized recombinant FSH dosing with ampules or vials, using conventional syringe	Follistim AQ Cartridge dosing with the Follistim Pen
75 IU	50 IU
150 IU	125 IU
225 IU	175 IU
300 IU	250 IU
375 IU	300 IU
450 IU	375 IU

* Each value represents an 18% difference rounded to the nearest 25 IU increment.

2.2 Recommended Dosing in Anovulatory Women Undergoing Ovulation Induction

The dosing scheme is stepwise and is individualized for each woman *[see Clinical Studies (14.1)]*.

- A starting daily dose of 50 international units of Follistim AQ Cartridge is administered *[see Dosage and Administration (2.1)]* subcutaneously daily for at least the first 7 days.
- Subsequent dosage adjustments are made at weekly intervals based upon ovarian response. If an increase in dose is indicated by the ovarian response, the increase should be made by 25 or 50 international units of Follistim AQ Cartridge at weekly intervals until follicular growth and/or serum estradiol levels indicate an adequate ovarian response.
  The following should be considered when planning the woman's individualized dose:
  - Appropriate Follistim AQ Cartridge dose adjustment(s) should be used to prevent multiple follicular growth and cycle cancellation.
  - The maximum, individualized, daily dose of Follistim AQ Cartridge is 250 international units.
- Treatment should continue until ultrasonic visualizations and/or serum estradiol determinations approximate the pre-ovulatory conditions seen in normal individuals.
- When pre-ovulatory conditions are reached, 5,000 to 10,000 international units of urinary hCG are used to induce final oocyte maturation and ovulation.
  The administration of hCG must be withheld in cases where the ovarian monitoring suggests an increased risk of OHSS on the last day of Follistim AQ Cartridge therapy *[see Warnings and Precautions (5.1, 5.2, 5.10)]*.

- The woman and her partner should be encouraged to have intercourse daily, beginning on the day prior to the administration of hCG and until ovulation becomes apparent *[see Warnings and Precautions (5.10)]*.
- During treatment with Follistim AQ Cartridge and during a two-week post-treatment period, the woman should be assessed at least every other day for signs of excessive ovarian stimulation.
  It is recommended that Follistim AQ Cartridge administration be stopped if the ovarian monitoring suggests an increased risk of OHSS or abdominal pain occurs. Most OHSS occurs after treatment has been discontinued and reaches its maximum at about seven to ten days post-ovulation.

2.3 Recommended Dosing in Normal Ovulatory Women Undergoing Controlled Ovarian Stimulation as Part of an In Vitro Fertilization (IVF) or Intracytoplasmic Sperm Injection (ICSI) Cycle

The dosing scheme follows a stepwise approach and is individualized for each woman.

- A starting dose of 200 international units (actual cartridge doses) of Follistim AQ Cartridge is administered *[see Dosage and Administration (2.1)]* subcutaneously daily for at least the first 7 days of treatment.
- Subsequent to the first 7 days of treatment, the dose can be adjusted down or up based upon the woman's ovarian response as determined by ultrasound evaluation of follicular growth and serum estradiol levels. Dosage reduction in high responders can be considered from the 6th day of treatment onward according to individual response.

  The following should be considered when planning the woman's individualized dose:
  - For most normal responding women, the daily starting dose can be continued until pre-ovulatory conditions are achieved (seven to twelve days).
  - For low or poor responding women, the daily dose should be increased according to the ovarian response. The maximum, individualized, daily dose of Follistim AQ Cartridge is 500 international units.
  - For high responding women [those at particular risk of abnormal ovarian enlargement and/or ovarian hyperstimulation syndrome (OHSS)], decrease or temporarily stop the daily dose, or discontinue the cycle according to individual response *[see Warnings and Precautions (5.1, 5.2, 5.10)]*.
- When a sufficient number of follicles of adequate size are present, dosing of Follistim AQ Cartridge is stopped and final maturation of the oocytes is induced by administering urinary hCG at a dose of 5,000 to 10,000 international units. The administration of hCG should be withheld in cases where the ovarian monitoring suggests an increased risk of OHSS on the last day of Follistim AQ Cartridge therapy *[see Warnings and Precautions (5.1, 5.2, 5.10)]*.
- Oocyte (egg) retrieval should be performed 34 to 36 hours following the administration of hCG.

2.4 Recommended Dosing for Induction of Spermatogenesis in Men

- Pretreatment with hCG is required prior to concomitant therapy with Follistim AQ Cartridge and hCG. An initial dosage of 1,500 international units of urinary hCG should be administered at twice weekly intervals to normalize serum testosterone levels. If serum testosterone levels have not normalized after 8 weeks of hCG treatment, the urinary hCG dose can be increased to 3,000 international units twice weekly *[see Clinical Studies (14.3)]*.
- After normal serum testosterone levels have been reached, Follistim AQ Cartridge should be administered by subcutaneous injection concomitantly with hCG treatment. Follistim is given at a dosage of 450 international units per week, as either 225 international units twice weekly or 150 international units three times per week, in combination with the same hCG dose used to normalize testosterone levels. Based on delivery of a higher dose of follitropin beta with the Follistim AQ Cartridge and pen injector *[see Dosage and Administration (2.1)],* a lower dose of Follistim AQ Cartridge may be considered.

  The concomitant therapy should be continued for at least 3 to 4 months before any improvement in spermatogenesis can be expected. If a man has not responded after this period, the combination therapy may be continued. Treatment response has been noted at up to 12 months.

3 DOSAGE FORMS AND STRENGTHS

Follistim AQ Cartridge is a clear and colorless solution available as:
Injection: 300 international units per 0.36 mL in a single-patient-use cartridge
Injection: 600 international units per 0.72 mL in a single-patient-use cartridge
Injection: 900 international units per 1.08 mL in a single-patient-use cartridge

4 CONTRAINDICATIONS

Follistim AQ Cartridge is contraindicated in women and men who exhibit:

- Prior hypersensitivity to recombinant hFSH products
- High levels of FSH indicating primary gonadal failure
- Presence of uncontrolled non-gonadal endocrinopathies (e.g., thyroid, adrenal, or pituitary disorders) *[see Indications and Usage (1.1, 1.2, 1.3)]*
- Hypersensitivity reactions to streptomycin or neomycin. Follistim AQ may contain traces of these antibiotics
- Tumors of the ovary, breast, uterus, testis, hypothalamus or pituitary gland

Follistim AQ Cartridge is also contraindicated in women who exhibit:

- Pregnancy *[see Use in Specific Populations (8.1)]*
- Heavy or irregular vaginal bleeding of undetermined origin
- Ovarian cysts or enlargement not due to polycystic ovary syndrome (PCOS)

5 WARNINGS AND PRECAUTIONS

Follistim AQ Cartridge should be used only by physicians who are experienced in infertility treatment. Follistim AQ Cartridge contains a potent gonadotropic substance capable of causing Ovarian Hyperstimulation Syndrome (OHSS) *[see Warnings and Precautions (5.2)]* with or without pulmonary or vascular complications *[see Warnings and Precautions (5.3)]* and multiple births *[see Warnings and Precautions (5.5)]*. Gonadotropin therapy requires the availability of appropriate monitoring facilities *[see Warnings and Precautions (5.10)]*.

Careful attention should be given to the diagnosis of infertility and in the selection of candidates for Follistim AQ Cartridge therapy *[see Indications and Usage (1.1, 1.2, 1.3) and Dosage and Administration (2.2, 2.3, 2.4)]*.

Switching to Follistim AQ Cartridge from other brands (manufacturer), types (recombinant, urinary), and/or methods of administration (Follistim Pen, conventional syringe) may necessitate an adjustment of the dose *[see Dosage and Administration (2)]*.

5.1 Abnormal Ovarian Enlargement

In order to minimize the hazards associated with abnormal ovarian enlargement that may occur with Follistim AQ therapy, treatment should be individualized and the lowest effective dose should be used *[*see *Dosage and Administration (2.2, 2.3)]*. Use of ultrasound monitoring of ovarian response and/or measurement of serum estradiol levels is important to minimize the risk of overstimulation *[see Warnings and Precautions (5.8)]*.

If the ovaries are abnormally enlarged on the last day of Follistim AQ therapy, hCG should not be administered in order to reduce the chances of developing Ovarian Hyperstimulation Syndrome (OHSS). Intercourse should be prohibited in patients with significant ovarian enlargement after ovulation because of the danger of hemoperitoneum resulting from ruptured ovarian cysts *[see Warnings and Precautions (5.3)]*.

5.2 Ovarian Hyperstimulation Syndrome (OHSS)

OHSS is a medical entity distinct from uncomplicated ovarian enlargement and may progress rapidly to become a serious medical condition. OHSS is characterized by a dramatic increase in vascular permeability, which can result in a rapid accumulation of fluid in the peritoneal cavity, thorax, and potentially, the pericardium. The early warning signs of OHSS developing are severe pelvic pain, nausea, vomiting, and weight gain. Abdominal pain, abdominal distension, gastrointestinal symptoms including nausea, vomiting and diarrhea, severe ovarian enlargement, weight gain, dyspnea, and oliguria have been reported with OHSS. Clinical evaluation may reveal hypovolemia, hemoconcentration, electrolyte imbalances, ascites, hemoperitoneum, pleural effusions, hydrothorax, acute pulmonary distress, and thromboembolic reactions *[see Warnings and Precautions (5.3)]*. Transient liver function test abnormalities suggestive of hepatic dysfunction with or without morphologic changes on liver biopsy have also been reported in association with OHSS.

OHSS occurs after gonadotropin treatment has been discontinued, and it can develop rapidly, reaching its maximum about seven to ten days following treatment. Usually, OHSS resolves spontaneously with the onset of menses. If there is a risk for OHSS evident prior to hCG administration *[see Warnings and Precautions (5.1)]*, the hCG must be withheld. Cases of OHSS are more common, more severe, and more protracted if pregnancy occurs; therefore, women should be assessed for the development of OHSS for at least two weeks after hCG administration.

If serious OHSS occurs, gonadotropins, including hCG, should be stopped and consideration should be given as to whether the patient needs to be hospitalized. Treatment is primarily symptomatic and overall should consist of bed rest, fluid and electrolyte management, and analgesics (if needed). Because the use of diuretics can accentuate the diminished intravascular volume, diuretics should be avoided except in the late phase of resolution as described below. The management of OHSS may be divided into three phases as follows:

- *Acute Phase:*
  Management should be directed at preventing hemoconcentration due to loss of intravascular volume to the third space and minimizing the risk of thromboembolic phenomena and kidney damage. Fluid intake and output, weight, hematocrit, serum and urinary electrolytes, urine specific gravity, BUN and creatinine, total proteins with albumin: globulin ratio, coagulation studies, electrocardiogram to monitor for hyperkalemia, and abdominal girth should be thoroughly assessed daily or more often based on the clinical need. Treatment, consisting of limited intravenous fluids, electrolytes, and human serum albumin is intended to normalize electrolytes while maintaining an acceptable but somewhat reduced intravascular volume. Full correction of the intravascular volume deficit may lead to an unacceptable increase in the amount of third space fluid accumulation.
- *Chronic Phase:*
  After the acute phase is successfully managed as above, excessive fluid accumulation in the third space should be limited by instituting severe potassium, sodium, and fluid restriction.
- *Resolution Phase:*
  As third space fluid returns to the intravascular compartment, a fall in hematocrit and increasing urinary output are observed in the absence of any increase in intake. Peripheral and/or pulmonary edema may result if the kidneys are unable to excrete third space fluid as rapidly as it is mobilized. Diuretics may be indicated during the resolution phase, if necessary, to combat pulmonary edema.

OHSS increases the risk of injury to the ovary. The ascitic, pleural, and pericardial fluid should not be removed unless there is the necessity to relieve symptoms such as pulmonary distress or cardiac tamponade. Pelvic examination may cause rupture of an ovarian cyst, which may result in hemoperitoneum, and should therefore be avoided. If bleeding occurs and requires surgical intervention, the clinical objective should be to control the bleeding and retain as much ovarian tissue as possible.

During clinical trials with Follistim or Follistim AQ Cartridge therapy, OHSS occurred in 7.6% of 105 women (OI) and 6.4% of 751 women (IVF or ICSI) treated with Follistim and Follistim AQ Cartridge, respectively.

5.3 Pulmonary and Vascular Complications

Serious pulmonary conditions (e.g., atelectasis, acute respiratory distress syndrome) have been reported in women treated with gonadotropins. In addition, thromboembolic reactions both in association with, and separate from OHSS have been reported following gonadotropin therapy. Intravascular thrombosis, which may originate in venous or arterial vessels, can result in reduced blood flow to vital organs or the extremities. Women with generally recognized risk factors for thrombosis, such as a personal or family history, severe obesity, or thrombophilia, may have an increased risk of venous or arterial thromboembolic events, during or following treatment with gonadotropins. Sequelae of such reactions have included venous thrombophlebitis, pulmonary embolism, pulmonary infarction, cerebral vascular occlusion (stroke), and arterial occlusion resulting in loss of limb and rarely in myocardial infarction. In rare cases, pulmonary complications and/or thromboembolic reactions have resulted in death. In women with recognized risk factors, the benefits of ovulation induction, in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) treatment need to be weighed against the risks. It should be noted that pregnancy itself also carries an increased risk of thrombosis.

5.4 Ovarian Torsion

Ovarian torsion has been reported after treatment with Follistim AQ Cartridge and after intervention with other gonadotropins. This may be related to OHSS, pregnancy, previous abdominal surgery, past history of ovarian torsion, previous or current ovarian cyst and polycystic ovaries. Damage to the ovary due to reduced blood supply can be limited by early diagnosis and immediate detorsion.

5.5 Multi-fetal Gestation and Birth

Multi-fetal gestation and births have been reported with all gonadotropin treatments including Follistim AQ Cartridge treatment. The woman and her partner should be advised of the potential risk of multi-fetal gestation and births before starting treatment.

5.6 Congenital Anomalies

The incidence of congenital malformations after IVF or ICSI may be slightly higher than after spontaneous conception. This slightly higher incidence is thought to be related to differences in parental characteristics (e.g., maternal age, sperm characteristics) and to the higher incidence of multi-fetal gestations after IVF or ICSI. There are no indications that the use of gonadotropins during IVF or ICSI is associated with an increased risk of congenital malformations.

5.7 Ectopic Pregnancy

Since infertile women undergoing IVF or ICSI often have tubal abnormalities, the incidence of ectopic pregnancies might be increased. Early confirmation of an intrauterine pregnancy should be determined by β-hCG testing and transvaginal ultrasound.

5.8 Spontaneous Abortion

The risk of spontaneous abortions (miscarriage) is increased with gonadotropin products. However, causality has not been established. The increased risk may be a factor of the underlying infertility.

5.9 Ovarian Neoplasms

There have been infrequent reports of ovarian neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for controlled ovarian stimulation; however, a causal relationship has not been established.

5.10 Laboratory Tests

For Women:

In most instances, treatment with Follistim AQ Cartridge will result only in follicular growth and maturation. In order to complete the final phase of follicular maturation and to induce ovulation, hCG must be given following the administration of Follistim AQ Cartridge or when clinical assessment indicates that sufficient follicular maturation has occurred. The degree of follicular maturation and the timing of hCG administration can both be determined with the use of sonographic visualization of the ovaries and endometrial lining in conjunction with measurement of serum estradiol levels. The combination of transvaginal ultrasonography and measurement of serum estradiol levels is also useful for minimizing the risk of OHSS and multi-fetal gestations.

The clinical confirmation of ovulation is obtained by the following direct or indirect indices of progesterone production as well as sonographic evidence of ovulation.

Direct or indirect indices of progesterone production are:

- Urinary or serum luteinizing hormone (LH) rise
- A rise in basal body temperature
- Increase in serum progesterone
- Menstruation following the shift in basal body temperature

The following provide sonographic evidence of ovulation:

- Collapsed follicle
- Fluid in the cul-de-sac
- Features consistent with corpus luteum formation

Sonographic evaluation of the early pregnancy is also important to rule out ectopic pregnancy.

For Men:

Clinical monitoring for spermatogenesis utilizes the following indirect or direct measures:

- Serum testosterone level
- Semen analysis

5.11 Follistim Pen

The Follistim Pen is intended only for use with Follistim AQ Cartridge. The Follistim Pen is not recommended for the blind or visually impaired without the assistance of an individual with good vision who is trained in the proper use of the injection device.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Abnormal Ovarian Enlargement *[see Warnings and Precautions (5.1)]*
- Ovarian Hyperstimulation Syndrome *[see Warnings and Precautions (5.2)]*
- Atelectasis *[see Warnings and Precautions (5.3)]*
- Thromboembolism *[see Warnings and Precautions (5.3)]*
- Ovarian Torsion *[see Warnings and Precautions (5.4)]*
- Multi-fetal Gestation and Birth *[see Warnings and Precautions (5.5)]*
- Congenital Anomalies *[see Warnings and Precautions (5.6)]*
- Ectopic Pregnancy *[see Warnings and Precautions (5.7)]*
- Spontaneous Abortion *[see Warnings and Precautions (5.8)]*
- Ovarian Neoplasms *[see Warnings and Precautions (5.9)]*

6.1 Clinical Study Experience

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

Ovulation Induction

In a single cycle, multi-center, assessor-blind, parallel group, comparative study, a total of 172 chronic anovulatory women who had failed to ovulate and/or conceive with clomiphene citrate therapy, were randomized and treated with Follistim (105) or a urofollitropin comparator. Adverse reactions with an incidence of greater than 2% in either treatment group are listed in Table 2.

Table 2: Common Adverse Reactions Reported at a Frequency of ≥2% in an Assessor-Blind, Comparative Study of Anovulatory Women Receiving Ovulation Induction

System Organ Class/Adverse Reactions	Treatment Number (%) of Women	
	Follistim N=105 n (%)	Comparator N=67 n (%)
Gastrointestinal disorders		
Abdominal discomfort	3 (2.9)	1 (1.5)
Abdominal pain	3 (2.9)	2 (3.0)
Abdominal pain lower	3 (2.9)	1 (1.5)
Reproductive system and breast disorders		
Ovarian cyst	3 (2.9)	2 (3.0)
Ovarian hyperstimulation syndrome	8 (7.6)	3 (4.5)
General disorders and administration site conditions		
Pyrexia	0 (0.0)	2 (3.0)

Adverse reactions reported commonly (greater than or equal to 2% of women treated with Follistim) in other ovulation induction clinical trials were headache, abdominal distension, constipation, diarrhea, nausea, pelvic pain, uterine enlargement, vaginal hemorrhage and injection site reaction.

In Vitro Fertilization/Intracytoplasmic Sperm Injection

In a single cycle, multi-center, double-blind, parallel group, comparative study, a total of 1509 women were randomized to receive controlled ovarian stimulation with either Follistim AQ Cartridge (751 women were treated with Follistim AQ Cartridge) or a comparator and pituitary suppression with a gonadotropin releasing hormone (GnRH) antagonist as part of an in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) cycle. Table 3 lists adverse reactions with an incidence of greater than 2% in the group of women treated with Follistim AQ Cartridge.

Table 3: Common Adverse Reactions Reported at a Frequency of ≥2% in a Randomized, Double-blind, Active-controlled, Comparative Study of Normal Ovulatory Women Undergoing Controlled Ovarian Stimulation as Part of an In Vitro Fertilization or Intracytoplasmic Sperm Injection Cycle

System Organ Class/Adverse Reactions	Follistim AQ Cartridge Treatment N = 751 n[a] (%)
Nervous System disorders	
Headache	55 (7.3%)
Gastrointestinal disorders	
Nausea	29 (3.9%)
Reproductive system and breast disorders	
Ovarian Hyperstimulation Syndrome	48 (6.4%)
Pelvic discomfort	62 (8.3%)
Pelvic Pain	41 (5.5%)
General disorders and Administration site conditions	
Fatigue	17 (2.3%)

[a] n = number of women with the adverse reaction

Induction of Spermatogenesis

In an open-label, non-comparative clinical trial, 49 men with hypogonadotropic hypogonadism were enrolled to receive pretreatment with hCG, followed by combination therapy with hCG and Follistim for induction of spermatogenesis. Of the 49 men, 30 received weekly Follistim doses of 450 international units; 24 of these 30 men received a total of 48 weeks of treatment with Follistim. Adverse reactions occurring with an incidence of greater than 2% in the 30 men treated with Follistim are listed in Table 4.

Table 4: Common Adverse Reactions Reported at a Frequency of ≥2% in an Open-Label Clinical Trial in Men with Hypogonadotropic Hypogonadism

System Organ Class/Adverse Reactions	Follistim Treatment N=30 n (%)
Nervous system disorders	
Headache	2 (6.7)
General disorders and administration site disorders	
Injection site reaction	2 (6.7)
Injection site pain	2 (6.7)
Skin and cutaneous tissue disorders	
Acne	2 (6.7)
Rash	1 (3.3)
Reproductive system and breast disorders	
Gynecomastia	1 (3.3)
Neoplasms benign, malignant and unspecified	
Dermoid cyst	1 (3.3)

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Follistim and/or Follistim AQ Cartridge. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal disorders
Abdominal distension, abdominal pain, constipation, diarrhea

General disorders and administration site conditions
Injection site reaction

Reproductive system and breast disorders
Breast tenderness, metrorrhagia, ovarian enlargement, vaginal hemorrhage

Skin and subcutaneous tissue disorders
Rash

Vascular disorders
Thromboembolism *[see Warnings and Precautions (5.3)]*

7 DRUG INTERACTIONS

No drug-drug interaction studies have been performed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Follistim AQ Cartridge is contraindicated for use in pregnant women and offers no benefit during pregnancy.

8.2 Lactation

Risk Summary
It is not known whether this drug is excreted in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Follistim AQ Cartridge and any potential adverse effects on the breastfed child from Follistim AQ Cartridge or from the underlying maternal condition.

8.4 Pediatric Use

Follistim AQ Cartridge is not indicated for use in pediatric patients. Clinical studies have not been conducted in the pediatric population.

8.5 Geriatric Use

Clinical studies of Follistim AQ Cartridge have not been conducted in patients 65 years of age and older.

10 OVERDOSAGE

Aside from the possibility of Ovarian Hyperstimulation Syndrome *[see Warnings and Precautions (5.2, 5.3)]* and multiple gestations *[see Warnings and Precautions (5.5)]*, there is no additional information concerning the consequences of acute overdosage with Follistim AQ Cartridge.

11 DESCRIPTION

Follitropin beta, a gonadotropin [human follicle-stimulating hormone (hFSH)], is a glycoprotein hormone produced by recombinant DNA technology in a Chinese hamster ovary (CHO) cell line. It has a dimeric structure containing two glycoprotein subunits (alpha and beta). The alpha and beta subunits have 92 and 111 amino acids, respectively, and their primary and tertiary structures are indistinguishable from that of hFSH. The molecular weight is approximately 40 kDa.

Follistim AQ Cartridge (follitropin beta) injection is a sterile clear and colorless solution, containing either 300 International Units, 600 International Units, or 900 International Units of follitropin beta in disposable single-patient-use cartridges for subcutaneous use only with the Follistim Pen.

Each cartridge delivers 300 International Units in 0.36 mL and the inactive ingredients: benzyl alcohol (3.6 mg; preservative), methionine (0.18 mg), polysorbate 20 (0.072 mg), sodium citrate (4.64 mg), sucrose (18 mg), and Water for Injection USP. Hydrochloric acid NF and/or sodium hydroxide NF are used to adjust the pH to 7.

Each cartridge delivers 600 International Units in 0.72 mL and the inactive ingredients: benzyl alcohol (7.2 mg; preservative), methionine (0.36 mg), polysorbate 20 (0.144 mg), sodium citrate (9.3 mg), sucrose (36 mg), and Water for Injection USP. Hydrochloric acid NF and/or sodium hydroxide NF are used to adjust the pH to 7.

Each cartridge delivers 900 International Units in 1.08 mL and the inactive ingredients: benzyl alcohol (10.8 mg; preservative), methionine (0.54 mg), polysorbate 20 (0.216 mg), sodium citrate (13.9 mg), sucrose (54 mg), and Water for Injection USP. Hydrochloric acid NF and/or sodium hydroxide NF are used to adjust the pH to 7.

Under current storage conditions, Follistim AQ may contain up to 11% of oxidized follitropin beta.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Women:

Follicle-stimulating hormone (FSH), the active component in Follistim AQ Cartridge, is required for normal follicular growth, maturation, and gonadal steroid production.

In women, the level of FSH is critical for the onset and duration of follicular development, and consequently for the timing and number of follicles reaching maturity. Follistim AQ Cartridge stimulates ovarian follicular growth in women who do not have primary ovarian failure. In order to effect the final phase of follicle maturation, resumption of meiosis and rupture of the follicle in the absence of an endogenous LH surge, human chorionic gonadotropin (hCG) must be given following treatment with Follistim AQ Cartridge when patient monitoring indicates appropriate follicular development parameters have been reached.

Men:

Follistim when administered with hCG stimulates spermatogenesis in men with hypogonadotropic hypogonadism. FSH, the active component of Follistim, is the pituitary hormone responsible for spermatogenesis.

12.3 Pharmacokinetics

Pharmacokinetic parameters for Follistim AQ Cartridge were evaluated in an open-label, single-center, randomized study in 20 healthy women. Serum FSH values from a single subcutaneous injection of reconstituted Follistim lyophilized powder administered by conventional syringe were compared to those values following a single subcutaneous injection of Follistim AQ Cartridge administered with the Follistim Pen injector. Administration of follitropin beta with the Follistim Pen resulted an 18% increase in $AUC_{0-\infty}$ and C_{max}. The 18% difference in serum FSH concentrations resulting from administration of the two formulations was due to differences between the anticipated and actual volume delivered with the conventional syringe. The pharmacokinetic parameters for Follistim AQ Cartridge are as follows:

Table 5: Mean (SD) Pharmacokinetic Parameters of a Single Subcutaneous Injection of 150 IU of Follistim AQ Cartridge (n=20)

	$AUC_{0-\infty}$ (IU/L*h)	C_{max} (IU/L)	t_{max} (h)	$t_{½}$ (h)	CL_{app} (L/h/kg)
Follistim AQ Cartridge	215.1 (45.8)	3.4 (0.7)	12.9 (6.2)	33.4 (4.2)	0.01 (0.003)

$AUC_{0-\infty}$ Area under the curve
C_{max} Maximum concentration
t_{max} Time to maximum concentration
$t_{½}$ Elimination half-life
CL_{app} Clearance

Absorption:

Women:

The bioavailability of Follistim following subcutaneous and intramuscular administration was investigated in healthy, pituitary-suppressed women given a single 300 international units dose. In these women, the area under the curve (AUC), expressed as the mean ± SD, was equivalent between the subcutaneous (455.6 ± 141.4 IU*h/L) and intramuscular (445.7 ± 135.7 IU*h/L) routes of administration. However, equivalence could not be established with respect to the peak serum FSH levels (C_{max}). The C_{max} achieved after subcutaneous administration and intramuscular administration was 5.41 ± 0.72 international units/L and 6.86 ± 2.90 international units/L, respectively. After subcutaneous or intramuscular injection the apparent dose absorbed was 77.8% and 76.4%, respectively.

The pharmacokinetics and pharmacodynamics of a single, intramuscular dose (300 international units) of Follistim were also investigated in a group (n=8) of gonadotropin-deficient, but otherwise healthy women. In these women, FSH (mean ± SD) AUC was 339 ± 105 international units*h/L, C_{max} was 4.3 ± 1.7 international units/L. C_{max} occurred at approximately 27 ± 5.4 hours after intramuscular administration.

A multiple dose, dose proportionality, pharmacokinetic study of Follistim was completed in healthy, pituitary-suppressed, female subjects given subcutaneous doses of 75, 150, or 225 international units for 7 days. Steady-state blood concentrations of FSH were reached with all doses after 5 days of treatment based on the trough concentrations of FSH just prior to dosing (C_{trough}). Peak blood concentrations with the 75, 150, and 225 international units dose were 4.30 ± 0.60 international units/L, 8.51 ± 1.16 international units/L and 13.92 ± 1.81 international units/L, respectively.

Men:

No PK studies were conducted using Follistim AQ Cartridge in men. Exposures of follitropin beta from Follistim AQ Cartridge and Follistim are expected to be equivalent after adjusting for the 18% difference in dose *[see Dosage and Administration (2)]*.

Serum levels of FSH were measured in a clinical study that compared the effects of two different dosing schedules of Follistim (150 international units three times a week or 225 international units twice a week) administered by subcutaneous injection concurrently with chorionic gonadotropin for induction of spermatogenesis in hypogonadotropic hypogonadal men. Administration of Follistim was started at Week 17. Mean serum trough concentrations of FSH remained fairly constant over the treatment period. At the end of treatment (Week 64), the mean serum trough concentrations of FSH were 2.09 international units/L in the 150 international units group and 3.22 international units/L in the 225 international units group. Serum trough concentrations of FSH measured prior to the first Follistim injection on the Mondays of active treatment period (Weeks 17 to 64) and one week after the end of treatment period are presented in Figure 1.

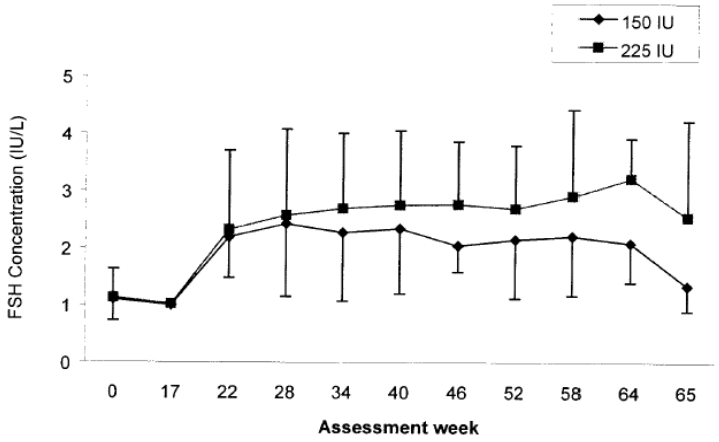


Figure 1: Mean (SD) Serum Trough Concentrations of FSH in Men Following Subcutaneous Administration of Follistim Using Two Different Dosing Schedules (150 International Units Three Times a Week or 225 International Units Twice a Week)

Distribution:

The volume of distribution of Follistim in healthy, pituitary-suppressed, women following intravenous administration of a 300 international units dose was approximately 8 L.

Metabolism:

The recombinant FSH in Follistim AQ Cartridge is biochemically very similar to urinary FSH and it is therefore anticipated that it is metabolized in the same manner.

Elimination:

The elimination half-life ($t_{½}$) following a single subcutaneous injection of 150 IU of Follistim AQ Cartridge in women was 33.4 (4.2) hours. The clearance was 0.01 (0.003) L/h/kg.

Use in Specific Populations:

Body weight: The effect of body weight on the pharmacokinetics of Follistim was evaluated in a group of European and Japanese women who were significantly different in terms of body weight. The European women had a body weight of (mean ± SD) 67.4 ± 13.5 kg and the Japanese subjects were 46.8 ± 11.6 kg. Following a single intramuscular dose of 300 international units of Follistim, the AUC was significantly smaller in European women (339 ± 105 international units*h/L) than in Japanese women (544 ± 201 international units*h/L). However, clearance per kg of body weight was essentially the same for the respective groups (0.014 and 0.013 L/hr/kg).

Geriatric Use: The pharmacokinetics of Follistim has not been studied in geriatric subjects.

Pediatric Use: The pharmacokinetics of Follistim has not been studied in pediatric subjects.

Renal Impairment: The effect of renal impairment on the pharmacokinetics of Follistim has not been studied.

Hepatic Impairment: The effect of hepatic impairment on the pharmacokinetics of Follistim has not been studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term toxicity studies in animals have not been performed with Follistim to evaluate the carcinogenic potential of the drug. Follistim was not mutagenic in the Ames test using *S. typhimurium* and *E. coli* tester strains and did not produce chromosomal aberrations in an *in vitro* assay using human lymphocytes.

14 CLINICAL STUDIES

14.1 Ovulation Induction

The efficacy of Follistim for ovulation induction was evaluated in a randomized, assessor-blind, parallel-group comparative, multicenter safety and efficacy study of 172 chronic anovulatory women (105 subjects on Follistim) who had previously failed to ovulate and/or conceive during clomiphene citrate treatment. The study results for ovulation rates are summarized in Table 6 and those for pregnancy rates are summarized in Table 7.

Table 6: Cumulative Ovulation Rates

Cycle	Follistim (n=105)
First treatment cycle	72%
Second treatment cycle	82%
Third treatment cycle	85%

Table 7: Cumulative Ongoing*, † Pregnancy Rates

Cycle	Follistim (n=105)
First treatment cycle	14%
Second treatment cycle	19%
Third treatment cycle	23%

* All ongoing pregnancies were confirmed after at least 12 weeks after the hCG injection.
† Study was not powered to demonstrate this outcome.

14.2 Controlled Ovarian Stimulation as Part of an In Vitro Fertilization (IVF) or Intracytoplasmic Sperm Injection (ICSI) Cycle

The efficacy of Follistim AQ Cartridge was evaluated in a randomized, double-blind, active-controlled study of 1,509 healthy normal ovulatory women (mean age, body weight, and body mass index of 32 years, 68 kg and 25 kg/m^2, respectively) treated for one cycle with controlled ovarian stimulation and pituitary suppression with a GnRH antagonist as part of an in vitro fertilization or intracytoplasmic sperm injection cycle. This 2008 study was conducted in Europe and North America (United States and Canada). Approximately 54% of the subjects were from North America. The overall results, as well as the results from North America only, for clinical pregnancy are summarized in Table 8.

Table 8: Pregnancy Results from Treatment With Follistim AQ Cartridge and a GnRH Antagonist in Normal Ovulatory Women Undergoing Controlled Ovarian Stimulation as Part of an In Vitro Fertilization or Intracytoplasmic Sperm Injection Cycle.* Intent-to-Treat Population (ITT)

Parameter	Follistim AQ Cartridge Overall data (n=750)	Follistim AQ Cartridge North American data (n=403)
Clinical pregnancy rate/cycle initiation†	41.1%	48.9%

* Single treatment cycle results
† Clinical pregnancy was assessed ≥6 weeks after transfer of one or two embryos.

14.3 Induction of Spermatogenesis

The safety and efficacy of Follistim administered by subcutaneous injection concomitantly with chorionic gonadotropin for injection (hCG) has been examined in a multicenter, open-label, non-comparator clinical study for induction of spermatogenesis in hypogonadotropic hypogonadal men. The study compared the effects of two different Follistim dosing schedules on semen parameters and serum levels of follicle stimulating hormone (FSH). The multicenter study involved a 16-week pretreatment phase with urinary hCG at a dosage of 1,500 international units twice a week to normalize serum testosterone levels. If serum testosterone levels did not normalize after 8 weeks of hCG treatment, the urinary hCG dose could have been increased to 3,000 international units twice a week. This phase was followed by a 48-week treatment phase. Men who were still azoospermic after the pretreatment phase were randomized to receive either 225 international units Follistim together with 1,500 international units urinary hCG twice a week or 150 international units Follistim three times a week together with 1,500 international units urinary hCG twice weekly. Men who required 3,000 international units of urinary hCG twice a week in the pretreatment phase were continued on that dosage during the treatment phase. The mean age of patients in both treatment groups was approximately 30 years (range 18 to 47 years). At baseline, mean left and right testis volumes were 4.61 ± 2.94 mL and 4.57 ± 3.00 mL, respectively, in the group receiving three weekly injections of Follistim. For the group receiving two weekly injections of Follistim, the mean left and right testis volumes were 6.54 ± 2.45 mL and 7.21 ± 2.94 mL, respectively, at baseline. The primary efficacy endpoint was the percentage of patients with a mean sperm density of ≥1 x 10^6/mL on their last two treatment assessments. The outcomes of treatment in the 30 men enrolled in the treatment phase are summarized in Table 9.

Table 9: Number of Men Receiving Follistim Who Achieved a Mean Sperm Density of ≥10^6/mL on Their Last Two Treatment Assessments

	Follistim 150 international units three times a week (n=15)		Follistim 225 international units twice a week (n=15)		Overall (n=30)	
Sperm Density of ≥10^6/mL	**n**	**%**	**n**	**%**	**n**	**%**
Yes	6	40	7	47	13	43
No	9	60	8	53	17	57

Overall, the median time to reach a sperm concentration of 10^6 per mL was 165 days (range 25 to 327 days) in patients who demonstrated a sperm concentration of at least 10^6 per mL. The median time to reach a sperm concentration of at least 10^6 per mL was 186 days (range 25 to 327 days) for the 150 international units group and 141 days (range 43 to 204 days) for the 225 international units group. No pregnancy data were collected during the trial.

The local tolerance data were comparable between the two treatment groups. The mean percentage of days without pain calculated for all subjects in the treatment period was 91.3% for patients in the 150 international units (three times a week) and 76.0% for patients in the 225 international units (two times a week) Follistim treatment groups. In the 225 international units (twice per week) group, local symptoms judged as severe by the investigator were: itching in 1 patient (7%), pain in 2 patients (13%), bruising in 2 patients (13%), swelling in 2 patients (13%), and redness in 1 patient (7%). In the 150 international units (three times per week) group, 1 event in 1 patient (bruising, 7%) was judged as severe. No patient discontinued treatment due to injection site reaction or injection site pain.

16 HOW SUPPLIED/STORAGE AND HANDLING

Follistim AQ Cartridge (follitropin beta) injection is a clear and colorless solution in a disposable, prefilled single-patient-use glass cartridge with grey rubber piston and an aluminum crimp-cap with grey rubber inlay supplied in a box containing disposable, 29 gauge, ultra-fine, ½-inch, sterile BD Micro-Fine™ Pen Needles (for use with Follistim Pen available separately) and in the following presentations:

NDC 78206-129-01 Follistim AQ Cartridge 300 international units per 0.36 mL with silver crimp-caps and 5 BD Micro-Fine Pen Needles

NDC 78206-130-01 Follistim AQ Cartridge 600 international units per 0.72 mL with gold crimp-caps and 7 BD Micro-Fine Pen Needles

NDC 78206-131-01 Follistim AQ Cartridge 900 international units per 1.08 mL with blue crimp-caps and 10 BD Micro-Fine Pen Needles

Pharmacy Storage: Store refrigerated 2°C to 8°C (36°F to 46°F) until dispensed. Do not freeze.

Patient Storage: Store unused cartridge refrigerated at 2°C to 8°C (36°F to 46°F) until the expiration date, or at room temperature at up to 25°C (77°F) for 3 months or until expiration date, whichever occurs first. After first use, store at 2°C to 25°C (36°F to 77°F) and discard after 28 days. Store in the original carton to protect from light. Do not freeze.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Dosing and Use of Follistim AQ Cartridge with Pen

Instruct women and men on the correct usage and dosing of Follistim AQ Cartridge in conjunction with the Follistim Pen. Make sure that individuals who have used other gonadotropin products delivered by a syringe are aware of differences arising from use of the pen. Women and men should read and follow all instructions in the Follistim Pen “Instructions for Use” Manual prior to administration of Follistim AQ Cartridge.

Advise women and men of the number of doses which can be extracted from the full unused Follistim AQ Cartridge that you have prescribed.

Therapy Duration and Necessary Monitoring in Women and Men Undergoing Treatment

Prior to beginning therapy with Follistim AQ Cartridge, inform women and men about the time commitment and monitoring procedures necessary to undergo treatment *[see Dosage and Administration (2), Warnings and Precautions (5.10)]*.

Instructions on a Missed Dose

Inform women and men that if they miss or forget to take a dose of Follistim AQ Cartridge, the next dose should not be doubled and they should call the healthcare provider for further dosing instructions.

Ovarian Hyperstimulation Syndrome

Inform women regarding the risks with use of Follistim AQ Cartridge of Ovarian Hyperstimulation Syndrome *[see Warnings and Precautions (5.2)]* and associated symptoms including lung and blood vessel problems *[see Warnings and Precautions (5.3)]* and ovarian torsion *[see Warnings and Precautions (5.4)]*.

Multi-fetal Gestation and Birth

Inform women regarding the risk of multi-fetal gestations with the use of Follistim AQ Cartridge *[see Warnings and Precautions (5.5)]*.

Manufactured by: Organon USA LLC, a subsidiary of
ORGANON & Co.,
Jersey City, NJ 07302, USA
U.S. License No.2331

For patent information: www.organon.com/our-solutions/patent/

uspi-og8328-SOi-2307r000

处方信息要点

这些重点不包括有效安全地使用 FOLLISTIM AQ Cartridge 的所有必需信息。请查看 FOLLISTIM AQ Cartridge 的完整处方信息。

FOLLISTIM® AQ Cartridge (follitropin beta) injection, for subcutaneous use
美国首次批准日期：1997

---------- 适应症及用法 ----------

Follistim AQ Cartridge 是一种促性腺激素，适用于：

专治以下女性疾病：

- 对功能性不孕而非原发性卵巢功能衰竭导致的无排卵性不孕妇女进行促排卵和妊娠 (1.1)
- 使在体外受精 (IVF) 或卵胞浆内单精子注射 (ICSI) 周期过程中接受控制性卵巢刺激治疗的正常排卵的女性受孕 (1.2)

专治以下男性疾病：

- 通过诱导精子生成，治疗原发性和继发性低促性腺素功能减退症 (HH) 男性而非因原发性睾丸衰竭导致的不育症 (1.3)

---------- 用法用量 ----------

请参阅剂量换算表 1 了解带笔式注射器的 Follistim AQ Cartridge (2.1)

对于接受排卵诱导的不排卵女性 (2.2)：

- 至少在最初 7 天内，Follistim AQ Cartridge 每天初始剂量为 50 国际单位，通过皮下注射。之后每隔一个星期，在原剂量的基础上增加 25 或 50 国际单位，直到卵泡生长和/或血清雌激素水平能够适当做出反应。
  - 当达到可接受的排卵前状态时，即可注射 5,000 至 10,000 国际单位的尿人绒毛膜促性腺激素 (hCG)，使卵母细胞最终成熟。
  - 从注射 hCG 前一天开始，女性患者与其伴侣应每天进行性生活，直到排卵明显为止。

对于在体外受精或卵胞浆内单精子注射周期过程中接受控制性卵巢刺激治疗的正常排卵的女性 (2.3)：

- 至少在治疗的最初 7 天内，Follistim AQ Cartridge 每天初始剂量为 200 国际单位（实际药液管剂量），通过皮下注射。后续剂量根据卵巢反应进行上下调整，需要对卵泡生长进行超声波检查并测定血清雌激素水平才能决定。根据个体反应，从治疗第 6 天起可以考虑对反应强烈者减少剂量。
  - 使用 5,000-10,000 国际单位剂量的尿 hCG，诱发卵母细胞最终成熟。
  - 注射后 34 至 36 小时即可取卵（卵子）。

男性精子生成诱导 (2.4)：

- 必须仅使用尿 hCG（1,500 国际单位，每周两次）进行前期治疗。进行 hCG 治疗 8 周之后，如果血清睾酮水平仍未达到正常标准，可将剂量增加到 3,000 国际单位，每周两次。
- 血清睾酮水平达到正常之后，Follistim AQ Cartridge 每周给药剂量为 450 国际单位（每次 225 国际单位，每周两次；或每次 150 国际单位，每周三次），通过皮下注射，hCG 剂量与前期治疗过程中用来调节睾酮水平的剂量相同。

---------- 剂型及规格 ----------

注射剂：Follistim AQ Cartridge，300 国际单位/0.36 mL，药液管仅供单个患者使用 (3)
注射剂：Follistim AQ Cartridge，600 国际单位/0.72 mL，药液管仅供单个患者使用 (3)
注射剂：Follistim AQ Cartridge，900 国际单位/1.08 mL，药液管仅供单个患者使用 (3)

---------- 禁忌症 ----------

患有以下病症的女性和男性：

- 对重组 hFSH 产品有前期超敏反应 (4)
- 卵泡刺激素 (FSH) 水平偏高，表明患有原发性性腺衰竭 (4)
- 存在异常的非性腺内分泌病症状 (4)
- 与链霉素或新霉素有关的超敏反应 (4)
- 卵巢、乳房、子宫、睾丸、下丘脑或垂体肿瘤 (4)

有以下情况的女性：

- 妊娠 (4, 8.1)
- 不明原因导致的严重或无规律性阴道出血 (4)
- 非多囊卵巢综合征 (PCOS) 导致的卵巢囊肿或肥大 (4)

---------- 警告和注意事项 ----------

Follistim AQ 治疗可能导致：

- 异常卵巢肥大 (5.1)
- 卵巢过度刺激综合征 (OHSS) (5.2)
- 肺部和血管并发症 (5.3)
- 卵巢扭转 (5.4)
- 多胎妊娠和分娩 (5.5)
- 先天畸形 (5.6)
- 异位妊娠 (5.7)
- 自然流产 (5.8)
- 卵巢肿瘤 (5.9)

----------不良反应----------

对于正在接受排卵诱导治疗的女性，最常见的不良反应 (≥2%) 是卵巢过度刺激综合征、卵巢囊肿、腹部不适、腹痛和下腹痛。(6.1)

对于正在 IVF 或 ICSI 周期过程中接受控制性卵巢刺激的女性，最常见的不良反应 (≥2%) 是骨盆不适、头痛、卵巢过度刺激综合征、骨盆疼痛、恶心和疲劳。(6.1)

对于正在接授精子生成诱导治疗的男性，最常见的 (≥2%) 不良反应是头痛、痔疮、注射部位反应、注射部位疼痛、男性乳房增大、皮疹和皮样囊肿。(6.1)

若需报告疑似不良反应，请致电 1-844-674-3200 联系 Organon & Co. 旗下子公司 Organon USA LLC，或者致电 1-800-FDA-1088 联系 FDA 或访问 www.fda.gov/medwatch。

---------- 特定人群用药 ---------- 哺乳期：目前尚不清楚该药物是否会通过母乳排出。(8.2)

有关患者咨询信息和 FDA 批准的患者说明书，请参阅第 17 节。

修订日期：2023 年 7 月

完整处方信息：内容*

*****此处并未列出完整处方信息中省略的章节或小节。

完整处方信息

1 适应症及用法

FOLLISTIM® AQ Cartridge (follitropin beta) injection 适用于：

专治以下女性疾病：

1.1 对功能性不孕而非原发性卵巢功能衰竭导致的无排卵性不孕妇女进行促排卵和妊娠

开始使用 Follistim AQ Cartridge 治疗之前：

- 患者必须进行全面的妇科和内分泌评估。
- 应排除原发性卵巢功能衰竭。
- 应排除妊娠的可能性。
- 应确保输卵管畅通。
- 应评估男性伴侣的生育状况。

1.2 使在体外受精 (IVF) 或卵胞浆内单精子注射 (ICSI) 周期过程中接受控制性卵巢刺激治疗的正常排卵的女性受孕

开始使用 Follistim AQ Cartridge 治疗之前：

- 女性应进行全面的妇科和内分泌评估，对不孕症的原因进行诊断。
- 应排除妊娠的可能性。
- 应评估男性伴侣的生育状况。

专治以下男性疾病：

1.3 原发性和继发性低促性腺素性功能减退症 (HH) 男性的精子发生诱导，这些患者的不育原因不是由于原发性睾丸衰竭

开始使用 Follistim AQ Cartridge 治疗之前：

- 患者应进行全面的内科和内分泌评估。
- 确定患有低促性腺素功能减退症，排除原发性睾丸衰竭症。
- 通过人绒毛膜促性腺激素 (hCG) 治疗，使血清睾酮水平达到正常范围。
- 应评估女性伴侣的生育状况。

2 用法用量

2.1 剂量信息概述

- 给药之前，在溶液和容器允许的情况下，应目测注射药物是否有颗粒和变色。如果发现溶液不清澈、有颜色或有颗粒，则不应使用。
- 请勿将任何其他药物加入 Follistim AQ Cartridge 中。
- 与使用传统注射器及针头注射 Follistim 配制药液相比，使用 Follistim AQ Cartridge 及笔式注射器装置对促卵泡素 β 的给药量平均高出 18%。注射 Follistim AQ Cartridge 时，应考虑较低的起始剂量和较低的剂量调整（与重组 Follistim 配制药液相比）。为此，提供以下剂量换算表：

表 1：使用 Follistim Pen 进行 Follistim AQ Cartridge 皮下注射剂量换算表*

安瓿或小瓶装冻干重组卵泡刺激素 (FSH)，使用传统注射器给药	Follistim AQ Cartridge，使用 Follistim Pen 给药
75 IU	50 IU
150 IU	125 IU
225 IU	175 IU
300 IU	250 IU
375 IU	300 IU
450 IU	375 IU

* 每个值均按 18% 的差异计算，按最小增量为 25 IU 取整。

2.2 接受排卵诱导的不排卵女性的推荐用量

给药方案应逐步加量，并根据每位女性的具体情况而定 *[参阅临床研究 (14.1)]*。

- 至少在最初 7 天内，Follistim AQ Cartridge 每天初始剂量为 50 国际单位 *[参阅用法用量 (2.1)]*，通过皮下注射。
- 后续用量根据卵巢反应情况每周进行调整。如果卵巢反应显示需要增加剂量，每周应增加的 Follistim AQ Cartridge 剂量为 25 或 50 国际单位，直到卵泡生长和/或血清雌激素水平显示卵巢反应充分。
  在为女性制定个性化给药剂量方案时，应考虑以下事项：
  - 适当调整 Follistim AQ Cartridge 剂量，以防多个卵泡生长和周期取消。
  - 个性化的 Follistim AQ Cartridge 每日最大剂量为 250 国际单位。
- 治疗应持续到超声波透视检查和/或血清雌激素测量结果接近正常女性排卵前的状态。
- 达到排卵前条件时，注射 5,000 至 10,000 国际单位的尿 hCG，诱发卵母细胞最终成熟和排卵。
  如果 Follistim AQ Cartridge 治疗最后一天的卵巢监测表明卵巢过度刺激综合征 (OHSS) 风险增加，则必须暂停使用 hCG *[参阅警告和注意事项 (5.1, 5.2, 5.10)]*。
- 从注射 hCG 前一天开始，应鼓励女性患者与其伴侣每天进行性生活，直到排卵明显为止 *[参阅警告和注意事项 (5.10)]*。
- 在使用 Follistim AQ Cartridge 治疗期间以及治疗后两周内，女性至少应每隔一天评估一次，排查是否出现卵巢过度刺激症状。
  如果卵巢监测结果表明 OHSS 风险增加或出现腹痛，建议停止 Follistim AQ Cartridge 给药。大多数 OHSS 发生在治疗停止后，并在排卵后七到十天左右达到高峰。

2.3 在体外受精 (IVF) 或卵胞浆内单精子注射 (ICSI) 周期过程中接受控制性卵巢刺激治疗的正常排卵女性的推荐剂量

给药方案应逐步加量，并根据每位女性的具体情况制定个性化方案。

- 至少在治疗的最初 7 天内，Follistim AQ Cartridge 每天初始剂量为 200 国际单位（实际药液管剂量）*[参阅用法用量 (2.1)]*，通过皮下注射。
- 治疗 7 天之后，后续剂量根据卵巢反应进行调整，需要通过超声波检查卵泡生长和测定血清雌激素水平才能决定。根据个体反应，从治疗第 6 天起可以考虑对反应强烈者减少剂量。

  在为女性制定个性化给药剂量方案时，应考虑以下事项：
  - 对于大多数反应正常的女性，可以每天持续使用初始剂量，直到达到排卵前状态（7 到 12 天）。
  - 对于反应低或反应不良的女性，每日剂量必须根据卵巢反应适量增加。个性化的 Follistim AQ Cartridge 每日最大剂量为 500 国际单位。
  - 对于反应强烈的女性 [为卵巢异常肿大和/或卵巢过度刺激综合征 (OHSS) 的高危人群]，必须根据个人反应情况减少每日剂量或暂停给药，或者中断周期*[参阅警告和注意事项 (5.1, 5.2, 5.10)]*。
- 当存在足够数量和足够大小的卵泡时，停止 Follistim AQ Cartridge 给药，通过注射 5,000 至 10,000 国际单位的尿 hCG，诱导卵母细胞的最终成熟。如果 Follistim AQ Cartridge 治疗最后一天的卵巢监测表明卵巢过度刺激综合征 (OHSS) 风险增加，则应暂停 hCG 给药 *[参阅警告和注意事项 (5.1, 5.2, 5.10)]*。
- 注射 hCG 之后 34 至 36 小时即可取卵（卵子）。

2.4 男性精子生成诱导推荐剂量

- 进行 Follistim AQ Cartridge 和 hCG 伴随治疗法前，必须使用 hCG 进行前期治疗。为了使血清睾酮水平达到正常范围，尿 hCG 的起始用量应达到 1,500 国际单位，每周给药两次。进行 hCG 治疗 8 周之后，如果血清睾酮水平仍未达到正常标准，可将尿 hCG 剂量增加到 3,000 国际单位，每周两次 *[参阅临床研究 (14.3)]*。
- 达到正常血清睾酮水平之后，应通过皮下注射方式进行 Follistim AQ Cartridge 给药，同时伴随 hCG 治疗。Follistim 的每周用量为 450 国际单位，亦即每次 225 国际单位，每周两次，或者每次 150 国际单位，每周三次；伴随 hCG 治疗的剂量与前期调节睾酮水平使用的剂量相同。因为使用 Follistim AQ Cartridge 和笔式注射器时卵泡素 β 注射液剂量更高 *[参阅用法用量 (2.1)]*，应考虑使用较低的 Follistim AQ Cartridge 剂量。

  伴随治疗至少持续 3 至 4 个月，直到精子生成状况有所改善。如果经过这段时间的治疗之后，患者没有反应，则应继续使用联合治疗方案。观察到治疗效果的时间最长达 12 个月。

3 剂型及规格

Follistim AQ Cartridge 是一种透明无色的溶液，可供选择：

注射剂：300 国际单位/0.36 mL，药液管供单个患者使用
注射剂：600 国际单位/0.72 mL，药液管供单个患者使用
注射剂：900 国际单位/1.08 mL，药液管供单个患者使用

4 禁忌症

具有以下症状的女性和男性禁止使用 Follistim AQ Cartridge：

- 既往对重组人卵泡刺激素 (hFSH) 产品有超敏反应
- FSH 水平偏高，表明患有原发性性腺衰竭
- 存在异常的非性腺内分泌病症状（如甲状腺、肾上腺或脑垂体紊乱）*[参阅适应症及用法 (1.1, 1.2, 1.3)]*
- 对链霉素或新霉素有超敏反应。Follistim AQ 可能含有微量的此类抗生素
- 卵巢、乳房、子宫、睾丸、下丘脑或垂体肿瘤

具有以下情况的女性禁止使用 Follistim AQ Cartridge：

- 妊娠 *[参阅特殊人群用药 (8.1)]*
- 不明原因导致的严重或无规律性阴道出血
- 非多囊卵巢综合征 (PCOS) 导致的卵巢囊肿或肥大

5 警告和注意事项

Follistim AQ Cartridge 必须在不孕不育治疗经验丰富的医生指导下使用。Follistim AQ Cartridge 是一种强效的促性腺物质，有可能导致卵巢过度刺激综合征 (OHSS) *[参阅警告和注意事项 (5.2)]*，伴或不伴肺部或血管并发症 *[参阅警告和注意事项 (5.3)]* 以及多胞胎妊娠 *[参阅警告和注意事项 (5.5)]*。促性腺激素治疗要求同时使用必要的监测设备*[参阅警告和注意事项 (5.10)]*。

对不孕不育症进行诊断，以及选择患者接受 Follistim AQ Cartridge 治疗时，应引起高度*重视 [参阅适应症及用法 (1.1, 1.2, 1.3) 以及用法用量 (2.2, 2.3, 2.4)]*。

从其他品牌（制造商）、类型（重组、泌尿）和/或给药方法（Follistim Pen、传统注射器）*改为使用* Follistim AQ Cartridge 时，必要时需调整剂量 *[参阅用法用量 (2)]*。

5.1 卵巢异常肿大

*为了*尽可能减小 Follistim AQ 治疗导致的卵巢异常肿大危害，治疗时必须因人而异，并应使用最低有效剂量 *[参阅用法用量 (2.2, 2.3)]*。对卵巢反应进行超声波监测和/或对血清雌激素水平进行测定，对最大限度地降低卵巢过度刺激风险非常重要 *[参阅警告和注意事项 (5.8)]*。

如果在接受 Follistim AQ 治疗的最后一天，卵巢异常肿大，则为了减少卵巢过度刺激综合征 (OHSS) 的发生几率，应停止进行 hCG 给药。如果患者排卵后出现明显的卵巢肿大，则应禁止进行性生活，因为卵巢囊肿可能会破裂，从而导致腹腔积血 *[参阅警告和注意事项 (5.3)]*。

5.2 卵巢过度刺激综合征 (OHSS)

OHSS 是一种有别于无并发症卵巢肿大的医学症状，可能快速恶化成一种严重的病症。OHSS 的主要特征表现为毛细血管通透性大幅增加，可导致腹腔、胸腔以及可能心包内液体迅速积聚。OHSS 的早期警告体征为严重的盆腔疼痛、恶心、呕吐和体重升高。据报告，OHSS 会引起腹痛、腹胀、胃肠道症状（包括恶心、呕吐和腹泻）、卵巢严重肿大、体重升高、呼吸困难和少尿。临床评估可能还会发现以下症状：低血容积、血液浓缩、电解质失衡、腹水、腹腔积血、胸腔积血、胸水、急性肺窘迫和血栓栓塞反应 *[参阅警告和注意事项 (5.3)]*。也曾有报告与 OHSS 有关的一过性肝功能检查异常表明存在肝功能缺陷，伴有或不伴有肝活检提示的形态学变化。

OHSS 出现于促性腺激素治疗中断后，并且可能会快速恶化，治疗后第 7 到 10 天症状最为严重。通常，OHSS 会在月经来潮时自行消退。如果在进行 hCG 给药之前，明显存在 OHSS 发病风险 *[参阅警告和注意事项 (5.1)]*，则必须停止 hCG 给药。如果发生妊娠，OHSS 病例更为常见、更严重、更持久，因此注射 hCG 之后至少两周内，应评估女性是否出现 OHSS。

如果发生了严重的 OHSS，则无论患者是否需要住院，均应立即停止包括 hCG 在内的任何促性腺激素给药。治疗主要是对症进行，总体上应包括卧床休息、体液和电解质调节以及镇痛药（如有需要）。使用利尿剂会导致血管内液体容量减少现象更为明显，因此应避免使用利尿剂，除非是在下文所述的消退期的晚期。OHSS 的治疗可划分为三个阶段，如下文所述：

- *急性期：*
  治疗应侧重于防止因第三间隙血管内容量减少导致出现血浓缩，最大限度地减少血栓栓塞症状和肾脏损害风险。液体摄入量和排出量、体重、血细胞比容、血清和尿液电解质、尿比重、尿素氮和肌酐、总蛋白和白蛋白：应根据临床需要每天或更频繁地全面评估球蛋白比率、凝血功能检查、心电图以监测高钾血症和腹围。限量静脉内液、电解质、人血清白蛋白等治疗旨在使电解质恢复正常并维持在可接受范围内，但有时会导致血管内液体容量减少。全面矫正血管内液体容量不足，可能会导致第三间隙积液增加到不可接受的范围。
- *慢性期：*
  成功渡过上述急性期之后，应通过制定严格的钾、钠和液量限制，控制第三间隙中的积液过量症状。
- *消退期：*
  随着第三间隙积液重新流入血管内，红细胞压积下降，在摄入量没有增加的情况下，可以明显看到尿排出量增加。如果肾脏在激活的同时无法快速分泌第三间隙积液，可能导致外周性水肿和/或肺水肿。在消退期，如有必要，可以使用利尿剂来治疗肺水肿。

OHSS 会增加卵巢受损风险。除非有必要减轻一些临床症状（如肺窘迫或心脏压塞），否则不应消除腹腔、胸腔和心包积液。进行盆腔检查可能导致卵巢囊肿破裂，从而引起腹腔积血，因此应避免进行盆腔检查。如果发生出血并需要进行外科干涉，临床治疗的目标应侧重在止血方面，尽可能多地保留卵巢组织。

在 Follistim 或 Follistim AQ Cartridge 治疗的临床试验中，在接受 Follistim 和 Follistim AQ Cartridge 治疗的 105 名排卵诱导 (OI) 女性患者中，OHSS 的发作率为 7.6%，在 751 名接受 IVF 或 ICSI 治疗的女性患者中，OHSS 的发作率为 6.4%。

5.3 肺部和血管并发症

在接受促性腺激素治疗的女性中，有报告称会引起重症肺部疾病（如肺不张、急性呼吸窘迫综合征）。此外，在接受促性腺激素疗法治疗的过程中，还发现会引起与 OHSS 相关或无关的血栓栓塞反应。血管内血栓症可能会在静脉或动脉血管内发生，导致重要器官或四肢的血流量减少。对于存在普遍认可的血栓症风险的女性，如有个人或家族病史、过度肥胖或血栓形成倾向，在接受促性腺激素治疗的过程中或治疗之后，静脉或动脉血栓栓塞发病率较高。这些反应的后遗症包括血栓性静脉炎、肺栓塞、肺梗塞、脑血管闭塞（卒中），以及导致截肢的动脉闭塞，在极少数情况下还会导致心肌梗死。在极少数情况下，肺部并发症和/或血栓栓塞直接导致死亡。对于已确认存在血栓症风险的女性患者，必须权衡排卵诱导、体外受精 (IVF) 或 卵胞浆内单精子注射 (ICSI) 治疗的益处与风险。值得注意的是，妊娠本身也会增加血栓形成的风险。

5.4 卵巢扭转

据报告，接受 Follistim AQ Cartridge 治疗和进行其他促性腺激素干预之后，可能会出现卵巢扭转。这可能与 OHSS、妊娠、既往接受过腹部手术、卵巢扭转既往病史、既往或当前卵巢囊肿以及多囊卵巢症状有关。通过早期诊断和及时扭转，可以控制因血液供给减少导致的卵巢损坏。

5.5 多胎妊娠和分娩

所有接受促性腺激素治疗，包括 Follistim AQ Cartridge 治疗，均有报告称出现多胎妊娠和分娩。开始治疗之前，应告知女性患者及其配偶存在多胎妊娠和分娩的潜在风险。

5.6 先天畸形

相对于自然受孕，接受 IVF 或 ICSI 之后的先天畸形发病率稍有偏高。这种发病率偏高的主要原因是父母身体特征各不相同（如孕妇年龄、精子特性），以及接受 IVF 或 ICSI 之后多胎妊娠几率较大。目前尚无任何证据表明，IVF 或 ICSI 治疗期间使用促性腺激素与先天畸形风险增大相关。

5.7 异位妊娠

由于正在接受 IVF 或 ICSI 治疗的不孕女性通常患有输卵管异常疾病，因此异位妊娠的发病率可能会增加。应通过 β-hCG 检验和经阴道超声波检查，早期确认宫内妊娠。

5.8 自然流产

使用促性腺激素药物时，自然流产（小产）的风险会增加。但是，目前尚未找出确切的因果关系。流产风险增加可能是导致潜在不孕不育症的一个因素。

5.9 卵巢肿瘤

少数报告称，为进行控制性卵巢刺激而接受多种药物治疗的女性发生了卵巢肿瘤（良性和恶性）；但目前尚未找到确切的因果关系。

5.10 实验室检查

对于女性：

在多数情况下，Follistim AQ Cartridge 治疗只会促进卵泡生长和成熟。为了完成卵泡成熟最后阶段并诱导排卵，注射 Follistim AQ Cartridge 之后或临床评估表明卵泡充分成熟，必须给予注射 hCG。通过使用卵巢和子宫内膜内层超声成像，结合测量血清雌激素水平，确定卵泡成熟程度以及 hCG 注射时间。结合运用经阴道超声诊断和血清雌激素水平测量，对尽可能降低 OHSS 和多胎妊娠风险也非常有帮助。

使用以下孕激素分泌直接或间接指数和排卵超声迹象，对排卵进行临床确认。

孕激素分泌直接或间接指数包括：

- 尿液或血清促黄体激素 (LH) 升高
- 基础体温升高
- 血清孕激素升高
- 基础体温产生变化之后月经来临

以下表现为排卵的超声证据：

- 卵泡缩小
- 穹窿部的液体
- 符合黄体形成的特征

对早期妊娠进行超声评估是排除异位妊娠的重要手段。

对于男性：
精子生成的临床检测采用以下直接或间接措施：
- 血清睾酮水平
- 精液分析

5.11 Follistim Pen
Follistim Pen 仅用于 Follistim AQ Cartridge 给药。如果没有具有良好视力且经过注射设备正规使用培训的人员的帮助，盲人或视障人士不建议使用 Follistim Pen。

6 不良反应
以下各种严重的副作用已在说明书的其他章节讨论：
- 卵巢异常肿大 *[参阅警告和注意事项 (5.1)]*
- 卵巢过度刺激综合征 *[参阅警告和注意事项 (5.2)]*
- 肺不张 *[参阅警告和注意事项 (5.3)]*
- 血栓栓塞 *[参阅警告和注意事项 (5.3)]*
- 卵巢扭转 *[参阅警告和注意事项 (5.4)]*
- 多胎妊娠和分娩 *[参阅警告和注意事项 (5.5)]*
- 先天畸形 *[参阅警告和注意事项 (5.6)]*
- 异位妊娠 *[参阅警告和注意事项 (5.7)]*
- 自然流产 *[参阅警告和注意事项 (5.8)]*
- 卵巢肿瘤 *[参阅警告和注意事项 (5.9)]*

6.1 临床研究经验
因为临床试验是在广泛变化的条件下进行，某个药物在临床试验中观察到的不良反应率不能直接和另一种药物的临床试验中的不良反应率相比，亦不一定能反映实践中观察到的不良反应率。

排卵诱导
在单周期过程中，通过多中心、评价者盲法、平行分组和比对研究，一共随机抽取了 172 名无法排卵和/或通过克罗米芬疗法促进妊娠的持续不排卵女性，给予 Follistim (105) 或尿促卵泡素对照药的治疗。各个治疗组中发病率大于 2% 的不良反应已在表 2 中列出。

表 2：对接受排卵诱导治疗的无排卵女性患者进行评价者盲法、对比研究过程中发生率 ≥2% 的常见不良反应

	女性治疗数量 (%)	
系统器官分类/不良反应	**Follistim N=105 n (%)**	**对照药 N=67 n (%)**
胃肠疾病		
腹部不适	3 (2.9)	1 (1.5)
腹痛	3 (2.9)	2 (3.0)
下腹痛	3 (2.9)	1 (1.5)
生殖系统与乳房疾病		
卵巢囊肿	3 (2.9)	2 (3.0)
卵巢过度刺激综合征	8 (7.6)	3 (4.5)
全身性疾病及给药部位各种反应		
发热	0 (0.0)	2 (3.0)

其他排卵诱导临床试验报告的常见不良反应（发病率大于或等于接受 Follistim 治疗的女性的 2%）有头痛、腹胀、便秘、腹泻、恶心、盆腔疼痛、子宫增大、阴道出血和注射部位反应。

体外受精/卵胞浆内单精子注射
在单周期过程中，通过多中心、双盲法、平行分组和比对研究，一共随机抽取了 1509 名女性患者，接受 Follistim AQ Cartridge（其中 751 名）或对照药的控制性卵巢刺激，同时在体外受精 (IVF) 或卵胞浆内单精子注射 (ICSI) 周期过程中使用促性腺激素释放激素 (GnRH) 治疗。在接受 Follistim AQ Cartridge 治疗的女性患者组中，发病率大于 2% 的不良反应已在表 3 中列出。

表 3：对在体外受精或卵胞浆内单精子注射周期过程中接受控制性卵巢刺激治疗的正常排卵女性进行双盲、活性药物对照、对比研究过程中发生率 ≥2% 的常见不良反应

系统器官分类/不良反应	Follistim AQ Cartridge 治疗 N = 751 n[a] (%)
神经系统疾病	
头痛	55 (7.3%)
胃肠疾病	
恶心	29 (3.9%)
生殖系统与乳房疾病	
卵巢过度刺激综合征	48 (6.4%)
盆腔不适	62 (8.3%)
盆腔疼痛	41 (5.5%)
全身性疾病及给药部位各种反应	
疲劳	17 (2.3%)

[a]n = 出现不良反应的女性患者人数

精子发生诱导

在开放标签、非比对临床试验中，一共登记了 49 名低促性腺素性功能减退症男性，前期进行 hCG 治疗，后期进行 hCG 和 Follistim 联合治疗，诱导精子生成。在 49 名男性患者中，其中 30 名患者每周 Follistim 注射剂量为 450 国际单位；30 名患者中共有 24 名患者接受了总共长达 48 周的 Follistim 治疗。在 30 名接受 Follistim 治疗的男性中，发病率大于 2% 的不良反应已在表 4 中列出。

表 4：对低促性腺素性功能减退症男性进行开放标签临床试验过程中发生率 ≥2% 的常见不良反应

系统器官分类/不良反应	Follistim 治疗 N=30 n (%)
神经系统疾病	
头痛	2 (6.7)
全身性紊乱和用药部位症状	
注射部位反应	2 (6.7)
注射部位疼痛	2 (6.7)
皮肤与皮下组织疾病	
痤疮	2 (6.7)
皮疹	1 (3.3)
生殖系统与乳房疾病	
男性乳房增大	1 (3.3)
良性、恶性和不明类别肿瘤	
皮样囊肿	1 (3.3)

6.2 上市后经验

Follistim 和/或 Follistim AQ Cartridge 在批准使用后，发现了下列不良反应。由于这些不良反应是从大小不确定的人群中自愿报告，因此并不一定能可靠地估计其发生频率或确定与药物暴露之间的因果关系。

胃肠疾病

腹胀、腹痛、便秘、腹泻

全身性疾病及给药部位各种反应

注射部位反应

生殖系统与乳房疾病

乳房触痛、子宫不规则出血、卵巢肿大、阴道出血

皮肤及皮下组织类疾病

皮疹

血管疾病

血栓栓塞 *[参阅警告和注意事项 (5.3)]*

7 药物相互作用

尚未实施任何药物与药物间的相互作用研究。

8 特定人群用药

8.1 妊娠

风险总结

Follistim AQ Cartridge 禁用于孕妇，在妊娠期间没有任何益处。

8.2 哺乳期

风险总结

目前尚不清楚该药物是否会通过母乳排出。母乳喂养的发育和健康益处应与母亲对 Follistim AQ Cartridge 的临床需求以及 Follistim AQ Cartridge 或潜在母体状况对母乳喂养儿童的任何潜在不良影响一起考虑。

8.4 儿科使用

Follistim AQ Cartridge 不适用于儿科患者。尚未在儿童群体中开展临床研究。

8.5 老年人使用

尚未对 65 岁及以上的人群进行 Follistim AQ Cartridge 的临床研究。

10 药物过量

除了导致卵巢过度刺激综合征 (OHSS) *[参阅警告和注意事项 (5.2, 5.3)]*和多胎妊娠 *[参阅警告和注意事项 (5.5)]* 之外，对于 Follistim AQ Cartridge 急性过量使用引起的后果，尚未找到任何其他信息。

11 说明

促卵泡素 β 是一种性腺激素 [人类促卵泡激素 (hFSH)]，是一种通过重组 DNA 技术在中国仓鼠卵巢 (CHO) 细胞株中产生的糖蛋白激素。它具有含有两个糖蛋白亚基（α 和 β）的二聚体结构。α 亚基和 β 亚基分别有 92 个和 111 个氨基酸，它们的一级结构和三级结构与 hFSH 的一级结构和三级结构相同。分子量约为 40 kDa。

Follistim AQ Cartridge（促卵泡激素 β）注射液是一种无菌透明无色溶液，含有 300 国际单位、600 国际单位或 900 国际单位的促卵泡激素 β，装于一次性供单个患者使用的药液管中，仅供 Follistim Pen 进行皮下注射使用。

每个药液管提供 300 国际单位/0.36 mL 和非活性成分：苯甲醇（3.6 mg；防腐剂）、蛋氨酸（0.18 mg）、聚山梨醇酯 20（0.072 mg）、柠檬酸钠（4.64 mg）、蔗糖（18 mg）和注射用水 USP。盐酸 NF 和/或氢氧化钠 NF 用于将 pH 值调节到 7。

每个药液管提供 600 国际单位/0.72 mL 和非活性成分：苯甲醇（7.2 mg；防腐剂）、蛋氨酸（0.36 mg）、聚山梨醇酯 20（0.144 mg）、柠檬酸钠（9.3 mg）、蔗糖（36 mg）和注射用水 USP。盐酸 NF 和/或氢氧化钠 NF 用于将 pH 值调节到 7。

每个药液管提供 900 国际单位/1.08 mL 和非活性成分：苯甲醇（10.8 mg；防腐剂）、蛋氨酸（0.54 mg）、聚山梨醇酯 20（0.216 mg）、柠檬酸钠（13.9 mg）、蔗糖（54 mg）和注射用水 USP。盐酸 NF 和/或氢氧化钠 NF 用于将 pH 值调节到 7。

根据目前的贮存条件，Follistim AQ 可能包含高达 11% 的氧化促卵泡素 β。

12 临床药理学

12.1 作用机制

女性：

促卵泡激素 (FSH) 是 Follistim AQ Cartridge 中的活性成分，是正常卵泡生长、成熟和性腺中性激素产生过程中必不可少的物质。

在女性中，FSH 水平对于卵泡的开始和持续发育，以及早期卵泡达到成熟的时间和数量至关重要。对于无原发性卵巢功能衰竭症的女性，Follistim AQ Cartridge 有助于刺激卵巢卵泡生长。为了影响卵泡成熟的最后阶段，在没有达到内生黄体生成素高峰之前恢复细胞成熟分裂和卵泡破裂，如果在患者监测中发现卵泡发育参数达到适当范围，必须在进行 Follistim AQ Cartridge 治疗之后，给予注射人绒毛膜促性腺激素 (hCG)。

男性：

与 hCG 一起注射时，Follistim 可以刺激低促性腺素性功能减退症男性的精子生成。Follistim 中的活性物质 FSH 是影响精子生成的脑垂体激素。

12.3 药代动力学

Follistim AQ Cartridge 药代动力学参数来自对 20 名健康女性的开放标签、单中心、随机研究。将使用 Follistim Pen 单次皮下注射 Follistim AQ Cartridge 后的血清 FSH 值，与使用传统注射器单次皮下注射 Follistim 冻干粉末配制药液后的血清 FSH 值进行了对比。使用 Follistim Pen 进行促卵泡素 β 给药，将 $AUC_{0-\infty}$ 和 C_{max} 提高了 18%。两种配方之间存在 18% 的血清 FSH 浓度差异，是由于传统注射器的预期和实际给药量不同。Follistim AQ Cartridge 的药物代谢动力学参数如下：

表 5：单次皮下注射 150 IU Follistim AQ Cartridge 的平均（标准差）药代动力学参数 (n=20)

	$AUC_{0-\infty}$ (IU/L*h)	**C_{max} (IU/L)**	**t_{max} (h)**	**$t_{½}$ (h)**	**CL_{app} (L/h/kg)**
Follistim AQ Cartridge	215.1 (45.8)	3.4 (0.7)	12.9 (6.2)	33.4 (4.2)	0.01 (0.003)

$AUC_{0-\infty}$ 曲线下面积
C_{max} 最大血药浓度
t_{max} 达到最大浓度时间
$t_{½}$ 清除半衰期
CL_{app} 清除率

吸收：

女性：

通过皮下和肌内注射 Follistim 之后的生物利用度调查在健康的、经过垂体降调节之后的女性中开展，一次性注射剂量为 300 国际单位。在这些女性患者中，皮下 (455.6 ± 141.4 IU*h/L) 和肌内 (445.7 ± 135.7 IU*h/L) 两种给药途径的曲线下面积（AUC，以平均值 ± 标准差表示）相等。但是，当血清 FSH 水平达到峰值 (C_{max}) 时，等式不成立。当皮下注射和肌内注射分别为 5.41 ± 0.72 国际单位/L 和 6.86 ± 2.90 国际单位/L 时，达到 C_{max}。进行皮下或肌内注射之后，体内明显可吸收的剂量分别为 77.8% 和 76.4%。

同时在一组 (n=8) 促性腺激素分泌不足但身体健康的女性中，对 Follistim 单次肌内剂量（300 国际单位）的药代动力学和药效动力学进行了调查。在这些女性中，FSH（平均值±SD）AUC 为 339±105 国际单位*h/L，C_{max} 为 4.3±1.7 国际单位/L。C_{max} 在肌肉注射后大约 27 ± 5.4 小时出现。

通过在一组健康的、经过垂体降调节之后的女性中连续 7 天皮下注射 75、150 或 225 国际单位的剂量，对 Follistim 的多剂量、剂量比例性和药物代谢动力学进行了研究。通过对比促卵泡生成素 (FSH) 在给药之前的谷浓度 (C_{trough})，经过 5 天的治疗之后，所有剂量的 FSH 血液浓度达到稳定状态。75、150 和 225 国际单位剂量的血液浓度峰值分别为 4.30 ± 0.60 国际单位/L、8.51 ± 1.16 国际单位/L 和 13.92 ± 1.81 国际单位/L。

男性：

尚未在使用 Follistim AQ Cartridge 的男性中进行药代动力学研究。在进行 18% 的剂量调整之后 Follistim AQ Cartridge 和 Follistim 中的促卵泡素 β 暴露量应该是相等的 *[参阅用法用量 (2)]*。

而在 Follistim 的临床研究中，采取了两种不同的 Follistim 给药方案（每次 150 国际单位每周三次，或每次 225 国际单位每周两次），均采用皮下注射方式，同时注射绒膜促性腺激素诱导低促性腺素性功能减退症男性精子生成，通过对比这两种方案的效果来测量 FSH 的血清水平。从第 17 周开始 Follistim 给药。在治疗期间，FSH 的平均血清浓度保持相当稳定。治疗结束时（第 64 周），150 国际单位治疗组的 FSH 平均血清谷浓度为 2.09 国际单位/L，225 国际单位治疗组的 FSH 平均血清谷浓度为 3.22 国际单位/L。在积极治疗期间（第 17 周至第 64 周）的每周一进行首次 Follistim 注射之前，以及治疗期结束一周之后，FSH 血清谷浓度的测量结果如图 1 所示。

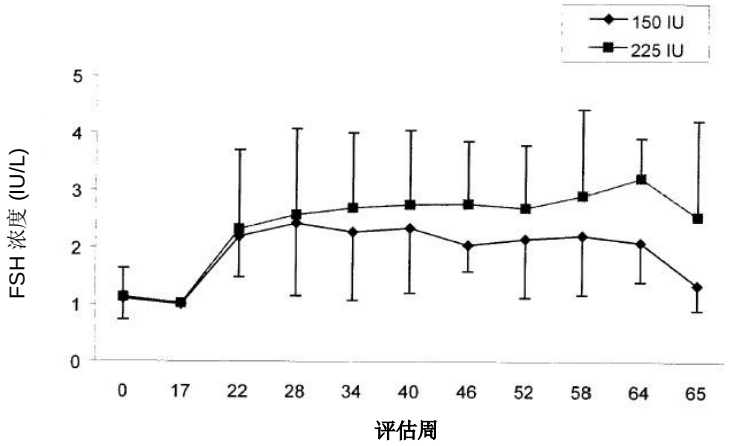


图 1：使用两种不同剂量方案（每次 150 国际单位每周三次，或每次 225 国际单位每周两次）进行 Follistim 皮下注射的男性的 FSH 血清谷浓度平均值（标准差）

分布：

对于健康的、经过垂体降调节之后的女性，在接受 300 国际单位剂量的静脉内注射之后，Follistim 的分布容积大约为 8 L。

代谢：

从生物化学角度来看，Follistim AQ Cartridge 中的重组 FSH 与尿液中的 FSH 十分相似，因此设想它也会通过同一方式进行代谢。

消除：

向女性单次皮下注射 150 IU 的 Follistim AQ Cartridge 消除半衰期 ($t_{½}$)为 33.4 (4.2) 小时。清除率为 0.01 (0.003) L/h/kg。

特殊人群用药：

体重：通过对一群在体重上存在明显差异的欧洲和日本受试者女性进行研究，评估体重对 Follistim 药代动力学的影响。欧洲女性体重（平均值±标准差）为 67.4±13.5 kg，日本受试者体重为 46.8±11.6 kg。单次肌肉注射 300 国际单位 Follistim 后，欧洲女性的 AUC（339±105 国际单位*h/L）明显小于日本女性的 AUC（544±201 国际单位*h/L）。但是，两个受试组每公斤体重的清除率基本相同，分别为 0.014 和 0.013 L/hr/kg。

老年人使用：尚未在老年受试者中进行 Follistim 的药代动力学研究。

儿科使用：尚未在儿童受试者中进行 Follistim 的药代动力学研究。

肾功能损害：尚未进行 Follistim 是否会造成肾功能损害影响的药代动力学研究。

肝功能损害：尚未进行 Follistim 是否会造成肝功能损害影响的药代动力学研究。

13 非临床毒理学

13.1 致癌性、致突变性和生育力受损

目前尚未通过对 Follistim 对动物造成的长期毒性执行研究来评估药物的致癌潜力。使用*鼠伤寒沙门氏菌*和*大肠埃希杆菌*测交品系进行埃姆斯试验之后，未发现 Follistim 具有诱变性，使用人淋巴细胞进行*体外*测定之后，也未发现会导致染色体畸变。

14 临床研究

14.1 排卵诱导

通过对 172 名曾经无法正常排卵和/或在进行克罗米酚柠檬酸盐治疗期间出现意外妊娠的持续不排卵女性（105 名 Follistim 受试者）进行随机、评价者盲法、平行分组比对、多中心安全性和疗效研究，评估 Follistim 对排卵诱导的影响。排卵率研究结果汇总在表 6 中，妊娠率研究结果汇总在表 7 中。

表 6：累积排卵率

周期	Follistim (n=105)
第一治疗期	72%
第二治疗期	82%
第三治疗期	85%

表 7：累积正在妊娠者*, † 受孕率

周期	Follistim (n=105)
第一治疗期	14%
第二治疗期	19%
第三治疗期	23%

* 注射人绒毛膜促性腺激素 (hCG) 至少 12 周之后，所有正在妊娠者均得以确认。

† 仅依靠研究不足以证明这一结果。

14.2 在体外受精 (IVF) 或卵胞浆内单精子注射 (ICSI) 周期过程中的控制性卵巢刺激治疗

通过对 1,509 名健康且正常排卵的女性（平均年龄 32 岁，平均体重 68 kg，平均体重指数为 25 kg/m^2）在体外受精或卵胞浆内单精子注射周期过程中，进行一个周期的控制性卵巢刺激和使用 GnRH 拮抗剂进行垂体降调节的随机、双盲、活性药物对照研究，以评估 Follistim AQ Cartridge 的疗效。该研究已于 2008 年在欧洲和北美（美国和加拿大）完成。约有 54% 的受试者来自北美。表 8 为临床妊娠的总体结果与仅北美地区的结果。

表 8：在体外受精或卵胞浆内单精子注射周期过程中接受控制性卵巢刺激的正常排卵女性接受 Follistim AQ Cartridge 和 GnRH 拮抗剂治疗的妊娠结果。* 意向治疗人群 (ITT)

参数	Follistim AQ Cartridge 总体数据 (n=750)	Follistim AQ Cartridge 北美数据 (n=403)
临床受孕率/周期开始 †	41.1%	48.9%

* 单次治疗周期结果

† 在移植一或二个胚胎后 ≥6 周时评估临床妊娠。

14.3 精子生成诱导

通过对低促性腺素性功能减退症男性的精子生成诱导进行多中心、开放标签、非对照药临床研究，对皮下注射 Follistim 以及绒膜促性腺激素注射 (hCG) 同步治疗的安全性和疗效进行调查。该研究对两组不同的 Follistim 给药方案的效果进行了对比，主要表现在精子参数和 FSH 血清水平上。这项多中心研究包含一个 16 周的前期治疗阶段：尿 hCG 的用量为 1,500 国际单位，每周两次，目的是为了使血清睾酮水平达到正常范围。进行 8 周的 hCG 治疗之后，如果血清睾酮水平仍然没有达到正常范围，则将尿 hCG 剂量增加到 3,000 国际单位，每周两次。这一阶段完成之后，是长达 48 周的治疗阶段。经过前期治疗阶段之后，如果男性患者的精子仍然缺乏活力，则通过随机方式接受治疗。治疗方案为 225 国际单位的 Follistim 以及 1,500 国际单位的尿 hCG 每周两次；或者 150 国际单位的 Follistim，每周三次以及 1,500 国际单位的尿 hCG，每周两次。在前期治疗阶段，如果男性的治疗方案为 3,000 国际单位的尿 hCG，每周两次；那么到了治疗阶段，这些患者将继续沿用同一给药用量方案。两个治疗组的患者平均年龄都约为 30 岁（18 岁到 47 岁不等）。在基线时，其中一个治疗组在接受 3 周的 Follistim 注射之后，平均左睾丸体积和右睾丸体积分别为 4.61 ± 2.94 mL 和 4.57 ± 3.00 mL。另一治疗组在接受 2 周的 Follistim 注射之后，平均左睾丸体积和右睾丸体积分别为 6.54 ± 2.45 mL 和 7.21 ± 2.94 mL。主要疗效终点是在最后两次治疗评估中，平均精子密度 ≥1 x 10^6/mL 的患者百分比。共有 30 名男性患者加入治疗阶段，治疗结果汇总在表 9 中。

表 9：在接受 Follistim 治疗过程中，最后两次治疗评估的平均精子密度≥ 10^6/mL 的男性数量

	Follistim 150 国际单位，每周三次 (n=15)		Follistim 225 国际单位，每周两次 (n=15)		总体 (n=30)	
精子密度 ≥10^6/mL	**n**	**%**	**n**	**%**	**n**	**%**
是	6	40	7	47	13	43
否	9	60	8	53	17	57

总体而言，精子浓度达到至少 10^6 /mL 的患者中，精子浓度达到至少 10^6 /mL 的中位时间为 165 天（范围为 25 至 327 天）。150 国际单位组达到至少 10^6/mL 的中位时间为 186 天（范围为 25 至 327 天），225 国际单位组达到至少 106/mL 的中位时间为 141 天（范围为 43 至 204 天）。试验期间未收集任何妊娠数据。

两个治疗组在局部不良反应数据方面进行了对比。对于采用 150 国际单位（每周三次）给药方案的所有受试者，在治疗期间没有感觉到疼痛的平均天数百分比为 91.3%。对于采用 225 国际单位（每周两次）Follistim 的治疗组，平均天数百分比为 76.0%。在 225 国际单位（每周两次）组中，研究者判断为严重的局部症状是：1 例患者 (7%) 出现瘙痒，2 例患者 (13%) 出现疼痛，2 例患者 (13%) 出现瘀伤，2 例患者 (13%) 出现肿胀，1 例患者 (7%) 出现发红。在采用 150 国际单位（每周三次）给药方案的治疗组中，只有 1 名患者的 1 个事件（瘀伤，7%）被认为比较严重。在注射部位出现反应或注射部位感到疼痛时，没有任何患者放弃治疗。

16 提供方式/储存和处理

Follistim AQ Cartridge（促卵泡激素 β）注射液是一种透明无色溶液，装在一次性预填充的供单个患者使用的玻璃药液管中，配有灰色橡胶活塞和带有灰色橡胶镶嵌物的铝制卷边盖，装在一个盒子里，其中包含一次性 29 号、超细、½ 英寸、无菌 BD MicroFine™ 笔针（与单独提供的 Follistim Pen 一起使用）并具有以下包装：

NDC 78206-129-01 Follistim AQ Cartridge 300 国际单位/0.36 mL，配有银色压接盖和 5 个 BD Micro-Fine Pen Needle

NDC 78206-130-01 Follistim AQ Cartridge 600 国际单位/0.72 mL，配有金色压接盖和 7 个 BD Micro-Fine Pen Needle

NDC 78206-131-01 Follistim AQ Cartridge 900 国际单位/1.08 mL，配有蓝色压接盖和 10 个 BD Micro-Fine Pen Needle

药品储存：分配前，请将本品冷藏保存于 2°C 至 8°C (36°F 至 46°F)。请勿冷冻。

患者储存：将未使用的药液管存放在 2°C 至 8°C (36°F 至 46°F) 的冷藏环境中直至到期日，或存放在最高 25°C (77°F) 的室温环境中 3 个月或直到到期日（以先到者为准）。首次使用后，请存放在 2°C 至 25°C (36°F 至 77°F) 的环境中，并在 28 天后丢弃。存放在原纸箱中，避光。请勿冷冻。

17 患者咨询信息

建议患者阅读 FDA 批准的患者说明书（患者信息）。

通过 Follistim Pen 使用 Follistim AQ Cartridge 的用量和用法

指导女性和男性如何正确借助 Follistim Pen 来使用 Follistim AQ Cartridge，并告知其正确用量。确保使用过注射器接受促性腺激素药物治疗的每位患者均了解使用笔式注射器的区别。在进行 Follistim AQ Cartridge 给药之前，女性和男性均应当阅读并遵循 Follistim Pen《使用说明》手册中的所有指导。

告知患者可从完整未使用过的 Follistim AQ Cartridge 中取用处方剂量的次数。

女性和男性患者接受治疗时的持续治疗时间和必要监测

开始 Follistim AQ Cartridge 治疗之前，应告知女性和男性患者在接受治疗时的持续时间和必要的监测程序 *[参阅用法用量 (2)、警告和注意事项 (5.10)]*。

药物漏用说明

告知女性和男性患者，如果他们错过或忘记注射某一次剂量的 Follistim AQ Cartridge，不应在下一次给药中使用双倍剂量，应该打电话咨询医生，了解后续给药方案。

卵巢过度刺激综合征

告知女性患者，使用 Follistim AQ Cartridge 时可能会引起卵巢过度刺激综合征风险 *[参阅警告和注意事项 (5.2)]* 和相关症状，包括肺部和血管问题 *[参阅警告和注意事项 (5.3)]*，以及卵巢扭转症状 *[参阅警告和注意事项 (5.4)]*。

多胎妊娠和分娩

告知女性患者，使用 Follistim AQ Cartridge 时可能会导致多胎妊娠 *[参阅警告和注意事项 (5.5)]*。

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