Figure 9. Change from Baseline in 6-Minute Walk Distance (meters) at Weeks 4, 8, and 12 in Study 1: Mean (95% Confidence Interval)

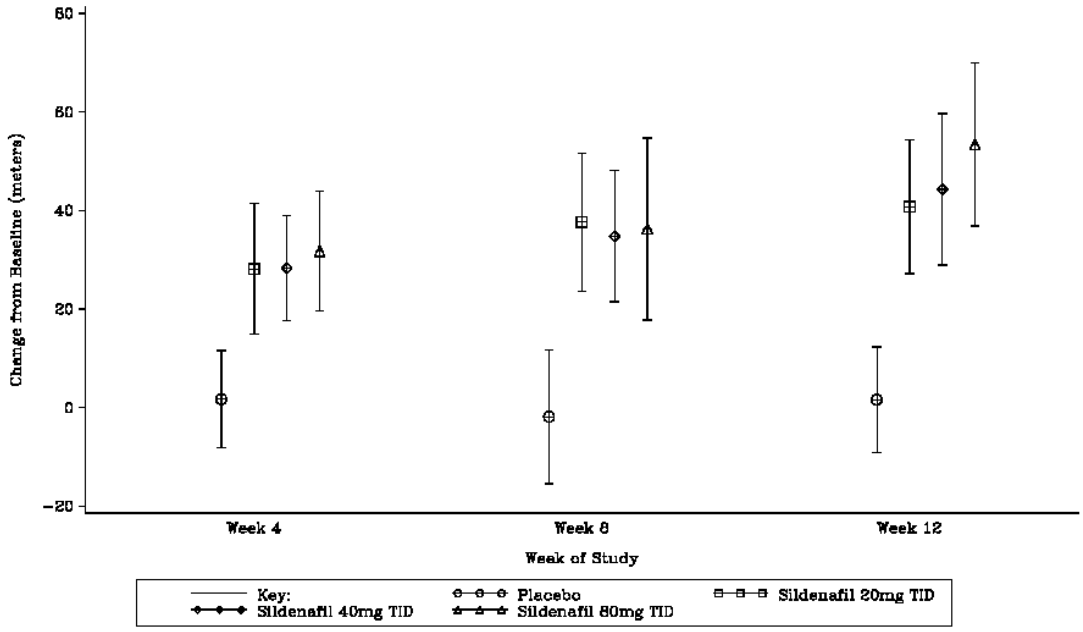
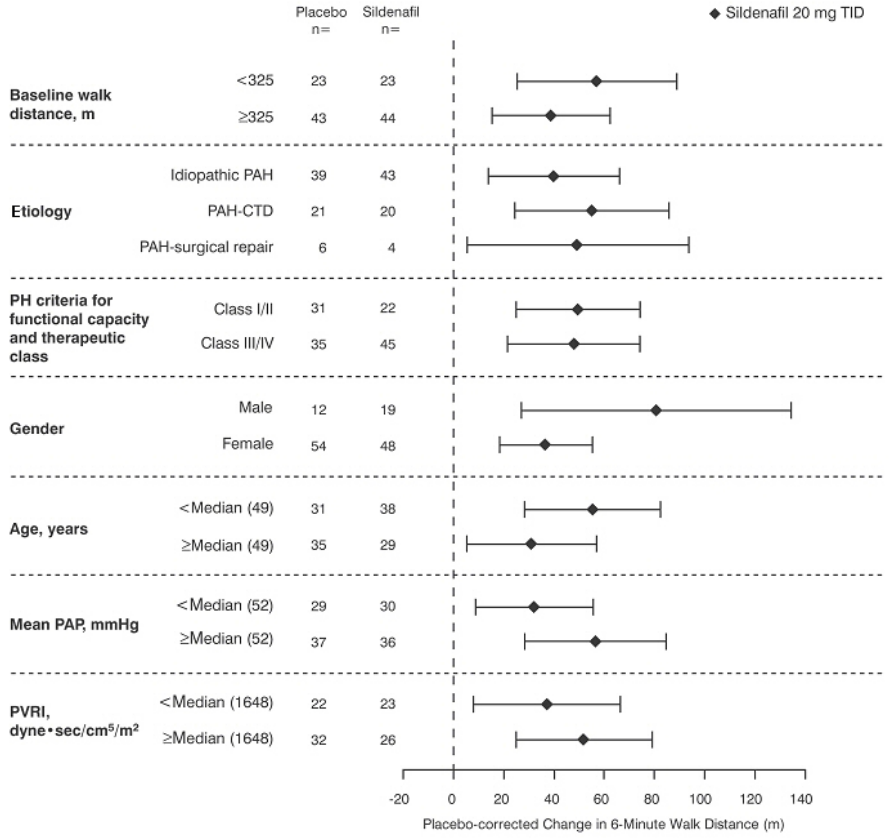


Figure 10 displays subgroup efficacy analyses in Study 1 for the change from baseline in 6-Minute Walk Distance at Week 12 including baseline walk distance, disease etiology, functional class, gender, age, and hemodynamic parameters.

Figure 10. Placebo-Corrected Change From Baseline in 6-Minute Walk Distance (meters) at Week 12 by study subpopulation in Study 1: Mean (95% Confidence Interval)



Key: PAH = pulmonary arterial hypertension; CTD = connective tissue disease; PH = pulmonary hypertension; PAP = pulmonary arterial pressure; PVRI = pulmonary vascular resistance index; TID = three times daily.

Of the 277 treated patients, 259 entered a long-term, uncontrolled extension study. At the end of 1 year, 94% of these patients were still alive. Additionally, walk distance and functional class status appeared to be stable in patients taking REVATIO. Without a control group, these data must be interpreted cautiously.

Study 2 (REVATIO co-administered with epoprostenol)

A randomized, double-blind, placebo controlled study (Study 2) was conducted in 267 patients with PAH who were taking stable doses of intravenous epoprostenol. Patients had to have a mean pulmonary artery pressure (mPAP) greater than or equal to 25 mmHg and a pulmonary capillary wedge pressure (PCWP) less than or equal to 15 mmHg at rest via right heart catheterization within 21 days before randomization, and a baseline 6-minute walk test distance greater than or equal to 100 meters and less than or equal to 450 meters (mean 349 meters). Patients were randomized to placebo or REVATIO (in a fixed titration starting from 20 mg, to 40 mg and then 80 mg, three times a day) and all patients continued intravenous epoprostenol therapy.

At baseline patients had PPH (80%) or PAH secondary to CTD (20%);WHO functional class I (1%), II (26%), III (67%), or IV (6%); and the mean age was 48 years, 80% were female, and 79% were Caucasian.

There was a statistically significant greater increase from baseline in 6-minute walk distance at Week 16 (primary endpoint) for the REVATIO group compared with the placebo group. The mean change from baseline at Week 16 (last observation carried forward) was 30 meters for the REVATIO group compared with 4 meters for the placebo group giving an adjusted treatment difference of 26 meters (95% CI: 10.8, 41.2) (p = 0.0009).

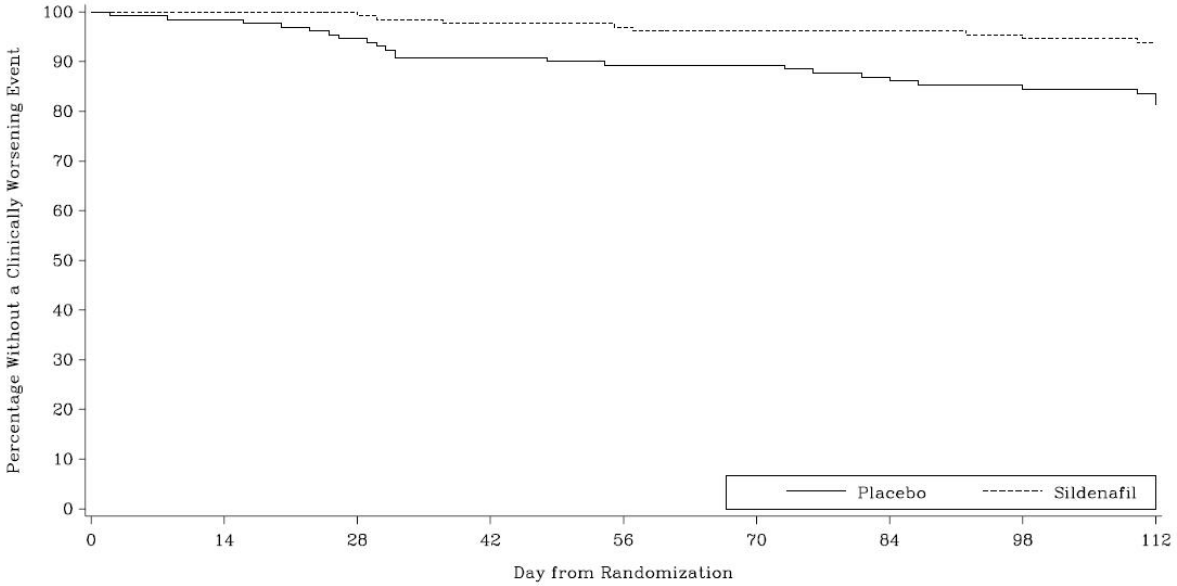
Patients on REVATIO achieved a statistically significant reduction in mPAP compared to those on placebo. A mean placebo-corrected treatment effect of -3.9 mmHg was observed in favor of REVATIO (95% CI: -5.7, -2.1) (p = 0.00003).

Time to clinical worsening of PAH was defined as the time from randomization to the first occurrence of a clinical worsening event (death, lung transplantation, initiation of bosentan therapy, or clinical deterioration requiring a change in epoprostenol therapy). Table 4 displays the number of patients with clinical worsening events in Study 2. Kaplan-Meier estimates and a stratified log-rank test demonstrated that placebo-treated patients were 3 times more likely to experience a clinical worsening event than REVATIO-treated patients and that REVATIO-treated patients experienced a significant delay in time to clinical worsening versus placebo-treated patients (p = 0.0074). Kaplan-Meier plot of time to clinical worsening is presented in Figure 11.

Table 4. Clinical Worsening Events in Study 2

	Placebo (N = 131)		**REVATIO (N = 134)**	
Number of subjects with clinical worsening first event	23		8	
	First Event	**All Events**	**First Event**	**All Events**
Death, n	3	4	0	0
Lung Transplantation, n	1	1	0	0
Hospitalization due to PAH, n	9	11	8	8
Clinical deterioration resulting in:				
Change of Epoprostenol Dose, n	9	16	0	2
Initiation of Bosentan, n	1	1	0	0
Proportion Worsened	0.187		0.062	
95% Confidence Interval	(0.12 - 0.26)		(0.02 - 0.10)	

Figure 11. Kaplan-Meier Plot of Time (in Days) to Clinical Worsening of PAH in Study 2



Improvements in WHO functional class for PAH were also demonstrated in subjects on REVATIO compared to placebo. More than twice as many REVATIO-treated patients (36%) as placebo-treated patients (14%) showed an improvement in at least one functional New York Heart Association (NYHA) class for PAH.

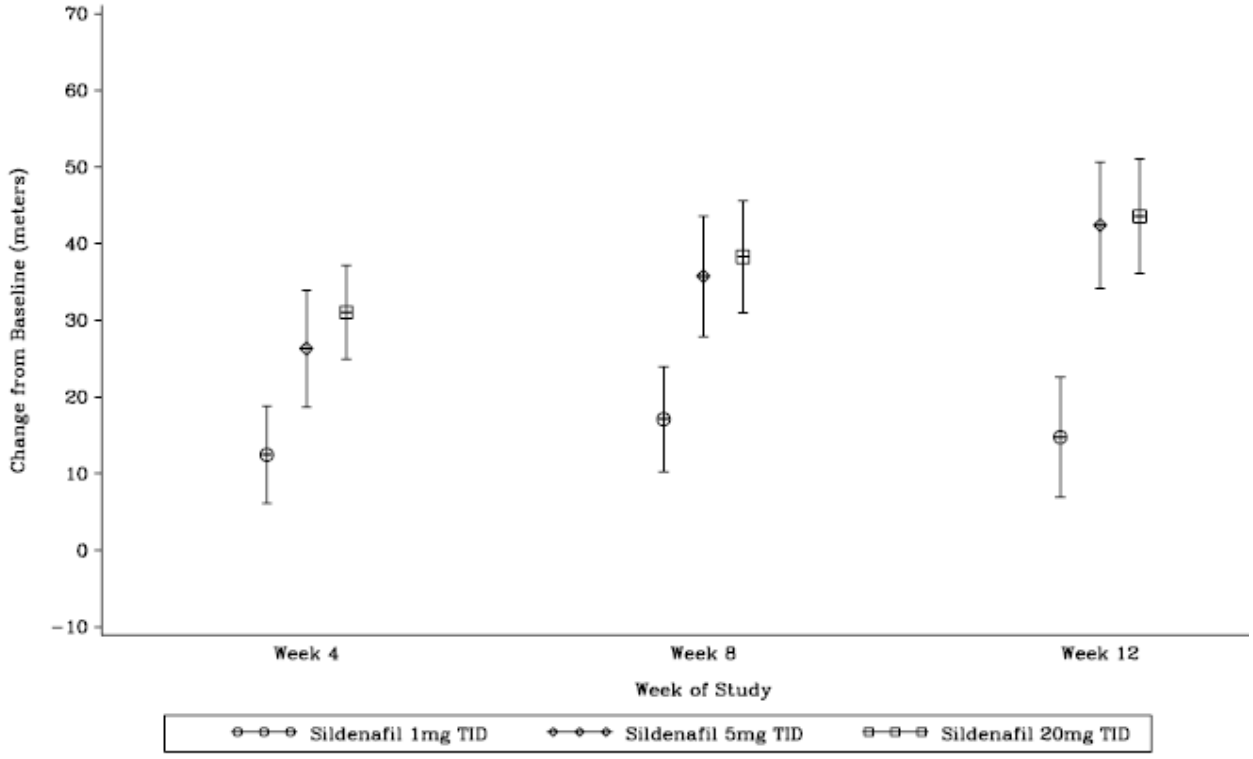
Study 3 (REVATIO monotherapy (1 mg, 5 mg, and 20 mg three times a day))

A randomized, double-blind, parallel dose study (Study 3) was planned in 219 patients with PAH. This study was prematurely terminated with 129 subjects enrolled. Patients were required to have a mPAP greater than or equal to 25 mmHg and a PCWP less than or equal to 15 mmHg at rest via right heart catheterization within 12 weeks before randomization, and a baseline 6-minute walk test distance greater than or equal to 100 meters and less than or equal to 450 meters (mean 345 meters). Patients were randomized to 1 of 3 doses of REVATIO: 1 mg, 5 mg, and 20 mg, three times a day.

At baseline patients had PPH (74%) or secondary PAH (26%); WHO functional class II (57%), III (41%), or IV (2%); the mean age was 44 years; and 67% were female. The majority of subjects were Asian (67%), and 28% were Caucasian.

The primary efficacy endpoint was the change from baseline at Week 12 (at least 4 hours after the last dose) in the 6-minute walk distance. Similar increases in walk distance (mean increase of 38-41 meters) were observed in the 5 and 20 mg dose groups. These increases were significantly better than those observed in the 1 mg dose group (Figure 12).

Figure 12. Mean Change from Baseline in Six Minute Walk (meters) by Visit to Week 12 – ITT Population Sildenafil Protocol A1481244



The plot represents the mean change from baseline +/− the Standard Error for each treatment at each visit up to week 12.

Source Data: Table 12.4.1.1 Date of Data Extraction: 23NOV2010 Date of Table Generation: 20JAN2011 (12:38)

Study 4 (REVATIO added to bosentan therapy – lack of effect on exercise capacity)

A randomized, double-blind, placebo controlled study was conducted in 103 patients with PAH who were on bosentan therapy for a minimum of three months. The PAH patients included those with primary PAH, and PAH associated with CTD. Patients were randomized to placebo or sildenafil (20 mg three times a day) in combination with bosentan (62.5-125 mg twice a day). The primary efficacy endpoint was the change from baseline at Week 12 in 6MWD. The results indicate that there is no significant difference in mean change from baseline on 6MWD observed between sildenafil 20 mg plus bosentan and bosentan alone.

16 HOW SUPPLIED/STORAGE AND HANDLING

REVATIO tablets are supplied as white, film-coated, round tablets containing sildenafil citrate equivalent to the nominally indicated amount of sildenafil as follows:

REVATIO Tablets			
Package Configuration	Strength	NDC	Engraving on Tablet
Bottle of 90 Tablets	20 mg	0069-4190-68	RVT20

Recommended Storage for REVATIO Tablets: Store at controlled room temperature 20°C - 25°C (68°F - 77°F) ; excursions permitted to 15°C - 30°C (59°F -86°F) [see USP Controlled Room Temperature].

REVATIO injection is supplied as a clear, colorless, sterile, ready to use solution containing 10 mg sildenafil/12.5 mL presented in a single-use glass vial.

REVATIO Injection		
Package Configuration	Strength	NDC
Vial individually packaged in a carton	10 mg /12.5 mL	0069-0338-01

Recommended Storage for REVATIO Injection: Store at controlled room temperature 20°C - 25°C (68°F - 77°F); excursions permitted to 15°C - 30°C (59°F - 86°F) [see USP Controlled Room Temperature].

REVATIO powder for oral suspension is supplied in amber glass bottles. Each bottle contains white to off-white powders containing 1.57 g of sildenafil citrate (equivalent to 1.12 g sildenafil). Following constitution, the volume of the oral suspension is 112 mL (10 mg sildenafil/mL). A 2 mL oral dosing syringe (with 0.5 mL and 2 mL dose markings) and a press-in bottle adaptor are also provided.

REVATIO Powder for Oral Suspension		
Package Configuration	Strength	NDC
Powder for oral suspension - bottle	10 mg/mL (when reconstituted)	0069-0336-21

Recommended storage for REVATIO for oral suspension: Store below 30°C (86°F) in the original package in order to protect from moisture.

Constituted Oral Suspension
Store below 30°C (86°F) or in refrigerator at 2°C to 8°C (36° F - 46°F). Do not freeze. The shelf-life of the constituted oral suspension is 60 days. Any remaining oral suspension should be discarded 60 days after constitution.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

- Inform patients of contraindication of REVATIO with regular and/or intermittent use of organic nitrates.
- Inform patients that sildenafil is also marketed as VIAGRA for erectile dysfunction. Advise patients taking REVATIO not to take VIAGRA or other PDE-5 inhibitors.
- Advise patients to seek immediate medical attention for a sudden loss of vision in one or both eyes while taking REVATIO. Such an event may be a sign of NAION.
- Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking REVATIO. These events may be accompanied by tinnitus and dizziness.
-

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com

LAB-0313-18.1

PATIENT INFORMATION

REVATIO® (re-VAH-tee-oh)
(sildenafil) tablets

REVATIO® (re-VAH-tee-oh)
(sildenafil)
oral suspension

Read this Patient Information before you start taking REVATIO and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or treatment. If you have any questions about REVATIO, ask your doctor or pharmacist.

What is the most important information I should know about REVATIO?

Never take REVATIO with any nitrate or guanylate cyclase stimulator medicines. Your blood pressure could drop quickly to an unsafe level.

Nitrate medicines include:

- **Medicines that treat chest pain (angina)**
- **Nitroglycerin in any form including tablets, patches, sprays, and ointments**
- **Isosorbide mononitrate or dinitrate**
- **Street drugs called "poppers" (amyl nitrate or nitrite)**

Guanylate cyclase stimulators include:

- **Riociguat (Adempas)**

Ask your doctor or pharmacist if you are not sure if you are taking a nitrate or a guanylate cyclase stimulator medicine.

What is REVATIO?
REVATIO is a prescription medicine used in adults to treat pulmonary arterial hypertension (PAH). With PAH, the blood pressure in your lungs is too high. Your heart has to work hard to pump blood into your lungs.
REVATIO improves the ability to exercise and can slow down worsening changes in your physical condition.

- REVATIO is not for use in children
- Adding REVATIO to another medication used to treat PAH, bosentan (Tracleer®), does not result in improvement in your ability to exercise.

REVATIO contains the same medicine as VIAGRA® (sildenafil), which is used to treat erectile dysfunction (impotence). Do not take REVATIO with VIAGRA or other PDE-5 inhibitors.

Who should not take REVATIO?

Do not take REVATIO if you:

- take nitrate medicines. See "**What is the most important information I should know about REVATIO?**"

- take guanylate cyclase stimulator medicines. See "**What is the most important information I should know about REVATIO?**"
- are allergic to sildenafil or any other ingredient in REVATIO. See "**What are the ingredients in REVATIO?"** at the end of this leaflet.

What should I tell my doctor before taking REVATIO?

Tell your doctor about all of your medical conditions, including if you
- have heart problems such as angina (chest pain), heart failure, irregular heartbeats, or have had a heart attack
- have a disease called pulmonary veno-occlusive disease (PVOD)
- have high or low blood pressure or blood circulation problems
- have an eye problem called retinitis pigmentosa
- have or had loss of sight in one or both eyes
- have any problem with the shape of your penis or Peyronie's disease
- have any blood cell problems such sickle cell anemia
- have a stomach ulcer or any bleeding problems
- are pregnant or planning to become pregnant. It is not known if REVATIO could harm your unborn baby.
- are breastfeeding. REVATIO passes into your breast milk, it is not known if it could harm your baby.

Tell your doctor about all of the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal products. REVATIO and certain other medicines can cause side effects if you take them together. The doses of some of your medicines may need to be adjusted while you take REVATIO.

Especially tell your doctor if you take
- Nitrate medicines. See "**What is the most important information I should know about REVATIO?**"
- Riociguat (Adempas). See "**What is the most important information I should know about REVATIO?**"
- Ritonavir (Norvir®) or other medicines used to treat HIV infection
- Ketoconazole (Nizoral®)
- Itraconazole (Sporanox)
- High blood pressure medicine

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine.

How should I take REVATIO?
- Take REVATIO exactly as your doctor tells you.

REVATIO may be prescribed to you as
- REVATIO tablets or REVATIO oral suspension
- Take REVATIO tablet or oral suspension 3 times a day about 4 to 6 hours apart
- Take REVATIO tablets or oral suspension at the same times every day.
- REVATIO oral suspension will be mixed for you by your pharmacist. Do not mix REVATIO oral suspension with other medicine or flavoring. Shake well for at least 10 seconds before each dose.
- If you miss a dose, take it as soon as you remember. If it is close to your next dose, skip the missed dose, and take your next dose at the regular time.
- Do not take more than one dose of REVATIO at a time.

- Do not change your dose or stop taking REVATIO on your own. Talk to your doctor first.
- **If you take too much REVATIO, call your doctor or go to the nearest hospital emergency room.**

What are the possible side effects of REVATIO?
- **low blood pressure.** Low blood pressure may cause you to feel faint or dizzy. Lie down if you feel faint or dizzy.
- **more shortness of breath than usual.** Tell your doctor if you get more short of breath after you start REVATIO. More shortness of breath than usual may be due to your underlying medical condition.
- **decreased eyesight or loss of sight in one or both eyes (NAION).** If you notice a sudden decrease or loss of eyesight, talk to your doctor right away.
- **sudden decrease or loss of hearing.** If you notice a sudden decrease or loss of hearing, talk to your doctor right away. It is not possible to determine whether these events are related directly to this class of oral medicines, including REVATIO, or to other diseases or medicines, to other factors, or to a combination of factors.
- **heart attack, stroke, irregular heartbeats, and death.** Most of these happened in men who already had heart problems.
- **erections that last several hours.** If you have an erection that lasts more than 4 hours, get medical help right away. If it is not treated right away, priapism can permanently damage your penis.

The most common side effects with REVATIO include:
Nosebleed, headache, upset stomach, getting red or hot in the face (flushing), trouble sleeping, as well as fever, erection increased, respiratory infection, nausea, vomiting, bronchitis, pharyngitis, runny nose, and pneumonia in children.

Tell your doctor if you have any side effect that bothers you or doesn't go away.

These are not all the possible side effects of REVATIO. For more information, ask your doctor or pharmacist.

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 REVATIO?
- Store REVATIO tablets at controlled room temperature, between 20°C -25°C (68°F to 77°F).
- Store REVATIO constituted oral suspension below 30°C (86°F) or in a refrigerator between 2°C to 8°C (36°F to 46°F).
- Do not freeze REVATIO oral suspension.
- Throw away REVATIO oral suspension after 60 days.

- **Keep REVATIO and all medicines away from children.**

General information about REVATIO
Medicines are sometimes prescribed for purposes that are not in the patient leaflet. Do not use REVATIO for a condition for which it was not prescribed. Do not give REVATIO to other people, even if they have the same symptoms you have. It could harm them.

This patient leaflet summarizes the most important information about REVATIO. If you would like more information about REVATIO talk with your doctor. You can ask your doctor or pharmacist for information about REVATIO that is written for health professionals.
For more information go to www.REVATIO.com or call 1-800-879-3477.

What are the ingredients in REVATIO?

REVATIO tablets
Active ingredients: sildenafil citrate
Inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, lactose monohydrate, and triacetin

REVATIO for oral suspension
Active ingredients: sildenafil citrate
Inactive ingredients: sorbitol, citric acid anhydrous, sucralose, sodium citrate dihydrate, xanthan gum, titanium dioxide , sodium benzoate, colloidal silicon dioxide anhydrous, and grape flavor

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.

This Patient Information has been approved by the U.S. Food and Drug Administration.

LAB-0335-11.1
Revised: January 2019

Instructions for Use

REVATIO® (re-VAH-tee-oh)
(sildenafil) oral suspension

Read this Instructions for Use for REVATIO oral suspension before you start taking and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

Important information:

- Your pharmacist should tell you how to measure REVATIO oral suspension by using the oral syringe provided in the pack.
- REVATIO oral suspension should only be given using the oral syringe supplied with each pack.
- REVATIO for oral suspension should not be mixed with any other medicine or flavoring.

Supplies you will need to take REVATIO oral suspension:

- Bottle of REVATIO oral suspension with syringe adaptor fitted in neck of bottle
- Oral syringe (as supplied by pharmacist). (See Figure A)

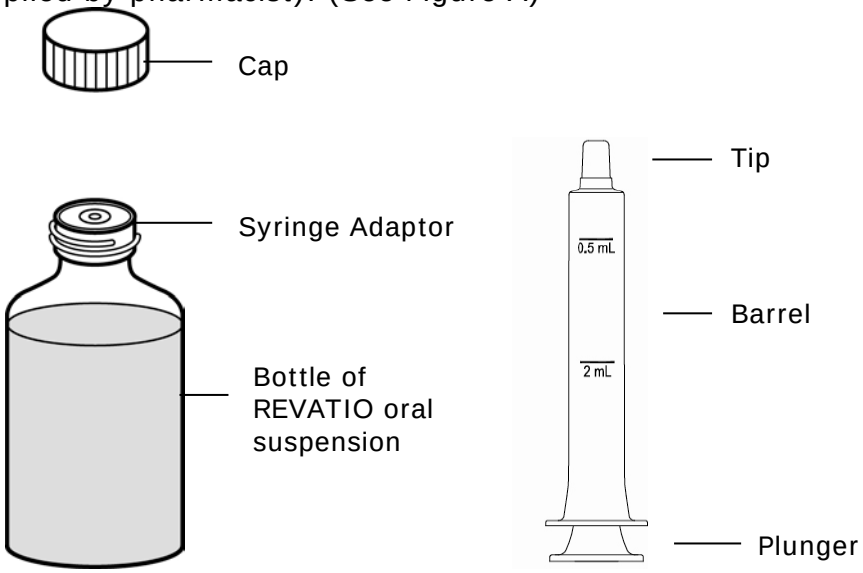


Figure A

1. Shake the bottle of REVATIO oral suspension for 10 seconds before each use. (See Figure B)
2. Remove the cap. Open the bottle by pushing downward on the cap and twisting it in the direction of the arrow (counter-clockwise). (See Figure B)

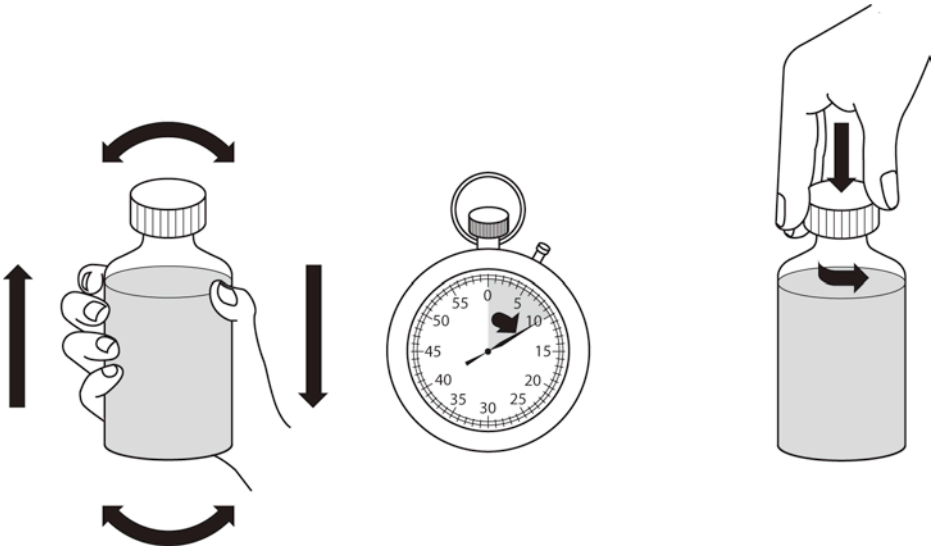


Figure B

3. Insert the tip of the oral syringe into the adaptor while the bottle is upright, on a flat surface. Fully push down (depress) the plunger of the syringe. (See Figure C)

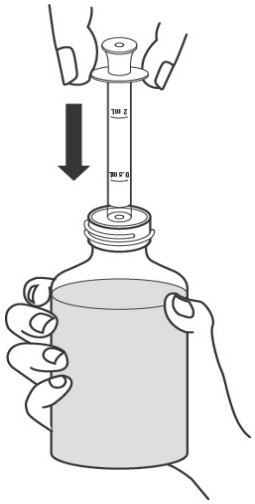


Figure C

4. Turn the bottle upside down while holding the oral syringe in place. Slowly pull back the plunger of the oral syringe until the bottom of the plunger is even with the graduation markings on the syringe for the prescribed dose for you. Take your dose of REVATIO oral suspension exactly as prescribed by your doctor. If air bubbles can be seen, slowly push the oral suspension in the syringe back into the bottle. Repeat steps 3 and 4. (See Figure D)

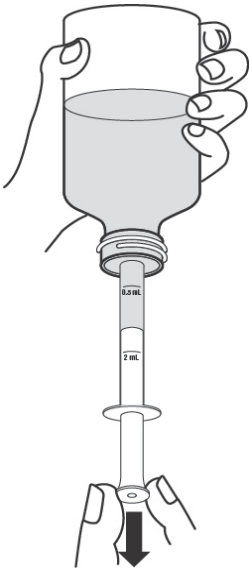


Figure D

5. Turn the bottle back upright with the oral syringe still in place. Remove the oral syringe from the bottle by pulling straight up on the barrel of the oral dosing syringe. (See Figure E)

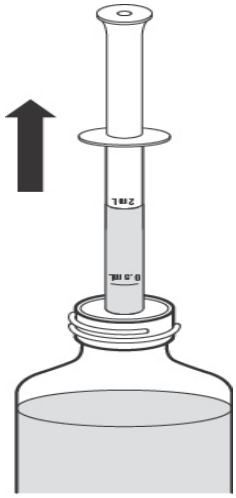


Figure E

6. Put the tip of the oral syringe into your mouth. Point the tip of the oral syringe towards the inside of the cheek. Slowly push down the plunger of the oral syringe. (See Figure F)

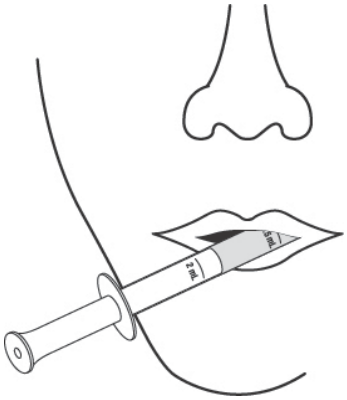


Figure F

7. Replace the cap on the bottle, leaving the bottle adaptor in place. Wash the oral syringe as instructed below.
8. The syringe should be washed after each dose. Pull the plunger out of the barrel and rinse both parts with water. (See Figure G)

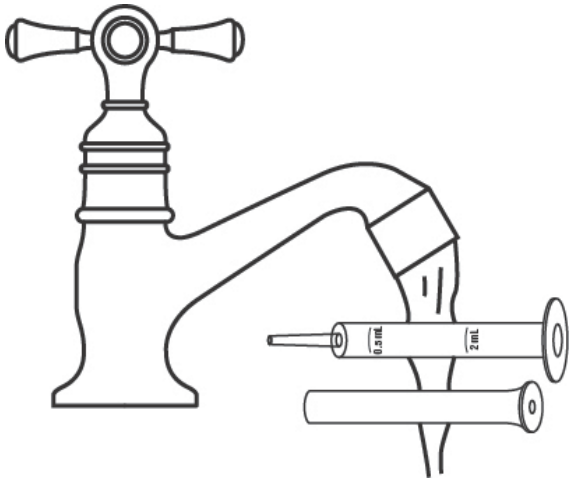


Figure G

9. Dry all parts with a clean paper towel. Push the plunger back into the barrel. Store the syringe with REVATIO oral suspension in a clean safe place.

Administer REVATIO oral suspension using the oral syringe supplied with each pack. Refer to the patient instructions for use for more detailed instructions for use. Discard any unused suspension after the expiration date written on the bottle.

How should I store REVATIO?

- Store REVATIO constituted oral suspension below 30°C (86°F) or in a refrigerator between 2°C to 8°C (36°F to46°F).
- Do not freeze REVATIO oral suspension
- Throw away (discard) REVATIO oral suspension after 60 days.

- **Keep REVATIO and all medicines away from children.**

This Instruction for Use has been approved by the U.S. Food and Drug Administration.

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com

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January 2014

Issued Jan/2014