PRESCRIBER GUIDE

STARTING PR LUPIN-TOLVAPTAN

Understanding, discussing and prescribing LUPIN-TOLVAPTAN

LUPIN-TOLVAPTAN is indicated to slow the progression of kidney enlargement and decline in kidney function in adult patients with autosomal dominant polycystic kidney disease (ADPKD).[1]

LUPIN GENESIS
PATIENT SUPPORT PROGRAM

LUPIN-TOLVAPTAN FOR PATIENTS WITH ADPKD

Tolvaptan is indicated to slow the progression of kidney enlargement and also to slow the decline in kidney function in patients with ADPKD. In such patients, kidney enlargement reflects renal cyst burden.[1]

Increased kidney size and renal cyst burden are indicative of disease progression.[2,3]

About this guide

This guide is written to support you in prescribing Tolvaptan. To:

- help you identify patients best suited for treatment with LUPIN-TOLVAPTAN
- help you understand the contraindications to LUPIN-TOLVAPTAN
- make you aware of the hepatic safety warning
- explain the conditions for safe use of LUPIN-TOLVAPTAN, including:
  - liver monitoring requirements, and Controlled Distribution Program (CDP) of the drug that will support you and your patients with the mandatory ongoing hepatic function monitoring
  - the consolidated Patient-Prescriber Agreement Form (PPAF) enrollment form that is a fully agreed engagement between you and each patient which both you and the patient must co-sign and date in person together at the same time as part of the prescription process
- help you understand and review the potential benefits and risks of LUPIN- TOLVAPTAN for each patient (supporting the full Product Monograph)
- give you an overview of recommended dosage and titration for LUPIN-TOLVAPTAN

Patient Selection Considerations for LUPIN-TOLVAPTAN[1]

From TEMPO 3:4, patients most likely to benefit from LUPIN-TOLVAPTAN appear to be those who have rapidly-progressing ADPKD (meeting modified Ravine criteria), are at early stage of CKD, TKV ≥ 750 mL, and estimated creatinine clearance ≥ 60 mL/min.

- From REPRISE, patients most likely to benefit from LUPIN-TOLVAPTAN appear to be those at high risk of progressive eGFR decline based on renal function for age (18 to 65 years of age with baseline eGFR between 25 and 65 mL/min/1.73 m^2).

ADPKD patients without evidence of hypertension, and especially those at an early stage of disease with excellent renal function, e.g., estimated creatinine clearance (eCrCL) ≥ 120 mL/min, consistent with renal glomerular (compensatory) hyperfiltration, appear to show little near-term benefit in terms of TKV progression or diminution of renal function decline.

Warnings and precautions for LUPIN-TOLVAPTAN

Contraindications

LUPIN-TOLVAPTAN is contraindicated in:

- Patients who have been asked to permanently discontinue Tolvaptan
- Patients with known or suspected hypersensitivity to Tolvaptan, benzazepine or benzazepine derivatives (e.g., mirtazapine) or any of the excipients
- Patients with hypovolemia
- Patients with hypernatremia
- Patients with anuria
- Patients who do not have access to fluids or who cannot respond to the physiologic sensation of thirst
- Patients with a history, signs or symptoms of significant liver impairment or injury, excluding uncomplicated polycystic liver disease
- Concomitant use of strong CYP3A inhibitors, e.g., ketoconazole, itraconazole, clarithromycin, telithromycin, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone
- Pregnancy
- Nursing women
- Patients with one of the following rare hereditary diseases: Galactose intolerance, Lapp lactase deficiency or Glucose-galactose malabsorption

Warning: Idiosyncratic hepatic toxicity

TOLVAPTAN use has led to idiosyncratic elevations of blood alanine and aspartate aminotransferases (ALT & AST), rarely associated with concomitant elevations of total bilirubin. To help mitigate the risk of liver injury, blood testing for hepatic transaminases and total bilirubin is required prior to initiation of Tolvaptan, then blood testing for hepatic transaminases is required:

- continuing monthly for 18 months;
- every 3 months for the next 12 months;
- every 3–6 months thereafter during treatment with LUPIN-TOLVAPTAN.

Therefore, LUPIN-TOLVAPTAN will be available for treatment of patients with ADPKD only through CDP conducted and maintained by, or for, the market authorization holder of LUPIN- TOLVAPTAN.

In TEMPO 3:4, a pivotal, double-blind, randomized, placebo-controlled multi-center trial in patients with ADPKD (N = 1,445; n = 961 tolvaptan, n = 484 placebo), two (2/957, 0.2%) tolvaptan-treated patients as well as a third patient from an open-label extension trial exhibited increases in hepatic enzymes (> 3 x upper limit of normal [ULN]) with concomitant elevations in total bilirubin (> 2 x ULN). The period of onset of hepatocellular injury, as reflected by ALT elevations > 3 x ULN, was within 3 to 14 months after initiating treatment, and these increases were reversible, with ALT returning to < 3 x ULN within 1 to 4 months. These concomitant elevations were gradually reversible with prompt discontinuation of tolvaptan; however, they represent a potential for significant liver injury.

In REPRISE, a pivotal double-blind, randomized, placebo-controlled, multi-center trial in patients with later stages of ADPKD (N = 1,519; n = 1,370 randomized; n = 683 randomized to tolvaptan, n = 687 randomized to placebo), all patients were monitored monthly for liver enzymes elevation and none of them showed this concomitant level of hepatic enzyme and bilirubin elevation.

Data from this trial suggests that monthly liver function monitoring during treatment helps detect liver enzyme elevation early on.

In post-marketing experience with tolvaptan in ADPKD, acute liver failure requiring liver transplantation has been reported.

Regular monitoring helps mitigate the risk of significant and/or irreversible liver injury. Concurrent monitoring for symptoms that may indicate liver injury (e.g., fatigue, anorexia, nausea, upper right abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice) is also warranted.

Actions for abnormal results

At the onset of symptoms or signs consistent with hepatic injury, or if abnormal ALT or AST increases are detected, LUPIN-TOLVAPTAN administration must be immediately interrupted and liver function tests (LFTs) – i.e., ALT, AST, total bilirubin, alkaline phosphatase – must be repeated and obtained as soon as possible, ideally within 48–72 hours. Testing should continue at an increased frequency until symptoms/signs/laboratory abnormalities stabilize or resolve, at which point cautious re-initiation of LUPIN-TOLVAPTAN may be considered.

Current clinical practice suggests that LUPIN-TOLVAPTAN treatment should be immediately interrupted upon confirmation of sustained or increasing transaminase levels, and permanently discontinued if significant increases and/or clinical symptoms of hepatic injury persist. Recommended guidelines for permanent discontinuation include:

- ALT or AST > 8 x ULN
- ALT or AST > 5 x ULN, for more than 2 weeks
- ALT or AST > 3 x ULN, and total bilirubin >2 x ULN or international normalized ratio (INR) >1.5
- ALT or AST > 3 x ULN, with persistent symptoms of hepatic injury as noted above

If ALT and AST levels remain < 3 x ULN, LUPIN-TOLVAPTAN therapy may be cautiously continued with frequent monitoring, as transaminase levels appear to stabilise during continued therapy in some patients without increases in other liver function tests.

Permanent discontinuation from receiving tolvaptan is a contraindication, and so once a patient has been permanently discontinued from receiving tolvaptan, treatment **must never be** restarted. The permanent discontinuation status of patients should be verified prior to initiation with tolvaptan.

Pregnancy prevention and other cautions and precautions

To prevent pregnancy while on LUPIN-TOLVAPTAN treatment, women of childbearing potential must have effective contraceptive measures in place before and during treatment.

For women of childbearing potential:

1. The program will ensure they have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/ml within 1 week prior to beginning treatment.
2. The program will verify each new patient until the report of a negative pregnancy test has been obtained.
3. Women of childbearing potential will be advised by program to use highly effective birth control prior and during the treatment course.

    a. Highly effective birth control is a method of birth control that results in low failure rate (i.e., less than 1% per year) when used consistently and correctly.

Please read the Product Monograph for full information regarding dehydration, concomitant use of CYP3A inhibitors or inducers, P-gp inhibitors, hepatotoxicity, hypernatremia, hyperkalemia, hyperuricemia, hypotension-related events, serum sodium abnormalities, hepatic impairment, and renal impairment.

LUPIN-TOLVAPTAN conditions of use

Lupin has established a CDP for LUPIN-TOLVAPTAN

All prescribers and patients must take part in the Program in order to prescribe/receive LUPIN-TOLVAPTAN in Canada.

This program shall facilitate blood testing and results confirmation between the patient, the pharmacy and you, to support long-term monitoring and safety. The Program will follow up with you for every required test, to find out if the test was done and to confirm the result (ALT or AST ≤ 3 x ULN). The Program supports you in reminding patients to go for their blood tests and will distribute LUPIN-TOLVAPTAN to the patient's pharmacy when the safe use conditions (e.g., blood tests) are met.

Who can prescribe LUPIN-TOLVAPTAN

LUPIN-TOLVAPTAN should be initiated and monitored under the supervision of a nephrologist or specialist with expertise in the management of patients with ADPKD and a full understanding of the benefits and risks of tolvaptan therapy including hepatic toxicity and monitoring requirements.

Online support education

The manufacturer of LUPIN-TOLVAPTAN recommends that you and all other members of the ADPKD management team complete the online training module: *LUPIN-TOLVAPTAN Educational Training Module.*

The module is available at **LupinGenesis.com**

The Consolidated Patient-Prescriber Agreement Form (PPAF) Enrollment Form

The prescription process for LUPIN-TOLVAPTAN requires that you and each patient together review and co-sign with date a consolidated PPAF enrollment form in person. The purpose of the consolidated PPAF enrollment form is to document the fully considered engagement of both the patient and the prescriber to the treatment of ADPKD with LUPIN-TOLVAPTAN.

LUPIN-TOLVAPTAN can only be prescribed to patients who have completed and signed the consolidated PPAF enrollment form with the prescriber. The form must be signed by the prescriber and the patient in person, and at the same time.

The prescriber and patient should discuss about the appropriate use of LUPIN-TOLVAPTAN before initiation of treatment, considering the potential benefits and risks of treatment, appropriate patient selection, and the need for mandatory ongoing hepatic function monitoring.

Both the patient and prescriber should keep a copy of the signed consolidated PPAF enrollment form for their records. A new consolidated PPAF enrollment form is required if the physician (prescriber) or brand of tolvaptan changes.

Initiating LUPIN-TOLVAPTAN for your patients

The CDP will facilitate initiation of LUPIN-TOLVAPTAN. The checklist is meant to ensure your patients have met all the conditions of prescription and are given all the necessary information to begin their treatment journey.

HOW TO INITIATE AND CONTINUE PATIENTS ON LUPIN-TOLVAPTAN

Steps for Prescriber | Steps for CDP

INITIATE

Meet conditions of prescription

- Educate patient about LUPIN-TOLVAPTAN
- Co-sign and date consolidated PPAF enrollment form with patient in person
- Submit consolidated PPAF enrollment form to the CDP
- Provide prescription and LFT orders

- Receives, validates and stores consolidated PPAF enrollment form
- Contacts patient to confirm enrollment and understanding of the CDP

CONTINUE

- Review LFT results*
- Communicate result status to the CDP
- Titrate/adjust dose if required

- Ships supply of LUPIN-TOLVAPTAN to patient's designated pharmacy if all consolidated PPAF enrollment form conditions are met
- Conducts follow-up of LFT result status with prescriber, using the LFT via Fax
- Sends blood test reminders to patient

* Any adverse event should be reported to Lupin at1-866-488-6017.

DOSING AND TITRATING LUPIN-TOLVAPTAN

LUPIN-TOLVAPTAN: Split-dose regimen

LUPIN-TOLVAPTAN total daily dose is given as a split-dose regimen, with a higher dose taken in the morning, and a second, lower dose taken 8 hours later.

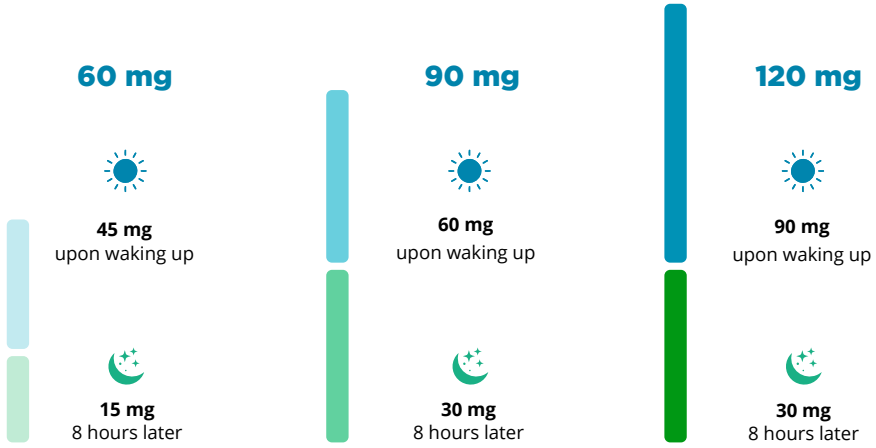
Dose titration process

Titration intervals should be at least 1 week. Titration should be done judiciously to ensure that high doses are not poorly tolerated through overly rapid up-titration. In addition, dosing may be down-titrated and up-titrated again as appropriate.

The dose should be up-titrated as shown:

Total daily dose

as a split-dose regimen of



Dose titration goal

The aim of dose titration is to block activity of vasopressin at the renal V_2-receptor as completely and constantly as possible, to achieve optimal effect on TKV progression or diminution of renal function decline while maintaining acceptable fluid balance.

Patients should normally be maintained on the highest tolerated dose.

The importance of adherence

Patients should be told that unnecessary treatment interruption should be avoided, and that daily adherence to LUPIN-TOLVAPTAN is important to achieve the best possible outcomes in terms of diminution of renal cyst progression and preservation of renal function.

Refer to the Product Monograph for full dosing and titration information.

Administration and missed doses

LUPIN-TOLVAPTAN should be taken:

- with or without food
- without grapefruit juice (and not after eating grapefruit, due to a significant increase in tolvaptan concentrations)

All patients on LUPIN-TOLVAPTAN should be encouraged to drink water liberally on an ongoing basis in order to match increased urine output and reduce the likelihood of dehydration and hypernatremia from the aquaretic effects of LUPIN-TOLVAPTAN. Treatment should be interrupted if the ability to drink or accessibility to water is limited.

Missed doses

If a patient misses a dose, he/she should take the next dose at the scheduled time and prescribed level. **Patients should not take 2 doses at the same time.**

Dosage adjustments to LUPIN-TOLVAPTAN: Drug-drug interactions

LUPIN-TOLVAPTAN is a substrate of CYP3A, and thus co-administration with CYP3A inhibitors or CYP3A inducers may lead to a change in exposure.

Concomitant use with strong CYP3A inducers should be avoided.

Where dose adjustments are recommended or required, response should be monitored, and the dose adjusted accordingly.

Below mentioned are the drug categories and their adjustments of LUPIN-TOLVAPTAN.

- **Strong CYP3A inhibitors:** Substantial dose reduction required for strong CYP3A inhibitors, especially for those also having P-glycoprotein (P-gp) inhibitory properties:
  - Split-dose regimens of 120 mg/day (90 + 30) and 90 mg/day (60 + 30): Down-adjust to 30 mg once daily upon waking.
  - Split-dose regimen of 60 mg/day (45 + 15): Down-adjust to 15 mg once daily upon waking.

  Treatment should proceed with caution. If these doses are not well tolerated, further down-titration should be carried out, or co-administration discontinued.
- **Moderate CYP3A inhibitors:** Dose reduction required.
- **P-gp inhibitors:** Dose reduction may be required in patients concomitantly treated with P-gp inhibitors, based on clinical response. If P-gp inhibitor also acts as a strong CYP3A inhibitor, substantial dose reduction of JINARC is required (see above).
- **CYP3A substrates:** In healthy subjects, tolvaptan, a CYP3A substrate, had no effect on the plasma concentrations of some other CYP3A substrates (e.g., warfarin or amiodarone). However, tolvaptan increased plasma levels of lovastatin by 1.3 to 1.4-fold, indicating a potential effect on weak substrates of CYP3A substrates.

Dosage adjustments to other drugs, foods, and herbs

Below mentioned are the drug categories and their interaction effects.

- **Digoxin:** Steady state digoxin concentrations were statistically significantly increased (approximately 30% increase as determined by C_{max} and 20% increase as determined by AUC_t) when digoxin was co-administered with multiple 60 mg doses (QD) of tolvaptan; in vitro studies indicate that tolvaptan is a substrate and competitive inhibitor of p-glycoprotein. Patients receiving digoxin should be evaluated for excessive digoxin effects after adding Tolvaptan.
- **Warfarin, amiodarone, furosemide, and hydrochlorothiazide:** Co-administration of tolvaptan does not appear to alter the pharmacokinetics of warfarin, furosemide, hydrochlorothiazide, or amiodarone (or its active metabolite, desethylamiodarone) to a clinically significant degree.
- **Vasopressin analogues:** Co-administration not recommended. In addition to its V_2- receptor mediated renal aquaretic effects, tolvaptan blocks vascular vasopressin V_2- receptors involved in the release of coagulation factors (e.g., von Willebrand's factor) from endothelial cells. Therefore, the effect of vasopressin analogs such as desmopressin may be attenuated in patients using these therapies concomitantly with tolvaptan.
- **Grapefruit juice:** Co-administration of tolvaptan with 240 mL of grapefruit juice produced a doubling of peak tolvaptan concentrations (C_{max}) but had no effect on tolvaptan elimination half-life. LUPIN-TOLVAPTAN should not be taken with grapefruit juice.
- **St John's Wort:** Interactions with herbal products have not been established; however, St John's Wort should be avoided while taking LUPIN-TOLVAPTAN.
- **Furosemide or hydrochlorothiazide (HCTZ) - Pharmacodynamic interactions:** Tolvaptan use alone produces a greater 24-hour urine volume than does furosemide or HCTZ alone. However, concomitant administration of tolvaptan with furosemide or HCTZ results in a 24-hour volume that is similar to that after tolvaptan administration alone. Furosemide co-administered with tolvaptan produces a similar maximal rate of urine excretion compared to furosemide alone and 70% higher than tolvaptan alone. HCTZ co-administered with tolvaptan produces a slightly higher maximal excretion rate compared to tolvaptan alone and 66% higher compared to HCTZ alone.

Refer to the Product Monograph for full dosing and dose adjustment information.

CONTROLLED DISTRIBUTION PROGRAM: A VALUE-ADDED PROGRAM EXCLUSIVELY FOR LUPIN-TOLVAPTAN PATIENTS.

Key support services include:

- CDP facilitation of prescriber training and patient education.
- Careful consideration and discussion of the appropriateness of LUPIN-TOLVAPTAN treatment should be undertaken between the prescriber and patient before initiation of treatment, taking into account the potential benefits and risks of treatment, appropriate patient selection, and the need for mandatory ongoing hepatic function monitoring.
- Following agreement to undertake treatment with LUPIN-TOLVAPTAN, the prescriber and the patient both will co-sign and date the consolidated Patient-Prescriber Agreement Form (PPAF) enrollment form in person, which will also serve to confirm the patient enrollment in this program.
- It will facilitate distribution materials on additional risk minimization measures (aRMM) including educational materials to the target audience.
- LUPIN-TOLVAPTAN will be distributed only through the patient's designated pharmacy under this CDP.
- It will help in restriction of prescription to nephrologists or specialists with expertise in the management of patients with ADPKD and a full understanding of the benefits and risks of tolvaptan therapy including hepatic toxicity and monitoring requirements.
- It will help in monitoring liver function tests results to ensure conditions for safe use of the drug are met.

Clinical use:

- In order to select patients who might best benefit from the effects of LUPIN-TOLVAPTAN, clinical trials evaluated ADPKD patients having a total kidney volume (TKV) ≥ 750 mL, and/or renal function corresponding to a CKD-EPI eGFR ≥ 25 mL/min/1.73 m^2, at the time of initiation of treatment.
- LUPIN-TOLVAPTAN treatment should be initiated and monitored under the supervision of a nephrologist or specialist with expertise in the management of patients with ADPKD and a full understanding of the benefit and risks of tolvaptan therapy including hepatic toxicity and monitoring requirements.
- Careful consideration and discussion of the appropriateness of LUPIN-TOLVAPTAN treatment should be undertaken between the prescriber and patient before initiation of therapy, taking into account the potential benefits and risks of treatment. Upon mutual agreement to undertake treatment with LUPIN-TOLVAPTAN, a signed, duly documented, manufacturer and product-specific consolidated PPAF enrollment form is required outlining the relevant patient selection criteria to be considered, expected benefits and risks of treatment, and the need for mandatory hepatic function monitoring.
- All approved suppliers of tolvaptan for ADPKD must send a written request to the CDP to ascertain the patient permanent discontinuation status of all patients prior to patient initiation, which will be provided within 48 hours of receipt of the written request. If any patients are permanently discontinued subsequent to treatment, this information must be provided within 48 hours in writing to the CDP. The CDP will serve as the central repository of the Permanent Discontinuation List for tolvaptan in ADPKD.
- **CDP**: LUPIN-TOLVAPTAN is available for treatment of patients with ADPKD only through a manufacturer and product-specific Controlled Distribution Program (CDP) conducted and maintained by, or for, the market authorisation holder of LUPIN-TOLVAPTAN. A duly signed manufacturer and product-specific consolidated PPAF enrollment form is required for enrollment in the CDP. For more information on the program, please call 1-866-488-6017
- Patients may not be switched from one brand of tolvaptan for ADPKD to another without the completion of a new manufacturer and product-specific (consolidated PPAF enrollment form) form co-signed by the prescribing physician and patient.
- Safety and effectiveness have not been established in geriatrics (> 65).
- Use not recommended in pediatrics (< 18).

Contraindications:

LUPIN-TOLVAPTAN is contraindicated in:

- Patients who have been asked to permanently discontinue tolvaptan
- Patients with known or suspected hypersensitivity to tolvaptan, benzazepine or benzazepine derivatives (e.g., mirtazapine) or any of the excipients
- Patients with hypovolemia
- Patients with hypernatremia
- Patients with anuria
- Patients who do not have access to fluids or who cannot respond to the physiologic sensation of thirst
- Patients with a history, signs or symptoms of significant liver impairment or injury, excluding uncomplicated polycystic liver disease
- Concomitant use of strong CYP3A inhibitors, e.g., ketoconazole, itraconazole, clarithromycin, telithromycin, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone
- Pregnancy
- Nursing women
- Patients with one of the following rare hereditary diseases: Galactose intolerance, Lapp lactase deficiency or Glucose-galactose malabsorption because lactose is a non-medicinal ingredient in LUPIN-TOLVAPTAN.

Most serious warnings and precautions:

Idiosyncratic hepatic toxicity: Tolvaptan use has led to idiosyncratic elevations of blood ALT & AST, rarely associated with concomitant elevations of total bilirubin. To help mitigate the risk of liver injury, blood testing for hepatic transaminases and total bilirubin is required prior to initiation of LUPIN-TOLVAPTAN, then blood testing for hepatic transaminases is required:

- monthly for 18 months
- every 3 months for the next 12 months
- every 3–6 months thereafter during treatment with LUPIN-TOLVAPTAN.

Therefore, LUPIN-TOLVAPTAN is indicated for treatment of patients with ADPKD only through a controlled hepatic safety monitoring and distribution program conducted and maintained by, or for, the market authorization holder of LUPIN-TOLVAPTAN.

Other relevant warnings and precautions:

- Risk of dehydration
- Interactions with moderate CYP3A inhibitors, CYP3A inducers or P-glycoprotein inhibitors
- Hepatotoxicity: Acute liver failure
- Anaphylaxis
- Hypernatremia: Concomitant use with hypertonic saline solutions or drugs that may increase serum sodium should be avoided
- Hyperkalemia
- Hyperuricemia
- Hypotension: Co-administration with antihypertensive medications may cause increase in hypotension-related adverse events, including dizziness or syncope
- Serum sodium abnormalities must be corrected prior to LUPIN-TOLVAPTAN initiation
- Use of contraception in women of childbearing potential
- Vasopressin analogues: Co-administration not recommended
- Caution when driving vehicles or operating machinery

For more information:

Refer to the Product Monograph for adverse reactions, interactions, dosing, monitoring tests and conditions of clinical use.
The Product Monograph is also available by calling 1-866-488-6017

References:

1. Tolvaptan Product Monograph. Lupin Pharma Canada Ltd. Mmm DD, YYYY.
2. Chapman AB, Bost JE, Torres VE et al. Clin J Am Soc Nephrol 2012;7:479–86.
3. Grantham JJ, Torres VE, Chapman AB et al. N Engl J Med 2006;354:2122–30.