Package leaflet: Information for the user

Itraconazole 10 mg/ml concentrate and solvent for solution for infusion

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Itraconazole is and what it is used for

Itraconazole is one of a group of medicines called "antifungals". These medicines are used to treat infections caused by fungi including yeasts. Itraconazole is used to treat fungal infections of the internal organs.

2. What you need to know before you are given Itraconazole

You must not be given Itraconazole if you:
- are allergic to itraconazole or any of the other ingredients of this medicine (listed in section 6)
- are pregnant, think you might be pregnant or are trying to become pregnant, (see the section on *"Pregnancy"*)
- have seriously reduced kidney function
- cannot have sodium chloride by injection
- are taking any of the following medicines:
  - terfenadine or mizolastine (antihistamines for allergies)
  - bepridil, ivabradine or ranolazine - used to treat angina (crushing chest pain)
  - nisoldipine, lercanidipine or eplerenone (used for high blood pressure)
  - cisapride (used for stomach upsets)
  - domperidone (for nausea and vomiting)
  - midazolam by mouth or triazolam (used to help you sleep or for anxiety)
  - lovastatin or simvastatin (used to lower cholesterol)
  - lurasidone, pimozide or sertindole (for conditions affecting thoughts, feelings and/or behaviour)
  - dihydroergotamine or ergotamine (for migraine headaches)
  - ergometrine (ergonovine) or methylergometrine (methylergonovine) used after giving birth
  - disopyramide, dronedarone, quinidine or dofetilide (for irregular heart beat rhythms)
  - telithromycin (for pneumonia) when used in patients with severe kidney or liver problems
  - colchicine (for gout) when used in patients with kidney or liver problems
  - halofantrine (for malaria)
  - irinotecan (for cancer)
  - dabigatran (for blood thinning)
  - ticagrelor (for blood clots)
  - quetiapine (for psychosis)

- aliskiren (for hypertension)
- darifenacin (for urinary incontinence)
- fesoterodine (for irritated urinary bladder) when used in patients with certain kidney or liver problems
- sildenafil when used to treat pulmonary hypertension (increased blood pressure in the blood vessels in the lungs)
- solifenacin (for irritated urinary bladder) when used in patients with certain kidney or liver problems
- vardenafil (for erectile dysfunction) when used in men older than 75 years of age.

Also, upon completing your course of Itraconazole, do not take any of the medicines listed above for 2 weeks.

Warnings and precautions
Tell your doctor immediately if you:
- have any unusual feelings of tingling, numbness or weakness in your hands or feet whilst taking Itraconazole
- experience any hearing loss symptoms. In very rare cases patients taking Itraconazole have reported temporary or permanent hearing loss.

You must tell your doctor before you are given Itraconazole if you suffer from or have suffered in the past from any of the following:
- any liver problems or jaundice (yellowing of the skin). If your doctor decides to give you Itraconazole the dose may have to be changed. Your doctor may give you instructions on symptoms to watch out for and ask you to have your blood checked. In addition, there may be specific medication you may not be able to take.
- an allergic reaction to any other antifungal medicine.
- heart problems, including heart failure (also called congestive heart failure or CHF), Itraconazole could make it worse. If your doctor decides to give you Itraconazole you should be told about the symptoms listed below to watch out for. If you get any of the following stop taking Itraconazole and tell your doctor straight away. These may be signs of heart failure:
    - shortness of breath
    - unexpected weight gain
    - swelling of your legs or stomach
    - feel unusually tired
    - wake up short of breath at night
- are on a low salt diet.
- a kidney disorder, you may be monitored more closely or your dose of Itraconazole may have to be changed. In addition, there may be specific medication you may not be able to take.

Children and adolescents
Itraconazole is not normally given to children and adolescents. Your doctor may prescribe it in special cases.

Other medicines and Itraconazole
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines including medicines obtained without a prescription or herbal medicines.

There are some medicines that you **must not take** whilst being given Itraconazole. These are listed above under the heading *"You must not be given Itraconazole:"*.

Tell your doctor if you are using the following as they may stop Itraconazole from working properly:
- rifampicin, rifabutin or isoniazid (antibiotics used to treat tuberculosis)
- phenytoin, carbamazepine or phenobarbital (anti-epileptics)
- efavirenz or nevirapine (medicines used for HIV/AIDS)
- St John's Wort (a herbal medicine).

You must not be given Itraconazole within 2 weeks of taking these medicines.

Tell your doctor if you are using the following medicines as they are not recommended with Itraconazole unless your doctor feels it is necessary:

- medicines for cancer (namely axitinib, dabrafenib, dasatinib, ibrutinib, lapatinib, nilotinib, sunitinib or trabectedin)
- simeprevir (for Hepatitis C)
- riociguat, when used to treat pulmonary hypertension (increased blood pressure in the blood vessels in the lungs)
- rifabutin (for tuberculosis)
- carbamazepine (for epilepsy)
- colchicine (for gout)
- everolimus or temsirolimus (given after an organ transplant)
- fentanyl (for pain)
- apixaban (for blood clots)
- rivaroxaban (for blood clots)
- salmeterol (for breathing problems)
- tamsulosin (for male urinary incontinence)
- vardenafil (for erectile dysfunction) when used in men 75 years of age and younger
- atorvastatin (for lowering levels of cholesterol)
- ciclesonide (for inflammation, asthma and allergies)
- ebastine (for allergies)
- eletriptan (for migraine headaches)
- tolterodine (for irritated urinary bladder)
- felodipine (for the heart or blood vessels).

Also, upon completing your course of Itraconazole, do not take any of the medicines listed above for 2 weeks.

Tell your doctor before taking any of the following medicines as the dose of Itraconazole or other treatments may need to be altered:

- ciprofloxacin, clarithromycin or erythromycin (anitibiotics for infections)
- medicines that act on the heart or blood vessels (bosentan, digoxin, nadolol, calcium channel blockers such as, dihydropyridines, verapamil)
- telithromycin (for pneumonia)
- medicines that slow down blood clotting or thin the blood, such as the coumarins (e.g. warfarin) or cilostazol
- methylprednisolone, budesonide, fluticasone or dexamethasone, medicines given by mouth and injection for inflammation, asthma and allergies
- ciclosporin, tacrolimus or rapamycin (also known as sirolimus), which are usually given after an organ transplant
- medicines used in HIV-infected patients, such as maraviroc, ritonavir, ritonavir-boosted darunavir, ritonavir-boosted fosamprenavir, indinavir or saquinavir
- telaprevir (used in the treatment of Hepatitis C virus)
- medicines for cancer (such as bortezomib, busulphan, docetaxel, erlotinib, gefitinib, imatinib, ixabepilone, ponatinib, trimetrexate or a group of medicines known as vinca alkaloids)
- alfentanil, buprenorphine, oxycodone or sufentanil (for pain)
- methadone for treatment of drug abuse (opioid-dependency)
- buspirone, alprazolam, brotizolam, perospirone or midazolam when given by injection into a vein (for anxiety or to help you sleep)
- reboxetine (for depression)
- repaglinide or saxagliptin (for diabetes)
- aripiprazole, haloperidol or risperidone (for psychosis)
- aprepitant (for nausea and vomiting)

- fesoterodine, oxybutynin or solifenacin (for irritated urinary bladder)
- sildenafil or tadalafil (for erectile dysfunction)
- praziquantel (for fluke and tapeworms)
- bilastine (for allergies)
- meloxicam (for joint inflammation and pain)
- cinacalcet (for an over active parathyroid)
- tolvaptan (to treat low blood sodium or some kidney problems)
- alitretinoin (oral) (for eczema)

Pregnancy
You must not be given Itraconazole if you are pregnant, unless your doctor has told you to. If you are of childbearing age and could become pregnant, you should use contraceptives to make sure that you do not become pregnant while you are receiving your medicine. As Itraconazole remains in the body for some time after you stop receiving it, you should continue to use some form of contraception until your next period after your treatment with Itraconazole has finished.

If you do find that you are pregnant after receiving a course of Itraconazole, tell your doctor straight away.

Before taking any medicine - always tell your doctor if you are pregnant, think you might be pregnant or are trying to become pregnant.

Breast-feeding
You must stop breast-feeding before you are given Itraconazole, as small amounts of the medicine could be present in your breast milk.

Driving and using machines
Itraconazole can sometimes cause dizziness, blurred/double vision or hearing loss. If you have these symptoms, do not drive or use machines.

Itraconazole contains sodium
This medicine contains approximately 177 mg sodium (main component of cooking/table salt) in each dose. This is equivalent to 9 % of the recommended maximum daily dietary intake of sodium for an adult.

3. How Itraconazole is given

Your medicine will be given to you by your doctor or nurse. Itraconazole concentrate is mixed with the sodium chloride solution in the bag and is then given by slow injection into a vein. This is called an intravenous (IV) infusion and will usually take about an hour. For the first two days, you will be given two infusions each day. From Day 3 onwards you will be given one infusion each day.

How much you will be given
The recommended dosage is as follows:

Adults
Day 1 and Day 2 of the treatment: Two 1-hour infusions of 200 mg itraconazole will be given each day as a 60 ml infusion.

From Day 3 onwards: One 1-hour infusion of 200 mg itraconazole will be given each day as a 60 ml infusion.

Elderly
Itraconazole is not normally given to the elderly. Your doctor may prescribe it in special cases.

If a dose is missed or you are given too much Itraconazole

Since this medicine will be given to you by a doctor or nurse, it is unlikely that you will be given too much or that a dose will be missed. However, if you are worried, tell your doctor or nurse.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Medicines can cause serious allergic reactions.

Stop taking Itraconazole and contact your doctor immediately if you have:

- any sudden wheeziness, difficulty in breathing, swelling of the face, rash, itching (especially affecting the whole body) or a severe skin disorder (widespread rashes with peeling skin and blisters in the mouth, eyes and genitals, or rashes with small pustules or blisters)
- severe lack of appetite, feeling sick, being sick, unusual tiredness, abdominal (stomach) pain, unusually dark urine, or pale stools. These may be symptoms of severe liver problems.

You must also let your doctor know immediately if you have any of the side effects below:

- Symptoms that resemble heart failure such as shortness of breath, unexpected weight gain, swelling of the legs, unusual fatigue (tiredness), repeated waking at night
- A tingling sensation, sensitivity to light, numbness or weakness in the limbs
- Blurred vision/double vision, ringing in your ears, lose the ability to control your urine or increased need to urinate (pass water)
- If you experience any symptoms of hearing loss
- Severe upper stomach pain, often with nausea and vomiting due to inflammation of the pancreas (pancreatitis).

Other side effects include:

Very common side effects (may affect more than 1 in 10 people):

- feeling sick (nausea)
- being sick (vomiting)
- diarrhoea
- cough
- rash
- general swelling.

Common side effects (may affect up to 1 in 10 people):

- headache, dizziness
- stomach ache, constipation
- increases in specific liver function tests (hepatic enzyme increased), inflammation of the liver (hepatitis), yellowing of the skin (jaundice)
- itching, hives
- fever or high temperature
- shortness of breath
- certain blood disorder which may increase the risk of infections (possible symptom of low levels of granulocytes)
- high blood sugar levels
- muscle cramps or irregular heart beat (possible symptoms of low blood levels of magnesium)
- confusion
- sleepiness
- tremors
- increase in heart rate

- high blood pressure
- low blood pressure
- fluid in the lungs
- indigestion
- hair loss
- excess sweating
- muscle pain
- kidney problems
- chest pain
- pain
- chills
- fatigue
- increase in blood urea levels
- abnormal urine findings
- injection site swelling.

Uncommon side effects (may affect up to 1 in 100 people):
- unpleasant taste
- muscle cramps or irregular heart beat (possible symptoms of high blood levels of potassium)
- certain blood disorder which may increase the risk of bleeding or bruising (possible symptoms of low levels of platelets)
- difficulty speaking
- decreased feeling or sensitivity, especially in the skin
- increase in blood creatine phosphokinase levels.

The following side effect has been reported in patients being given itraconazole with an unknown frequency:
- excess of triglycerides (fats) in the blood.

The following side effects have been reported in patients taking other formulations of itraconazole:
- infection of the upper respiratory tract
- inflammation of the nose
- inflammation of the sinuses
- certain blood disorder which may increase the risk of infections (possible symptom of low levels of white blood cells)
- muscle cramps or irregular heart beat (possible symptoms of low blood levels of potassium)
- excess gas in the intestinal tract
- painful joints
- excessive urine production
- abnormal menstrual bleeding
- erectile dysfunction.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Itraconazole

Keep this medicine out of the sight and reach of children.

Itraconazole will be kept in the hospital pharmacy.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Itraconazole concentrate: Do not store above 25 °C. Keep the ampoule in the outer carton in order to protect from light. Do not freeze.

Bag containing Sodium Chloride: Do not store above 25 °C.

Protect the mixed solution from direct sunlight. Once mixed, the product should be used immediately.

Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8 °C. From a microbiological point of view the prepared infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Itraconazole concentrate contains:
- The active substance is itraconazole (10 mg of itraconazole per ml).
- The other ingredients are hydroxypropyl-β-cyclodextrin, propylene glycol, hydrochloric acid, sodium hydroxide and water for injections.

What Sodium Chloride Solution for infusion contains:
- sodium chloride and water for injections.

Also see section 2 *"Itraconazole contains sodium"*.

What Itraconazole concentrate and solvent looks like and contents of the pack
It is a kit containing a clear, colourless or faintly yellow coloured concentrated solution for intravenous (IV) infusion, which means the solution needs to be diluted before use.

Itraconazole concentrate comes in a 25 millilitre (ml) ampoule, together with a bag containing a clear, colourless Sodium Chloride solution and an extension line. These two solutions will be mixed together to give a clear, colourless solution before they are given directly into your veins.

One ml of Itraconazole concentrate contains 10 milligrams (mg) of itraconazole. When the Itraconazole concentrate is added to the bag containing sodium chloride solution, each ml of the mixed solution contains 3.33 mg itraconazole.

The Sodium Chloride bag is a plastic polypropylene infusion bag, which contains 50 ml of Sodium Chloride solution. One ml of solution contains 9 mg sodium chloride. It is used to dilute the Itraconazole concentrate making it easier to be given.

Marketing Authorisation Holder
Neon Healthcare Limited, 8 The Chase, John Tate Road, Hertford, SG13 7NN, UK.

Manufacturer
Altan Pharmaceuticals, S.A., Avda. de la Constitución, 198-199, Polígono Industrial Monte Boyal, Casarrubios del Monte, 45950 Toledo, Spain.

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The following information is intended for healthcare professionals only:

Itraconazole 10 mg/ml concentrate and solvent for solution for infusion

Please refer to the Summary of Product Characteristics (SmPC) for further information.

Preparation and handling

Itraconazole has the potential to precipitate when 25 ml of Itraconazole concentrate are diluted in solutions other than 50 ml Sodium Chloride 0.9 % w/v solution for infusion. The full amount of 25 ml of Itraconazole concentrate from the ampoule must be diluted into the Sodium Chloride Infusion Bag, which is intended to be used exclusively in combination with Itraconazole concentrate. Only the components of a unit sales pack (e.g. saline bag, an extension line with a 2-way stopcock and 0.2 µm in-line filter, and Itraconazole ampoule) must be used. Itraconazole cannot be co-administered with other drugs or fluids (see *"Incompatibilities"*).

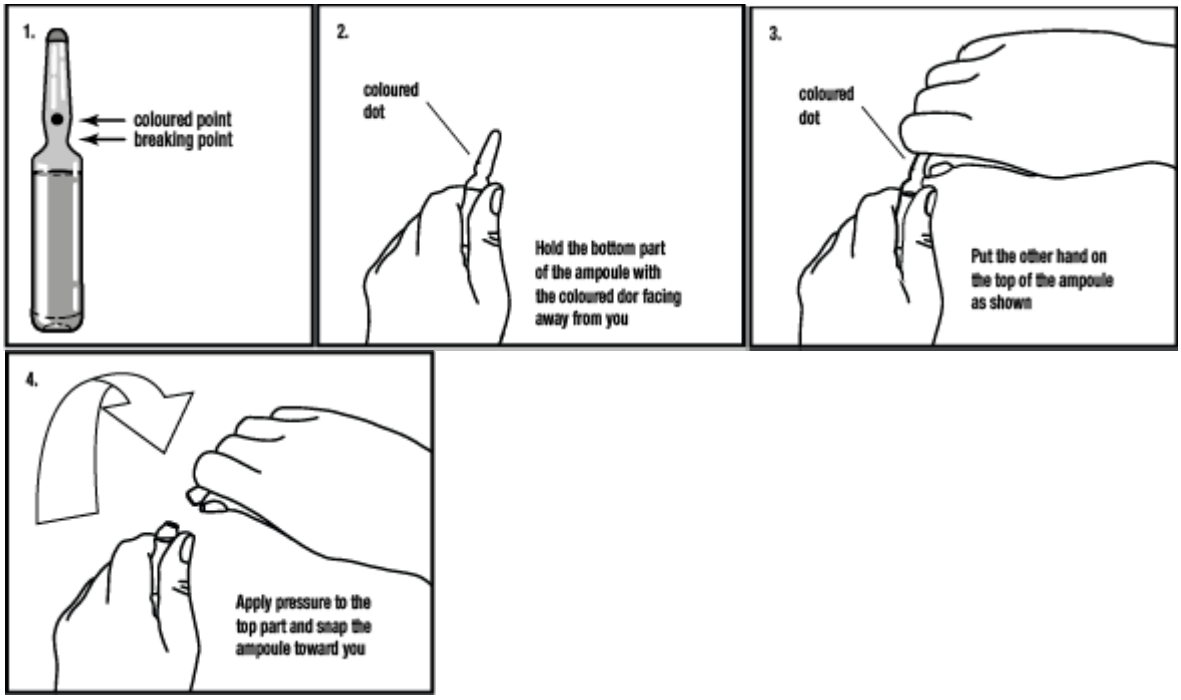
Prior to starting the admixing process, the Itraconazole concentrate and the solvent (Sodium Chloride) must be visually inspected. Only clear solutions free from foreign particles should be used for the preparation of the admixture.

The full amount of Itraconazole concentrate must be injected into the Sodium Chloride bag in a slow single action (up to 60 seconds). During the admixing process opalescence may appear but will clear after gently mixing. When visually inspecting the bag after admixing and prior to administration, product intrinsic aggregates may be observed. These aggregates do not affect the quality of the product. The dedicated extension line with the 0.2 µm in-line filter must be used to prevent aggregates from reaching the recipient's circulation.

Itraconazole should be prepared for administration according to the following instructions:

Opening sodium chloride bag:
Tear outer wrap at notch and remove infusion bag.

Opening ampoule:
Break the ampoule as shown:



The admixing should begin immediately after opening the ampoule.

Flush procedure before the infusion:
Before the infusion, the catheter should be flushed to avoid compatibility problems between residual amounts of other drugs and itraconazole.

- Fill the extension line provided with the kit containing the 0.2 µm in-line filter with sterile Sodium Chloride 0.9 % w/v solution and connect directly to the indwelling intravenous catheter.
- Flush the extension line provided with the kit and indwelling intravenous catheter with sterile Sodium Chloride 0.9 % w/v solution.

Admixing Itraconazole concentrate and Sodium Chloride 0.9 % w/v solution for infusion:

- Each component must be at room temperature.
- Admix only in the infusion bag provided.
- Using aseptic technique and an additive delivery needle of appropriate length (not supplied with the kit), draw up all the concentrate from the ampoule and subsequently add the Itraconazole concentrate to the infusion bag by puncturing the resealable additive port and inject.
- Add the entire volume (25 ml) of Itraconazole concentrate while holding the bag in upright position in a slow single action (up to 60 seconds) this approach will avoid the concentrate collecting in the tubing which would hinder proper mixing. During the admixing process some opalescence may appear. This is a normal phenomenon for the product and will disappear after the full content of the 25 ml of Itraconazole has been diluted into the Sodium Chloride infusion bag and after gentle mixing.Withdraw needle after injecting the Itraconazole concentrate into the bag.
- Gently mix the content of the bag once the Itraconazole concentrate is completely transferred to the bag. The admixture will become clear but product intrinsic aggregates (described as fibrous to flake-like, non-crystalline, white particles) may be observed. These aggregates do not affect the quality of the product.
- The admixture should be used immediately and should be protected from direct sunlight. During administration, exposure to normal room light is acceptable (see sections 6.3 and 6.4 of the SmPC).

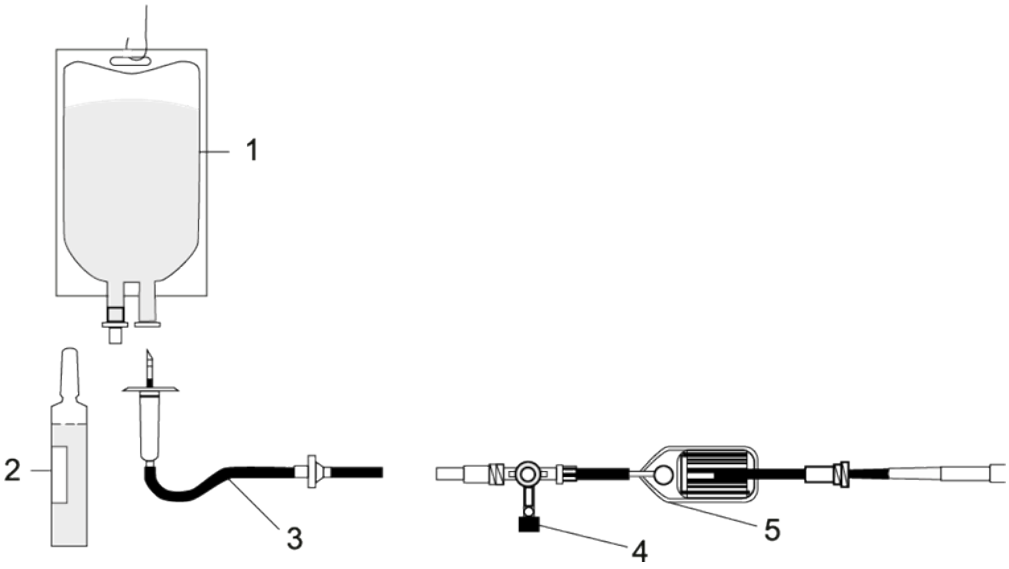
Infusion:

- The admixed solution is intended for single-dose infusion only. No administration should occur if the solution is a milky white colour that does not disappear after gentle mixing, or contains foreign matter, or if the infusion bag is damaged.
- The infusion bag should now contain 25 ml Itraconazole concentrate and 50 ml Sodium Chloride 0.9 % w/v solution for infusion.
- Note: An infusion line with drip chamber is not supplied with the kit. Close the flow control device (e.g., rotary clamp) on the infusion line. Remove the breakable part of the outlet port. Using aseptic technique, push the pin of the infusion line in the flexible port of the infusion bag.
- Slowly release the flow control device and fill the drip chamber to half full by squeezing (pumping) it.
- Open the flow control device until all the air has been expelled from the infusion line.
- Connect the infusion line to the two-way stopcock of the extension line.
- The Itraconazole infusion is now ready for intravenous infusion to the patient.
- Adjust the infusion rate to 1 ml/min (approximately 25 drops/min) by means of a flow control device (e.g. rotary clamp or infusion pump).
- Administer 60 ml of the solution to the patient over approximately one hour.
- Stop the infusion when 60 ml is administered.
- Note that 200 mg of itraconazole has been administered.
- Flush the line as per the flushing procedure described below.

Flush procedure after the infusion:

- After the infusion a complete flush procedure must be started to clean the catheter. This is done to avoid compatibility problems between residual amounts of itraconazole and other drugs which later could be administered through the same catheter.
- Flush the extension line and catheter with 15–20 ml of sterile Sodium Chloride 0.9 % w/v solution at the level of the 2-way stop cock, just before the 0.2 µm in-line filter.
- Perform the flush in a continuous run of 30 seconds to 15 minutes.
- After flushing, disconnect and discard the bag, the infusion line and the extension line.
- Do not re-sterilise or re-use the Itraconazole infusion set.
- To avoid precipitation, other medication should only be administered via the catheter after flushing.
- If using a multi-lumen catheter, other medication may not be administered until the Itraconazole infusion has been completed and the catheter has been flushed.

1. Sodium Chloride infusion bag
2. Itraconazole ampoule
3. Infusion line with drip chamber (not provided)
4 & 5. Extension line with 2-way stopcock and in-line filter.



Incompatibilities
Itraconazole has the potential to precipitate when Itraconazole concentrate is diluted in solutions other than the 50 ml Sodium Chloride 0.9 % w/v solution for infusion supplied.

Posology
Adults
Itraconazole is given on the first two days in a loading dose twice daily, followed by once daily dosing.

Day 1 and 2 of the treatment: 1-hour infusion of 200 mg (60 ml of the admixed solution) Itraconazole twice daily (see *"Preparation and handling"*).

From Day 3 onwards: one 1-hour infusion of 200 mg (60 ml of the admixed solution) Itraconazole each day. Safety for periods longer than 14 days has not been established.

Paediatric population
Since clinical data on the use of Itraconazole in paediatric patients are unavailable, Itraconazole should not be used in children unless the potential benefit outweighs the potential risk (see section 4.4 of the SmPC).

Elderly

Since clinical data of the use of Itraconazole in elderly patients are limited, it is advised to use Itraconazole in these patients only if the potential benefit outweighs the potential risk (see section 4.4 of the SmPC).

Renal impairment
Limited data are available on the use of intravenous itraconazole in patients with renal impairment.

Hydroxypropyl-β-cyclodextrin, a required component of Itraconazole intravenous formulation, is eliminated through glomerular filtration. Therefore, in patients with severe renal impairment defined as creatinine clearance below 30 ml/min the use of Itraconazole is contraindicated (see section 4.3 of the SmPC).

In patients with mild and moderate renal impairment, Itraconazole should be used with caution. Serum creatinine levels should be closely monitored and, if renal toxicity is suspected, consideration should be given to changing to the oral capsule formulation (see sections 4.4. and 5.2 of the SmPC).

Hepatic impairment
Limited data are available on the use of itraconazole in patients with hepatic impairment. Caution should be exercised when this drug is administered in this patient population (see section 5.2 of the SmPC).