Package leaflet: Information for the patient

Yondelis 0.25 mg powder for concentrate for solution for infusion
Yondelis 1 mg powder for concentrate for solution for infusion
trabectedin

Read all of this leaflet carefully before you start using 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.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Yondelis is and what it is used for

Yondelis contains the active substance trabectedin. Yondelis is an anti-cancer medicine that works by preventing the tumour cells from multiplying.

Yondelis is used for the treatment of patients with advanced soft tissue sarcoma, when previous medicines have been unsuccessful or the patients are unsuited to receive them. Soft tissue sarcoma is a malignant disease that starts somewhere in the soft tissues, such as the muscles, fat or other tissues (for example cartilages or vessels).

Yondelis in combination with pegylated liposomal doxorubicin (PLD: another anti-cancer medicine) is used for the treatment of patients with ovarian cancer that has come back after at least 1 previous therapy and are not resistant to anti-cancer medicines containing platinum compounds.

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

Do not use Yondelis

- if you are allergic to trabectedin or any of the other ingredients of this medicine (listed in section 6).
- if you have any serious infections.
- if you are breast-feeding.
- if you will receive yellow fever vaccine.

Warnings and precautions

Talk to your doctor before using Yondelis

Yondelis or its combination with PLD must not be used if you have severe liver, kidney or cardiac damage.

Tell your doctor if you know or suspect that you have any of the following before starting the treatment with Yondelis:

- Liver or kidney problems.
- Cardiac problems or a history of cardiac problems.
- Left ventricular ejection fraction (LVEF) under the lower limit of normal.
- Received high anthracycline dose treatment in the past.

You should seek medical attention immediately if any of the following conditions appear:

- If you develop a fever as Yondelis may cause side-effects affecting your blood and liver.
- If you still feel sick, vomit or are unable to drink fluids and therefore pass less urine despite being given anti-sickness medicines.
- If you experience severe muscle pain or weakness as it could be a sign of damage to your muscles (rhabdomyolysis; see section 4).
- If you notice that Yondelis infusion leaks out of your vein while you are being given it. It could lead to damage and death of your tissue cells around the injection site (tissue necrosis, see also section 4) which may require surgery.
- If you have an allergic reaction (hypersensitivity). In this case you may experience one or more of the following signs: fever, difficulty in breathing, redness or flushing of the skin or a rash, feeling sick (nausea) or being sick (vomiting; see section 4).
- If you notice unexplained partial or general swelling (oedema), with possible lightheadedness, dizziness or thirst (low blood pressure). It could be a sign of a condition (capillary leak syndrome) that can cause excessive accumulation of fluid in your tissues, and requires urgent medical evaluation by your doctor.

Children and adolescents

Yondelis should not be used in children below 18 years of age with paediatric sarcomas.

Other medicines and Yondelis

Tell your doctor if you are taking, have recently taken or might take any other medicines.

You must not use Yondelis if you will receive yellow fever vaccine and it is not recommended that you use Yondelis if you will receive a vaccine containing live virus particles. The effect of medicines containing phenytoin (for epilepsy) may be decreased if given together with Yondelis and this is therefore not recommended.

If you use any of the following medicines during your treatment with Yondelis, you need to be closely monitored as the effects of Yondelis are:

- decreased (examples are medicines containing rifampicin (for bacterial infections), phenobarbital (for epilepsy) or St. John's Wort (*Hypericum perforatum*, an herbal medicine for depression)) or
- increased (examples are medicines containing ketoconazole or fluconazole (for fungal infections), ritonavir (for human immunodeficiency virus [HIV] infection), clarithromycin (for bacterial

infections), aprepitant (to prevent nausea and vomiting), ciclosporin (inhibit the defensive system of the body) or verapamil (for high blood pressure and heart conditions)).

Thus the use of any of these medicines together with Yondelis should be avoided, if possible.

If you are given Yondelis or the combination Yondelis+PLD together with a medicine that might cause damage to the liver or to the muscles (rhabdomyolysis), you may need to be closely monitored, as there could be an increased risk of liver or muscle damage. Medicines containing statins (for lowering cholesterol levels and preventing cardiovascular disease) is an example of medicines that may cause muscle damage.

Yondelis with alcohol

Alcohol consumption must be avoided during treatment with Yondelis as this may harm the liver.

Pregnancy, breast-feeding and fertility

Pregnancy

Yondelis should not be used during pregnancy. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine.

Adequate contraceptive precautions must be used by women of childbearing potential when receiving Yondelis and for 3 months following the end of treatment.

If a pregnancy should occur you must tell your doctor immediately and genetic counselling is recommended since Yondelis can cause genetic damage.

Breast-feeding

Yondelis must not be given to patients who are breast-feeding. Therefore you must stop breast-feeding before you start your treatment and you must not begin breast-feeding again until your doctor has confirmed that it is safe to do so.

Fertility

Adequate contraceptive precautions must be used by men in fertile age when receiving Yondelis and for 5 months following the end of treatment.

Patients should seek advice on ovules or sperm conservation prior to treatment because of the risk of irreversible infertility due to therapy with Yondelis.

Genetic counselling is also recommended for patients wishing to have children after therapy.

Driving and using machines

During your treatment with Yondelis you may feel tired and experience a loss of strength. Do not drive or use any tools or machines if you are experiencing any of these side effects.

Yondelis contains potassium

This medicine contains potassium, less than 1 mmol (39 mg) per vial, and can therefore be considered as essentially “potassium-free”.

3. How to use Yondelis

Yondelis is given to you under the supervision of a physician experienced in the use of chemotherapy. Its use should be confined to qualified oncologists or other health professionals specialised in the administration of cytotoxic medicines.

For the treatment of soft tissue sarcoma, the usual dose is 1.5 mg/m^2 of body surface area. During the treatment period, your doctor will carefully monitor you and decide the most appropriate dosage of Yondelis to give to you. The recommended dose in Japanese patients is lower than the usual dose for all other races, and is 1.2 mg/m^2 of body surface area.

For the treatment of ovarian cancer, the usual dose is 1.1 mg/m^2 body surface area after the administration of 30 mg/m^2 body surface area of PLD.

Before Yondelis is given to you, it is reconstituted and diluted for intravenous use. Every time you are given Yondelis for the treatment of soft tissue sarcoma, it will take about 24 hours for all of the solution to enter your blood. It will take 3 hours for the treatment of ovarian cancer.

In order to avoid irritation at the site of injection it is recommended that Yondelis is given to you through a central venous line.

You will be given a medicine before and as needed during the treatment with Yondelis in order to protect your liver and to reduce the risk of side effects such as feeling sick (nausea) and vomiting.

The infusion is given to you every 3 weeks, although occasionally your doctor may recommend dose delays to ensure that you receive the most appropriate dose of Yondelis.

The length of your whole treatment period will depend on your progress and how well you feel. Your doctor will tell you how long your treatment lasts. If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine or its combination with PLD can cause side effects, although not everybody gets them.

If you are not sure what the side effects below are, you should ask your doctor to explain them to you in more detail.

<u>Serious side effects caused by the treatment with Yondelis:</u>

Very common: may affect more than 1 in 10 people

- You could have increased levels of the yellow pigment bilirubin in the blood which might cause jaundice (a yellowing of the skin, mucous membranes and eyes).
- Your doctor will order regular blood tests to detect any abnormalities in the blood.

Common: may affect up to 1 in 10 people

- You may also have blood infections (sepsis) if your immune system is greatly compromised. *If you have fever you should seek medical attention immediately.*
- You could also feel pain in your muscles (myalgia). There could also be damage to your nerves which may result in muscle pain, weakness and numbness. You could experience general swelling or swelling of the limbs and a sensation of creeping on the skin.

- You may have a reaction at the site of injection. Yondelis infusion may leak out of your vein while you are being given it, leading to damage and death of your tissue cells around the injection site (tissue necrosis, see also section 2 “Warnings and precautions”) which may require surgery.

- You could have an allergic reaction. In this case you may experience fever, difficulty in breathing, redness or flushing of the skin or a rash, feeling sick (nausea) or being sick (vomiting).

- When Yondelis is used in combination with PLD, you may have syncope also called fainting. Furthermore, you could feel like your heart is beating too hard or too fast in your chest (palpitations), have a weakness in the ventricles, the heart's major pumping chambers (left ventricular dysfunction), or a sudden blockage in a lung artery (pulmonary embolism).

Uncommon: may affect up to 1 in 100 people

- You may feel severe muscle aches and pain, stiffness and muscle weakness. You also may experience a darkening of the urine colour. All the previously described, could be a sign of damage to your muscles (rhabdomyolysis).

- Your doctor may require blood tests in certain situations in order to avoid that you develop muscle damage (rhabdomyolysis). In very severe cases this could lead to kidney failure. *If you experience severe muscle pain or weakness, you should seek medical attention immediately.*

- You may experience difficulty in breathing, irregular heartbeat, decreased urine output, abrupt change in mental status, areas of mottled skin, extremely low blood pressure associated with abnormal laboratory test results (decrease in platelet count). If you get any of the above symptoms or signs, **seek medical care immediately**.

- You may experience an abnormal build-up of fluid in the lungs, which leads to swelling (pulmonary oedema).

- You may notice unexplained partial or general swelling (oedema), with possible lightheadedness, dizziness or thirst (low blood pressure). It could be a sign of a condition (capillary leak syndrome) that can cause excessive accumulation of fluid in your tissues. If you get the above symptoms or signs, **seek medical care immediately**.

- You may notice that Yondelis infusion leaks out of your vein (extravasation) while you are being given it. Then you will notice some redness, swelling, itchiness and discomfort at the injection site. If you get any of these symptoms or signs, **tell your nurse or doctor immediately.**

  It could lead to damage and death of your tissue cells around the injection site (tissue necrosis) which may require surgery.

  Some of the symptoms or signs of extravasation may not be visible until several hours after it occurred. There may be blistering, peeling and darkening of the skin over the site. It is possible for it to take a few days before the full extent of tissue damage is visible. If you get any of the previous described symptoms or signs, **seek medical care immediately**.

Rare: may affect up to 1 in 1,000 people

- You may experience yellowing of your skin and eyeballs (jaundice), pain in the upper right area of your abdomen, nausea, vomiting, a general sense of not feeling well, difficulty in concentrating, disorientation or confusion, sleepiness. These signs could be indicative of the

inability of the liver to perform its normal function. If you get any of the previous described symptoms or signs, **seek medical care immediately**.

Other less serious side effects:

Very common: may affect more than 1 in 10 people

- You may:
  - feel tired
  - feel difficulty breathing and coughing
  - feel pain in your back and joints
  - feel an excess of fluid in the body (oedema)
  - bruise more easily
  - have nose bleeds
  - be more prone to infections. An infection could also give you a raised temperature (fever).

  If you develop any of these symptoms you should seek medical attention immediately.

- You may present some digestive symptoms such as loss of appetite, sick (nausea) or vomit, pain in the abdomen, diarrhoea or constipation. *If you still feel sick, vomit or are unable to drink fluids and therefore pass less urine, despite being given anti-sickness medicine, you should immediately seek medical help.*

- You may experience headache and sleeping problems.

- You could have mucosal inflammation as a swelling redness of the inside of the mouth leading to painful ulcers and mouth sores inflammation of the mouth (stomatitis), or as an inflammation of the gastrointestinal tract when Yondelis is used with PLD.

- Patients receiving Yondelis plus PLD for ovarian cancer may also have the hand and foot syndrome. It may present as red skin of the palms, fingers, and soles of the feet that later may become swollen and violaceous. The lesions may either dry out and desquamate, or blister with ulceration.

Common: may affect up to 1 in 10 people

- You may experience, loss of water from the body, weight loss, digestive discomfort and a change in your sense of taste.

- You may lose hair (alopecia).

- You could also experience dizziness, low blood pressure and flushing or skin rash.

- Higher skin pigmentation could occur in patients receiving Yondelis with PLD for ovarian cancer.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via:

United Kingdom
Yellow Card Scheme
Website: 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 Yondelis

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

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

Store in a refrigerator (2ºC - 8ºC).

Information on in-use stability of the reconstituted and diluted solutions is included in the section for medical and healthcare professionals.

Do not use this medicine if you notice visible particles after the reconstitution or dilution of the medicine.

Any unused medicine or waste material should be disposed of in accordance with local requirements for cytotoxic medicines.

6. Contents of the pack and other information

What Yondelis contains:

- The active substance is trabectedin.
  Yondelis 0.25 mg: Each vial of powder contains 0.25 mg of trabectedin.
  Yondelis 1 mg: Each vial of powder contains 1 mg of trabectedin.

- The other ingredients are sucrose, potassium dihydrogen phosphate, phosphoric acid (for pH-adjustment) and potassium hydroxide (for pH-adjustment).

What Yondelis looks like and contents of the pack

Yondelis is a powder for concentrate for solution for infusion. The powder has a white to off-white colour and comes in a glass vial.

Each carton contains 1 vial of either 0.25 mg or 1 mg of trabectedin.

Marketing Authorisation Holder and Manufacturer:

Pharma Mar, S.A.
Avda. de los Reyes 1
Polígono Industrial La Mina
28770 Colmenar Viejo (Madrid)
Spain
Tel: +34 91 846 60 00
Fax: +34 91 846 60 01

For any information about this medicine, please contact the Marketing Authorisation Holder.

This leaflet was last revised in 12/2019

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Instructions for use – preparation, handling and disposal

Appropriate procedures for proper handling and disposal of cytotoxic medicines must be followed. Any unused medicine or waste material should be disposed of in accordance with local requirements for cytotoxic medicines.

You should have received training on the correct techniques to reconstitute and dilute Yondelis or its combination with PLD and you should wear protective clothing including mask, goggles and gloves during the reconstitution and dilution. Accidental contact with the skin, eyes or mucous membranes must be treated immediately with copious amounts of water. You should not work with this medicine if you are pregnant.

Preparation for intravenous infusion

Yondelis must be reconstituted and further diluted prior to infusion (see also section 3). *Appropriate aseptic techniques must be used.*

Yondelis must not be administered as a mixture with other medicines in the same infusion apart from the diluent. No incompatibilities have been observed between Yondelis and type I glass bottles, polyvinylchloride (PVC) and polyethylene (PE) bags and tubing, polyisoprene reservoirs and titanium implantable vascular access systems.

When Yondelis is used in combination with PLD, the intravenous line should be flushed well with 50 mg/ml (5%) glucose solution for infusion after administration of PLD and before administration of Yondelis. The use of any diluent other than 50 mg/ml (5%) glucose solution for infusion may cause precipitation of PLD. (See also PLD Summary of Product Characteristics for specific handling instructions).

Instructions for reconstitution

Yondelis 0.25 mg: Inject 5 ml of sterile water for injections into the vial.

Yondelis 1 mg: Inject 20 ml of sterile water for injections into the vial.

A syringe is used to inject the correct amount of sterile water for injections into the vial. Shake the vial until complete dissolution. The reconstituted solution results in a clear, colourless or slightly yellowish solution, essentially free of visible particles.

This reconstituted solution contains 0.05 mg/ml of trabectedin. It requires further dilution and is for single-use only.

Instructions for dilution

Dilute the reconstituted solution with sodium chloride 9 mg/ml (0.9%) solution for infusion or glucose 50 mg/ml (5%) solution for infusion. Calculate the required volume as follows:

$$\text{Volume (ml)} = \frac{\text{BSA } (m^2) \times \text{individual dose } (mg/m^2)}{0.05 \text{ mg/ml}}$$

BSA = Body Surface Area

Withdraw the appropriate amount of reconstituted solution from the vial. If intravenous administration is to be made via a central venous line, add the reconstituted solution to an infusion bag containing ≥ 50 ml of diluent (sodium chloride 9 mg/ml (0.9%) solution for infusion or glucose 50 mg/ml (5%) solution for infusion), the concentration of trabectedin in the infusion solution being ≤ 0.030 mg/ml.

If central venous access is not feasible and a peripheral venous line has to be used, add the reconstituted solution to an infusion bag containing ≥ 1,000 ml of diluent (sodium chloride 9 mg/ml (0.9%) solution for infusion or glucose 50 mg/ml (5%) solution for infusion).

Inspect the parenteral solution visually for particles prior to intravenous administration. Once the infusion is prepared, it should be administered immediately.

In-use stability of the solutions

Reconstituted solution
After reconstitution, chemical and physical stability has been demonstrated for 30 hours up to 25ºC.

From a microbiological point of view, the reconstituted solution should be diluted and used immediately. If not diluted and used immediately, in-use storage times and conditions prior to use of the reconstituted solution are the responsibility of the user and would normally not be longer than 24 hours at 2ºC to 8ºC, unless reconstitution has taken place in controlled and validated aseptic conditions.

Diluted solution
After dilution, chemical and physical stability has been demonstrated for 30 hours up to 25ºC.