

Endoxana® 50 mg Tablets

(cyclophosphamide)

Read all of this leaflet carefully before you take 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 pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes possible side effects not listed in this leaflet. See section 4.

The name of your medicine is Endoxana 50 mg Tablets but will be referred to as Endoxana throughout the leaflet.

Important things to know about Endoxana

Your doctor has prescribed Endoxana because you have cancer that can be treated.

Endoxana is a medicine that kills cancer cells but, as a result, also attacks normal cells. It can therefore have a number of side effects. Your doctor will not give you Endoxana unless he or she thinks that your cancer is more of a risk to you than any possible side effects. Your doctor will check you regularly and treat any side effects where possible.

Endoxana:

- will reduce your blood cell count, which may make you feel tired and be more likely to get infections.
- can affect your kidneys and bladder. You may be given another medicine called Mesna to help prevent any damage. If you notice blood in your urine, tell your doctor immediately.
- like most anti-cancer or chemotherapy medicines, you may lose your hair (anything from thinning to total loss), although it should start to grow back once your treatment has finished. It may also make you feel sick or be sick. Your doctor can give you advice or medicines to help.
- Men or women should not have a child during treatment with Endoxana or for at least 6 months after treatment. You should use an effective contraceptive. Ask your doctor for advice.

Now read the rest of this leaflet. It includes other important information on the use of Endoxana that might be especially important for you.

In this leaflet:

- What Endoxana is and what it is used for
- What you need to know before you take Endoxana
- How to take Endoxana
- Possible side effects
- How to store Endoxana
- What you need to know before you take Endoxana

1. What Endoxana is and what it is used for

Endoxana is a cytotoxic drug or anti-cancer drug. It works by killing cancer cells, this is sometimes called ‘chemotherapy’. It is used to treat lots of different cancers. Endoxana is often used together with other anti-cancer drugs or radiotherapy.

Occasionally, some doctors may prescribe Endoxana for other conditions not related to cancer, your doctor will tell you if this applies to you.

2. What you need to know before you take Endoxana Do not take Endoxana if:

- you have ever had an allergic reaction to the active ingredient or any of the other ingredients (listed in Section 6). An allergic reaction can include shortness of breath, wheezing, rash, itching or swelling of the face and lips
- your bone marrow is not working properly (especially if you have previously had chemotherapy or radiotherapy). You will have blood tests to check how well your bone marrow is working
- you have a urinary tract infection, which can be recognised as pain when passing urine (cystitis)
- you currently have any infections
- you have ever had kidney or bladder problems as a result of previous chemotherapy or radiotherapy.
- you have a condition which decreases your ability to urinate (Urinary outflow obstruction).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Endoxana if:

- you are already having, or have recently had, radiotherapy or chemotherapy
- you have diabetes
- you have liver or kidney problems. Your doctor will check how well your liver and kidneys are working by doing a blood test
- you have had your adrenal glands removed
- you have heart problems or have had radiotherapy in the area of your heart
- you have poor general health or are frail
- you are elderly.

Take special care with Endoxana

- Endoxana can have effects on your blood and immune system
- Blood cells are made in your bone marrow. Three different types of blood cell are made:
 - red blood cells, which carry oxygen around your body
 - white blood cells, which fight infection, and
 - platelets, which help your blood to clot.
- After taking Endoxana, your blood count of the three types of cells will drop. This is an unavoidable side effect of Endoxana. Your blood count will reach its lowest level about 5 to 10 days after you start taking Endoxana and will stay low until a few days after you finish the course. Most people recover to a normal blood count within 21 to 28 days. If you have had a lot of chemotherapy in the past, it may take a little longer to return to normal.
- You may be more likely to get infections when your blood count drops. Try to avoid close contact with people who have coughs, colds and other infections. Your doctor will treat you with appropriate medicine if they think you have, or are at risk, of an infection.
- Your doctor will check that the number of red blood cells, white blood cells and platelets is high enough before and during your treatment with Endoxana. They may need to reduce the amount you are given or delay your next dose.
- Endoxana can affect wound healing. Keep any cuts clean and dry, and check they are healing normally.

- It is important to keep your gums healthy, as mouth ulcers and infections can occur. Ask your doctor about this if you are unsure.
- Endoxana can damage the lining of your bladder, causing bleeding into your urine and pain on urination. Your doctor knows this can happen and, if necessary, he or she will give you a medicine called Mesna which will protect your bladder.
- Mesna can either be given to you as a short injection, or mixed into the drip solution with your Endoxana, or as tablets.
- More information on Mesna can be found in the Patient Information Leaflet for Mesna Injection and Mesna tablets.
- Most people having Endoxana with Mesna do not develop any problems with their bladder, but your doctor may want to test your urine for the presence of blood using a ‘dipstick’ or microscope.
- If you notice that you have blood in the urine, you must tell your doctor straight away as they may need to stop giving you Endoxana.
- Cancer medicines and radiation therapy can increase the risk of you developing other cancers; this can be a number of years after your treatment has stopped. Endoxana has an increased risk of causing cancer in the area of your bladder.
- Endoxana can cause damage to your heart or affect the rhythm of it beating. This increases with higher doses of Endoxana, if you are being treated with radiation or other chemotherapy medicines or if you are elderly. Your doctor will monitor your heart closely during treatment.
- Endoxana can cause inflammation or scarring in your lungs. This can occur more than six months after your treatment. If you start having difficulty breathing tell your doctor straight away.
- Endoxana can have life threatening effects on your liver. If you have sudden weight gain, liver pain and jaundice tell your doctor straight away.
- Hair thinning or baldness can occur. Your hair should grow back normally though it may be different in texture or colour.
- Endoxana can make you feel sick or be sick. This can last for about 24 hours after taking Endoxana. You may need to be given medicines to stop feeling or being sick. Ask your doctor about this.

Using other medicines and treatments

Tell your doctor or nurse if you are taking or have recently taken any other medicines, including medicines you have bought yourself. In particular, tell them about the following medicines or treatments as they may not work well with Endoxana:

The following medicines can reduce how effective Endoxana is:

- aprepitant (used to prevent being sick)
- bupropion (an anti-depressant)
- busulfan, thiotepa (used to treat cancer)
- ciprofloxacin, chloramphenicol (used to treat bacterial infections)
- fluconazole, itraconazole (used to treat fungal infections)
- Prasugrel (used to thin the blood)
- Sulfonamides, such as sulfadiazine, sulfasalazine, sulfamethoxazole (used to treat bacterial infections)

The following medicines can increase the toxicity of Endoxana:

- allopurinol (used to treat gout)
- azathioprine (used to reduce the activity of the immune system)
- chloral hydrate (used to treat insomnia)
- cimetidine (used to reduce stomach acid)
- disulfiram (used to treat alcoholism)
- glyceraldehyde (used to treat warts)
- protease inhibitors (used to treat viruses)
- ondansetron (used to prevent being sick)
- medicines that increase liver enzymes such as:
 - rifampicin (used to treat bacterial infections)
 - carbamazepine, phenobarbital, phenytoin (used to treat epilepsy)
 - St. John’s wort (a herbal remedy for mild depression)
 - Corticosteroids (used to treat inflammation)
- medicines that can increase the toxic effects on your blood cells and immunity
 - ACE inhibitors (used to treat high blood pressure)
 - natalizumab (used to treat multiple sclerosis)
 - paclitaxel (used to treat cancer)
 - thiazide diuretics such as hydrochlorothiazide or chlortalidone (used to treat high blood pressure or water retention)
 - zidovudine (used to treat viruses)
 - Clozapine (used to treat symptoms of some psychiatric disorders)
- medicines that can increase the toxic effects on your heart
 - anthracyclines such as bleomycin, doxorubicin, epirubicin, mitomycin (used to treat cancer)
 - cytarabine , pentostatin, trastuzumab (used to treat cancer)
 - radiation in the area of your heart
- medicines that can increase the toxic effects on your lungs
 - amiodarone (used to treat irregular heart beat)
 - G-CSF, GM-CSF hormones (used to increase white blood cell numbers after chemotherapy)
- medicines that can increase the toxic effects on your kidneys
 - amphotericin B (used to treat fungal infections)
 - Indomethacin (used to treat pain and inflammation)

Other medicines that can affect or be affected by Endoxana include:

- etanercept (used to treat rheumatoid arthritis)
- metronidazole (used to treat bacterial or protozoal infections)
- tamoxifen (used to treat breast cancer)
- bupropion (used to help stop smoking)
- coumarins such as warfarin (used to thin the blood)
- cyclosporine (used to reduce the activity of the immune system)
- succinylcholine (used to relax muscles during medical procedures)
- digoxin, β-acetyldigoxin (used to treat heart conditions)
- vaccines
- verapamil (used to treat high blood pressure, angina or irregular heart beat)

Using Endoxana with food and drink

Drinking alcohol can increase the nausea and vomiting caused by Endoxana.

Pregnancy, breast-feeding and fertility

Do not become pregnant while taking Endoxana. This is because it can cause miscarriage or damage your unborn baby. Tell your doctor if you are pregnant, think you might be pregnant or are trying to become pregnant.

- Men or women should not try to have a child during or for at least 6 to 12 months after treatment. You should use an effective contraceptive. Ask your doctor for advice.
- Endoxana can affect your ability to have children in the future. Talk to your doctor about freezing sperm samples or eggs before your treatment starts.

Do not breast-feed while being treated with Endoxana. Ask your doctor for advice.

Driving or using machines

Some of the side effects of treatment with Endoxana might affect your ability to drive and use machines safely. Your doctor will decide if it is safe for you to do so.

What to do if you see a different doctor, or have to go to hospital
If you see any other doctor or have to go to hospital for any reason, tell them what medicines you are taking. Do not take any other medicines unless your doctor knows you are taking Endoxana.

3. How to take Endoxana Taking this medicine

- Endoxana Tablets are to be taken by mouth. Do not chew them.
- If you are also having Mesna, your doctor will tell you how much you need to drink. You should take your tablets with enough liquid to make them easy to swallow.
- Endoxana is often given with other anti-cancer drugs or radiotherapy.

The usual dose

- Your doctor will decide how much of the medicine you need and when you should take it.
- The amount of Endoxana you will need to take depends on:
 - the type of illness you have
 - how big you are (a combination of your height and weight)
 - your general health
 - whether you are being given other anti-cancer drugs or having radiotherapy.
- The usual dose is between 100 mg (2 tablets) and 300 mg (6 tablets) per day. You can take all of one day’s tablets together, but you should try to take them about the same time each day, preferably in the morning. If you are not sure how to take your tablets, ask your doctor or pharmacist.

Endoxana is usually taken for several days in a row as a course, and then there is a break (a period when no tablets are taken) before the next course. Sometimes you may need to take different numbers of tablets on alternate days, for instance, 3 tablets one day and 4 the next.

Your doctor may need to change the amount of medicine you are given and monitor you more closely if you:

- have problems with your liver or kidneys
- you are elderly.

If you forget to take Endoxana

If you forget to take your Endoxana:

- you should take them as soon as you remember, if it is on the same day. If you have forgotten to take a whole day’s tablets, then you should talk to your doctor.
- Never take more tablets in one day than you were meant to
 - so never take two days worth of tablets on the same day in order to ‘catch up’.

If you take too much Endoxana

In the event of an overdose, or if a child swallows any of your tablets, talk to your doctor or local hospital emergency department immediately. Hospital admission for special treatment may be needed.

4. Possible side effects

Like all medicines, Endoxana can cause side effects, although not everybody gets them. Side effects can sometimes occur after ending the treatment. The following side effects may happen with this medicine.

Tell your doctor straight away, and go to hospital immediately if you notice any of the following serious side effects:

- allergic reactions, signs of this would be shortness of breath, wheezing, rash, itching or swelling of the face and lips (hypersensitivity). Severe allergic reactions could lead to difficulty in breathing or shock, with a possible fatal outcome (anaphylactic shock, anaphylactic/ anaphylactoid reaction)
- getting bruises without knocking yourself, or bleeding from your gums. This may be a sign that the platelet levels in your blood are getting too low
- a lowering of your white blood cell count - your doctor will check this during your treatment. It will not cause any signs, but you will be more likely to get infections. If you think you have an infection (a high temperature, feeling cold and shivery, or hot and sweaty, or any signs of infection such as a cough, or stinging on passing water) you may need antibiotics to fight infections because your blood count is lower than usual
- blood in your urine, pain while passing urine, or less urine being passed (hemorrhagic cystitis, haematuria)
- inflammation of your intestines or bowel which may resulting in bleeding (hemorrhagic enterocolitis)
- fits (convulsions)
- life threatening conditions which cause rash, ulcers, sore throat, fever, conjunctivitis, separation of skin layers (toxic epidermal necrolysis, Stevens-Johnson syndrome). Swelling, numbness, red lumps and peeling of skin on the hands and feet (Palmar-plantar erythrodysesthesia syndrome)
- life threatening decrease in the abilities of your kidney to adequately remove toxins and waste products from the blood (kidney failure). These changes to the tissues within your kidney can prevent them from working correctly, and induce kidney failure (renal tubular necrosis, renal tubular disorder)
- pneumonia. Signs of this could be chest pain when you breathe or cough, confusion, coughing, fever, sweating and chills, fatigue, shortness of breath, nausea, vomiting or diarrhoea
- severe infection spreading through the blood which may lead to a dangerous drop in blood pressure with a possible fatal outcome (sepsis, shock)

- effects on the brain (encephalopathy), signs of this can be problems in thinking or concentrating, reduced alertness, changes in personality, tiredness, fits, muscle twitching, and shaking
- a syndrome called reversible posterior leukoencephalopathy syndrome, which can cause swelling of the brain, headache, confusion, fits and loss of sight
- heart attack (myocardial infarction)
- decrease in your hearts ability to pump enough blood around your body which may be life threatening (cardiogenic shock, heart failure or cardiac arrest)
- life-threatening decrease of your lungs ability to transfer oxygen in to your blood (respiratory failure)
- a build-up of toxins in the body due to liver failure (hepatotoxicity). This may affect the brain causing confusion, reduced consciousness or coma (hepatic encephalopathy)

Tell your doctor straight away, if you notice any of the following serious side effects:

- haemolytic uremic syndrome - a condition causing abnormal break down of the red blood cells, decreased numbers of platelets in the blood and kidney failure
- cancer of your blood (leukaemia)
- cancer of the bone marrow (myelodysplastic syndrome)
- swelling of the brain due to too much water in your blood (water intoxication). Signs of this can be headache, changes in personality or behaviour, confusion, drowsiness
- formation of small blood clots in your blood vessels disrupting the normal blood flow around your body (disseminated intravascular coagulation)
- blood clot in the lungs which causes chest pain and breathlessness (pulmonary embolism)
- blood clot, usually in a leg, which causes pain swelling or redness venous thrombosis)
- low blood levels of sodium which can cause tiredness and confusion, muscle twitching, fits and coma (hyponatremia)
- tummy discomfort or severe tummy and back pain, this may be caused by inflammation of the pancreas (acute pancreatitis)
- high blood sugar levels which can cause thirst, tiredness and irritability (hyperglycaemia)
- low blood sugar levels which can cause confusion and sweating (hypoglycaemia)
- effects on the spinal cord (Myelopathy), which can cause numbness, weakness and tingling in the hands, loss of motor skills
- disease of the heart muscle (cardiomyopathy); inflammation of the tissues in or around your heart (myocarditis, pericarditis); build up of fluid in the sac around your heart (pericardial effusion). Increased pressure from this fluid can stop the heart filling properly (cardiac tamponade); abnormal ECG heart tracing (Electrocardiogram QT prolonged) – These could be considered causes of arrhythmia
- changes in your heart rhythm (arrhythmia) which may be noticeable (palpitations):
 - irregular heart beat (fibrillation)
 - faster heart beat (tachycardia), which may be life threatening (ventricular tachycardia)
 - slower heart beat (bradycardia)
- blood clot in the lungs which causes chest pain and breathlessness (pulmonary veno-occlusive disease)
- scarring of the lungs which causes shortness of breath (pulmonary fibrosis)
- conditions causing inflammation of the lungs which can cause breathlessness, cough and raised temperature or scarring of the lungs (pneumonitis, acute respiratory distress syndrome, obliterative bronchiolitis, organizing pneumonia, alveolitis allergic)
- fluid in or around the lungs (pulmonary oedema, pleural effusion)
- increased blood pressure in the lungs which can cause shortness of breath, fatigue, cough, angina, fainting, peripheral oedema (pulmonary hypertension)
- abnormal muscle breakdown which can lead to kidney problems (rhabdomyolysis)

Other possible side effects, listed by frequency, may be:

Very common: may effect more than 1 in 10 people

- reduction in the effectiveness of your immune system (immunosuppression)
- hair loss (alopecia)
- pain and difficultly passing urine (cystitis)
- very pale, lethargic and tired. This may be a sign of low red blood cells (anaemia). Usually, no treatment is required, your body will eventually replace the red blood cells. If you are very anaemic, you may need a blood transfusion

Common: may effect up to 1 in 10 people

- increased risk and severity of bacterial, fungal, viral, protozoal or parasitic infections due to the effect of cyclophosphamide on your immune system
- reactivation of infections you have had before (latent infections)
- increased levels of certain proteins produced by your liver called enzymes. Your doctor will do blood tests to test for these
- inflammation of the bladder lining which causes pain, bleeding, blood in the urine, reduced urine flow (haemorrhagic cystitis)
- inflammation of the linings of your body cavities (mucosal inflammation)

Uncommon: may effect up to 1 in 100 people

- loss of appetite (anorexia)
- reddening of the skin (flushing) which may be accompanied by feeling hot or sweating (hot flushing)

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

- secondary tumours in various parts of the body, often in the area of the bladder
- dehydration
- dizziness
- blurring, reduction or loss of sight
- changes in colour of your fingernails and skin.
- inflammation of this skin which may cause rash, blisters, itching, sores, oozing and scarring (dermatitis)
- absence of menstrual periods (amenorrhoea)
- chest pain

Very rare: may effect up to 1 in 10,000 people

- increase in the release of antidiuretic hormone from the pituitary gland. This affects the kidneys causing the low levels of sodium in your blood (hyponatremia) and water retention
- accumulation of fluid in the body (water retention), which may be seen as fluid beneath the skin or swelling in you limbs
- feeling sick and being sick (nausea, vomiting)
- constipation or diarrhoea
- ulcers in the lining of your digestive system (mucosal ulceration)
- inflammation of the lining of your mouth including ulcers (stomatitis)
- confusion
- ulceration or scaring (fibrosis) of the bladder
- inflammation of the eye (conjunctivitis)
- eye oedema (swelling)

Unknown: frequency cannot be estimated from the available data

- changes to your metabolism caused by the breakdown of the dying cancer cells (Tumour lysis syndrome)
- inflammation of your intestines or bowel which may resulting in bleeding (enteritis, cecitis)
- bleeding in your stomach or intestines (gastrointestinal haemorrhage)
- inflammation which causes abdominal pain or diarrhoea (colitis)
- swelling of the glands in your neck (parotid gland inflammation).
- a disorder of the nerves which can cause weakness, tingling or numbness (peripheral neuropathy). This could be in more than one set of nerves (polyneuropathy)
- pain from your nerves, which can also feel like an aching or burning sensation (neuralgia)
- tingling or numbness, often in the hands or feet (paresthesia)
- shaking (tremor)
- changes in your sense of touch (dysesthesia) or loss of sensation (hypoesthesia)
- changes in your sense of taste (dysgeusia) or loss of taste (hypogeusia)
- changes in your sense of smell (parosmia)
- increased tear formation (lacrimation)
- deafness or hearing impairment
- ringing in the ears (tinnitus)
- inflammation of the blood vessels (vasculitis)
- reduced blood supply to your hands and feet (peripheral ischemia). This may cause pain, weakness, numbness, ulcers, changes in skin colour or temperature
- difficulty in breathing or wheezing (bronchospasm)
- shortness of breath (dyspnea)
- decrease levels of oxygen in your body (hypoxia)
- cough
- blocked or runny nose
- pain at the back of your throat
- increased liver size (hepatomegaly)
- yellowing of the skin or whites of the eyes (jaundice)
- blockage of the small veins in your liver (veno-occlusive liver disease) which can cause weight gain, increased liver size, pain and jaundice
- conditions causing inflammation of the liver which can cause jaundice, weight loss and malaise (hepatitis)
- disruption of the formation of bile by the liver which can cause itchiness, jaundice, pale coloured stools, dark urine (cholestasis)
- a build-up of fluid in the abdomen causing swelling of the tummy and shortness of breath (ascites)
- dark red raised itchy rash (urticaria)
- redness and blistering of the skin appearing months or years after treatment (radiation recall dermatitis)
- itchy, red rash which can develop in to sores (erythema multiforme)
- excessive sweating (hyperhidrosis)
- swelling of the face
- itching (pruritus)
- serious illness which causes thickening of the skin and the connective tissue in your internal organs (scleroderma)
- muscle spasms
- muscle pain (myalgia) or joint pain (arthralgia)
- damage to the kidneys by toxins in the blood (toxic nephropathy)
- glucose in the urine (nephrogenic diabetes insipidus)
- inflammation of the urethra which causes pain and bleeding (haemorrhagic urethritis)
- death of the cells and tissues (necrosis)
- decrease in the size of the bladder (bladder contracture)
- changes to the cells in the lining of your bladder
- increase in the levels of creatinine or urea nitrogen in your blood. Your doctor will do blood tests to test for these
- premature labour
- infertility. Sperm production in men and egg production in women may be reduced or stop. In some cases this can be permanent
- reduced frequency of menstrual periods (oligomenorrhoea)
- decrease in testicle size (testicular atrophy)
- decrease in the hormone oestrogen in the blood
- increase in the hormone gonadotrophin in the blood
- use in young patients may result in some impairments of future fertility
- reduction in growth, deformity or death of a foetus while in the womb
- toxic effects on the foetus such as myelosuppression and gastroenteritis
- life threatening failure of multiple organs such as heart, lungs, kidney, liver (see symptoms throughout section 4)
- general physical deterioration
- flu-like symptoms such as headache, fever, chills, joint and muscle pain, weakness, tiredness
- swelling
- injection site reaction.

Reporting of side effects

If you get any side effects, talk to your doctor, nurse or pharmacist. 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. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Endoxana

- Keep out of the sight and reach of children.
- Do not use Endoxana after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.
- Do not store above 25°C. Store in the original package.
- If the medicines become discoloured or show any other signs of deterioration, consult your pharmacist who will tell you what to do.
- Medicines should not be disposed of via wastewater or household waste. If you have any medicine left over, take it back to your pharmacist.

6. Contents of the pack and other information

What Endoxana contains

The active substance is cyclophosphamide. Each coated tablet contains cyclophosphamide monohydrate equivalent to 50 mg cyclophosphamide. Other ingredients are: maize starch, lactose monohydrate, calcium hydrogen phosphate, talc, magnesium stearate, gelatin, glycerol 85%, sucrose, titanium dioxide E171, calcium carbonate, macrogol 35000, colloidal anhydrous silica, povidone, carmellose sodium, polysorbate 20, montan glycol wax.

What Endoxana looks like and contents of the pack

Endoxana Tablets are white, round, biconvex, coated tablets with a white core. They are available in blister pack sizes of 50 and 100 tablets

Manufacturer and Product Licence Holder

Manufactured by Baxter Oncology A.G., Kantstrasse 2, 33790 Halle/Kunsebeck, Germany and procured from the EU by Product Licence holder: Star Pharmaceuticals Ltd., 5 Sandridge Close, Harrow, Middlesex HA1 1XD. Repackaged by Servipharm Ltd.

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PL 20636/2653

Revision and issue date (Ref.) 09.08.17[5]

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