Package leaflet: Information for the user

Levact ® 25 mg and 100 mg

Powder for Concentrate for Solution for Infusion

Bendamustine hydrochloride

Read all of this leaflet carefully before you start using this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT *LEVACT* IS AND WHAT IT IS USED FOR

Levact is a medicine which is used for the treatment of certain types of cancer (cytotoxic medicine).

Levact is used alone (monotherapy) or in combination with other medicines for the treatment of the following forms of cancer:
- chronic lymphocytic leukaemia in cases where fludarabine combination chemotherapy is not appropriate for you,
- non-Hodgkin's lymphomas, which had not, or only shortly, responded to prior rituximab treatment,
- Multiple myeloma in cases where high-dose chemotherapy with autologous stem cell transplantation, thalidomide or bortezomib containing therapy is not appropriate for you.

2. BEFORE YOU USE *LEVACT*

Do not use *Levact*
- if you are hypersensitive (allergic) to the active substance bendamustine hydrochloride or any of the other ingredients of ***Levact***;
- while breastfeeding;
- if you have severe liver dysfunction (damage to the functional cells of the liver);
- if you have yellowing of the skin or whites of the eyes caused by liver or blood problems (jaundice);
- if you have severely disturbed bone marrow function (bone marrow depression) and serious changes in your number of white blood cells and platelets in the blood (white blood cells and/or thrombocyte values drop to < 3,000/µl or < 75,000/µl, respectively.);
- if you have had major surgical operations less than 30 days before starting treatment;
- if you have an infection, especially one accompanied by a reduction in white blood cells (leucocytopenia);
- in combination with yellow fever vaccines.

Take special care with *Levact*
- in case of reduced capability of the bone marrow to replace blood cells. You should have your number of white blood cells and platelets in the blood checked before starting treatment with ***Levact***, before each subsequent course of treatment and in the intervals between courses of treatment.
- in case of infections. You should contact your doctor if you have signs of infection, including fever or lung symptoms.
- in case of reactions on your skin during treatment with ***Levact***. The reactions may increase in severity.
- in cases of existing heart disease (e.g. heart attack, chest pain, severely disturbed heart rhythms).
- in case you notice any pain in your side, blood in your urine or reduced amount of urine. When your disease is very severe, your body may not be able to clear all the waste products from the dying cancer cells. This is called tumour lysis syndrome and can cause kidney failure and heart problems within 48 hours of the first dose of ***Levact***. Your doctor will be aware of this and may give you other medicines to help prevent it.
- in case of severe allergic or hypersensitivity reactions. You should pay attention to infusion reactions after your first cycle of therapy.

Men receiving treatment with ***Levact*** are advised not to conceive a child during treatment and for up to 6 months afterwards. Before starting treatment, you should seek advice on storing sperm because of the possibility of permanent infertility.

Unintentional injection into the tissue outside blood vessels (extravasal injection) should be stopped immediately. The needle should be removed after a short aspiration. Thereafter the affected area of tissue should be cooled. The arm should be elevated. Additional treatments like the use of corticosteroids are not of clear benefit (see section 4).

Using other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken other medicines, including medicines obtained without a prescription.

If ***Levact*** is used in combination with medicines which inhibit the formation of blood in the bone marrow, the effect on the bone marrow may be intensified.

If ***Levact*** is used in combination with medicines which alter your immune response, this effect may be intensified.

Cytostatic medicines may diminish the effectiveness of live-virus vaccination. Additionally cytostatic medicines increase the risk of an infection after vaccination with live vaccines (e.g. viral vaccination).

Pregnancy and breastfeeding

Pregnancy

Levact can cause genetic damage and has caused malformations in animal studies. You should not use ***Levact*** during pregnancy unless certainly indicated by your doctor. In case of treatment you should use medical consultation about the risk of potential adverse effects of your therapy for the unborn child and genetic consultation is recommended.

If you are a woman of childbearing potential you must use an effective method of contraception both before and during treatment with ***Levact***. If pregnancy occurs during your treatment with ***Levact*** you must immediately inform your doctor and should use genetic consultation.

If you are a man, you should avoid fathering a child during treatment with ***Levact*** and for up to 6 months after treatment has stopped. There is a risk that treatment with ***Levact*** will lead to infertility and you may wish to seek advice on conservation of sperm before treatment starts.

Breastfeeding

Levact must not be administered during breastfeeding. If treatment with ***Levact*** is necessary during lactation you must discontinue breastfeeding.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

No studies on the effects on the ability to drive and to use machines have been performed. Do not drive or operate machines if you experience side effects, such as dizziness or lack of coordination.

3. HOW TO USE *LEVACT*

Levact is administered into a vein over 30-60 minutes in various dosages, either alone (monotherapy) or in combination with other medicines.

Treatment should not be started if your white blood cells (leukocytes) have fallen to counts below 3,000 cells/µl and/or your blood platelets have fallen to counts below 75,000 cells/µl.

Your doctor will determine these values at regular intervals.

Chronic lymphocytic leukaemia

Levact 100 mg per square metre of your body surface area (based on your height and weight)	on Days 1 + 2
Repeat the cycle after 4 weeks up to 6 times	

Non-Hodgkin's lymphomas

Levact 120 mg per square metre of your body surface area (based on your height and weight)	on Days 1 + 2
Repeat the cycle after 3 weeks at least 6 times	

Multiple myeloma

Levact 120 – 150 mg per square metre of your body surface area (based on your height and weight)	on Days 1 + 2
Prednisone 60 mg per square metre of your body surface area (based on your height and weight) i.v. or per os.	on Days 1 – 4
Repeat the cycle after 4 weeks at least 3 times	

Treatment should be terminated if white blood cell (leukocyte) and/or platelet values drop to < 3,000/µl or < 75,000/µl, respectively. Treatment can be continued after white blood cell values have increased to > 4,000/µl and platelet values to > 100,000/µl.

Impaired liver or kidney function

Dependent on the degree of impairment of your liver function it may be necessary to adjust your dose (by 30% in case of moderate liver dysfunction). No dose adjustment is necessary in case of impairment of kidney function. Your attending doctor will decide whether a dosage adjustment is necessary.

How it is administered

Treatment with ***Levact*** should be undertaken only by doctors experienced in tumour therapy. Your doctor will give you the exact dose of ***Levact*** and use the necessary precautions.

Your attending doctor will administer the solution for infusion after preparation as prescribed. The solution is administered into a vein as a short-term infusion over 30 – 60 minutes.

Duration of use

There is no time limit laid down as a general rule for treatment with ***Levact***. Duration of treatment depends on disease and response to treatment.

If you are at all worried or have any questions regarding treatment with ***Levact***, please speak to your doctor or nurse.

If you forget to use *Levact*

If a dose of ***Levact*** has been forgotten, your doctor will usually retain the normal dosage schedule.

If you stop using *Levact*

The doctor treating you will decide whether to interrupt the treatment or to change over to a different preparation.

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

4. POSSIBLE SIDE FFECTS

Like all medicines, ***Levact*** can cause side-effects, although not everybody gets them.

The following definitions of frequency are used when assessing side-effects:

Very common: affects more than 1 user in 10
Common: affects 1 to 10 users in 100
Uncommon: affects 1 to 10 users in 1,000
Rare: affects 1 to 10 users in 10,000
Very rare: affects less than 1 user in 10,000
Not known: frequency cannot be estimated from the available data

Tissue changes (necrosis) have been observed very rarely following unintentional injection into the tissue outside blood vessels (extravascular). A burning sensation where the infusion needle is inserted may be a sign for administration outside the blood vessels. The consequence of administration in this way can be pain and poorly healing skin defects.

The dose-limiting side-effect of ***Levact*** is impaired bone-marrow function, which usually returns to normal after treatment. Suppressed bone marrow function increases the risk of infection.

Very common:
- Low counts of white blood cells (leukocytopenia)
- Decrease in the red pigment of the blood (haemoglobin)
- Low counts of platelets (thrombocytopenia)
- Infections
- Feeling sick (nausea)
- Vomiting
- Mucosal inflammation
- Increased blood level of creatinine
- Increased blood level of urea
- Fever
- Fatigue

Common:
- Bleeding (haemorrhage)
- Disturbed metabolism caused by dying cancer cells releasing their contents into the blood stream
- Reduction in red blood cells which can make the skin pale and cause weakness or breathlessness (anaemia)
- Low counts of neutrophils (neutropenia)
- Hypersensitivity reactions such as allergic inflammation of the skin (dermatitis), nettle rash (urticaria)
- A rise in liver enzymes AST/ALT
- A rise in the enzyme alkaline phosphatase
- A rise in bile pigment
- Low potassium blood levels
- Disturbed function (dysfunction) of the heart
- Disturbed heart rhythms (arrhythmia)
- Low or high blood pressure (hypotension or hypertension)
- Disturbed lung function
- Diarrhoea
- Constipation
- Sore mouth (Stomatitis)
- Loss of appetite
- Hair loss
- Skin changes
- Missed periods (amenorrhoea)
- Pain
- Insomnia
- Chills
- Dehydration

Uncommon:
- Accumulation of fluid in the heart sac (escape of fluid into the pericardial space)

Rare:
- Infection of the blood (sepsis)
- Severe allergic hypersensitivity reactions (anaphylactic reactions)
- Signs similar to anaphylactic reactions (anaphylactoid reactions)
- Drowsiness
- Loss of voice (aphonia)
- Acute circulatory collapse
- Reddening of the skin (erythema)
- Inflammation of the skin (dermatitis)
- Itching (pruritus)
- Skin rash (macular exanthema)
- Excessive sweating (hyperhidrosis)

Very rare:
- Primary atypical inflammation of the lungs (pneumonia)
- Break-down of red blood cells
- Rapid decrease in blood pressure sometimes with skin reactions or rash (anaphylactic shock)
- Disturbed sense of taste
- Altered sensations (paraesthesia)
- Malaise and pain in the limbs (peripheral neuropathy)
- Disease of the nervous system (anticholinergic syndrome)
- Neurological disorders
- Lack of coordination (ataxia)
- Inflammation of the brain (encephalitis)
- Increased heart rate (tachycardia)
- Heart attack, chest pain (myocardial infarct)
- Heart failure
- Inflammation of the veins (phlebitis)
- Formation of tissue in the lungs (fibrosis of the lungs)
- Bleeding inflammation of the gullet (haemorrhagic oesophagitis)
- Bleeding of stomach or gut
- Infertility
- Multiple organ failure

There have been reports of secondary tumours (myelodysplastic syndrome, AML, bronchial carcinoma) following treatment with ***Levact***. No clear relationship with ***Levact*** could be determined.

A small number of cases of severe skin reactions (Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis) have been reported. The relationship with ***Levact*** is unclear.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE *LEVACT*

Keep out of the reach and sight of children.

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

Keep the container in the outer carton to protect the content from light.

Note on shelf-life after opening or preparing the solution

Solutions for infusions prepared according to the directions listed at the end of this leaflet are stable in polyethylene bags at room temperature / 60% relative humidity for 3.5 hours, and in a refrigerator they are stable for 2 days. ***Levact*** contains no preservatives. The solutions should not therefore be used after these lengths of time.

It is the responsibility of the user to maintain aseptic conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What *Levact* contains

The active substance is bendamustine hydrochloride.

One vial of Levact 25 mg Powder for Concentrate for Solution for Infusion contains 25 mg of bendamustine hydrochloride

One vial of Levact 100 mg Powder for Concentrate for Solution for Infusion contains 100 mg of bendamustine hydrochloride

After reconstitution 1 ml of the concentrate contains 2.5 mg bendamustine hydrochloride.

The other ingredient is Mannitol.

What *Levact* looks like and contents of the pack

Brown glass vials with rubber stopper and an aluminium flip-off cap.

The powder appears white and crystalline.

Levact is available in packs containing 5 and 20 injection vials with 25 mg of bendamustine hydrochloride and 5 injection vials with 100 mg of bendamustine hydrochloride.

Marketing Authorisation Holder

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This leaflet was last revised in 08/2010.

This leaflet is also available in large print, Braille or as an audio CD. To request a copy, please call the RNIB Medicine Information Line on:

0044 1733 37 53 70

You will need to give details of the product name and reference number. These are as follows:
Product name: Levact 25 mg & Levact 100 mg
Reference number: PA 731/5/1 & PA 731/5/2

The following information is intended for medical or healthcare professionals only:

As with all similar cytotoxic substances, stricter safety precautions apply as far as nursing staff and doctors are concerned, due to the potentially genome-damaging and cancer-causing effect of the preparation. Avoid inhalation (breathing in) and contact with the skin and mucous membranes when handling ***Levact*** (wear gloves, protective clothing, and possibly a face mask!). If any parts of the body become contaminated, clean them carefully with soap and water, and flush the eyes with 0.9% (isotonic) saline solution. If possible, it is advisable to work on a special safety work bench (laminar flow) with a disposable absorbent sheet that is impermeable to liquids. Contaminated articles are cytostatic waste. Please comply with national guidelines on the disposal of cytostatic material! Pregnant staff must be excluded from working with cytostatics.

The solution ready for use must be prepared by dissolving the contents of an injection vial of ***Levact*** exclusively in water for injections, as follows:

1. Preparation of the concentrate
   - One injection vial of ***Levact*** containing 25 mg of bendamustine hydrochloride is first dissolved in 10 ml by shaking
   - One injection vial of ***Levact*** containing 100 mg of bendamustine hydrochloride is first dissolved in 40 ml by shaking
2. Preparation of the solution for infusion

As soon as a clear solution is obtained (generally after 5 – 10 minutes), the total recommended dose of ***Levact*** is immediately diluted with 0.9% (isotonic) saline solution to obtain a final volume of approximately 500 ml. ***Levact*** must not be diluted with other solutions for infusion or injection. ***Levact*** must not be mixed in an infusion with other substances.