ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Beromun 1 mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1 mg tasonermin*, corresponding to 3.0-6.0 x 10^7 IU (International Units).

*tumor necrosis factor alfa-1a (TNFα-1a) produced by recombinant DNA technology in *E. coli*.

Excipient(s) with known effect:
Each vial contains 20.12 mg (0.87 mmol) sodium. After reconstitution in 0.9 % physiological sodium chloride solution the amount is 37.82 mg (1.64 mmol) sodium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion (powder for infusion).

The powder is white to off-white.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Beromun is indicated in adults. as an adjunct to surgery for subsequent removal of the tumour so as to prevent or delay amputation, or in the palliative situation, for irresectable soft tissue sarcoma of the limbs, used in combination with melphalan via mild hyperthermic isolated limb perfusion (ILP).

4.2 Posology and method of administration

This treatment should be undertaken in specialised centres by surgical teams experienced in the management of limb sarcomas and ILP procedure, with an intensive care unit readily available and with the facilities for continuous monitoring for medicinal product leakage into the systemic circulation.

Posology

Beromun:
Upper limb: 3 mg total dose by ILP
Lower limb: 4 mg total dose by ILP

Melphalan:
Melphalan dose should be calculated according to the litre-volume method of Wieberdink (Wieberdink J, Benckhuysen C, Braat RP, van Slooten EA, Olthius GAA. Dosimetry in isolation perfusion of the limbs by assessments of perfused tissue volume and grading of toxic tissue reactions. *Eur J Cancer Clin Oncol* 1982; 18: 905-910.), to a maximum dose of 150 mg.
13 mg/l perfused upper limb volume
10 mg/l perfused lower limb volume

Paediatric population
The safety and efficacy of Beromun in children under 18 years have not been established. No data are available.

Method of administration

Precautions to be taken before handling or administering the medicinal product
When preparing and handling Beromun solutions, the use of gloves is recommended. If Beromun dry powder or reconstituted solution should come into contact with the skin or mucous membranes, they should be washed thoroughly with water.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

Beromun should be administered by mild hyperthermic ILP. The perfusion circuit (roller pump, oxygenator with integrated reservoir, heat exchanger, connecting tubing) should be prepared prior to surgery and primed with 700 to 800 ml of perfusate, with haematocrit of 0.25 to 0.30.

Perfusion level should be chosen to adequately encompass affected tissue (external iliac, common femoral, femoro-popliteal, popliteal, axillary and brachial being accepted routes) and catheters introduced. External heat loss from the limb should be prevented by application of thermal blankets and limb temperature continuously monitored by thermistor probes inserted into subcutaneous tissue and muscle. Hand and foot, if not affected, should be protected by Esmarch (expulsion) bandages. A tourniquet should be applied to the proximal limb.

After connection of the limb to the isolated circuit, flow rate should be adjusted to 35 to 40 ml/litre limb volume/minute and leakage from limb to systemic circulation checked using a radioactive tracer technique (see section 4.4). Adjustment of flow rate and tourniquet may be required to ensure leakage from perfusion circuit to systemic circulation is stable (systemic level of radioactivity has reached a plateau) and does not exceed 10 %. Beromun should only be administered if leakage is less than 10 %.

Once the temperature in the distal subcutaneous tissue of the limb has reached >38°C, (but not exceeding 39°C), and pH of the perfusate is between 7.2 and 7.35, Beromun should be injected as a bolus into the arterial line of the circuit. After 30 minutes perfusion of Beromun alone, melphalan should be added as a bolus into the reservoir of the circuit, or slowly into the arterial line of the circuit. The temperature should then be increased to >39°C (but not exceeding 40°C) in two different sites of measurement in the tumour area. The duration of the perfusion including melphalan should be 60 minutes. Thus, the duration of the total perfusion should be 90 minutes.

At the end of the perfusion, the perfusate should be collected into the reservoir while washout fluid is added simultaneously to the circuit and circulated at the same flow rate of 35 to 40 ml/litre limb volume/minute. Washout should be continued until the colour of the perfusate is clear pink, transparent (see section 4.4).

Surgical resection of the tumour remnant should be undertaken whenever possible. When necessary a second ILP can be considered 6-8 weeks after the first ILP (see section 4.4).

4.3 Contraindications

Contraindications to Beromun ILP, subdivided by components of the procedure, are:

Contraindications to Beromun:

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Significant cardiovascular disease, e.g. congestive heart failure (New York Heart Association Class II, III or IV), severe angina pectoris, cardiac arrhythmias, myocardial infarction within a 3 months period prior to treatment, venous thrombosis, occlusive peripheral arterial disease, recent pulmonary embolism.

Severe pulmonary dysfunction.

A recent history of, or active peptic ulcer.

Severe ascites.

Significant haematological dysfunction, e.g. leucocytes < 2.5 x 10^9/l, haemoglobin < 9 g/dl, platelets < 60 x 10^9/l, haemorrhagic diathesis or active bleeding disorder.

Significant renal dysfunction, e.g. nephrotic syndrome, serum creatinine > 150 µmol/l, or creatinine clearance of < 50 ml/min.

Significant hepatic dysfunction, e.g. > 2 x upper limits of normal levels of aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase; or bilirubin levels > 1.25 x upper limits of normal.

Hypercalcaemia > 12 mg/dl (2.99 mmol/l).

Patients with contraindications to the use of vasopressor substances.

Patients with contraindications to the use of anticoagulants.

Simultaneous treatment with cardiotoxic substances (e.g. anthracyclines).

Pregnancy and lactation (see section 4.6).

Contraindications to melphalan:

Please refer to the Summary of Product Characteristics for melphalan.

Contraindications to the ILP procedure:

Severe ascites.

Severe lymphoedema of the limb.

Patients with contraindications to the use of vasopressor agents.

Patients with contraindications to the use of anticoagulants.

Patients with contraindications to radioactive tracer monitoring.

Patients with contraindications to limb hyperthermia.

Patients in whom the blood supply to the extremity distal to the tumour is suspected to be highly dependent on tumour associated blood vessels. This can be clarified by an arteriogram.

Pregnancy and lactation.

4.4 Special warnings and precautions for use

ILP should be undertaken in specialised centres by surgical teams experienced in the management of limb sarcomas and ILP procedure, with an intensive care unit readily available and with the facilities for continuous monitoring for medicinal product leakage into the systemic circulation. Beromun must not be administered systemically.

Please refer to the Summary of Product Characteristics of melphalan prior to commencing an ILP procedure.

Induction of general anaesthesia and subsequent mechanical ventilation should be applied according to standard methods. It is important to maintain a constant level of anaesthesia in order to prevent large fluctuations in systemic blood pressure, which can affect leakage between systemic circulation and perfusion circuit.

During the ILP, central venous pressure and arterial pressure monitoring is strongly recommended. Furthermore, blood pressure, urine output and electrocardiographic monitoring should be routinely undertaken in the first 24 to 48 hours post-ILP, or longer if indicated. A Swan-Ganz catheter may be considered for monitoring pulmonary artery pressure and wedge pressure during the ILP and in the post-operative period.

Prophylaxis and treatment of fever, chills and other influenza-like symptoms associated with Beromun administration can be achieved by pre-ILP administration of paracetamol (oral or by suppository) or an alternative analgesic/antipyretic.

For the prophylaxis of shock, patients should always be maximally hydrated prior to, during and after the perfusion procedure. This is to ensure optimal haemodynamic conditions and ensure a high urinary output, especially after the perfusion, to allow for rapid clearance of any residual tasonermin. Additional resuscitation fluids (crystalloid and colloid solutions) should be available for volume expansion in case of a significant fall in blood pressure. Colloids and hydroxyethyl starch fluids are preferred, as they are less likely to leak out of the vascular system. In addition, as the clinical situation dictates, a vasopressor agent, e.g. dopamine, can be considered for administration during the ILP procedure, as well as in the post-operative period. In the event of severe shock before the end of the ILP, the limb perfusion should be discontinued and appropriate therapy administered.

In order to minimise the risk of leakage of the perfusate into the systemic circulation, the perfusion flow rate should not exceed 40 ml/litre limb volume/minute. Potential leakage should be measured by radioactively labelled albumin or erythrocytes injected into the perfusion circuit, with appropriate measures for continuous monitoring of radioactivity leakage into the systemic circulation. Adjustment of flow rate and tourniquet may be required to ensure leakage is stable (systemic level of radioactivity has reached a plateau) and does not exceed 10%. The perfusion should be terminated if the cumulative leakage into the systemic circulation is > 10%. In such cases, a standard wash-out procedure should follow, using at least 2 litres of dextran 70 intravenous infusion or similar fluid.

Following the ILP, a standard wash-out procedure should always be employed, using dextran 70 intravenous infusion or similar fluid. After lower limb perfusion, 3 to 6 litres should be used, and after upper limb perfusion, 1 to 2 litres. Popliteal and brachial perfusions may not need more than 1 litre. Wash-out should continue until a clear (pink, transparent) venous outflow is obtained.

Measures should be taken to ensure that the periods of interrupted oxygen supply to the limb are as brief as possible (20 minutes maximum).

Surgical resection of the tumour remnant should be undertaken whenever possible. When necessary a second ILP can be considered 6-8 weeks after the first ILP.

If a second ILP is indicated, physicians should take into account the leakage rate of the previous ILP.

The maximum tolerated dose (MTD) of tasonermin for ILP is 4 mg, which is 10 times the systemic MTD. Therefore, whenever there is significant systemic leakage of tasonermin, serious undesirable effects are to be expected. Doses of up to 6 mg of other TNFα preparations have been administered via ILP, but this dose was found to be unacceptable in terms of loco-regional toxicity.

Combinations with cardiotoxic substances (e.g. anthracyclines) should be avoided because it is possible that tasonermin could enhance cardiotoxicity, as has been observed in preclinical 13-week toxicological investigations. Concurrent administration of agents likely to cause significant hypotension is not recommended (see section 4.5).

A number of therapeutic measures are routinely used during the ILP and in the immediate post-operative period. These include standard anaesthetic agents, analgesics, antipyretics, intravenous fluids, anticoagulants and vasopressor agents. There is no evidence that any of these agents counteracts the pharmacodynamic effects of tasonermin. No significant interactions have so far been noted, but caution should be exercised (see section 4.5).

If signs of systemic toxicity appear for example fever, cardiac arrhythmias, shock/hypotension, adult respiratory distress syndrome (ARDS), general supportive measures should be employed and the patient immediately transferred to an Intensive Care Unit for monitoring. Volume expanders and vasopressors are recommended. Artificial respiratory support may be required if ARDS develops. Renal and hepatic function should be closely monitored. Haematological disorders, in particular leukopaenia, thrombocytopaenia and clotting dysfunction, might be expected.

Cases of compartment syndrome characterised by pain, swelling and neurological symptoms, as well as muscle damage affecting the perfused limb have been observed in isolated patients treated with Beromun. Therefore patients should be monitored during the first three days after the ILP. In case the clinical diagnosis of compartment syndrome is made the following treatment should be considered:

- Fasciotomy of all muscle compartments of the limb affected,
- Forced diuresis and alkalinisation of the urine, if a muscle damage occurs with increased myoglobin levels in plasma and urine.

The reconstituted medicinal product contains up to 151.27 mg (6.58 mmol) sodium per recommended dose. To be taken into consideration by patients on a controlled sodium diet.

The container of this medicinal product contains latex rubber. May cause severe allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Beromun has been co-administered with interferon-gamma in the ILP setting but no added value has been demonstrated. The addition of interferon-gamma to the tasonermin perfusate seems not to be associated with significant increases in endogenous production of tasonermin or other inflammatory cytokines as shown in patients with severe trauma. Clinical data however indicate that the overall incidence of adverse events is increased if patients are simultaneously exposed to tasonermin and interferon-gamma.

Combinations with cardiotoxic substances (e.g. anthracyclines) should be avoided because it is possible that tasonermin could enhance cardiotoxicity, as has been observed in preclinical 13-week toxicological investigations (see section 4.4).

A number of therapeutic measures are routinely used during the ILP and in the immediate post-operative period. These include standard anaesthetic agents, analgesics, antipyretics, intravenous fluids, anticoagulants and vasopressor agents. There is no evidence that any of these agents counteracts the pharmacodynamic effects of tasonermin. No significant interactions have so far been noted, but caution should be exercised (see section 4.4).

Concurrent administration of agents likely to cause significant hypotension is not recommended (see section 4.4).

The Summary of Product Characteristics for melphalan should be consulted for information on the interactions of melphalan.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of tasonermin in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryonal development and postnatal development (see section 5.3). The potential risk for humans is unknown. Beromun is contraindicated in pregnancy (see section 4.3).

Breastfeeding
It is not known whether tasonermin is excreted in human milk. Because of the unknown risk to the infant, breast-feeding is contraindicated within 7 days of ILP (see section 4.3).

Fertility
No data on the possible effect of this medicinal product on male and female fertility are available.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

Undesirable effects may be related to Beromun, to melphalan, or to the ILP procedure and associated measures, or to a combination of these factors.

The most frequent adverse reactions reported in clinical trials were fever, nausea, vomiting, fatigue, arrhythmia, chills, pain, wound infection and skin reaction. Adverse reactions are either local, affecting the limb treated with ILP, or systemic. Systemic adverse reactions include mild constitutional reactions and toxic effects on different organ systems.

Tabulated summary of adverse reactions

Adverse reactions have been ranked under headings of frequency using the following convention: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000).

Infections and infestations		
	Common:	Infection, wound infection
	Uncommon:	Sepsis
Blood and lymphatic system disorders		
	Common:	Leukopenia, thrombocytopenia
Immune system disorders		
	Common:	Hypersensitivity reaction
Nervous system disorders		
	Common:	Nerve injury, peripheral neurotoxicity, altered state of consciouness, headache
Cardiac disorders		
	Very common:	Arrhythmia
	Common:	Cardiac failure
Vascular disorders		
	Common:	Venous thrombosis, arterial thrombosis, shock, hypotension

	Uncommon:	Peripheral arterial occlusive disease

Respiratory, thoracic and mediastinal disorders

Common:	Adult respiratory distress syndrome
Uncommon:	Pulmonary oedema

Gastrointestinal disorders

Very common:	Nausea, vomiting
Common:	Diarrhoea, constipation
Uncommon:	Abdominal pain upper, gastritis erosive

Hepatobiliary disorders

Very common:	Hepatotoxicity

Skin and subcutaneous tissue disorders

Very common:	Skin reaction
Common:	Skin necrosis, oedema peripheral
Uncommon:	Onychomadesis (loss of nails)

Musculoskeletal and connective tissue disorders

Common:	Compartment syndrome, myalgia

Renal and urinary disorders

Common:	Proteinuria
Uncommon:	Renal failure acute

General disorders and administration site conditions

Very common:	Fever, chills, pain, fatigue
Common:	Night sweats

Investigations

Uncommon:	Blood creatinine increased

Surgical and medical procedures

Common:	Extremity necrosis, severe enough to warrant amputation

Description of selected adverse reactions

Extremity necrosis and compartment syndrome might be severe enough to warrant amputation.

Late onset of peripheral arterial occlusive disease (PAOD) of the lower limbs has been reported in patients several years after ILP, predominantly in patients presenting with established cardiovascular risk factors, or who had undergone additional irradiation therapy of the concerned limb.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Should accidental overdose occur, ILP should be terminated immediately and the limb washed out using at least 2 litres of dextran 70 intravenous infusion or similar fluid (see also section 4.4).

If signs of systemic toxicity appear, for example fever, cardiac arrhythmias, shock/hypotension, adult respiratory distress syndrome (ARDS), general supportive measures should be employed and the

patient immediately transferred to an Intensive Care Unit for monitoring. Volume expanders and vasopressors are recommended. Artificial respiratory support may be required if ARDS develops. Renal and hepatic function should be closely monitored. Haematological disorders, in particular leukopaenia, thrombocytopaenia and clotting dysfunction, might be expected.

There is no specific antidote for tasonermin currently available. Treatment with anti-TNFα antibodies is not recommended.

Please refer to the Summary of Product Characteristics for melphalan for information on overdose of melphalan.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other immunostimulants, ATC code: L03AX11

Mechanism of action
In vivo antitumour activity is probably based on direct and indirect effects:

Direct inhibition of tumour cell proliferation: Tasonermin is cytotoxic or cytostatic *in vitro* for a variety of tumour cell lines of different histogenesis.

Direct effects on tumour vasculature: Tasonermin affects the morphology and reduces proliferation of endothelial cells and modifies expression of specific cell surface and secretory proteins (including adhesion molecules and proteins modulating coagulation, interleukins and haematopoietic growth factors). These changes in turn lead to a procoagulant state, resulting in microvascular thrombosis. Further, adherence and extravasation of leukocytes is increased, leading to infiltration of the tumour by lymphocytes, monocytes, and granulocytes. The reason for the differential sensitivity of the tumour vasculature (high) versus normal vasculature (low) are currently unknown.

Indirect and direct immunomodulation: Tasonermin has profound effects on cellular components of the immune system. Proliferation of activated B- and T-lymphocytes, development of cytotoxic T-cells and immunoglobulin-secreting cells is enhanced, monocytes/macrophages are activated for killing of tumour cells, granulocytes are activated to display enhanced phagocytic activity, respiratory burst and degranulation, and adherence to endothelium. Further, in addition to its direct effects, tasonermin modulates immune responses by inducing production of cytokines as well as low molecular weight mediators (prostaglandins, platelet activating factor). Several lines of evidence suggest that these immunomodulatory activities are of relevance for the antitumour effects; e.g. the antitumour activities of tasonermin are much less pronounced in immunodeficient animals. Further, animals that reject experimental tumours following tasonermin treatment may develop specific immunity for this tumour cell type.

Pharmacodynamic effects
Tasonermin has been shown to be active in the classic assay for tumour necrosis factor, producing haemorrhagic necrosis of tumour nodules in murine syngeneic and human xenogeneic tumour systems after local or systemic injection. The systemic application of tasonermin is limited by its toxic effects, the effective dose predicted from preclinical studies being substantially higher than the observed human maximum tolerated dose.

Clinical efficacy
The loco-regional application of Beromun, along with melphalan, has been shown to be highly effective for local control of irresectable soft tissue sarcomas of the limbs. However, the treatment is specifically a loco-regional treatment and is not expected to influence survival. A matched-pair survival analysis of patients treated by Beromun and melphalan ILP as compared to a historical control failed to demonstrate any survival difference ($p=0.5$).

5.2 Pharmacokinetic properties

Systemic pharmacokinetics
The systemic pharmacokinetic information on tasonermin is sparse. A dose-dependency has been observed as indicated by a decrease in clearance and an increase in half-life at increasing doses. The terminal half-life at the maximum tolerated intravenous dose (150 μg/m^2) was 15-30 min.

Pharmacokinetics in ILP
ILP allows the administration of high and fairly stable concentrations of tasonermin to the limb. Data obtained from 51 ILP patients demonstrated maximum concentrations of tasonermin in the perfusion circuit are reached 30 min after the onset of ILP and range between 3000 and 4000 ng/ml. Under conditions of less than 2% systemic leakage (observed in 38 of 51 patients), maximum systemic circulation concentrations of tasonermin were reached 5 min after the start of ILP and are approximately 200 times less than in the perfusion circuit. Under conditions of greater than 2 % systemic leakage (observed in 13 of 51 patients) maximum systemic concentrations of tasonermin were still at least ten times lower than in the perfusion circuit.

5.3 Preclinical safety data

The toxicological profile of tasonermin has been investigated in preclinical studies using mice, rats, rabbits, dogs and monkeys. Haematological and circulatory changes, decreased well-being and weight gain as well as alterations in the function of liver and kidneys were the main adverse effects observed on repeated tasonermin administration. The haematological changes included anaemia, increased haematocrit and increased or decreased leukocytes and platelets depending upon species and treatment duration. The circulatory changes included decreased blood pressure and, in some studies, increased heart rate and decreased contractility. The synthesis capacity of the liver was lowered as indicated by increased liver enzymes. Altered renal function comprised increased water and sodium excretion as well as increased urea and creatinine. No NOTEL (No Observed Toxic Effect Level) could be established in the preclinical studies with the exception of a 7-day administration of 0.1 μg/kg in monkeys. The changes observed at the low dose of the 13-week studies can be classified as minimal and fully reversible.

Tasonermin does not cross the intact blood-brain barrier to a significant extent in mice. In the Rhesus monkey, whole body radiography following administration of radiolabelled tasonermin indicated no specific distribution pattern. Tasonermin did not cross the placenta or pass into necrotic tumour. In the Rhesus monkey, pharmacokinetic studies following intravenous injection of tasonermin indicated a non-specific, non-saturable excretion via glomerular filtration in the kidney. A second specific and saturable elimination mechanism involving tasonermin receptors seems likely.

No evidence has been found of any mutagenic effect, neither *in vivo* nor *in vitro*. No reproduction toxicity or carcinogenicity studies were performed due to testing being inappropriate as the intended clinical use of Beromun is in ILP for soft tissue sarcoma treatment.

To cover the intended clinical use of Beromun, ILP experiments were performed in hind legs of healthy rats using different doses in the same tasonermin concentration as in the clinical situation in the human. Except for slight aggravation of ischaemic effects in higher doses, standard histological examinations of the skin, muscle, bone, nerves and vessels revealed no difference in findings between tasonermin-treated and control animals. No late detrimental effects of tasonermin were seen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen phosphate dihydrate
Disodium phosphate dodecahydrate

Human serum albumin.

6.2 Incompatibilities

At ILP, no incompatibilities with other constituents of the perfusate, with hyperthermia or with the membrane oxygenator and the silicone tubing are known. Perfusate samples of several ILPs showed plateau levels of tasonermin (as measured by ELISA) up to 100 minutes after start of perfusion, with no decay attributable to degradation.

Please refer to the Summary of Product Characteristics for melphalan for details regarding incompatabilities with melphalan.

6.3 Shelf life

3 years

Reconstituted solution
Chemical and physical in-use stability has been demonstrated for up to 48 hours at 25°C.

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

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder vial
Type I glass vial with chlorobutyl rubber stopper and sealed with aluminium flip-off cap.

Each pack contains 4 vials.

6.6 Special precautions for disposal and other handling

Instructions for reconstitution
The content of one vial of Beromun powder should be reconstituted with 5.3 ml sterile 0.9% sodium chloride solution for injection. A homogeneous solution will be obtained by shaking gently. The solution of the reconstituted product should be inspected visually for particulate matter prior to administration. The solution has a clear to light yellow colour.
The formulation does not contain a preservative and is for single use only. Once opened, the content of a vial should normally be used immediately (see section 6.3). For instructions on administration, see section 4.2.

Disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BELPHARMA s.a.
2, Rue Albert 1er
L-1117 Luxembourg
Grand Duchy of Luxembourg

8. MARKETING AUTHORISATION NUMBER

EU/1/99/097/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 April 1999
Date of latest renewal: 13 April 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER (S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER (S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

AGC Biologics
Vandtaarnsvej 83B
DK-2860 Soeborg
Copenhagen
Denmark

Name and address of the manufacturer responsible for batch release

Eumedica NV
Chemin de Nauwelette 1
B-7170 Manage
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Beromun 1 mg powder for solution for infusion
Tasonermin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 1 mg tasonermin, corresponding to 3.0-6.0 x 10^7 IU.

3. LIST OF EXCIPIENTS

Sodium dihydrogen phosphate dihydrate, disodium phosphate dodecahydrate, human serum albumin

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion

4 vials of powder for solution for infusion

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For administration by ILP
Intraarterial use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

For single use only. Upon reconstitution the product should be used immediately.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BELPHARMA s.a.
2, Rue Albert 1er
L-1117 Luxembourg
Grand Duchy of Luxembourg

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/097/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number} [product code]
SN: {number} [serial number]
NN: {number} [national reimbursement number or other national number identifying the medicinal product]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR BEROMUN

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Beromun 1 mg powder for infusion
Tasonermin
Intraarterial use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mg

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Beromun 1 mg powder for solution for infusion
Tasonermin

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.

What is in this leaflet:

1. What Beromun is and what it is used for

Beromun contains the active substance tasonermin (tumor necrosis factor alfa-1a), produced by recombinant DNA technology. It belongs to a class of medicines known as immunostimulants, which help your body's immune system fight cancer cells.

Beromun is used, together with melphalan containing medicine, for the treatment of soft tissue sarcoma of the arms and legs. By reducing the size of the tumour, the treatment is intended to facilitate the removal of the tumor by surgery or to prevent severe damage to the surrounding healthy tissue and thus to delay or prevent the need for arm or leg amputation.

2. What you need to know before you use Beromun

Do not use Beromun
- if you are allergic to tasonermin or any of the other ingredients of this medicine (listed in section 6).
- if you have significant heart problems
- if you have severe lung disease
- if you have or have recently had a stomach ulcer
- if you have too low numbers of blood cells or bleeding problems
- if you have moderate to severe liver or kidney disease
- if you cannot use vasopressors (used to increase low blood pressure), anticoagulants (used to prevent blood clotting) or radioactive tracers
- if you are also using medicines with heart toxicity
- if you have raised levels of calcium in your blood
- if you have certain infections which do not respond to antibiotics
- if you have severe swelling of the affected arm or leg due to local fluid build-up, or severe fluid build-up in the abdomen
- if you are pregnant or planning to become pregnant.
- if you are breast-feeding, you must stop for at least seven days after receiving Beromun

Warnings and precautions
Beromun will be administered by a doctor who is experienced and skilled in isolated limb perfusion (ILP). This technique ensures that Beromun is kept within the affected arm or leg. It is important that

it does not reach other parts of your body, because this so-called *systemic leakage* could cause serious side effects on the main organs of the body.

During the IPL and the seven to ten day period afterwards you will need to stay in hospital, your doctor will carefully monitor your blood pressure, circulation and any side effects. You may have to stay in an intensive care unit (ICU) directly after the ILP for a short time.

A condition called “compartment syndrome” may develop within the first three days after Beromun administration. Symptoms of muscle damage at the perfused limb include pain, swelling, as well as neurological symptoms (e. g. paraesthesia, paralysis), all of which should be reported immediately to the attending doctor.

Other medicines and Beromun
Tell your doctor if you are using, have recently used or might use any other medicines. In particular, you should tell your doctor if you are using medicines to lower blood pressure (to treat hypertension).

For ILP, you will also receive other medicines to control pain, fever, blood pressure and blood clotting, as well as general anaesthesia.

Pregnancy and breast-feeding
You must not use Beromun if you are pregnant.
You must not breast-feed for at least seven days after treatment with Beromun.

Driving and using machines
Not relevant

Beromun contains sodium
This medicine contains 151.27 mg (6.58mmol) sodium in each recommended dose. This is equivalent to 7.6% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Beromun

Beromun will be administered by isolated limb perfusion (ILP), together with the anti-tumour agent melphalan. This will occur whilst you are unconscious, under the influence of a general anaesthetic.

The blood flow to and from your affected limb will be stopped using a tourniquet. Blood, supplied with oxygen by a heart and lung machine, is pumped into your affected limb via a catheter in the main artery, while it is drained (pumped out) from the main vein. Beromun and then melphalan are injected into this circuit, over a total of 90 minutes the affected limb will be exposed to Beromun.

The recommended dose of Beromun depends on the affected limb, usually 3 mg for the arm and 4 mg for the leg. Beromun powder has to be dissolved before use. The resulting solution will be administered into an artery in your affected arm or leg by ILP for an initial period of 30 minutes. After that, melphalan will be added and the ILP continued for another 60 minutes.
Finally, your limb will be washed out to remove the rest of Beromun and melphalan.

ILP allows that tumour cells in your limb can be exposed to a very high dose of Beromun and melphalan, enhancing their anti-tumour effect, but without reaching the rest of the body, where they could cause serious side effects.

You will usually not receive a second ILP with Beromun. If you do, this will not be until at least six weeks after your first ILP.

If you use more Beromun than you should
As Beromun is always administered by experienced and qualified hospital doctors, accidental overdose is extremely unlikely. However, should this occur, your doctor will immediately wash out your affected limb to remove Beromun, and the ILP will be stopped. If there is any risk of serious side effects, your doctor will immediately transfer you to an intensive care unit to closely monitor you and start adequate treatment.

If there is significant systemic leakage of Beromun
If more than 10% of your Beromun dose reaches the main part of your body, your doctor will take similar measures as in the case of overdose.

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

4. Possible side effects

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

Side effects may be caused by Beromun, melphalan, the ILP technique or a combination of these factors. Some of the side effects can be serious, particularly if Beromun reaches other parts of your body (systemic leakage). In approximately 2% of cases, Beromun may cause tissue damage in your affected arm or leg which is severe enough to require amputation. If there is any risk of serious side effects, your doctor will immediately transfer you to an intensive care unit to closely monitor you and start adequate treatment.

The following side effects were observed during treatment with this medicine (grouped by how likely they are to happen).

<u>Very common (may affect more than 1 in 10 people)</u>
- disturbances in your heart beat (arrhythmia)
- feeling sick, vomiting
- liver damage
- blistering of the skin
- fever (usually mild to moderate), chills
- pain in the affected arm or leg
- tiredness (fatigue)

<u>Common (may affect up to 1 in 10 people)</u>
- infections
- local wound infections
- reductions in numbers of certain white blood cells and platelets
- hypersensitivity (allergic) reactions
- nerve damage
- decreased consciouness
- headache
- heart problems which can cause shortness of breath or ankle swelling
- blood clot formation in the artery or vein of the affected arm or leg (thrombosis)
- low blood pressure, shock
- severe breathing problems
- constipation, diarrhoea
- skin necrosis (death of skin cells) in the affected arm or leg
- swelling of the ankles, feet or fingers caused by fluid build up in the affected arm or leg
- “compartment syndrome”, a medical condition characterised by pain, swelling and neurological symptoms, as well as muscle damage in the affected arm or leg
- muscle pain
- protein in urine
- night sweats

- tissue necrosis (death of tissue cells) in the affected arm or leg, which is severe enough to require amputation

Uncommon (may affect up to 1 in 100 people)
- blood poisoning (sepsis)
- fluid in the lungs
- stomach ache
- inflammation of the gastric mucosa (gastritis)
- temporary loss of finger or toe nails of the affected arm or leg
- kidney failure
- blood tests showing changes in the way the kidneys are working
- narrowing or closing of limb vessels carrying blood from the heart

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 the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Beromun

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 vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C). Upon reconstitution the product should be used immediately.

6. Contents of the pack and other information

What Beromun contains
- The active substance is tasonermin. Each vial contains 1 mg tasonermin. The content of one vial of Beromun powder should be reconstituted with 5.3 ml sterile 0.9% sodium chloride solution for injection
- The other ingredients (excipient(s)) are sodium dihydrogen phosphate dihydrate, disodium phosphate dodecahydrate and human serum albumin.

What Beromun looks like and contents of the pack
Beromun is a white to off-white powder for solution for infusion (powder for infusion) supplied in a glass vial with rubber stopper and sealed with aluminium flip-off cap.
Each pack contains 4 vials of powder.

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Grand Duchy of Luxembourg

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

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This leaflet was last revised in

Other sources of information

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

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.