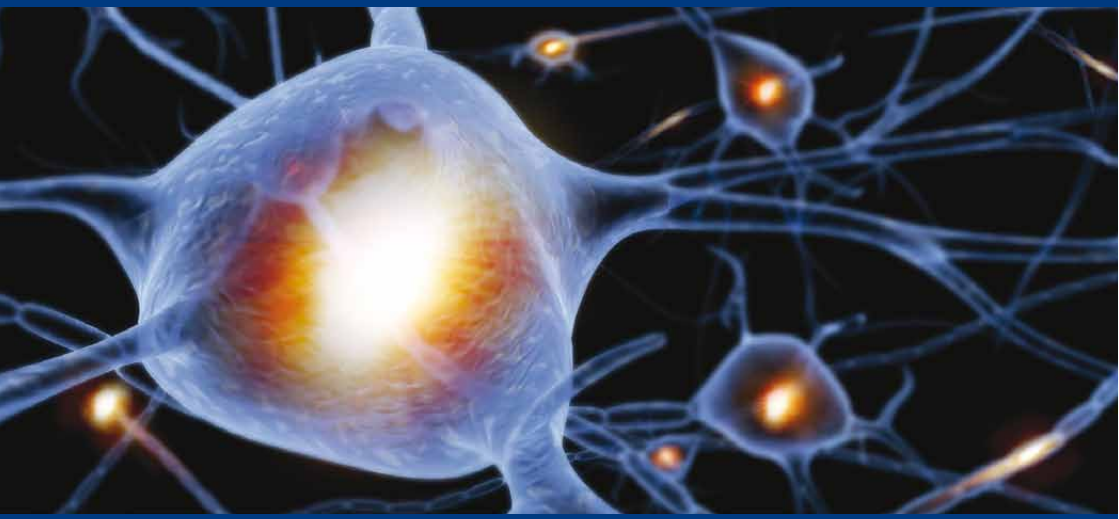
Peripheral Neuropathy

Causes & Treatment

Information
for patients and
their relatives

English



MYELOMA
EURONET

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Peripheral Neuropathy (PNP)
Causes & Treatment

Information for
patients and their relatives

Contents

Foreword

Dear reader,

this brochure aims to help you to understand peripheral neuropathy as a complication of multiple myeloma or as a consequence of its treatment. Peripheral neuropathy is a nerve disorder which is primarily manifested in the hands and feet. In order to prevent lasting consequential damages, this condition must be recognised at an early stage. You have the task of observing your body attentively, so that the first signs of neuropathy can be medically treated and / or managed immediately.

We would like to thank Prof. Monika Engelhardt from the university hospital in Freiburg, the support group Leukämiehilfe Rhein-Main e.V. and Guy Sherwood from IWMF for their expert advice and support during the creation of this brochure.

Kind regards,

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The present text is a translation of the german brochure. Please note that some passages refer only to the german situation and are not necessarily applicable to the english-speaking world.

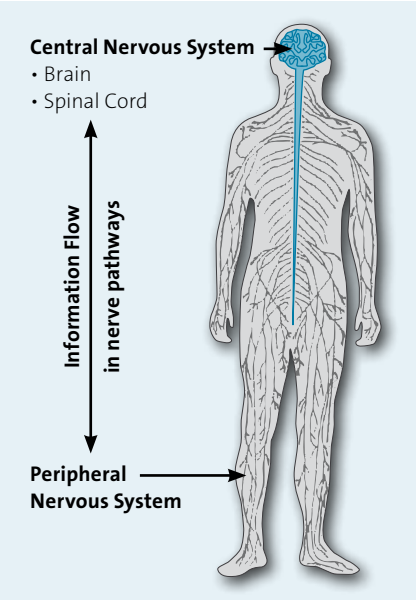
What is peripheral neuropathy?

Do you recognise these symptoms? Do your legs burn or tingle? Do you have the feeling that you have a stone in your shoe? You may have stabbing pains in your hands and / or feet?

In very general terms, neuropathies are conditions of the nerve cells.

In the case of *peripheral neuropathy* (gr. **περιφερειακός** – away from the centre, o **νεύρον** – the nerve and **η πάθεια**, derived from the verb **παθαίνω** – be ill, suffer) the nerve fibres of the so-called peripheral nervous system are affected. We talk about *poly*neuropathy (gr. **πολύ** – much), when many of these peripheral nerves have been affected.

The human nervous system is divided into two parts: the central nervous system which includes the brain and the spinal cord. The remaining nerves which come from the brain and the spinal cord and are, for their part, connected to the nerve tracts in the whole body, form the peripheral nervous system.



The central nervous system processes all the information that arrives as electrical impulses via the nerve cells of the peripheral nervous system. It issues commands which are fed back to muscles, sensory organs and internal organs and thus precisely control the processes in the body.

Fig 1: The human nervous system

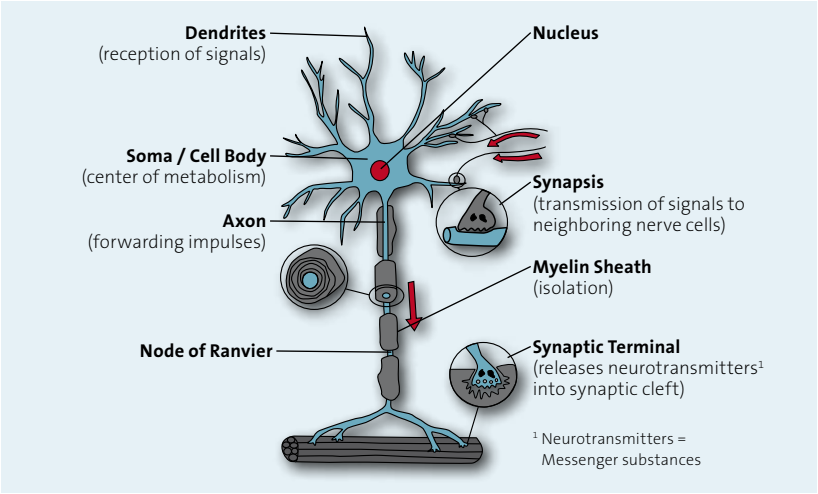


Fig 2: Structure of a nerve cell

As the peripheral nervous system plays an important role in controlling the movements of the body, peripheral neuropathy leads to restrictions of movement and disrupts the body's sensitivity. Peripheral neuropathy can also damage the autonomic nervous system.

Nervous System				
Peripheral Nervous System			Central Nervous System	
Autonomic (vegetative) Nervous System		Somatic Nervous System	Brain	Spinal Cord
Para-sympathetic Nervous System (salivation)	Sympathetic Nervous System (mobilization)			

Tab. 1: Arrangement of the nervous system

What are the causes of peripheral neuropathy?

Peripheral neuropathy is observed in several illnesses. It occurs, for example, in patients who are suffering from diabetes or a vitamin deficiency. Alcoholics are also familiar with it. It is, however, also possible to have a genetic tendency towards peripheral neuropathy. Nerve cells, particularly in the extremities, begin to die and, therefore, cannot perform their tasks anymore.

This brochure deals with peripheral neuropathy that, apart from in multiple myeloma, can also be triggered in other cancers, as a result of the treatment of the illness or the illness itself.

Peripheral neuropathy in multiple myeloma

Multiple myeloma is a form of cancer in which the plasma cells in the bone marrow are affected. Plasma cells develop from the B cells after a maturing process. They produce antibodies in a healthy body and are, therefore, important for resistance.

Multiple myeloma emerges due to the malignant alteration of these cells. Myeloma cells (abnormal / malignant plasma cells) produce non-functional antibodies, so-called paraprotein. The body can no longer sufficiently protect itself from infection. In approximately 99 percent of patients, the paraproteins can be detected in urine and blood through various methods of gel electrophoresis.

In myeloma patients, peripheral neuropathy can occur as a complication to the myeloma itself. The antibodies that emerged as a result of multiple myeloma are considered to be the causes for this. Peripheral neuropathy can also occur in connection with cryoglobulinemia (a special kind of vascular inflammation) and POEMS syndrome.

The medical treatment of myeloma usually only begins when the typical symptoms can be identified. These are, for example:

- Presence of anaemia
- Renal damage (renal failure)
- Local bone disintegration (osteolysis)

Then standard chemotherapy, steroids (prednisone or dexamethasone), new substances, such as bortezomib, thalidomide or lenalidomide are used and an autologous stem cell transplant is performed.

Peripheral neuropathy as a consequence of treatment

It is not uncommon for chemotherapeutic agents, such as vincristine, or new substances, such as bortezomib or thalidomide, which are used to combat multiple myeloma, to also cause peripheral neuropathy. Some patients frequently remain silent out of fear that their treatment would be stopped if they mention the side effects. This is a mistake with serious consequences. Peripheral neuropathy is a complication that should be taken very seriously. It damages the body and can have a lasting effect and painfully restricts the quality of life of those affected. However, if peripheral neuropathy is diagnosed and treated at an early stage, it frequently recedes.

For you as the patient, it is, therefore, of the utmost importance that you are given comprehensive information and thus can observe your body attentively.

BE AWARE! If you suspect that there are indications of the beginnings of peripheral neuropathy, do not hesitate to inform the doctor of these symptoms. There are often possibilities of altering the treatment in such a way that it still combats your myeloma and spares your nerve cells at the same time.

What are the symptoms of peripheral neuropathy?

Peripheral neuropathy is frequently first noticed in the feet. Discomfort, such as tingling, prickling („pins and needles"), burning or sensations of numbness and furriness, occurs here. Many patients have the feeling of having a foreign object in their shoe. These symptoms can all also be accompanied by stabbing pains. Patients describe these sensory complaints as „stocking-shaped". Later, the same symptoms occur in the hands in a „glove shape". The extent of the pain is different from patient to patient and moves on a scale from „slight" to „very severe". The sensitivity to pain itself is increased, so that even slight contact can trigger pain.

In contrast to this, a pronounced, completely unexpected, **in**sensitivity to pain is observed in other patients. They suddenly do not feel temperature stimuli, such as heat or cold, injuries and burns, anymore. Ulcers will often develop from harmless wounds. For such patients, a weakening of the reflexes can also be detected at a relatively early point.

The following figure shows the possible deviations from normality of sensory feeling in the event of peripheral neuropathy. These can occur individually or collectively.

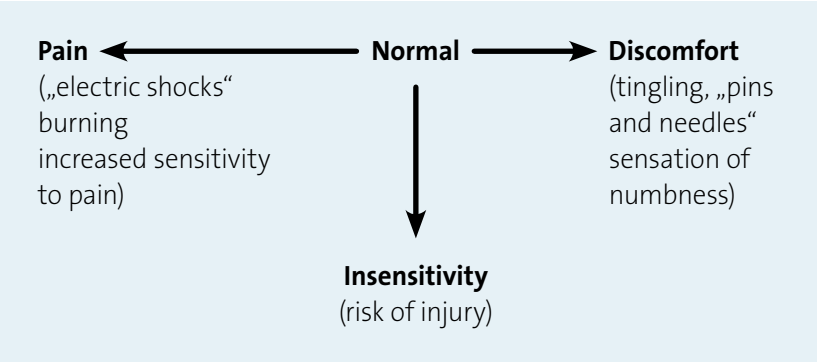


Fig 3: Noticeable features of peripheral neuropathy

In addition to the sensory disorders, impairments in movements also occur. Fine motor skills should be mentioned here, in particular. As sensory and motor nerves are equally affected, patients, for example, experience difficulties with writing, tying their shoelaces or buttoning up their clothes. Reaching for small objects becomes difficult: they fall out of the patient's hand without apparent reason. Standing up from a seated position is only managed with difficulty. In rare instances, it may occur that patients stumble when walking because they do not notice the bumps in the ground anymore. They are no longer able to control and balance their movements at will. Muscle twitches and muscle cramps, involuntary spontaneous movements, paralyses and a reduction of muscle mass (weakness, powerlessness) are also visible side effects of peripheral neuropathy, which occur less frequently.

Symptoms which originate from damage to the nerve cells of the autonomic nervous system are, for example: too little perspiration (warm, dry skin) or increased perspiration, problems with urine retention, diarrhea, constipation. Hearing disorders (reduced hearing, ringing in the ears) can also occur. As reduced muscle tension leads to a drop in blood pressure, such patients also suffer from feelings of dizziness. A racing heart or skipped beats are also common. Hair growth can be impaired. For male patients, impotence may occur.

Sensory symptoms	Motor symptoms	Autonomic symptoms
Discomfort (tingling, burning, sensations of numbness, „pins and needles“) in the hands and feet Increased sensitivity to pain Hypersensitivity of the skin Stabbing pains in the hands and feet Insensitivity to pain and temperature	Coordination disorders Impairments of fine motor skills Muscle weakness Muscle cramps Uncertainty when walking/stumbling Involuntary movements Paralyses Altered gait	Warm, dry skin or heavy perspiration Diarrhea/ constipation Cardiac arrhythmia Blood pressure disorders/dizziness Hearing disorders Incontinence Impotence

Tab. 2: Most frequent symptoms of peripheral neuropathy

What levels of severity are there in peripheral neuropathy?

Most international scales for assessing the level of severity of neuropathy (WHO criteria: *World Health Organisation* criteria / NCI-CTC – scale: *National Cancer Institute – Common Toxicity Criteria*) extend from level 0 (mild) to level 4 (life-threatening or extent of a physical/mental disability). Level 2 is considered to disrupt function, levels 3 and 4 involve impairment of everyday life. The handicap in everyday life perceived subjectively by the patient may, however, begin with a level 1 neuropathy.

For this reason, it is important that you discuss any discomfort IMMEDIATELY with your doctor.

How is peripheral neuropathy diagnosed?

Peripheral neuropathy is diagnosed on the basis of questionnaires (see appendix), and by means of sensitivity and muscle tests and laboratory investigations. In rare cases, electro-diagnostic tests or a nerve biopsy are used.

The questionnaires that the patient completes attempt to find out the extent to which the patient is impaired in his everyday life. Sensitivity and muscle tests are used to investigate surface and depth sensitivity, muscle reflexes and muscle power.

Surface sensitivity
The tests are carried out on both feet, the lower legs and thighs, the lower and upper arms and on the shoulders. The following steps are tested:

- sense of touch (test using cotton applicators)
- sense of pain (test using a pointed object)
- sense of cold/heat (test using metal/plastic)

Depth sensitivity
This is tested through perception of vibrations and sense of position.

- Perception of vibrations (128 Hz tuning fork on the metacarpophalangeal joint and the inner ankle of the shinbone)
- Mobility of the fingers and toes helps to estimate the sense of position

The muscle reflexes are checked with the reflex hammer in both extremities. Muscle power is also tested on both sides. The level of severity is determined on the basis of these results.

Sensitivity and muscle tests	Laboratory tests	Electro-diagnostic tests	Nerve biopsy
Surface sensitivity: - Sense of touch - Sense of pain - Sense of temperature **Depth sensitivity:** - Preception of vibrations - Sense of position Muscle reflexes Muscle power	- TSH (thyroid gland) - Glucose values - Vitamin B12-concentration - Erythrocyte sedimentation rate - Protein analysis - Urine analysis	**Elektro-myography:** Measurement of electrical muscle activity **Elektro-neurography:** Determination of the functional condition of a peripheral nerve	Generally takes place on the sural nerve, directly beneath the skin of the lower leg – the sensitivity of the lower leg is hardly restricted by this

Tab. 3: Overview of the testing procedures for the diagnosis of peripheral neuropathy

How is peripheral neuropathy treated?

Peripheral neuropathy that occurs as a consequence of multiple myeloma is treated together with the underlying issue, i.e. multiple myeloma.

Before the start of a treatment, it is important to examine the patient for any existing neuropathy. If indications of peripheral neuropathy or its risk factors are present (vitamin deficiency, diabetes or alcohol consumption), it is necessary to do without a prolonged use of substances which are harmful to the nerves and impede the growth of cells (cytostatic drugs) and the use of highly dosed steroids, as much as possible.

If peripheral neuropathy has been caused by the myeloma treatment (by chemotherapy or, for example, by bortezomib or thalidomide), the alteration of the dose of the medication is the first sensible countermeasure. The dose and duration of the treatment should be reduced to the lowest level. Tight controls should accompany the adjustment. If there is no improvement, in spite of the reduction in the dose, or if the condition of the patient even deteriorates, the treatment must temporarily be stopped. After the neuropathic symptoms have abated, the treatment can be continued again. If the neuropathy reaches severity level 3 or 4, however, the treatment must be aborted for good.

The chemotherapeutic drug vincristine was previously used in myeloma therapy. This is known for triggering peripheral neuropathy. Thalidomide is now used in smaller doses than earlier (50-100 mg/day, compared to 400-800 mg/day).

Patients who are treated with bortezomib should regularly be examined for neuropathy, even if the dose has been adjusted from twice weekly to once weekly. As a result of these measures, peripheral neuropathy is now less common than was the case a few years ago. Nevertheless, patients should pay particular attention to symptoms of a peripheral neuropathy. With lenalidomide, another new treatment for multiple myeloma, peripheral neuropathy rarely occurs.

In your own interest, inform your doctor of all the discomfort that occurs immediately!

The treatment of neuropathy-related pain is also very important. The following substances are available: anti-spasmodic medication (anticonvulsive drugs, e.g. gabapentin), pain-reducing and uplifting medication (tricyclic antidepressants, serotonin and noradrenaline reuptake inhibitors, opioide, capsaisin). Acupuncture or relaxation procedures (e.g. autogenic training) may also be helpful.

In Germany, nursing staff and scientists from the university hospital in Ulm and the Viv - Arte® School of Movement are developing a special care training concept, which is tailored to the problems of neuropathy patients. The study for leukaemia and lymphoma patients aims to increase their physical and mental wellbeing. The training is to reduce nerve disorders caused by chemotherapy. The German José Carreras Leukämie-Stiftung e. V. is funding the study that is planned to take three years. The care training is divided into four modules: manual therapy (passive, integrative movement of muscles and limbs), gymnastic exercises (movements and stretches performed slowly and consciously), Galileo® vibration training and function training. The objective of the training is to relieve deep, internal tension, to stimulate physical awareness and to train muscle power, muscle performance, condition and coordination.
If patients can no longer control the performance of their everyday activities, they also receive function training.

The whole training lasts approximately 60 minutes per unit and is conducted twice a week over a period of eight weeks.

For more detailed information contact:
elisabeth.kirchner@uniklinik-ulm.de

Other physiotherapeutic measures, such as traditional physiotherapy, electrical stimulation, massages or Kneipp baths, may also be helpful. In the case of water treatments, the nursing staff is instructed to check the water temperature precisely beforehand, as the patient often no longer has a sense of temperature, or this is impaired. It is necessary to ensure careful foot and nail care, to avoid the risk of ulcers.

The top priority is the promotion of movement for peripheral neuropathy caused by certain myeloma treatments. The objective is to avoid a deficiency of self-care and ability to look after oneself. All everyday activities depend on movement.

Dietary supplements, vitamins (B1, B6, B12, C), folic acid, l-carnitine or alpha-lipoic acid can also be included in the treatment of peripheral neuropathy, but produce a significant improvement more rarely than the medication listed above.

It is important to point out that the effectiveness of all the therapy approaches mentioned in the treatment of peripheral neuropathy has not yet been scientifically proven, and that these approaches are still being tested.

It is, therefore, all the more important to diagnose the illness in the early stages, so that appropriate action can be taken to ensure that it does not progress.

Here, you, the patient, are an important link in the chain of activity. Pay attention to the signs of your body, observe it, and do not be afraid to tell your doctor about them. As a specialist, he/she can adapt your treatment to the requirements of your body.

Please observe the enclosed questionnaire. It will help you in your discussion with your doctor. If this is missing, you can request it from the addresses given.

Glossary

Acupuncture
Insertion of needles into specific energy points in the body

Antibody
Defensive substance in the blood serum that is formed from B cells; defeats pathogens

Antidepressants
Medication against depression

Autogenic training
A relaxation technique based on autosuggestion (idea influenced by oneself)

Autonomic nervous system
Automatic control of vital functions; conducts signals from the internal organs to the central nervous system and vice versa

B cells
A kind of white blood cells that produces antibodies, as soon as they meet a foreign pathogen

Diabetes mellitus
Metabolic disorder with increased blood sugar level

Electrical stimulation
Stimulation of peripheral nerve fibres with electrical impulses

Fine motor skills
Subtle, sophisticated movements (e.g. finger dexterity, facial expression)

Motor skills
All the voluntary movements of the body

NCI-CTC
Criteria of the American National Cancer Institute for the classification of the level of severity of side effects, such as, for example, of peripheral neuropathy

Neurotransmitter
Substance which transfers information from nerve cell to nerve cell via the synapses

Noradrenaline
Neurotransmitter that enhances attention, activity and reaction times; has an anti-depressant effect

POEMS syndrome
Complex of symptoms from peripheral neuropathy, organomegaly (abnormal enlargement of organs, such as, for example, the liver = hepatomegaly or the spleen = splenomegaly), endocrinopathy (disease of endocrine glands, such as, for example, diabetes mellitus), monoclonal gammopathy (such as typically occurs in multiple myeloma) and changes to the skin

Reflex
Involuntary, direct reaction, such as, for example, patellar reflex or Achilles tendon reflex, can be checked or triggered by the doctor‘s reflex hammer

Sensorimotor
The interaction of sensations and movements

Sensory
Relating to the sensory organs

Serotonin
Neurotransmitter with an anti-depressant effect that relieves pain and dispels anxiety

Serotonin/noradrenaline reuptake inhibitors
Substances which inhibit the reuptake of the neurotransmitters serotonin and noradrenaline into the nerve cells, increasing their concentration in the brain; anti-depressant

Steroids
A class of drugs; some steroids also occur in the body as hormones, for example testosterone or oestrogen

Symptom
Indication of an illness

Synapses
Point of contact between nerve cells

Treatment
Administration, use of a medicine

Viv-Arte®
School of movement

WHO
World Health Organisation

Additional Resources

- **American Cancer Society**
  www.cancer.org
- **Cancerworld**
  www.cancerworld.org
- **The European Myeloma Network**
  www.myeloma-europe.org
- **European Myeloma Platform**
  www.emp-myeloma.eu
- **International Myeloma Foundation**
  www.myeloma.org
- **International Waldenstrom`s Macroglobulinemia Foundation**
  www.iwmf.com
- **Israel – AMEN Foundation**
  www.amen.org.il/site_files/index.en.1024.html
- **LeukemiaNet**
  www.leukemia-net.org

- **Leukemia and Lymphoma Society**
  www.leukemia-lymphoma.org

- **Leukemia Research Foundation**
  www.leukemia-research.org

- **Lymphoma Forum and Lymphoma Association**
  www.lymphoma.org.uk

- **Lymphoma Research Foundation**
  www.lymphoma.org

- **Multiple Myeloma Research Foundation**
  www.themmrf.org

- **Myeloma Euronet**
  www.myeloma-euronet.org

- **Myeloma Patients Europe**
  www.myelomapatientseurope.org

- **National Cancer Institute**
  www.cancer.gov

About Myeloma Euronet

Myeloma Euronet, a non-profit network organization of multiple myeloma patient groups, is an European initiative dedicated to raising the awareness of multiple myeloma, an increasingly common form of bone marrow cancer.

Myeloma Euronet provides information on the diagnosis, treatment and care of persons living with multiple myeloma and supports its member organisations in the fulfillment of their mission.

Myeloma Euronet also advocates, independently and in collaboration with organisations with similar objectives, on behalf of those affected by multiple myeloma.

The goals of Myeloma Euronet are to:

- Advocate the cause of myeloma among EU health care policy makers and share best practice in shaping appropriate policies at the European level
- Raise European awareness of multiple myeloma amongst relevant stakeholders and the public
- Provide information on appropriate diagnosis, treatment, care and support for myeloma patients and their families
- Build partnerships among members of Myeloma Euronet in order to share experience and expertise
- Encourage the growth of new multiple myeloma patient groups throughout Europe, especially in cities and countries where they are not found in the moment

Myeloma Euronet was launched at the 10th Congress of the European Hematology Association (EHA) in Stockholm on 3 June 2005. It is an international non-profit association (Association Internationale sans but lucratif, AISBL) registered in Belgium.

Myeloma Euronet's Secretariat is located in Ruesselsheim, Germany:

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Myeloma Euronet has members in 23 European countries and is a member of the:

- European Cancer Patient Coalition (ECPC) www.ecpc-online.org
- European CanCer Organisation (ECCO) www.ecco-org.eu
- International Lymphoma Coalition (ILC) www.lymphomacoalition.org
- European Organisation for Rare Diseases (EURORDIS) www.eurordis.org

Myeloma Euronet is working in the Patient Advisory Committees of the:

- European Hematology Association (EHA) Scientific Working Group "Quality of Life & Symptoms" www.ehaweb.org
- European Society for Medical Oncology (ESMO) www.esmo.org
- European Group for Blood & Marrow Transplantation (EBMT) www.ebmt.org
- European Medicines Agency (EMA) www.ema.europa.eu

October 2011, the European Myeloma Platform (EMP) and Myeloma Euronet (ME) merged to become Myeloma Patients Europe.

More information about Myeloma Euronet can be found at our multi-lingual, award-winning Web site at **www.myeloma-euronet.org.** This Web site is available in the following languages: Arabic (in part), Czech, English, French, German, Greek, Italian, Polish, Portuguese, Romanian, Russian, Spanish and Turkish. The Web site also provides a wealth of information about myeloma, useful links to other support organisations, a list of events, a quiz, surveys and many other useful resources.

We Need Your Help!

Myeloma Euronet relies heavily on voluntary donations and fund-raising to support our much needed projects and services. If you would like to support us in our efforts, we would be very grateful if you could make a donation by using the bank information given below or let us know if there is any other way for you to help us.

This could be, e.g. by helping us translate our Web site into more languages, assisting us in our fundraising efforts, covering the design and/or printing of information materials on multiple myeloma, providing a travel grant for one of our members to attend a Myeloma conference or Infoday, etc. If you have an idea for a fundraising event, or have any questions, please don't hesitate to get in touch with us – we'd love to hear from you!

Donate by bank transfer
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Bank code: 370 501 98
Sparkasse Koeln Bonn
Germany

International Bank Account Number:
DE74 3705 0198 1937 0135 20
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Myeloma Euronet – the voice of Myeloma patients in Europe