

ATTACHMENT 2

PART I

SUMMARY OF PRODUCT CHARACTERISTICS

HUMECTANT SWEEP 300 ml

CONTENTS: PART I

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I. SUMMARY OF PRODUCT CHARACTERISTICS**I.A. BASIC DATA ABOUT THE PRODUCT****1. Name of the proprietary medicinal product:**HUMET[®]-R Syrup, 300 ml**1.a) INN of the active ingredient(s):**

Name of the active ingredients	Quantity / 300 ml	Unit	Reference standards
1. Humic acid	2.25	g	manufacturer's stand. specification
2. Potassium	1.10	g	BP
3. Magnesium	450	mg	BP/USP/DAB
4. Iron	420	mg	USP/Ph.Eur.
5. Zinc	300	mg	Sigma for anal. use
6. Manganese	90	mg	Sigma for anal. use
7. Copper	60	mg	USP
8. Vanadium	15	mg	Sigma for anal. use
9. Cobalt	6	mg	Sigma for anal. use
10. Molybdenum	5.25	mg	Sigma for anal. use
11. Selenium	3.75	mg	Sigma for anal. use

2. Pharmaceutical form:

suspension syrup

Route of administration: oral

Dosage: From well-shaken syrup, once daily, after a main meal, 10 ml is recommended for adults as dosed by the measuring device in the box, and one half of the adult dose is recommended for children with a body weight below 40 kg. Drink the syrup slowly, in draughts, as mixed with 100 to 200 ml water or fruit juice. Medical consultation is essential when the product is given to children younger than 3 years of age.

3. Name and address of:**3.1. authorization holder:**

HORIZON-MULTIPLAN LTD.
H-1121 Budapest, Konkoly Thege u. 29-33.
Phone: 361/160-1828 FAX: 361/160-3704

3.2. applicant:

HORIZON-MULTIPLAN LTD.
H-1121 Budapest, Konkoly Thege u. 29-33.
Phone: 361/160-1828 FAX: 361/160-3704

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3.3. manufacturer of the active substance:

HORIZON-MULTIPLAN LTD.

(Humic acid on basis of original proprietary process)

SIGMA-ALDRICH Hungary Ltd., Budapest

(mineral components)

3.4. exclusive representative:

Tibor Farkas

LUPUS, Bratislavská 25

900 24 Veľký Biel

Tel: 07/ 91 61 35

Date: Budapest, 08.03.96

.....
István Gömörý
Executive director

.....
Albert Molnár
Marketing & sales director

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I.B. SUMMARY OF BASIC CHARACTERISTICS OF THE PRODUCT

1. Name of the Product:

HUMET®-R syrup, 300 ml

2. Qualitative and quantitative composition of the product with INN of the active ingredient(s) and excipients:

Name of the active ingredients	Quantity/ 300mL	Unit	Reference standards
1. Humic acid	2.25	g	manufacturer's stand. specification
2. Potassium (K_2HPO_4)	1.10	g	BP
3. Magnesium ($MgSO_4 \times 7H_2O$)	450.0	mg	BP/USP/DAB
4. Iron ($FeSO_4 \times 7H_2O$)	420.0	mg	USP/Ph.Eur.
5. Zinc ($ZnSO_4 \times 7H_2O$)	300.0	mg	Sigma for anal. use
6. Manganese ($MnSO_4 \times H_2O$)	90.0	mg	Sigma for anal. use
7. Copper ($CuSO_4 \times 5H_2O$)	60.0	mg	USP
8. Vanadium ($NaVO_3$)	15.0	mg	Sigma for anal. use
9. Cobalt ($CoSO_4 \times 7H_2O$)	6.0	mg	Sigma for anal. use
10. Molybdenum ($(NH_4)_6Mo_7O_{24}$)	5.25	mg	Sigma for anal. use
11. Selenium (Na_2SeO_3)	3.75	mg	Sigma for anal. use
- other excipients -			
flavouring Orange super concentrate	150.0	ml	stand. food quality

3. Pharmaceutical form (route of administration):

suspension syrup

Size of the dispersion medium of the suspension: < 200 μ m

Type of the suspension on basis of

- its administration: oral

- its type of medium: suspension syrup

Traditional suspension

4. Pharmacological properties:

physical - not known

incompatibilities:

chemical - not known

5. *Clinical data:*

5.1. therapeutic indications:

- for general roboration in convalescence periods and for the elderly,
- to help trace element deficiency conditions,
- to strengthen resistance of the organism and to prevent diseases in epidemic periods,
- to improve mental and physical performance
- to eliminate iron deficiency, to supplement iron-requirement in conditions with blood loss (e.g. in women's periods),

5.2. contra-indications:

- the first third of pregnancy,
- renal diseases

5.3. undesirable effects (frequency and seriousness): not known

5.4. special precaution for use: as under point 5.9 hereunder and as under point 7. of the enclosed "Information for users"

5.5. use during pregnancy and lactation: from the 4th month of the pregnancy and during lactation as under point 5.7 hereunder and as under point 7. of the enclosed "Information for users".

5.6. interaction with other medicaments and other form of interactions: none if taken 3 hours before or after any other medication.

5.7. posology, method and route of drug administration (for adults, where necessary for children and elderly patients):

From well-shaken syrup, once daily, after a main meal, 10 ml is recommended for adults as dosed by the measuring device in the box, and one half of the adult dose is recommended for children below 40 kg.

Drink the syrup slowly, in draughts, as mixed with 100 to 200 ml water or fruit juice.

Medical consultation is essential when the product is given to children younger than 3 years of age.

5.8. overdose (symptoms, emergency procedures, antidotes):

5.9. special warnings:

- If you are under medication, consultation with your physician about the use of HUMET_®-R is necessary.
 - Other drugs or paramedicaments used concomitantly with HUMET_®-R should be taken 3 hours before or after taking the product.
 - HUMET_®-R is not recommended to take in combination with other micro- or macro element products.
 - In diabetes, consider that each dose of the product contains 3.3 g carbohydrate.
 - Faeces might be discoloured to dark brown in the period the product is consumed.
-

6. Pharmaceutical data

6.1. Description of the product:

HUMET[®]-R SYRUP 300 ml
Macro and micro element supplement.

6.2. Nature of container:

bottle of 300 ml:	brown, type PFP28
security caps:	type AF 6134-100 Ø 28 mm
bottle label:	size 162 x 63 mm
individual cardboard box:	size 66,5 x 66,5 x 158 mm
direction for use:	inside the box

6.3. Pack size: holding 20 bottles, size 355 x 284 x 170 mm

6.4. Shelflife:

12 months from the date of manufacture (see date stamped on top of box).

6.5. Special precautions for storage:

Once opened, the bottle should be stored well-tight in a dark place, preferably in refrigerator (+2 - +8 C) and should be consumed within one month.

7. Information for users

HUMET[®]-R SYRUP

Roborant, macro and micro element supplement

Active ingredients: The product contains 2.25 g humic acid, 1.10 g potassium, 450 mg magnesium, 420 mg iron, 300 mg zinc, 90 mg manganese, 15 mg vanadium, 6 mg cobalt, 3.2 mg molybdenum and 3.75 mg selenium in 300 ml flavoured syrup.

Indications:

- for general roboration in convalescence periods and for the elderly,
- to help trace element deficiency conditions,
- to strengthen resistance of the organism and to prevent diseases in epidemic periods,
- to improve mental and physical performance
- to eliminate iron deficiency, to supplement iron-requirement in conditions with blood loss (e.g. in women's periods),

Contra-indications:

- the first third of pregnancy,
- renal diseases

Dosage: From well-shaken syrup, once daily, after a main meal, 10 ml is recommended for adults as dosed by the measuring device in the box, and one half of the adult dose is recommended for children below 40 kg.

Drink the syrup slowly, in draughts, as mixed with 100 to 200 ml water or fruit juice.

Medical consultation is recommended when the product is given to children younger than 3 years of age.

Shelf life: use before the date indicated on the top of the box and the bottle.

Storage: store at 15 to 25 °C. Once opened, the bottle should be stored well-tight on a dark place, preferably in refrigerator and should be consumed within one month.

Warning:

- If you are under medication, consultation with your physician about the use of HUMET®-R is necessary.
- Other drugs or paramedicaments used concomitantly with HUMET®-R should be taken 3 hours before or after taking the product.
- HUMET®-R is not recommended to take in combination with other micro- or macro element products.
- In diabetes, consider that each dose of the product contains 3.3 g carbohydrate.
- Faeces might be discoloured to dark brown while the product is consumed.

A paramedical product!

Registration No.: OGYI-430/1993

Manufactured by: HORIZON-MULTIPLAN Ltd.
1525 Budapest, P.O.Box 49.

I.C. EXPERT REPORTS ON CHEMICAL, PHARMACEUTICAL
AND CLINICAL DOCUMENTATION

I. Annex 1

I.D. PROPOSAL FOR INFORMATION OF PHYSICIANS AND
PHARMACISTS

HUMET_R SYRUP

Roborating product for macro- and micro element supplementation; its effect was confirmed by animal experiments.

A paramedical product.

For a long time, it has been well-known in medicine that certain metals of the natural elements in the periodic table are essential for the living organism.

Intake of macro and micro elements, and their correct proportion in the body are inevitable for the healthy (optimal) function of the organism. In our age, nutrition is not always able to meet the complete macro and micro element requirement of the organism, so these substances should be supplemented. Up-to-date research has suggested that trace elements should be supplemented not in the form of monotherapy, but as complex treatment where interactions among elements are considered as well.

HUMET-R syrup, a product of HORIZON-MULTIPLAN Ltd, meets these requirements.

A specific feature of HUMET-R syrup is that essential elements (a total of 10 kinds of macro- and micro elements) are bound to humic acids, organic carriers present in the organism, as well. Humic acids in the product contain 16 kinds of amino acids whose presence can be verified by amino acid analysis.

Role of the 10 kinds of macro- and micro elements in HUMET_R-R syrup is as follows:

(On the base of MSD Medical Handbook - 1994 /The Merck Manual/):

Micro element	Role in the organism
Potassium	Muscular activity, neural transmission, intracellular acid-basis balance and water retention
Magnesium	Bone and tooth formation, stimulus conductance, muscular contraction, enzyme activation
Iron	Haemoglobin and myoglobin synthesis, enzyme component

Zinc	Enzyme and insulin component, maintenance of skin intactness, wound healing, growth, immune system strengthening, nail and hair growth
Manganese	Enzyme component, bone formation, growth, maintenance of skin intactness, hair pigmentation, hair growth
Copper	Enzyme component, haemopoiesis, bone formation
Vanadium	Cholesterol synthesis, prevention of dental caries
Cobalt	Component of B ₁₂ molecule, increases haemoglobin concentration
Molybdenum	Component of redox catalysing enzymes, prevention of dental caries
Selenium	Antioxidant (protects from harmful effects of free radicals), strengthens the immune system, supports heart function, protects from myocardial infarction

Active ingredients: The product contains 2.25 g humic acid, 1.10 g potassium, 450 mg magnesium, 420 mg iron, 300 mg zinc, 90 mg manganese, 15 mg vanadium, 6 mg cobalt, 5.2 mg molybdenum and 3.75 mg selenium in 300 ml flavoured syrup.

Indications:

- for general roboration in convalescence periods and for the elderly,
- to help trace element deficiency conditions,
- to strengthen resistance of the organism and to prevent diseases in epidemic periods,
- to improve mental and physical performance
- to cease iron deficiency, to supplement iron-requirement in conditions with blood loss (e.g. in women's periods).

Counter-indications:

- the first third of pregnancy,
- renal disease

Dosage: From well-shaken syrup, once daily, after a main meal, 10 ml is recommended for adults as dosed by the measuring device in the box, and one half of the adult dose is recommended for children below 40 kg. Drink the syrup slowly, in draughts, as mixed with 100 to 200 ml water or fruit juice.

Medical consultation is essential when the product is given to children younger than 3 years of age.

Shelf life: use before the date indicated on the top of the box and the bottle.

Storage: store at 15 to 25 °C.

Once opened, the bottle should be stored well-tight on a dark place, preferably in refrigerator. Broken product should be consumed within one month.

Warning:

- If you are under medication, consultation with your physician about the use of HUMET_®-R is necessary.
- Other drugs or paramedical products used concomitantly with HUMET_®-R should be taken 3 hours before taking the product.
- HUMET_®-R is not recommended to take in combination with other micro- or macro element products.
- In diabetes, consider that each dose of the product contains 3.3 g carbohydrate.
- Faeces might be discoloured to dark brown in the period the product is consumed.

Registration No.: OGYI-430/1993

Manufactured by: HORIZON-MULTIPLAN Ltd.
1525 Budapest, P.O.Box 49.

HUMET®-R SYRUP

Produced and distributed by
HORIZON-MULTIPLAN Ltd.
H-1525 P.O.Box 49,
Budapest, Hungary
Tel.: (36-1)-160-1828
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Refereed by Sándor Takács MD, D.Sc.Med.

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Introduction

Micro elements act either as structural parts of the enzymes or as activators of the latter. Deficiency in micro elements or an excess of their antagonists will impair enzymatic activity so may lead to deficiency syndromes, resp. signs of enzymatic malfunction.

Nutrition ought to supply our need of micro elements. This way of supply may be, however, often unsatisfactory since often not even the soil contains the required amount. So both animal and vegetable foods vary in their content of the micro elements and are not infrequently deficient, quantitatively as well as in regard of the necessary proportions. Efforts to regularly provide both humans and their environment with the necessary amount and composition of micro elements have been made world-wide.

Relying on the most recent results of research, the experts of HORIZON-MULTIPLAN Ltd. have developed a micro element carrier of natural origin that provides for both the supply of the physiologically most important micro elements and promotes their absorption. This natural carrier is a mixture of humic acids.

The colloidal solution of humic acids as the basic ingredient of the syrup HUMET_®-R is a carrier of choice for the following reasons:

- its variegated biofunctional groups can bind the metallic macro- and micro elements added to it in amounts conforming to the international recommendations with specific, i.e. dissimilar, strength so ensures an uptake always meeting the actual needs;
- it contains the trace metals in chelate bond, that is, in a biological structure resembling that of the transport proteins of our body, so uptake conditions are most favourable for their utilisation,
- metals incorporated, but undesirable for normal life functions, such as lead or cadmium, become strongly bound to humic acid so their excretion gets considerably faster.

Chemistry and biochemistry

HUMET_®-R, the potent revitalising preparation, is a humic acid compound produced by using a special way of extraction and is complemented by macro- and micro-metals in doses recommended by the WHO to which a fruit-flavoured syrup is added

The standard 300 ml bottle contains 2.25 g of humic acids, 1.10 g of potassium, 450 mg of magnesium, 420 mg of iron, 300 mg of zinc, 90 mg of manganese, 60 mg of copper, 15 mg of vanadium, 6 mg of cobalt, 5.25 mg of molybdenum and 3.75 mg of selenium in the flavoured syrup

Humic acids as a mixture of active biopolymers of different molecular weight occur in the human organism as well. The importance of these compounds is due to the chelating capacity of their bioactive nucleus the structure of which varies slightly from molecule to molecule.

The metal binding property of the humic acids closely resembles the behaviour of the active sites in the human functional and transport proteins

The elements in HUMET_®-R and their physiological role

IRON (Fe)

It is responsible for the basic functions of the oxygen carriers haemoglobin and myoglobin, and of the electron carrier cytochromes. Iron deficiency is a rather frequent ailment with manifest clinical symptoms and signs such as fatigability, headache, inflammation of the oral mucosa and gums, loss of appetite, etc. In chronic iron deficiency hypochrome anaemia with microcytosis and a form of osteomedullary hyperplasia with a scarcity of haemosiderin develop

Iron uptake is heavily affected by the presence or absence of other micro elements. On the other hand, iron ingestion may promote the excretion of lead.

POTASSIUM (K)

Representing the main intracellular cation, it has a primary role in the conduction of nervous impulses as well as in a number of other fundamental life processes. Potassium deficiency is rare and develops mainly during medical treatment (e.g. diuretic therapy), though there are diseases too in which it occurs

MAGNESIUM (Mg)

A natural calcium antagonist which effects in addition to calcium the metabolism of phosphorus and sodium. It is an activator of glycolysis and has an essential part in protein metabolism. It is a modifier of muscle activity and helps maintain circulatory equilibrium. Also germinative functions are reported to depend on it. When lacking, cramps, etc. may develop.

ZINC (Zn)

A number of enzymes contain it as the active part of their prosthetic group. Its importance in the synthesis of the nucleides DNA and RNA as well as of proteins is outstanding and so is its contribution to the stereo-chemical structure of insulin. Its presence in adequate amounts in people

exposed to lead and cadmium intoxication is particularly essential since these metals are then less toxic as evidenced by the results of its therapeutic administration. Chronic zinc deficiency is associated with typical signs (skin lesions, baldness, testicular dysgenesis, sexual retardation, hepato-splenomegaly, impaired growth processes, delayed healing of wounds, derangement of immunological resistance, etc.) Its concentration may decrease as a side effect of corticoid and/or diuretic therapy or of prolonged administration of contraceptives too, but it is common in sickle cell anaemia, lung tumours and myocardial infarction. Zinc deficiency is particularly menacing in alcohol abuse, especially when liver cirrhosis had developed.

COPPER (Cu)

Haemopoiesis, cell respiration, enzymatic processes, and the catecholamine metabolism of the brain are the primary sites of its action. It interacts with the equilibrium of iron and zinc too. As shown by infertility studies, it affects reproduction. Cadmium toxicity is more severe when copper supply is deficient. Longer periods of inadequate copper supply are associated with anaemia, lesions of the bone marrow, retarded growth, cerebral dysfunction and myocardial degeneration.

MANGANESE (Mn)

It has an active role in osteogenesis. Its uptake is less efficient because of the competitive antagonism of the usually ample supply of calcium. It plays an essential part in maintaining the synthesis and integrity of biological membranes by being part of the enzyme pharnesyl pyrophosphate synthetase responsible for the synthesis of membrane cholesterol.

Another enzyme with a membrane protective role is a superoxide dismutase containing manganese which collaborates with the enzyme Cu^{2+} - Zn^{2+} - superoxide dismutase in the neutralisation of toxic intracellular superoxides.

Lasting manganese deficiency gives rise to dermatitis, symptoms resembling diabetes when an oral glucose test is employed, pigmentation disorders of the hair, impaired growth and infertility.

SELENIUM (Se)

It is an active part of the enzyme glutathion peroxidase which protects us (scavenger effect) from intracellular free radicals so it is important everywhere where there is a chance of an increased production of free radicals (irradiation effects, tumours, increased degradation of fats and proteins, starvation, etc.). When uptake is deficient, the function of muscle tissues suffer and the carcinogenic effect of heavy metals (Pb in animals, possibly Cd in humans) is augmented. Adequate supply prevents the development of cardiomyopathy, muscle dystrophy and colorectal cancer.

COBALT (Co)

It interacts with the metabolism of iron, increases haemoglobin concentration in the erythrocytes. It is the metal in the prosthetic group of vitamin B_{12} . It forms a part of the enzymes β -lysine isomerase, glycerol dehydrogenase, etc.

MOLYBDENUM (Mo)

Several enzymes catalysing redox-processes contain it. It plays a part in copper metabolism and prevents the incorporation of tungsten which competes with other metals necessary for our body. It protects against caries.

VANADIUM (V)

It affects the metabolism of manganese and plays a part in osteogenesis. It inhibits cholesterol synthesis and the development of caries.

Effects

Humic acids and their biological effects have been dealt with in a number of studies

- Medicine and agriculture have profited by their antitoxic effects since long.
- The number of adhesions following surgical interventions in animal experiments could be decreased by applying humic acids externally
- Peat moor waters were found to compensate for deficient trace element supply and to improve haematopoiesis.
- Humic acids could significantly reduce the toxic effects of heavy metals in unicellular algae.

By restoring the desirable balance among the provided micro elements, HUMET_®-R can correct certain disorders of the system of metal containing enzymes and improve the adaptation of the body. In addition to offering a correct amount of micro elements, and in part because of it, it can contribute to promoting the natural excretion of heavy metals.

This particular and flexible capacity of humic acids to bind and release metals is attributable to the broad range of functional groups in their mixture. Additional effects also occur, such as surface activity and adsorption capacity, due to the colloidal nature of the preparation.

When ingested, the humic acid suspension may in part become hydrolysed by the gastric juice. However, as soon as subjected to the bases of intestinal juice, the original conditions are restored. The exchange of the micro elements takes place through an interaction with the enzymes of the intestinal mucosa. The absorbed micro elements become bound to the transport proteins albumin, transferrin and metallothionein. On the other hand, since heavy metals are supposed to circulate and become excreted, at least in part, via the bile and the intestinal juice, the re-established chelating capacity of the humic acids can bind them and so prevent heavy metal reabsorption.

The primary advantage of HUMET_®-R is therefore that, owing to its humic acid content, it provides the metals in a form that masks their ionic nature and (in the suggested dosage) in amounts that conform to the recommendations of the World Health Organisation.

Adding it to the normal diet helps satisfy the daily need of several of the most important micro elements and some of the macro elements of the body. In this way, disorders of the enzyme systems and all associated functional disturbances can be avoided or normalised.

By establishing the balance between the micro elements, it relieves the body from the burden of maintaining compensatory mechanisms.

Toxicology and mutagenicity

- LD₅₀ was experimentally evidenced to be above 10 g/kg b.w. in the rat in the acute toxicological study and so was declared to qualify as practically non-toxic.
- In the cumulative test of toxicity HUMET_®-R did not produce any toxic effects.
- The preparation was found to be free from any mutagenic effects in the "AMES" test of mutagenicity.

Clinical studies

These studies were carried out in the Laboratory for Occupational Health of the Institute of Hygiene and Public Health of the Hungarian Railways (MÁV Közegészségügyi Intézet, Budapest).

After informed consent, 104 subjects from among the persons regularly screened for occupational health risks at this institute (age range 18-65 years) volunteered to take HUMET_®-R as prescribed and undergo the initial and closing blood chemistry. They were free from complaints and consented to avoid any drugs during the three weeks of study.

Of them, 14 had a lower than 8 nmol/l = 20.0 µg/l level of serum ferritin. Figure 1 shows the changes that took place after 3 weeks of HUMET_®-R administration.

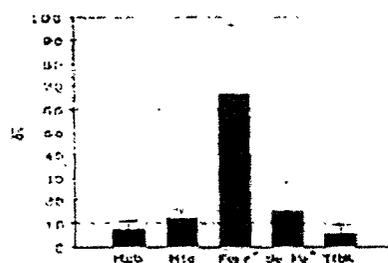


Fig. 1. Percentage change in blood chemistry and haematology following 3 weeks of HUMET_®-R administration (n= 14; serum ferritin levels below 20 µg/l). Abbreviations (and initial / final levels of substance; mean ±SEM). Hgb= haemoglobin (7.80 ±0.44 / 8.37 ±0.29 mmol/l); Htc= haematocrit (0.36 ±0.02 / 0.41 ±0.01 l/l); Ferr= serum ferritin (4.89 ±0.55 / 8.14 ±1.73 nmol = 12.23 ±1.37 / 20.35 ±4.33 µg/l); Se Fe= serum iron (12.58 ±1.48 / 14.46 ±2.58 µmol/l); TIBC= total iron-binding capacity (76.49 ±2.16 / 80.51 ±3.14 µmol/l); asterisk= difference significant at P<0.05

As shown in Figure 1, the preparation HUMET_®-R could effectively supply the essential micro elements and replenish the iron stores, irrespective of nutrition.

Information for users

HUMET_®-R SYRUP

Roborant, macro and micro element supplement

Active ingredients: The product contains 2.25 g humic acid, 1.10 g potassium, 450 mg magnesium, 420 mg iron, 300 mg zinc, 90 mg manganese, 15 mg vanadium, 6 mg cobalt, 5.2 mg molybdenum and 3.75 mg selenium in 300 ml flavoured syrup

Indications:

- for general roboration in convalescence periods and for the elderly,
- to help trace element deficiency conditions,
- to strengthen resistance of the organism and to prevent diseases in epidemic periods,
- to improve mental and physical performance
- to eliminate iron deficiency, to supplement iron-requirement in conditions with blood loss (e.g. in women's periods).

Contra-indications,

- the first third of pregnancy
- renal diseases

Dosage: From well-shaken syrup, once daily, after a main meal, 10 ml is recommended for adults as dosed by the measuring device in the box, and one half of the adult dose is recommended for children below 40 kg.

Drink the syrup slowly, in draughts, as mixed with 100 to 200 ml water or fruit juice.

Medical consultation is recommended when the product is given to children younger than 3 years of age

Shelf-life: use before the date indicated on the top of the box and the bottle.

Storage: store at 15 to 25 °C. Once opened, the bottle should be stored well-tight on a dark place, preferably in refrigerator and should be consumed within one month.

Warning:

- If you are under medication, consultation with your physician about the use of HUMET_®-R is necessary
- Other drugs or paramedicaments used concomitantly with HUMET_®-R should be taken 3 hours before or after taking the product.
- HUMET_®-R is not recommended to take in combination with other micro- or macro element products.
- In diabetes, consider that each dose of the product contains 3.3 g carbohydrate.
- Faeces might be discoloured to dark brown while the product is consumed.

A paramedical product!

Registration N°: OGYI-430/1993

Manufactured by: HORIZON-MULTIPLAN Ltd.
1525 Budapest, P.O. Box 49.

Appendix

Recently, a regrettably high incidence of metal intoxication of variable severity has been reported. Environmental pollution with heavy metals owing to technological or industrial (glass, dye and enamel ware production, for instance) contamination may cause nation-wide concern. Both in regard of health risk and morbidity, lead and cadmium are the primary menace.

CADMIUM (Cd)

It is one of the major sources as well as an indicator of environmental pollution. It is an important metal for industrial plastic, dye and pesticide production and battery manufacturing (where it can cause occupational harms). The main sources of cadmium uptake are vegetables and fruit (because of soil contamination), foods getting in contact with certain plastic implements and wrap materials, and tobacco smoke.

It gets stored by the kidneys with a very long half-life time so exerts lasting effects. Cadmium is an inhibitor of enzymes containing zinc as the active element. Subjects exposed to higher cadmium doses develop renal dysfunction, imbalance of phosphorus and calcium metabolism and consecutive osteomalacia, and zinc and copper dismetabolism. Animal experiments have clearly evidenced its teratogenic (developmental disorders) and cancerogenic effects (lung cancer). It severely interferes with the bioavailability and storage of iron and may cause iron-deficient anaemia.

There is no cadmium in the new-born as toxic accumulation in the body is solely due to environmental pollution.

The main biological antagonist of cadmium is zinc which when used therapeutically can reduce or counteract cadmium toxicity. Also selenium interacts with cadmium and selenium administration can prevent the toxic effects of cadmium. Copper administration has a similar effect while iron-deficient anaemia caused by cadmium intoxication can be effectively treated with adequate doses of the suitable iron compounds.

Figure 2 demonstrates the effect of administering HUMET₆-R to 26 subjects exposed to cadmium intoxication (blood cadmium levels above 0.08 $\mu\text{mol/l}$).

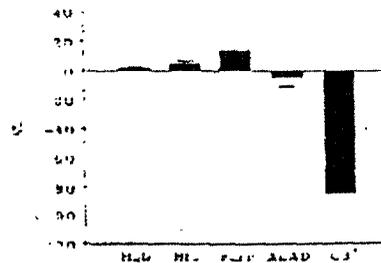


Fig. 2 Percentage change in blood chemistry and haematological status following 3 weeks of HUMET₆-R administration in subjects exposed to cadmium intoxication (N=26, blood Cd above 0.08 $\mu\text{mol/l}$). Abbreviations (with initial / final levels of substance; mean \pm SEM): Hgb= haemoglobin (18.91 \pm 0.25 / 19.02 \pm 0.15 mmol/l); Hct= haematocrit (0.42 \pm 0.01 / 0.44 \pm 0.01 l/l); Ferr= serum ferritin (77.8 \pm 0.5 / 87.8 \pm 39.8 $\mu\text{mol/l}$); ALAD= δ -amino-levulinic acid dehydrogenase (761.5 \pm 74.3 / 873.8 \pm 55.2 $\mu\text{mol/l}$); Cd= blood cadmium (0.23 \pm 0.05 / 0.04 \pm 0.01 $\mu\text{mol/l}$). The asterisk denotes significance of change at P<0.05.

LEAD (Pb)

Lead incorporation represents a major risk to health and affects many people exposed to environmental lead pollution caused by gasoline driven vehicles, industrial emission, etc.

Lead within the body interferes with haemoglobin synthesis and iron metabolism at several points of attack. It reduces the life span of erythrocytes and considerably impairs conduction velocity in the sensory and motor nerves. By destructing the proliferative tissues of the testicles, lead intoxication may cause infertility. It accumulates in the bones, liver and kidneys from which it is excreted very slowly, in constant balance with the actual blood level.

No direct teratogenic effect of lead has been reported although in vitro DNA synthesis was impeded by it. Its cancerogenic effects have been evidenced, however.

Lead and iron are competitive antagonists so lead intoxication gives rise to severe iron-deficient anaemia while iron excess inhibits the absorption and storage of lead. Suitable iron therapy can reduce the risk of lead intoxication.

Also zinc competes with lead so zinc deficiency aggravates lead toxicity. When lead intoxication has developed, severe zinc deficiency is bound to arise with complications. Zinc administration can be used to inhibit lead deposition within the body and promote its excretion.

Selenium treatment is also effective in mitigating the toxic manifestations of lead intoxication, inclusive of the cancerogenic effect. Selenium also promotes the excretion of lead by the faeces. In this way, selenium has an important role both in neutralising the toxic effects of lead and prophylactically.

Figure 3 demonstrates the effects of a 3-week administration of HUMET₉-R to 21 patients with blood lead levels above 1 $\mu\text{mol/l}$. As seen, HUMET₉-R may be of considerable help in reducing the blood level of both cadmium and lead through promoting the excretion of these toxic metals.

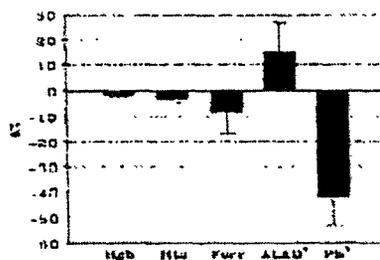


Fig. 3. Percentage change in blood chemistry and haematological status following 3 weeks of HUMET₉-R administration in subjects exposed to lead intoxication (N= 21; blood Pb above 1.0 $\mu\text{mol/l}$). Abbreviations (with initial / final levels of substance; mean \pm SEM): Hgb= haemoglobin (9.42 \pm 0.18 / 9.26 \pm 0.17 $\mu\text{mol/l}$); Hct= haematocrit (0.45 \pm 0.01 / 0.44 \pm 0.01 l); Ferr= serum ferritin (98.8 \pm 39.7 / 90.3 \pm 33.0 μmol ; 246.9 \pm 99.3 / 225.8 \pm 82.5 $\mu\text{g/l}$); ALAD= δ -amino-levulinic acid dehydrogenase (761.5 \pm 74.3 / 875.3 \pm 77.9 $\mu\text{mol/l}$); Pb= blood lead (1.74 \pm 0.19 / 1.01 \pm 0.16 $\mu\text{mol/l}$). The asterisk denotes significance of change at P<0.05.