

Fertilovit® for a new life

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A-Bregenz, 27.04.2016

To Romanian authorities / to whom it may concern

Gonadosan Distribution GmbH, Römerstrasse 2, 6900 Bregenz, Austria, hereby informs.

Fertilovit® M plus

Food for special medical purposes for the dietary management of male fertility issues related to limited semen quality.

What is Fertilovit® M plus?

Fertilovit® M plus is a food for special medical purposes for the dietary management of male fertility issues related to limited semen quality.

As has been shown by a considerable number of studies, male fertility is declining all over the world. One in ten couples experience problems conceiving and in 30 % these can be assigned to male fertility issues. Assisted reproductive techniques (ART) offer a range of possibilities to support people with fertility issues.

Clomiphene cycles, insemination, IVF or ICSI are very effective to support the fusion of oocyte and spermatozoa. However, sperms with severe oxidative damage will substantially lower success rates of any fertility treatment. Diminished sperm count and quality can be caused by a variety of factors. Pollution, hormones in the environment, poor eating habits and others have been claimed to be responsible. More and more research has focused on oxidative stress and its detrimental effects on sperm health. Oxidative stress occurs in our bodies as a result of exposure to environmental factors such as smoking, alcohol consumption, pollution, pesticides and other chemicals, stress and/or trauma. The term oxidative stress refers to damage that is inflicted on the body's cells and tissues by reactive oxygen species. Oocytes and spermatozoa are particularly susceptible to this kind of damage. Normally the body has its own powerful range of defence mechanisms, the body's own antioxidants, however, these are not always available in sufficient quantity.

Fertility benefits from a healthy lifestyle and well-balanced nutrition

The good news first: Because spermatozoa are continually formed anew, a healthy man can always make a difference regarding sperm count and motility by making healthy lifestyle choices. A well-balanced diet with abundant antioxidants and other micronutrients important for cell division and spermatogenesis plays an important role. It can support reproductive health effectively. However, if you find it hard to stick to a healthy diet in everyday life with all its demands in job and leisure, taking a specific supplement might prove a valuable amendment.

Antioxidants

Antioxidants are vital substances that safeguard the DNA, proteins and lipids of all the body's cells (including spermatozoa) from oxidative stress. Wellknown antioxidants include vitamins

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C and E as well as lycopene, a carotenoid from tomatoes. Vitamin C is the main antioxidant in seminal plasma, however is quickly eliminated from the body. Therefore the majority of vitamin C usually cannot exert its positive effects. Hence Fertilovit® M plus contains vitamin C with sustained release, making the most of its protective capacity. Vitamin E, being a lipid-soluble antioxidant, is important for safeguarding the cell membranes in particular.

Selenium and zinc for healthy fertility

It is generally acknowledged that the trace elements selenium and zinc are necessary for male fertility.

Zinc is an essential trace element which is crucial for many biochemical pathways within the body. It supports normal immune system function, growth and protein synthesis, simultaneously being vital for normal cell division and DNA synthesis. In addition to that it is essential for normal male fertility and reproduction and helps to maintain healthy testosterone levels. Selenium is an essential trace element as well and is involved in many key pathways of metabolism. Being part of so-called selenoproteins it plays a major role as part of protective enzymes, safeguarding cells from reactive oxygen species. Other selenoproteins are involved in thyroid hormone metabolism, which is vitally important for healthy reproduction and fertility. Thus it is no surprise that the thyroid is the body organ richest in selenium (except the brain). In addition to that selenium is needed for spermatogenesis.

Amino acids

Healthy sperm development requires a sufficient supply with a variety of micronutrients. Amongst others, certain amino acids play a vital role for sperm health. Arginine, for example, is vitally needed for the production of protamines, which help to package and thus stabilize sperm DNA. Arginine, however, has a very limited bioavailability. Yet it has been shown that supplementation of its precursor, the amino acid L-citrulline, can effectively boost arginine levels. An additional effect of both amino acids is that they can produce the mediator nitric oxide (NO).

The preparation has been tested in one of Europe's biggest ART clinics. Men who wish to conceive are recommended to take it from at least three months prior to conception.

Administration form:

Capsules

Packaging sizes (Net quantity):

60 capsules (48 g)

The composition of **Fertilovit® M plus** accounts for the special men with limited semen quality. **Fertilovit® M plus** can contribute to sperm quality and fertility and is particularly effective in men who smoke, who suffer from stress or experience nutrition-related impairment of sperm quality.

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Supplement facts:

	Daily dose (2 capsules)	% NRV*
Vitamin C	100 mg	125
Vitamin E	100 mg	833
Folic acid	500 µg	250
Zinc	25 mg	250
Selenium	100 µg	182
L-citrulline	300 mg	-
L-carnitine	300 mg	-
N-acetyl-L-cysteine	50 mg	-
Glutathione	50 mg	-
Coenzyme Q10	15 mg	-
Lycopene	4mg	-

*Percentage of Nutrition Reference Values (according to regulation 1169/2011/EU)

Fertilovit® M plus contains neither lactose, gluten, nor gelatin.

Directions

Preferably, to achieve optimal sperm health, you should start taking **Fertilovit® M plus** for at least 90 days before trying for pregnancy, as the sperm production cycle (spermatogenesis) takes 74 – 78 days. However, taking **Fertilovit® M plus** can be started at any time. Take two Fertilovit® M plus capsules daily, one in the morning and one in the evening. **Fertilovit® M plus** is a nutritionally incomplete food for special medical purposes. Some of its ingredients exceed defined maximum quantities. The product must be used under medical supervision. Do not exceed the recommended dosage. **Fertilovit® M plus** cannot and must not replace a healthy lifestyle and a well-balanced diet. Please store out of reach of children.

Scientifically Proven Effects of the Ingredients

Vitamin C

Vitamin C is the major antioxidant in seminal plasma of fertile men. Here its concentration is ten times higher than in blood plasma. Vitamin C protects spermatozoa against aggressive ROS (reactive oxygen species) and can improve sperm number and quality. However, the human body excretes vitamin C quickly. Therefore **Fertilovit® M plus** contains vitamin C that is released gradually in small quantities, thus providing a long term effect.

Zinc

Zinc is an important component of sperms: If the body lacks zinc, sperm production decreases considerably. In addition to this the motility of sperms diminishes as well. Studies have shown that taking a zinc supplement can improve sperm quality.

Vitamin E (D-alpha-tocopheryl succinate)

Vitamin E is localised in the cell membrane. Being an antioxidant it protects the membrane against oxidative stress. In various scientific studies men, who took a vitamin E supplement, had sperms that were significantly more resilient, motile and altogether healthier.

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Folic acid

Folic acid guards the sensitive DNA contained in the sperm head. Men with abundant folic acid have been found to have less sperms that cause a genetic disorder in case of conception. In addition to this, folic acid has been shown to lower homocysteine levels. This supports sperm development as well.

Selenium

Selenium is a highly effective antioxidant, which safeguards sperms' DNA. Additionally, studies have revealed that selenium can enhance motility of sperms.

Lycopene

Lycopene is a carotinoid featuring excellent antioxidant as well as anti-inflammatory properties. This has a positive effect on latent inflammations of the urogenital tract, reducing oxidative stress. Lycopene supplementation has been linked to an increase in sperm number and motility.

L-carnitine

In several studies L-carnitine ameliorated sperm motility substantially.

Coenzyme Q10

The body needs coenzyme Q10 (CoQ10) predominantly for energy production. However, it has powerful antioxidant properties, too, and can reduce the production of reactive oxygen species in seminal plasma markedly. Giving coenzyme Q10 to infertile men has been shown to result in a significant increase of pregnancy rates.

Glutathione (reduced) / N-acetyl-L-cysteine

Glutathione is the prevailing antioxidant in the human body. It safeguards cells from oxidative stress. However, glutathione's absorption within the gastro-intestinal tract is limited. Its main precursor, N-acetyl-L-cysteine, on the other hand, is easily absorbed and has been shown to effectively boost glutathione-synthesis within the body. Therefore **Fertilovit® M plus** contains N-acetyl-L-cysteine, raising intracellular glutathione levels considerably.

Citrulline

Citrulline is the body's main precursor for the production of the amino acid arginine. Supplementing citrulline has been shown to raise arginine levels substantially. The body uses arginine for making the polyamines spermine and spermidine, which are present in seminal fluid in high concentrations. Spermine stabilizes sperm DNA, whereas spermidine plays an important role in cellular repair mechanisms. Spermidine levels have been found to decrease continually with increasing age. Arginine is also needed for the production of protamines, which are necessary for packaging of sperm DNA, thus stabilizing the DNA. Arginine's precursor citrulline raises arginine levels effectively over an extended period of time. A welcome side effect of raised arginine levels is that it also promotes male erection by releasing the mediator NO (nitric oxide).

Contra-indications

Men have a known intolerance to any of the ingredients should not consume **Fertilovit® M plus**.

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Representative bibliography

Fertilovit® M plus

- In observational studies, dietary supplementation with **Fertilovit® M plus** improved semen quality of IVF (in vitro fertilization) patients in terms of motility, sperm count and nuclear vacuolization (Wirleitner et al., 2012, Ajayi et al., 2013, attached). In a subsequent observational study, supplementation of subfertile men with **Fertilovit® M plus** improved top-blastocyst rate in couples undergoing IVF/IMSI (Intracytoplasmic Morphologically Selected Sperm Injection) (Wogatzky et al, 2014, attached).

Vitamin C

- Contributes to normal energy metabolism: EFSA 2009; 7(9):1226 ; 2010;8(10):1815
- Contributes to normal function of the immune system: EFSA 2009; 7(9):1226 ; 2010;8(10):1815
- Contributes to protecting cells from oxidative stress: EFSA 2009; 7(9):1226 ; 2010;8(10):1815
- Vitamin C reduces sperm agglutination (Dawson 1983)
- Increases sperm count (Dawson 1987)
- Supplementation is especially effective in smokers (Dawson 1992)

Vitamin E

- Contributes to protecting cells from oxidative stress: EFSA 2010;8(10):1816
- In combination with selenium supplementation has a very good effect on motility in infertile men (Keskes-Ammar et al, 2003).

Folic acid

- Contributes to normal blood formation: EFSA 2009; 7(9):1213)
- Contributes to normal homocysteine metabolism: EFSA 2009; 7(9):1213)
- Contributes to normal function of the immune system: EFSA 2009; 7(9):1213
- Has a role in cell division: EFSA 2009; 7(9):1213 ; 2010;8(10):1760
- Promotes protamine packaging (Huang et al, 1999)
- Young et al (2008): Men with a diet low in folic acid have more sperms with chromosomal aberrations. The risk of having sperms with aneuploidy increases by 3.6 % per 100 mg of folic acid intake.
- Raises sperm counts (Wai Yee Wong et al, Fertil Steril 2002)

Zinc

- Contributes to normal DNA-synthesis: EFSA 2010;8(10):1819
- Contributes to normal fertility and normal reproduction: EFSA 2009; 7(9):1229
- Maintains a normal testosterone level in blood: EFSA 2010;8(10):1819
- Contributes to normal function of the immune system: EFSA 2009; 7(9):1229
- Contributes to protecting cells from oxidative stress: EFSA 2009; 7(9):1229
- Has a role in cell division: EFSA 2009; 7(9):1229
- Contributes to normal macro nutrient metabolism: EFSA 2010;8(10):1819
- Raises sperm counts when combined with folic acid (Wong et al 2002)

Selenium

- Contributes to normal spermatogenesis: EFSA 2009; 7(9):1220

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- Contributes to normal function of the immune system: EFSA 2009; 7(9):1220; 2010;8(10):1727
- Contributes to normal thyroid function: EFSA 2010;8(10):1727; 2009; 7(9):1220
- Contributes to protecting cells from oxidative stress: EFSA 2009; 7(9):1220; 2010;8(10):1727
- Has long been recognized as essential in animal reproduction (Rayman 2002)
- Improves motility in subfertile patients with low selenium status, however not all patients respond (Scott et al, 1998)
- Protects sperm DNA from oxidative stress by promoting protamin packaging (Pfeifer et al, 2001)

L-carnitine

- Increases sperm motility: Vitali 1995, Vicari 2002, DeRosa 2005, Balercia et al 2005, Cheng 2008
- Li et al 2005: pregnancy rates are raised too
- Khademi 2005: effect especially strong in smokers
- In various studies the beneficial effect on motility was accompanied by increased vitality and count (Vitali 1995, Vicari 2002, Lenzi et al, 2003 und 2004, Balercia et al, 2005, DeRosa et al, 2005, Chenget al, 2008)
- Reduces excess acetyl-CoA in the sperm mitochondria, leading to diminished build up of ROS (Gülcin 2005)

Lycopene

- Anti-inflammatory and anti-oxidative effect (Gupta 2002, Heber 2002)
- Reduces the production of ROS by leukocytes in semen.
- Lycopene supplementation in vitro protected sperm DNA from oxidative damage (Zini 2009)
- Improved sperm quality (Tremellen 2009)

Coenzyme Q10

- Higher fertilisation rate when used in vitro (Lewin 1997)
- Increased sperm count and motility in in vivo study (Tanimura 1967)
- Supplementation leads to reduced H2O2 in seminal plasma of infertile men (Alleva 1997)

Glutathione (reduced) / N-acetyl-L-cysteine (NAC)

- Glutathione as a supplement improved sperm motility in a number of studies (Lenzi 1992, Hong 1994, Perinaud 1997)
- Glutathione protects DNA from oxidative damage (Lopes 1998)
- Glutathione is not easily absorbed by the GI tract, but supplementation of its precursor NAC has been demonstrated to raise intracellular glutathione levels effectively (Yim et al, 1994)

Dr. Daniel Matthes, Regulatory Affairs

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