SIGHI Medication Manual

Medication for Systemic Mast Cell Activation Disorders (MCAD)

(mast cell activation syndrome MCAS, systemic mastocytosis SM, mast cell leukemia MCL, histaminosis)

- *Therapeutic strategy for MCAD*
- *Active ingredients of medications, medical products, food supplements and foods for special medical purposes: Mechanisms of action, application, advantages and disadvantages*
- *Recommendations for use in basic therapy, symptomatic adjunctive therapy and in special situations (premedication before medical interventions and dental treatments, allergies, anaphylactic shock, infections, vaccinations, pregnancy and lactation, mental illnesses)*
- *Guidance for the assessment of compatibility of products*
- *With references to the scientific literature*

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Author: Heinz Lamprecht, MSc

Translated by Dr. med. Matthew Chaney

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www.mastzellaktivierung.info

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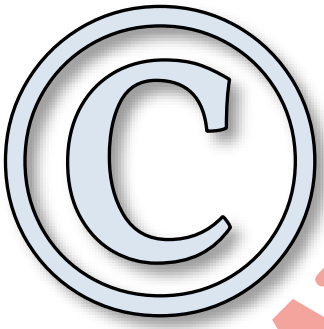

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Disclosure of possible conflicts of interest

The author is involved in the resale of a medical product. This is however a not-for-profit purchasing group with the sole aim of passing on the price advantages as far as possible to those affected. Thus, a conflict of interest in the sense of an incentive to represent a product more positively than it is or to distort or suppress information in any other way, does not exist in the author's opinion. The author has no (personal, financial or business) relationship with the manufacturers. The SIGHI does not sustain itself by selling medical products, but through its credibility. The author strove to make the selection and evaluation of the products specified here according to his best knowledge and belief for the benefit of those concerned.

Table of Contents:

1 Preliminary remarks

1.1 Disclaimer, disclosure duty

This medication manual was created by a university educated professional in the natural sciences (MS in Environmental Sciences, ETH Zürich) without a formal medical education. The information contained herein can be incomplete, incorrect, or outdated. Also, certain active ingredients or products listed here may be unsuitable in your individual case for particular medical reasons.

This document is updated continually. Whenever possible you should access the current version at www.mastzellaktivierung.info, rather than using a printed or locally stored version. Never use the information provided here as the sole source, but instead seek advice from your doctor or pharmacist.

If a medical professional prescribes or directly hands out medications to you, inform him about diseases that you have and about all the medications and medical products including supplements and over the counter remedies that you take occasionally or on a regular basis.

To be aware of potential risks and side effects always carefully read the enclosed information leaflet:

Switzerland: www.swissmedicinfo.ch **(official),** https://compendium.ch, https://ch.oddb.org**.**

Germany: http://oddb.org**.**

Austria: https://aspregister.basg.gv.at**.**

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1.2 Abbreviations. Definitions

→: a leading arrow (→) means "see", for example regarding references to page numbers or section numbers. Words or abbreviations with a preceding arrow are explained in the current section (1.2).

A: Austria

CH: Switzerland

D: Germany

DAO: Diamine oxidase, ABP1. An enzyme, produced mainly in the intestinal mucosa and in the kidneys, which can break down histamine, putrescine and other biogenic amines.

Drag: Dragee. A →tablet with a sugar coating.

Fct: film-coated tablet. A →tablet that is coated with a thin polymer layer.

Histamine: A biogenic amine, that due to its numerous features as an endogenous messenger, a neurotransmitter and inflammatory mediator can be described as the most important symptom inducing mast cell mediator. Histamine is not only produced by the body, but is also a degradation product of proteins in rotting or fermented foods.

Histaminosis: We define histaminosis as the **condition** in which the histamine status in the body deviates so far from the **ideal range** (either locally or systemically), that well-being or physical / mental performance are impaired to a significant degree. Usually the deviation is such that the levels are above the normal range, i.e. there is a histamine surplus. This term does not refer to the cause of this condition, which may have physical causes (originating in the body) or be due to environmental factors. Possible physical causes are for example the excessive release from mast cells, basophilic granulocytes or other histamine storing cells (e.g. due to MCAD, allergies, autoimmune diseases, certain tumors) or disorders in degradation (i.e. insufficient enzymatic activity of DAO).

Histamine intolerance (abbreviation: HIT):

The term "intolerance" comes from the Latin: *intolerantia*, derived from *tolerare* = "to bear", "to endure", with the negating prefix "*in-*".

Different conceptions are encountered about how histamine intolerance should be defined:

In the strictest sense histamine intolerance is an acquired or congenital reduction of the function of the histamine degrading enzyme diamine oxidase (DAO).

In a broader sense HIT can be defined as a disturbance at any point in the various enzymatic degradation pathways of histamine and other biogenic amines (enzymopathy, quantitative or qualitative enzyme deficiencies).

We recommend only referring to HIT when histamine degredation disorders with a *proven* enzymatic cause are present and to otherwise use the term →histamine incompatibility.

Histamine incompatibility: Only histamine degradation disorders with a demonstrable enzymatic cause should be referred to as a histamine **intolerance** (in analogy to lactose and fructose intolerances, which are also caused by lacking enzymes or reduced enzyme activity). For all other "histamine disorders" or histamine mediated intolerance reactions of **unknown or not enzyme related cause** it would be better to use the concept of histamine **incompatibility**.

Intravenous, i.v.: Using a vein, i.e. a venous blood vessel (leading to the heart), as the route of administration administration for a substance. For example, by injection or infusion.

Cap: Capsules, a medication form consisting of a solid shell and a filling.

MCAD: Abbreviation of "mast cell activation disease". Otherwise referred to as "systemic mast cell activation disease". An umbrella term for diseases in which one or more acquired or inherited genetic mutations or epigenetic alterations lead to an incorrect permanent activation, an increased sensitivity, or excessive proliferation of mast cells and thereby lead to an excessive non-specific release of mast cell mediators. MCAD include the very common →MCAS, the rare →SM, and the extremely rare →MCL.

MCAS: Abbreviation of "mast cell activation syndrome". Otherwise referred to as →systemic mast cell activation syndrome.

MCL: Abbreviation for "mast cell leukemia".

Oral (per os, peroral): Route of administration of a substance via the mouth, i.e. to swallow.

SM: Abbreviation for "systemic mastocytosis".

Systemic mastocytosis (SM):

A subtype of →MCAD.

Systemic mast cell activation syndrome (MCAS): A subtype of →MCAD.

Tab: Tablets, a solid form of medications, formed by compression of powders or granulates under pressure.

1.3 Fundamentals of MCAD medical treatment

According to the current state of knowledge, mast cell activation diseases (MCAD) have their origin in particular, complex patterns of multiple genetic and epigenetic mast cell activating factors, for which to date there is no curative (healing the root causes) therapy. Treatment is therefore mainly limited to keeping the intensity of the symptoms under control for life and to reducing the frequency of acute reactions.

- ✱ ***The mainstay of treatment is identifying and avoiding the mast cell activating triggering stimuli. To a certain degree the strength of a reaction to particular stimuli is different among different individuals. Due to the wide variety of stimuli with which one is confronted daily, identifying the triggering stimulus proves to be a difficult and lengthy task. See www.mastzellaktivierung.info.***
- ✱ ***Medications are in most cases useful or even indispensable to support the treatment, but in the medium term and long term can not replace strict avoidance of triggers!***

The symptoms have to be alleviated as much as possible by **avoiding the triggers** (see www.mastzellaktivierung.info) [MOLDERINGS ET AL. 2011; SIGHI]. In particular, all histamine liberators contained in food, sweets, beverages, and tobacco products should be strictly avoided. To the degree that one reacts to histamine rich foods, these should be limited to a tolerable amount.

In most cases symptoms will still emerge despite avoiding the triggers as well as possible. Under these conditions additional **pharmacological therapy** is necessary. The main objective is to reduce the release and synthesis of mediators (by stabilizing the mast cells and where apropiate by reducing their amount). A second important principle is blocking the effect of released mast cell mediators.

- ✱ ***Mast cell activation diseases (MCAD) do not have a homogeneous presentation, but instead every affected person has their individual constellation of symptoms with an individual degree of severity that is subject to temporal fluctuations. Therefore, an individually adapted therapy needs to be found for each patient.***

With MCAD, there is no uniform clinical presentation and the degree of severity is very individual. Therefore, no universally valid recommendations regarding treatment and dosage of medications can be given, but instead the medical therapy should be guided by the unique type and severity of symptoms [MOLDERINGS ET AL. 2011; SIGHI].

The basic medication at standard doses usually already has a quite beneficial effect, but the quality of life can be further improved by dosage adjustments and additional active ingredients. Over time, the affected person will find out through patient experimentation, the specific combinations and dosages out of the numerous possible treatment options that will help him best in particular situations [AFRIN ET AL. 2016; SIGHI]. In the course of goal-directed experimenting, the patient will depend on the assistance of a physician at least regarding the prescription medications.

2 Overview: Who needs which medication when?

2.1 Medical treatment for systemic mast cell activation disorders (MCAD)

2.1.1 Therapeutic strategy for MCAD

▶ **Treatment in the chronic phase:**

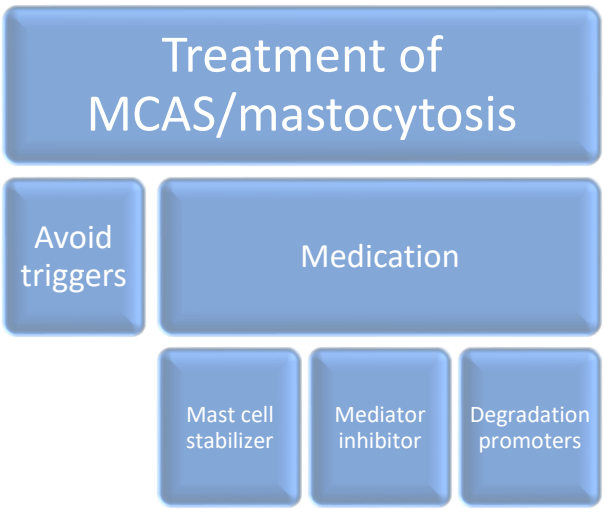
- **Basic medication:** Even without being in contact with mast cell-activating substances the level of release of mast cell mediators is often so high that it should be treated with medication on a permanent basis. In section 2.1.2 (page 16) we describe the basic medication to stabilize the mast cells and to control the symptoms while the condition is at the long-term baseline level of severity.
- **Symptomatic supplemental treatment:** Each affected person has an individual symptomatology. Which particular symptoms arise at which body site and with what intensity depends, among other things, on the particular set of causally involved mast cell mutations, which organs or tissues are affected by mutated mast cells and to which mast cell-activating substances one has been exposed. In section 2.1.3 (page 17) we present possibilities to specifically supplement the basic medication if necessary and to adapt it for the symptoms occurring in the particular case.

▶ **Treatment in the acute phase:** Not all triggering substances are reliably avoidable. This can lead to temporal fluctuations in symptom severity. Disease relapses can flare up both slowly (within hours to days) and very quickly (within minutes). If signs of anaphylactic or **anaphylactoid reactions** arise, proceed as described in chapter 7.1 "Anaphylaxis, anaphylactic shock" on page 79. In cases without anaphylaxis in the prior medical history, in the event of non-alarming newly emerging or intensifying preexisting symptoms, the **dosage of the basic medication and/or symptomatic supplemental therapy can simply be increased** up to at most the maximum permissible daily amount. With antihistamines many affected people even need up to four to six times the usual daily dose on a long-term basis. Naturally pharmacological agents with a rapid onset of action are to be preferred, while the dosage of very slow-acting long term medications (e.g. ketotifen) does not have to be adapted to one-off acute events.

Also suitable for acute short-term treatment:

Benzodiazepines: Flunitrazepam per os for a maximum of 3 to 4 days; inhibits mediator release from mast cells. [HOMANN ET AL. 2010]

In severe cases: Vitamin C 750 mg as an intravenous infusion dissolved in a glucose solution 5% (0.5 l / day for 3 to 4 days). Page 67. [HOMANN ET AL. 2010]



Second-line therapy

Peroral potassium supplementation, on a probatory basis for 2-3 days [WIRZ AND MOLDERINGS 2017].

Antihypertensive treatment, if (undetected) nocturnal hypertension could be the cause [WIRZ AND MOLDERINGS 2017].

Dihydroergotamine (serotonine receptor agonist with a potentially unfavorable risk and side-effect profile) [AICH, AFRIN AND GUPTA 2015]. Must absolutely not be taken together with Triptans.

Triptans (e.g. sumatriptan) are proven in animal studies to stimulate mast cell proliferation and should therefore only be used with great caution. [DUBAYLE ET AL. 2005; WIRZ AND MOLDERINGS 2017; AICH, AFRIN AND GUPTA 2015]

APETx2 (selective ASIC3-inhibitor) [AICH, AFRIN AND GUPTA 2015]. See also: [DIOCHOT ET AL. 2004].

Endometriosis pain

Palmitoylethanolamide (PEA): see page 48 [INDRACCOLO AND BARBIERI 2010; IUVONE ET AL. 2016]

Cromoglicic acid or di-sodium cromoglycate: page 33 [ZHU ET AL. 2015].

Throat pain

Increase the dose of H1-antihistamines,

etoricoxib (page 41) [WIRZ AND MOLDERINGS 2017]

Bladder pain syndrome, chronic non-bacterial cystitis, mast cell-mediated interstitial cystitis

H1-antihistamines, e. g. cetirizine [AICH, AFRIN AND GUPTA 2015], hydroxyzine [MINOGIANNIS ET AL. 1998].

H2-antihistamines, e. g. ranitidine, cimetidine, famotidine [AICH, AFRIN AND GUPTA 2015].

Pentosan polysulphate (a noticeable improvement usually only occurs after more than six months of therapy.) [TEICHMAN 2002; CHIANG ET AL. 2000; CHIANG ET AL. DAVIS ET AL. 2008; ANDERSON AND PERRY 2006].

Stop estrogen (hormonal contraception) and take leuprorelin [THEOHARIDES ET AL. 2008].

NK1R antagonists: gabapentin and L-703606 [AICH, AFRIN AND GUPTA 2015].

CaMKII-inhibitor: KN-93 [AICH, AFRIN AND GUPTA 2015].

Amphetamines [MOLDERINGS ET AL. 2011].

Prostatitis, chronic pelvic pain syndrome

Quercetin (page 74) [SHOSKES ET AL. 1999].

Disodium cromoglycate (DNCG, page 33) [AICH, AFRIN AND GUPTA 2015]

H1-antihistamines: cetirizine [AICH, AFRIN AND GUPTA 2015].

H2-antihistamines: ranitidine [AICH, AFRIN AND GUPTA 2015].

NGF neutralizing antibody AB-256-NA [AICH, AFRIN AND GUPTA 2015].

Chronic pelvic pain syndrome in women

Zafirlukast (leukotriene antagonist, page 42) [AICH, AFRIN AND GUPTA 2015].

Anti-CCL2 / JE (AB479NA) and anti-CCL3 (AB450NA) [AICH, AFRIN AND GUPTA 2015].

Complex regional pain syndrome (CRPS)

LY303870 (NK1R antagonist) [AICH, AFRIN AND GUPTA 2015].

Venom-induced hyperalgesia, excessive sensitivity to pain

Disodium cromoglycate (DNCG, page 33) [AICH, AFRIN AND GUPTA 2015]

H1-antihistamines: chlorphenamine, mepyramine (= pyrilamine) [AICH, AFRIN AND GUPTA 2015].

H2-antihistamines: cimetidine (not available in Switzerland) [AICH, AFRIN AND GUPTA 2015].

Diarrhea

Colestyramine [MOLDERINGS ET AL. 2011; HOMANN ET AL. 2010].

Leukotriene receptor antagonists (page 42): e.g. montelukast. [MOLDERINGS ET AL. 2011; HOMANN ET AL. 2010]

Psyllium husks regularize bowel movements, are of use with diarrhea as well as with constipation (e. g. ground psyllium husks as available at www.dm.de) [SIGHI].

5-HT3 receptor antagonists: e.g. ondansetron [MOLDERINGS ET AL. 2011]

Nystatin [MOLDERINGS ET AL. 2011].

Anal eczema, inflamed rear end

After every bowel movement immediately wash the affected area thoroughly with water without using soap. For example, with a wet washcloth, using a bidet, a toilet shower, or a shower toilet (Closomat) or by sitting on the edge of the bathtub and using the shower head. Then gently pat dry with a cloth, do not rub. Do not use oily creams or ointments. If fatty substances are to be used at all, at the utmost some coconut oil or olive oil can be applied after cleaning with water.

During strenuous activities (e.g. multi-day bicycle tours or horse trekking) unscented baby powder might also be helpful.

Only use local cortisone for a short time period because it causes the skin to become thin. [SIGHI]

Nausea, vomiting

Clonazepam, diazepam [AFRIN ET AL. 2015]

Lorazepam [HOMANN ET AL. 2010]

Metoclopramide (Caution: DAO inhibitor!) [HOMANN ET AL. 2010]

Domperidon [HOMANN ET AL. 2010]

5-HT3 receptor antagonists: e.g. ondansetron [MOLDERINGS ET AL. 2011; HOMANN ET AL. 2010].

Sensitivity to histamine-rich foods

Diamine oxidase (DAO): to be taken as needed (depending on the amount of histamine expected in a meal) or as long-term medication. Only to be taken as a prophylactic measure, and only for problems elicited by foodstuffs. Page 62. [SIGHI]

2.1.3.3 Miscellaneous symptoms and disorders

Inability to fall asleep or stay asleep

Benzodiazepines (3.9.3 on page 50):

Triazolam [MOLDERINGS ET AL. 2011]

Oxazepam [MOLDERINGS ET AL. 2011]

Depression

Doxepin (page 50) [GONZÁLEZ-DE-OLANO ET AL. 2016].

Anxiety, panic attacks

Benzodiazepines (3.9.3 on page 50):

e.g. lorazepam, alprazolam, clonazepam.

Mast cell activation by neuronal excitation or irritation

In some people mast cells, eosinophil granulocytes and lymphocytes are overly sensitive to the excitation of nerve cells in the vicinity (mediator release by neuronal effector cell triggering).

Treatment options:

Stress reduction, relaxation techniques, sedative antihistamines of the first generation (page 25), low dose benzodiazepines 1 to 2 times a week (see page 50, e.g. oxazepam, diazepam). [VAEM.EU]

Asthma

Leukotriene antagonists [HOMANN ET AL. 2010].

(Caution with paracetamol (acetaminophen)! It can increase the bronchial constriction.) [SIGHI]

3 Medicinal products (Medications)

Definition: Medicinal products (medications) are products (substances or mixtures of substances) with the intended purpose to treat or prevent human or animal diseases, injuries or disabilities or with the capacity to influence physiological functions or permit and facilitate making a medical diagnosis. This definition covers products, which are manufactured for this purpose and proclaimed as such (regardless of whether they are suitable for the purpose), as well as substances which are suitable (regardless of whether they are manufactured to this end or promoted as such).

For medicinal products specific and stringent legal requirements have to be met regarding proof of efficacy, the procedure of approval, their production, advertising, putting on the market and their dispensation.

Other legally defined and recognized product categories with a relation to health, such as medical products and devices (page 60), foodstuffs for particular medical purposes (page 62), or dietary supplements (page 67) do not belong to the category of medicinal products.

3.1 Antihistamines (histamine receptor antagonists)

Other designations:

Histamine receptor blockers, histamine blockers, histamine receptor inhibitors.

Einzahl: das Antihistaminikum, der Histaminrezeptorantagonist.

Mode of action

Histamine is one of the most important symptom-causing mast cell mediators. Histamine, a chemical messenger, affects the targeted cells by binding to histamine receptors on their surface, triggering a specific biochemical process.

Antihistamines (histamine receptor antagonists, histamine receptor blockers) have their effect countering histamine-induced symptoms by specifically blocking a particular type of histamine receptor. Figuratively speaking, they clog certain keyholes (receptors) so that the key (histamine) no longer can fit there. Antihistamines therefore do not directly counteract the histamine and do not reduce the level of histamine in the body. Instead they temporarily suppress certain effects that histamine would have on the targeted cells mediated by one specific type of receptor.

Four distinct **histamine receptor types** have at present been discovered and are designated as H1, H2, H3, H4. Antihistaminergic substances usually bind very specifically to only one of the four different types of histamine receptors, without having effects on the other

ones. Therefore, an H1-AH (H1-receptor specific antihistamine) cannot the have the effects of an H2-AH and the same applies vice versa.

The H1-antihistamines can be used to suppress the most symptoms and therefore have the greatest therapeutic significance. Additionally, in the eventuality of excessive stomach acid production (heartburn, acid reflux) or other disorders of the digestive tract (especially diarrhea) taking an H2-antihistamine might be of benefit. H3- and H4-blockers are currently of little therapeutic importance.

The various substances with H1-receptor antagonistic activity all have the same mode of action, but they may differ in terms of their overall effect, potency, duration of action, tolerability etc. The individual substances differ in the characteristics regarding absorption into and distribution in the body as well as degradation and elimination from the body, and also in other properties (toxicity, side effects, taste, etc.). It is therefore not irrelevant which H1-antihistamine one takes and the particular substance should be specifically selected for the desired attributes. If the results are not satisfactory after a few weeks or months another substance can be used on a trial basis.

Sometimes certain H1-antihistamines are even claimed to have a certain mast cell stabilizing effect. This is probably explainable by antihistamines causing the H1-receptor density to be reduced (i.e. a reduced receptor production by the cells) as a consequence of a lack of their stimulation due to being blocked. For this reason, it is recommended for people with pollen allergies that they prophylactically begin with H1-antihistamines a few days or weeks before the beginning of the pollen season in order to minimize the stimulation of H1-receptors from the beginning. [MIZUGUCHI ET AL. 2011, MIZUGUCHI ET AL. 2010]

3.1.1 H1 antihistamines (H1 receptor antagonists)

- ***H1-antihistamines (abbr.: H1-AH) are among the most important active substances in the treatment of MCAD and other histamine-mediated disorders and symptoms. They have a favorable risk-benefit profile.***
- ***Their mechanism of action is to prevent histamine from having an effect by blocking the histamine-H_1-receptor through which the majority of the symptoms caused by histamine is mediated. With only one active substance a very wide range of symptoms can be treated.***
- ***Older substances also affect the central nervous system and cause drowsiness (and therefore can be used to treat insomnia). This is not the case for the newer substances.***
- ***They are taken either continuously on a long-term basis or as required. H1-AH can be taken both with the intent to prevent as well as the intent to cure.***

Application and dosage:

H1-antihistamines can be used for all types of histaminosis. The administration is usually →peroral, in severe cases additionally →intravenous. Topical external application in an ointment also exists (for example in soothing insect bites and itching).

Unless otherwise stated, they may either be taken on a regular basis or as required depending on the situation, preferably prophylactically (before expected symptoms arise), or alternatively curatively (to relieve existing symptoms).

4 Medical devices

Definition: Medical devices are objects or (pharmacologically inert) substances used for therapeutic or diagnostic purposes in humans. In contrast to medications the principal intended effect of medical devices is mainly of a physical or physicochemical nature, i.e. without uptake of a pharmacologically / metabolically / immunologically active substance in the body or without direct Intervening in the metabolism.

Market access and marketability are differently regulated for medical devices than for medications. In this matter the Medical Devices Directive of the European Council 93/42/EEC (with applicability in the EU and also in Switzerland) and the Medical Devices Ordinance of the Swiss Federal Council (CH) are authorative. Medical devices are not officially approved, but instead, depending on their risk classification, are monitored by an external body (conformity assessment body) for compliance with legal requirements before and during the placing of these on the market.

4.1 Clinoptilolite, zeolite

Other names / brands:

Zeolites, Megamin®, MANC® (Modified, Activated Natural Clinoptilolite), Froximun® Toxaprevent®.

Mode of action:

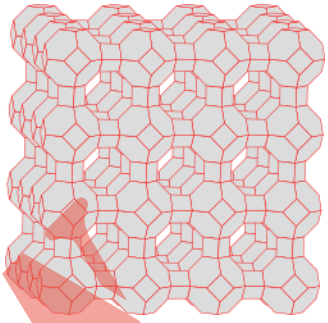
The crystalline mineral clinoptilolite belongs to the category of sedimentary rocks, but was originally formed in volcanic deposits. In chemical terms clinoptilolite is a group of hydrous aluminosilicates with calcium, potassium or sodium as connecting cations:

Clinoptilolite-Ca: $Ca_3(Si_{30}Al_6)O_{72}{\cdot}20H_2O$

Clinoptilolite-K: $K_6(Si_{30}Al_6)O_{72}{\cdot}20H_2O$

Clinoptilolite-Na: $Na_6(Si_{30}Al_6)O_{72}{\cdot}20H_2O$

The physical properties, not the chemical ones of this silicate structure are important:



As other zeolites clinoptilolite consists of a microporous scaffold structure of $[AlO_4]^-$- and $[SiO_4]^-$-tetrahedra. Water and other small molecules with specific properties can fit in the interstices of this crystal lattice. Due to this the material can be used as a molecular sieve or ion exchanger, in short: as a kind of "filter". For this purpose, the rock is ground finely. The finer the particle size, the greater the surface area and consequently the more pronounced the physical filter effect of this material. When buying, do not only compare the price per kg, but also the declared particle size.

In brief it is "flour" made of rocks, in which certain substances are captured and others are not.

Clinoptilolite is one of the most abundant zeolites and has many important industrial applications, where it is used in huge quantities in building materials, in horticulture, in animal feed, as a fertilizer carrier material, as stable bedding, cat litter, in household products, as a desiccant, and in environmental technology. Amongst other things, zeolites are used for the purification of substances, in wastewater treatment, and as an additive in laundry detergents to decalcify hard water.

Clinoptilolite is marketed as a **medical device** and certain claims of therapeutic abilities are associated with the products, for which we have so far found no convincing evidence, neither in literature nor in self-experiments (see also: [KERSCHNER 2015]).

The insoluble material is ingested in powder form and passes through the digestive tract unchanged, without being taken up by the body.

According to the manufacturers it should **"detoxify"** by absorbing harmful substances (binding them to itself) and thereby decreasing their uptake from food by the body. According to the manufacturers' claims ammonium, lead, mercury, **histamine and other amines** are bound. "*Essential substances, such as zinc, and iron are demonstrably not bound and left at the disposal of the body.*", is written in a leaflet.

Should this actually work, at best it would be the meal consumed at the same time and not the body that would be "*detoxified*". It seems to be proven that ammonium, cesium, strontium, and heavy metals are partially absorbed. Naturally this material does not have any innate "intelligence" which could distinguish which substances would be "harmful" or "useful" for humans. Anything is simply indiscriminately absorbed that fits into the interstices of the crystal lattice due to its molecular size, shape and charge. In our opinion it does not seem to be sufficiently researched whether this would also include useful or essential nutrients.

Six SIGHI members have volunteered and tested the preparation "Froximun Toxaprevent" in a self-experiment. None of the subjects could determine an effect after 1-2 months. This non-representative small trial of course does not prove the ineffectiveness of the preparation, but did not manage to convince us, that the effect is worth the price.

For this dirt-cheap substance of which tons are used in industry all of a sudden comparatively very high prices are charged for a few grams as soon as the stone flour is filled into capsules and packaged like a medication. Of course, there might be some differences in purity requirements and particle sizes, but whether they justify the high price is an open question.

Use:

Depending on the particular manufacturer the specifications are for example from 3 to 8 grams of powder (one teaspoon) in the morning stirred in water or in food and ingested.

Adverse effects

Clinoptilolite is regarded as a comparatively innocuous substance with few side effects. It is still not entirely without risks:

It is conceivable that with regular use the crystal particles could abrasively damage the intestinal mucosal cells or at least irritate and injure them.

A report by the EFSA (European Food Safety Authority) indicates that zeolites significantly increase the aluminum blood levels in animal studies performed on dairy cows [EFSA 2007]. Aluminium is suspected to be able to trigger Alzheimer's and other diseases.

In addition to pollutants, beneficial nutrients could possibly also be absorbed, which in the long term could lead to deficiencies. EFSA reports a "*dramatic depression of feed intake*" with a - albeit not severe - phosphate deficiency ("*hypophosphataemia*") as an observed result in a trial with dairy cows [EFSA 2007].

In an enclosed information leaflet one manufacturer warns that their product should not be taken with medications, but only with an interval of at least one hour. This shows that even manufacturers expect that desired substances could also be absorbed. Aspirin, theophylline, propanolol, and phenobarbital are absorbed to a slight degree in vitro. Regarding some medically used metal ions such as lithium or cisplatin, interactions with this substance can be expected. However, for most medications, interactions with clinoptilolite are unlikely due to their molecular size.

5 Foods for special medical purposes

Definition: "Dietary foods for special medical purposes", according to the legal definition of the EU, are foods that have been developed for patients whose nutritional needs cannot be met by eating normal food, caused by certain diseases, disorders, or specific complaints. Other somewhat shorter names are **"supplemental balanced diet"** or **"balanced diets"**, the abbreviation for **food for special medical purposes** is **FSMP**. In accordance with article 2 paragraph 2g of Regulation (EU) No 609/2013 they are intended for the dietary management of patients with:

a) limited, impaired or disturbed capacity to take, digest, absorb, metabolise or excrete ordinary food or certain nutrients contained therein, or metabolites; or

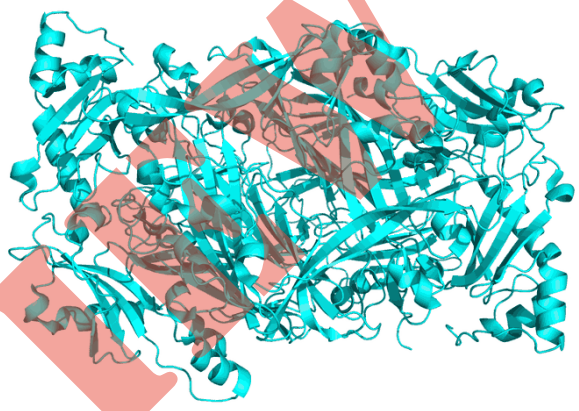
b) with other medically-determined nutrient requirements

The intended special purpose for use must be discernable from the labeling. In contrast to medications, the permissible defined purpose of FSMP is only to satisfy a specific nutritional requirement and not to treat diseases. The effectiveness must be proven by commonly accepted scientific data. There is no approval procedure for this; instead proof of efficacy would at most have to be presented upon request by the Food Safety Authority (or equivalent regulatory body). Advertising with disease-related statements is allowed for such products.

5.1 Diamine oxidase (DAO)

Other designations:

diamine oxidase, amiloride binding protein 1 (ABP1), amiloride-sensitive amine oxidase, kidney amine oxidase (KAO). Obsolete: histaminase.



Model representation of the crystal structure of diamine oxidase (DAO).

Mode of action:

Diamine oxidase (DAO) is an endogenous enzyme that specifically degrades certain biogenic amines (e.g. histamine, putrescine and cadaverine). DAO can be found in almost all organs and tissues in humans. It is produced in large quantities in the intestines, kidneys, and the placenta; however, it is lacking in the central nervous system. In the intestines, it degrades the histamine from the food and produced by the microbiota in order to prevent too much of it from entering the body.

If the enzyme activity is insufficient in the intestine either due to a diesease or due to external influences, a DAO product can be taken to supplement the endogenous enzyme activity. Diamine oxidase can be obtained from animal- or plant-based raw materials and isolated by precipitation in salt gradients or by other seperation processes.

6 Nutritional supplements

In addition to medications and medicinal products or dietary foods for special medical purposes, there are also nutritional supplements that can positively impact at MCAD. While the active ingredients of medications have been thoroughly investigated, are clearly defined and highly effective substances whose efficacy has been proven in studies, this is not always as clearly verified in the case of dietary supplements and their effects are often not very strong or even proven to exist beyond reasonable doubt. Therefore, medicinal treatment should primarily be based on medications and nutritional **supplements** should at most be used to complement this in reasonable, non-hazardous doses. A commonly voiced opinion is that nutritional supplements are more natural and therefore less harmful than medications. Here too, however, depending on the substance, overdoses are possible. Some supplements are also synthetically produced and various synthetic additives are usually included. Moreover, the harmfulness of a substance does not at all depend on whether it is of a "natural" or "synthetic" origin, or whether approval has been requested as a drug or as a nutritional supplement. Both among the natural and synthetic substances there are harmless as well as highly toxic substances.

6.1 Vitamin C

Other designations:

Ascorbic acid, E300, ascorbate.

More E-numbers of ascorbic acid derivatives: E301 (sodium ascorbate), E302 (calcium ascorbate), E304a (ascorbyl palmitate) and E304b (ascorbyl stearate).

Vitamin C is a general term for the substance L-(+)-ascorbic acid and its derivatives with the same effect. These include substances that can be converted in the body to L-(+)-ascorbic acid, such as dehydroascorbic acid (DHA). The salts of ascorbic acid are called ascorbates (e.g. magnesium ascorbate, calcium ascorbate, sodium ascorbate).

Mode of action:

Several scientific publications show that taking vitamin C lowers the histamine level in the blood [for example HAGEL ET AL. 2013; CLEMETSON 1980]. On the one hand, this happens because vitamin C inhibits histidine decarboxylase and thereby slows down the formation of histamine [MOLDERINGS ET AL. 2016]. On the other hand, vitamin C accelerates the degradation of histamine [JOHNSTON, MARTIN & CAI 1992; UCHIDA, MITSUI & KAWAKISHI 1989; CHATTERJEE ET AL. 1975]. Also, the release of histamine and prostaglandin (another inflammatory mediator) is inhibited [SHARMA AND WILSON 1980]. Ascorbic acid is also a necessary cofactor for many biochemical reactions. Ascorbic acid provides electrons for copper(I)-dependent monooxygenases and iron(III)-dependent dioxygenases. Many reports of concerned attest to a positive effect of vitamin C on overall well-being and relief of symptoms.

The human body can not synthesize vitamin C, which is an essential element of the human metabolism, but must acquire it from food. Vitamin C is used up (among other things) in the reaction with histamine. A high level of histamine exposure causes an increased need for vitamin C.

For very brief time a high dose of vitamin C (several grams) can be used therapeutically against urinary tract infections, since the microorganisms thrive less well in acidic urine.

Availability:

Fresh or frozen fruits, as well as raw or not overcooked vegetables are good natural sources of vitamin C (although the incompatible foods in MCAD, such as citrus fruits, should be

avoided). In pharmacies pure vitamin C powder is available over the counter, for example in bottles containing 100 g. In Germany it is much cheaper than in Switzerland and occasionally also available as a 100 g refill bag. There are also very many nutritional supplements (such as effervescent vitamin tablets), sweets, etc., which are fortified with vitamin C. However, they have the disadvantage that they often contain other incompatible, unhealthy or unnecessary ingredients.

Use and dosage:

Both the German and the Swiss Nutritional Society (Schweizerische Gesellschaft für Ernährung) recommend a daily intake of 100 mg of vitamin C per day for healthy people. With a healthy and balanced diet, this value is reached by normal food intake, so no additional supplementation is needed. In certain diseases - including allergies, chronic inflammatory diseases and MCAD - but the required amount is increased. We recommend an intake of approximately **100 to 1,000 mg per day** (= 0.1 to 1 grams per day), to be spread over several singular doses of each maximally 200 mg. A higher single dose brings little added benefit, because not much more can be absorbed, but can irritate the stomach. Taken for brief time periods amounts up to 5,000 mg are regarded as safe. Excess vitamin C is excreted by the body via the urine, since the body does not have any relative storage capacity for vitamin C and vitamin C is readily soluble in water.

Orally ingested vitamin C is rapidly absorbed (onset of effect within a few minutes), but only has an effect in the body for a short time. Therefore, it should be taken several times a day. A steady supply can be achieved for example through nutritional supplement in the form of delayed release capsules, which continually release the active ingredient over a prolonged time period. There are also cheaper options:

- Twice daily put a large glass of water, in which a pinch of pure vitamin C powder is dissolved in front of you (e.g. at work) and drink sips of it throughout the day.
- In a bowl, dissolve a pinch of pure vitamin C powder in a small amount of water or fruit juice, add oat flakes or millet flakes (no processed and refined forms of "breakfast cereals") and let them absorb the liquid. Then as usual add the milk, fruit juice, or other ingredients to the muesli flakes. The flakes will then slowly and continuously release the absorbed vitamin C during digestion.
- Eat fresh fruit or vegetables several times a day.

If the most rapid onset of action is the primary goal, then lozenges or chewable tablets are advantageous compared to other delivery forms, since vitamin C is especially quickly absorbed through the oral mucosa. On the other hand, ascorbic acid is an acid and in concentrated form can therefore damage the tooth enamel, especially in combination with sweets (caries).

In severe disease forms, vitamin C is also administered by infusion.

Buffered vitamin C (for example, magnesium ascorbate, calcium ascorbate, sodium ascorbate) irritates the stomach less, affects the teeth less, and is better tolerable for those sensitive to acids. Also, the body does not have to furnish the minerals for its neutralization. It is also more expensive than unbuffered vitamin C. Magnesium and calcium are also readily usable by the body. Magnesium ascorbate which is brown in color tastes pleasant, calcium ascorbate which is white in color may taste slightly bitter.

Side effects:

Vitamin C hardly has side effects. An overdose does by and large not entail complications. Too high doses (usually from about 5-15 g) can cause osmotically induced diarrhea.

Although vitamin C lowers the histamine level in the blood, at the same time it seems to also partially inhibit diamine oxidase (DAO), depending on the dosage, so that histamine degradation by DAO is slowed down [SATTLER ET AL. 1985]. It is conceivable that this might be unfavorable for people with disorders of DAO activity.

For MCAD patients that are particularly sensitive to acid, unbuffered vitamin C and other organic acids can sometimes also have mast cell activating activity.

The risk for calcium oxalate kidney stones could rise at high doses (from 2-3 g/d) in susceptible persons.

No additional vitamin C should be taken in case of iron storage diseases (hemochromatosis, thalassemia, sideroblastic anemia) and known glucose-6-phosphate dehydrogenase deficiency.

In all other cases we think that vitamin C use should be recommended. However, one should observe with which dose one achieves the best effects.

Mandated insurance coverage of costs (valid for Switzerland):

Vitamin C is regarded as a foodstuff and is therefore not covered by health insurances (except certain vitamin C preparations if prescribed by a physician). However, these preparations are many times more expensive than pure vitamin C powder bought over the counter so it is probably still often cheaper to cover the costs by oneself because of the deductibles and copayments.

6.2 Vitamin D_3 (cholecalciferol)

Other designations:

colecalciferol

Mode of action:

Vitamin D_3 is a prohormone (precursor of the hormone calcitriol) with very diverse, as yet not completely elucidated mechanisms of action.

Those affected report a positive effect of high dosed vitamin D_3 on their general condition. In particular regarding weather sensitivity from which certain individuals suffer and which cannot be avoided, has reportedly decreased significantly in several known cases. Recent studies now provide an explanation for these observations: There are vitamin D receptors on the surface of mast cells. Studies have shown that vitamin D is needed to keep the mast cells stable. Both in vitro and in vivo, vitamin D inhibits IgE-mediated activation of mast cells. Less inflammatory mediators were produced. A vitamin D deficiency, however, leads to mast cell activation. [LIU, LI, QIU ET AL. 2017; YIP ET AL. 2014]

Another study, however, indicates that D deficiency (that is widespread in the general population) may not be among the main causes of the frequent occurrence of the MCAS [WIRZ ET AL. 2017].

How does the body get vitamin D_3?

For historical reasons, vitamin D3 (cholecalciferol) is referred to as a "vitamin", but can in fact be synthesized by the body itself. The body itself covers almost the entire demand of vitamin D_3 by producing it in the skin with the help of the UVB portion of sunlight.

Nutrition only marginally affects the supply of vitamin D_3. It is only contained in significant quantities in oily fish (salmon, smoked eel, herring, anchovies). To a lesser degree small amounts are present in liver, eggs and dairy products.

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