Azepur99®

www.azelaic.com

Azepur99

Essential Guide azelaic acid

The **standard for azelaic acid** in pharma & cosmetics

Table of content

Company profile

Azelaic Products BV is a specialized supplier of azelaic acid for pharmaceutical and cosmetic applications. With satisfied customers all over the world, a long experience and a passion for quality, Azelaic Products BV is at your service for your azelaic acid business.

In compliance with international regulatory standards.

- EU GMP
- EU DMF
- US DMF (2019)
- US FDA Inspected and approved production site
- GDP+

World-wide delivery

- C&F main airports
- DAP

Lead time

- Within 10 working days from our warehouse

Azelaic Products B.V.
Mussenberg 1
6049 GZ Roermond
The Netherlands

Phone +31 475 782540
Mail service@azelaic.com
Web www.azelaic.com

Azepur99®

Azepur99® is a registered trademark

Disclaimer

Azelaic Products has compiled the information contained to be best of its knowledge and capabilities, respecting the rights of third parties. However, Azelaic Products accepts no responsibility or liability for any consequences arising from the use of this information. Azelaic Products will not be liable if the use of this information by third parties infringes a patent or any other right belonging to a third party.

Azelaic acid ; the active material

Azelaic acid (1,7-hepanedicarboxylic acid) is a naturally occurring dicarboxylic acid. It occurs amongst others in cereals like wheat, barley and rye. Extracts of these cereals have been used since 3000 years in Ayurveda products to treat hyperpigmentation (skin lightening). Azelaic acid also exhibits bactericidal properties, and was shown to be very effective for the treatment of acne vulgaris. Azelaic acid has also been shown to be effective for the treatment of baldness.

Azelaic acid obtained from natural resources is not commercially available; the extraction process is very difficult and expensive. On the other hand, azelaic acid can also be produced by ozonisation of oleic acid. Ozonisation is a hazardous reaction that can easily run out of control. The alternative is oxidation of oleic acid with peracetic or performic acid. This route goes via the 9,10-epoxide, followed by subsequent oxidation of the epoxide. The oxidation of oleic acid results in the formation of azelaic acid and nonanoic acid. Oleic acid required is obtained from hybrid sunflower oil and milk thistle oil. This choice of starting material enables to produce a grade of azelaic acid of more than 99% purity where regular azelaic grades are specified at 85-90%.

Azelaic acid is an odourless, white and highly crystalline solid with a melting point of 110°C. It is soluble in glycerol and glycols, but poorly soluble in water (2,1 g/l). The solubility of azelaic acid is pH dependant; the mono- and disodium salts are significantly better. Also micro-emulsions based on sorbitan esters using glycerol and lauryl alcohol as co-surfactants enable to dissolve azelaic acid.

AZELAIC ACID	INDUSTRIAL	COSMETIC	PHARMA
PURITY	80-98%	99,0%	99,2%
ORIGIN	ANIMAL / VEGETABLE	VEGETABLE	VEGETABLE
PACKING	25 KG BAGS JUMBO BAGS 1000 KG	HDPE DRUM	HDPE DRUM
POWDER FINENESS	FLAKES-POWDER	MAX. 30 MICRON	MAX. 30 MICRON
CERTIFICATIONS	VERY LIMITED	LIMITED	REQUIRED
TECHNICAL SUPPORT	VERY LIMITED	LIMITED	REQUIRED

For the treatment of acne vulgaris, rosacea, skin lightening and hair growth only the cosmetic or pharma grade can be used.

1. The tale of azelaic acid

1.1 On the processing of azelaic acid

The efficacy of azelaic acid for the treatment of health disorders, more particularly acne vulgaris, & hair growth & regrowth, alopecia areata rosacea, and its functionality for skin lightening, has been documented in quite some detail. However, significantly less information has been made available on the processing of azelaic acid:

1. solubility of azelaic acid,
2. configuration of the bio-availability of azelaic acid,
3. formulation strategy for clear products containing azelaic acid,
4. formulation strategy for multi-phase products containing azelaic acid,
5. formulation strategy for organogels containing azelaic acid.

Vegetable-based azelaic acid is commercially available as cosmetic grade, 99% purity and as pharmaceutical grade, 99,2% purity, under the trade name Azepur99.

1.2 Solubility of azelaic acid

Azelaic acid is only sparingly soluble in water: 2,1 g/l (20°C). At elevated temperature the solubility markedly increases with increasing temperature: at 50°C 22 g/l Azepur99 will dissolve. Saturated solutions of azelaic acid react slightly acidic: azelaic acid is a diprotic acid with dissociation constants (pKA values) of 4,55 & 5,50. The solubility of saturated linear α,ω-dicarboxylic acid (table 1) decreases quite significantly with increasing chain length while the dissociation constants do not show much variation (with the exception of oxalic and malonic acid).

TABLE 1: SOLUBILITY IN WATER OF LINEAR α,ω-DICARBOXYLIC ACIDS

DICARBOXYLIC ACID	FORMULA	SOLUBILITY
OXALIC ACID	$C_2H_2O_4$	220 G/L (25°C)
MALONIC ACID	$C_3H_4O_4$	763 G/L (25°C)
SUCCINIC ACID	$C_4H_6O_4$	83 G/L (25°C)
GLUTARIC ACID	$C_5H_8O_4$	639 G/L (20°C)
ADIPIC ACID	$C_6H_{10}O_4$	14 G/L (20°C)
PIMELIC ACID	$C_7H_{12}O_4$	50 G/L (20°C)
SUBERIC ACID	$C_8H_{14}O_4$	12 G/L (20°C)
AZELAIC ACID	$C_9H_{16}O_4$	2,1 G/L (20°C)
SEBACIC ACID	$C_{10}H_{18}O_4$	0,1 G/L (20°C)

The monosodium and disodium salt of azelaic acid are reasonably soluble in water, and very well soluble at elevated temperature. The sodium salts are best made in-situ by neutralisation of azelaic acid with sodium hydroxide. That enables processing of azelaic acid in the water phase of emulsion systems or in gel preparations, having said that the final emulsions or gels will react alkaline. Adjustment of the pH to acidic values comes with a price as in an acidic environment azelaic acid will be regenerated and may be subjected to crystallisation. The crystallised product will not contribute to the bio-availability of Azepur99.

Neutralisation with organic nitrogen bases is also possible, preferably with products that do not form stable N-nitrosamines. For pharmaceutical preparations tromethamine (TRIS, 2-amino-2-(hydroxymethyl)propane-1,3-diol) or AMP (2-amino-2-methyl-propan-1-ol) are preferred. Upon neutralisation of azelaic acid with TRIS or AMP simultaneously a powerful pH buffer is formed.

There is only a limited number of cosmetically/pharmaceutically suitable solvents available for azelaic acid, to enable preparing clear solutions at ambient temperature: polyethylene glycol and (poly)propylene glycol ethers. Ethoxydiglycol (Transcutol® P; Gattefosse) is probably the best solvent for azelaic acid available. Also butoxydiglycol is a good solvent for azelaic acid. These solvents enable the production of clear gels of azelaic acid, at high concentration (see also : ***Formulation of clear products***).

Some ester-based products are suitable to incorporate azelaic acid in emulsions: esters of dicarboxylic acids and/or esters derived from isostearic acid. Reference is made to (see also: ***Formulation of emulsions***).

1.3 Bio-availability of azelaic acid

From a medical/physical point of view bio-availability of azelaic acid is the most important parameter enabling the product to demonstrate its ultimate abilities. In currently commercial gel & emulsion preparations containing azelaic acid crystallization is frequently encountered; these preparations may contain up to 15-20% azelaic acid, but only a small percentage is bio-available.

Crystallisation of azelaic acid is best determined using optical microscopy using polarised light. Crystals of azelaic acid in emulsions or gels are birefringent and are easily detected. To avoid crystallisation suitable solvent(s) shall be used that is/are able to keep azelaic acid mono-molecularly in solution. That is applicable for emulsions in both the water or oil phase, but also for aqueous/hydrophilic gel preparations. Eventually also a solubiliser can be applied, but the amount of azelaic acid that can be solubilized is rather limited indeed. An exception are gels based on phospholipids, more particularly phosphatidylcholine. These are the so-called organogels that exhibit an extreme potential for transdermal transport for pharmaceutical and cosmetic actives (see: ***Formulation of organogels***).

1.4 Formulation clear products

Solubility and bio-availability are prime parameters for working with azelaic acid. The use of azelaic acid in the water phase of emulsions was already described (see: ***Solubility of azelaic acid***), and this also enables the use of azelaic acid in waterborne gels based on carbomers, cellulose ethers or polysaccharides such as xanthan gum or sclerotium gum. However, these gels are alkaline and show only a limited degree of bio-availability.

The solubility of azelaic acid in ethoxydiglycol is 360 g/l. A clear solution will be obtained that will not show crystallisation. Ethoxydiglycol is miscible with water in any proportion, and also soluble in many polar lipids. An example of such an application is given in table 2.

TABLE 2: CLEAR AZELAIC ACID SOLUTION

INGREDIËNT	CONCENTRATION
ETHOXYDIGLYCOL	61,0 %
AZELAIC ACID	20,0 %
AQUA	11,5 %
PEG-40 HYDROGENATED CASTOR OIL	4,5 %
DIMETHYL ADIPATE	3,0 %

The formulation according to table 2 enables transdermal transport, as ethoxydiglycol is swiftly absorbed through the skin. This results in transport of azelaic acid to the ratget location, such as in the hair follicles for the treatment of acne vulgaris. The preparation according to table 2 is very low viscous, but can effectively be converted into a transparent transdermal gel using hydroxypropylcellulose (HPC). For serum preparations 1-2% HPC is required, depending on the desired viscosity. For gel preparations 2-4% is needed. As an alternative for ethoxydiglycol butoxydiglycol may also be used although the solubility of azelaic acid is less, estimated at 15%.

For personal care & cosmetic products both ethoxydiglycol and butoxydiglycol are limited in use because of their extreme penetration power. According to EU Regulation 1223/2009 the maximum allowed concentration ethoxydiglycol in leave-on products is 2,6% while for % butoxydiglycol 9,0% is allowed. These concentration limitations are not applicable for medical devices and pharmaceutical products. Taking the risk of stating the obvious, anti-acne preparations, anti-rosacea preparations and products for the treatment of alopecia areata or hair growth products are not covered by EU Regulation 1223/2009.

Several other non-restricted glycol ethers may be used as solvent for azelaic acid, although the solubility of azelaic acid is markedly lower compared to ethoxydiglycol and butoxydiglycol. These products are commercially made available by DOW Chemical under the trademark Dowanol®. Some examples are:

- Triglycol Ethyl Ether. Common name: ethoxytriglycol. CAS: 112-50-5. No INCI name assigned. Excellent solvent for azelaic acid. Cosmetic limitations: none.
- Dipropylene Glycol Monomethyl Ether Acetate. INCI name: PPG-2 Methyl Ether Acetate. CAS: 88917-22-0. Cosmetic limitations: none.
- 1-Butoxy-2-propanol. INCI name: Propylene Glycol Butyl Ether. CAS: 5131-66-8. Cosmetic limitations: none.
- 1-Propoxypropan-2-ol. Common name: Propylene Glycol Propyl Ether. CAS: 1569-01-3. Cosmetic limitations: none.

There is a massive set of other glycol ethers available, many of those are used in large quantities in chemical/technical applications and some of those are suitable for use in personal care & cosmetic products. Attention shall be given to the residual monomer concentration (ethylene oxide/propylene oxide) and [substituted] p-dioxanes.

1.5 Formulation emulsions

Solubility and bio-availability are very important parameters for working with azelaic acid. The use of azelaic acid in the water phase of emulsions was already described (see: ***Solubility of azelaic acid***), and this enables the use of azelaic acid in waterborne gels based on carbomers, cellulose ethers or polysaccharides such as xanthan gum or sclerotium gum. However, these gels are alkaline and show only a limited degree of bio-availability.

For emulsion systems clarity of the azelaic acid solutions is not significant. Especially polar esters are advantageously applied, preferably in water-in-oil (W/O) emulsions. Good solvents for azelaic acid in the oil phase of emulsions are dimethyl, diisopropyl esters & diethylhexyl esters of succinic acid or adipic acid. Also some isostearic acid based esters, more particularly isopropyl isostearate and ethylhexyl isostearate, are good solvents for azelaic acid in the oil phase of the emulsion. For all emollients mentioned is applicable that hot processing must be used to properly formulate azelaic acid. The ratio of the before mentioned emollient(s) and azelaic acid used is best set at 2:1, assuring that crystallisation will not occur. Control on the presence of azelaic acid crystals is essential.

The choice of the emulsifier(s) for W/O emulsions is rather limited indeed. This limitation arises from the fact, that the emulsifier is also required to suppress crystallisation of azelaic acid. Superior results are achieved with PEG-30 dipolyhydroxystearate (Cithrol® DPHS/Croda Oleochemicals, formerly Arlacel® P135). This emulsifier also tolerates high electrolyte concentrations. Polyglyceryl-3 diisostearate (Cithrol® PG32IS/Croda Oleochemicals; previously Prisorine® 3700) is an excellent co-emulsifier for PEG-30 dipolyhydroxystearate that enables to tune the sensorial and organoleptic properties of the final emulsion. The azelaic acid loading of W/O-emulsions may be rather high, up to 15% without crystallisation.

Azelaic acid loading for oil-in-water (O/W) emulsions is significantly lower compared to W/O-emulsions, while simultaneously avoiding crystallisation of azelaic acid must be avoided. In O/W-emulsions non-ionic emulsifiers/emulsifier pairs must be used that form a liquid crystalline phase in the continuous phase of the emulsion (the water phase). There are numerous examples of emulsifiers that may be used. A small anthology, according to INCI, is given in table 3.

TABLE 3: LIQUID CRYSTALLINE EMULSIFIER COMBINATIONS

CETEARYL ALCOHOL / CETEARETH-6 / CETEARETH-25
STEARETH-2 / STEARETH-21
METHYL GLUCOSE SESQUISTEARATE / PEG-20 METHYL GLUCOSE SESQUISTEARATE
SORBITAN STEARATE / POLYSORBATE 60
SUCROSE STEARATE / SUCROSE DISTEARATE / CETEARYL ALCOHOL
CETEARETH-12 / CETEARETH-20 / GLYCERYL STEARATE

In these systems azelaic acid is “dissolved” in the liquid crystalline double layer as described by Israelachvili, Ninham & Bingham (1976), Friberg & Shinoda. Numerous (commercial) examples of inclusion of physiologically active ingredients in the liquid crystalline double layer of emulsions have been reported. Processing is best done by combining the emulsifier pair and azelaic acid at elevated temperature, followed by the addition of the water phase and the remaining ingredients of the oil phase.

In many situations the use of a hydrocolloid is required as the mechanical strength of the liquid crystalline double layer is frequently insufficient, and that may lead to emulsion instability. The addition of a hydrocolloid does not necessarily leads to an increased viscosity.

1.6 Formulation organogels

Solubility and bio-availability are prime parameters for working with Azepur99. The use of Azepur99 in the water phase of emulsions was already described in (see: Solubility), and this enables the use of Azepur99 in waterborne gels based on carbomers, cellulose ethers or polysaccharides such as xanthan gum or sclerotium gum. However, these gels are alkaline and show only a limited degree of bio-availability.

Organogels, for the first time introduced by Scartazzini, are formed from phospholipids, more particularly unsaturated phosphatidylcholine (PC). Phosphatidylcholine (Phospholipon® 85G; Lipoid), 5-10%, is dissolved in a suitable solvent that is also able to dissolve azelaic acid (5-10%): dimethyl, diisopropyl esters & diethylhexyl esters of succinic acid or adipic acid, and isostearic acid based esters, more particularly isopropyl isostearate and ethylhexyl isostearate. After complete dissolution of phosphatidylcholine, this may take considerable time, azelaic acid is added while gently heating. A clear, transparent and low viscous solution will be obtained. To this solution an aqueous solution of poloxamer 407 (Synperonic® PE/F127) is added. The viscosity of the product will increase whereby a viscous emulsion-gel will be formed (sometimes abbreviated to "emulgel").

These organogels are frequently used as a vehicle for transdermal application of pharmaceutical actives: pain relieve agents such as morphine or diclofenac, nicotine (smoking cessation), transdermal patches for contraceptives, etc. They distinguish themselves from regular emulsions & gels by the extreme degree of bio-availability, and thus high degree of functionality whereby the side effects are virtually completely suppressed compared to oral or intravenous application.

2. Applications of azelaic acid

Skin care applications of azelaic acid cover major skin care areas that represent highly significant market areas:

- Anti-acne,
- Anti-rosacea,
- Skin-lightning,
- Hair-growth & regrowth.

2.1 Azelaic acid for anti-acne products

Azelaic acid is considered as the absolute rising star for anti-acne products. The use of azelaic acid as anti-acne ingredient is highly favourable compared to the traditional anti-acne ingredients, as the side effects are minimal and can easily be controlled by adjustment of the concentration azelaic acid in the cream or gel.

2.1.1 Products used for the treatment of acne vulgaris

Next to ordinary acne (acne vulgaris) several other forms of acne are known, such as acne conglobata (a severe form of acne, mainly with males) and acne keloidalis. Acne ectopica (hidradenitis suppurativa, caused Staphylococcus epidermidis) is a form of acne that shows up in unusual places, such as the armpits, groin and on the buttocks. It can be very serious and painful. Recurrent infections and abscesses are highly inconvenient for the patient. This form of acne usually occurs after the age of 20, especially with smokers. Acne-like anomalies may also be caused by mechanical influences such as acne under a chin strap or head band (helmet), or because of contact with comedogenic products such as tar, oil, chlorine, steroids (oral contraceptives) and particular cosmetics. Mallorca acne may occur upon (over)exposure to direct sun light. It shows up as a large ensemble of white spots on the skin, and has little to do with the opportunistic behaviour of Propionibacterium acnes.

Medications for acne include benzoyl peroxide, salicylic acid, α-hydroxy acids, retinoids, antibiotics (doxycycline, clindamycin), nicotinamide (vitamin B3) and keratolytic preparations. Especially benzoyl peroxide and salicylic acid are under scrutiny; the FDA recommends a careful approach using these products. The use of topically or orally applied antibiotics is frequently identified as "healing is worse than the disease". The same can be said from the oral use of retinoids, that eventually may lead to birth defects.

These side effects are absent with when using azelaic acid. Azelaic acid is believed to function on the basis of its antimicrobial activity and normalization of keratinization (the process by which epithelial cells mature as they move towards the skin surface and then desquamated). The limitation for the use of azelaic acid is its solubility; nonetheless significant progress has been made by improving the solubility characteristics. The European Union considers azelaic acid as a cosmetic ingredient that can be applied without concentration restrictions. In the USA azelaic acid is FDA approved for the treatment of acne (and rosacea). A variety of commercial products containing 10-25% azelaic acid are available.

The effect of the topical acne treatment using azelaic acid on the transmembrane pH gradient of Propionibacterium acnes and Staphylococcus epidermidis was studied in vitro at external pH values found on human skin (pH 4.0-6.0).

The results indicate that the antibacterial activity of azelaic acid is associated with the perturbation of intracellular pH of the organisms.

The use of azelaic acid as anti-acne ingredient is highly favourable compared to the traditional anti-acne ingredients, as the side effects are minimal and can easily be controlled by adjustment of the concentration azelaic acid in the cream or gel.

APPLICABILITY

PRODUCTS FOR TREATMENT OF ACNE VULGARIS	COSMETIC USE	MEDICAL DEVICE USE	PHARMACEUTICAL USE
AZELAIC ACID	++	++	++
BENZOYL PEROXIDE	-	-	+
RETINOIDS	+/-	+/-	+
α-HYDROXY ACIDS	++	++	++
ADAPALENE	-	-	++
TARATOZENE	-	-	++
SALICYCLIC ACID	+	+	+
SULPHUR	+	+	+
ANTIBIOTICS	-	-	+

Legend: (++ Strongly recommended / Very suitable) (+ Limited recommended / Suitable) (+/- Limited allowed / Limited suitable) (- Forbidden)

FUNCTIONALITY

PRODUCTS FOR TREATMENT OF ACNE VULGARIS	COSMETIC FUNCTIONALITY	MEDICAL DEVICE FUNCTIONALITY	PHARMACEUTICAL FUNCTIONALITY
AZELAIC ACID	+	+	++
BENZOYL PEROXIDE	-	+/-	+/-
RETINOIDS	+/-	+/-	+
α-HYDROXY ACIDS	-	-	-
ADAPALENE	-	-	++
TARATOZENE	-	-	++
SALICYCLIC ACID	+/-	+/-	+
SULPHUR	+	+/-	+/-
ANTIBIOTICS	-	-	+

Legend: (++ Strongly recommended / Very suitable) (+ Limited recommended / Suitable) (+/- Limited allowed / Limited suitable) (- Forbidden)

ADVERSE EFFECTS

PRODUCTS FOR TREATMENT OF ACNE VULGARIS	CMR PROPERTIES	SKIN IRRITATION	SIDE EFFECTS	EXFOLIATION	PHOTO ACTIVITY	CYTOTOXI-CITY
AZELAIC ACID	-	-	-	-	-	-
BENZOYL PEROXIDE	++	++	++	-	-	++
RETINOIDS	+	++	+	+/-	++	+
α-HYDROXY ACIDS	-	+	-	++	+/-	-
ADAPALENE	++	+	++	-	+	++
TARATOZENE	++	+	++	-	++	++
SALICYCLIC ACID	++	++	+	+	-	+
SULPHUR	+	+/-	-	+	+/-	+
ANTIBIOTICS	++	-	++	-	+/-	++

Legend: (++ Very strong effects) (+ Noticeable effects) (+/- Hardly noticeable) (- Not noticeable)

2.1.2 General ingrediënt characteristics

Azelaic acid

Azelaic acid is considered as the rising star for anti-acne OTC products. Azelaic acid may be used in personal care & cosmetic products, in medical devices and in pharmaceutical products without concentration limitations. It shows no significant side effects, it has no cytotoxic properties and does not exhibit CMR properties.

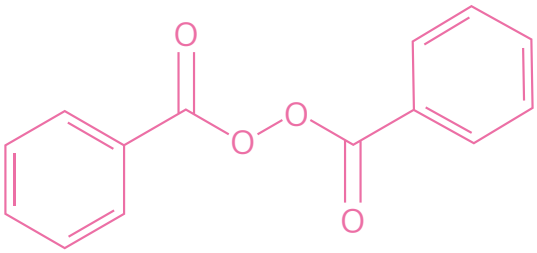
The major constraint for the use of azelaic acid is its solubility. However, the solubility problem of azelaic acid can be solved using particular solvent systems or using smart formulation techniques. Because of the poor solubility the bio-availability is also limited, but that problem may simultaneously be solved while tuning the solubility.

The mode of action of azelaic acid is not well-known, although it is considered likely that azelaic acid is detrimental for Propioni-bacterium acnes, but will not affect most other micro-organisms. P.acnes is an aerotolerant anaerobe gram-positive organism, identified as a commensal. The selectivity for P.acnes enables to normalise the P.acnes population while leaving the other native micro-organisms in peace.

The absence of adverse effects, compared to other products used for fighting acne, makes azelaic acid a preferred ingredient for anti-acne products.

Benzoyl peroxide

Probably the most frequently used anti-acne ingredient is benzoyl peroxide. It has outspoken anti-bacterial properties, but the disadvantage is its total lack of selectivity. Bacteria present on the skin and in the hair follicle are completely eliminated. This includes also P.acnes, the organism that is held responsible for the development of acne, and thus prevents acne from progressing.



Commercially available products may contain up to 10% benzoyl peroxide, while a minimum concentration required to fight acne is considered to be 2,5%. The absolute amount of benzoyl peroxide is dependent on the severity of the acne outbreak and observed skin irritation induced by benzoyl peroxide. Skin irritation is more frequently observed with darker skinned people compared to Caucasian skin. Racial distinction is, however, not a trustworthy approach. Prof.Proserpio distinguished five different skin types. That approach much better describes the actual situation:

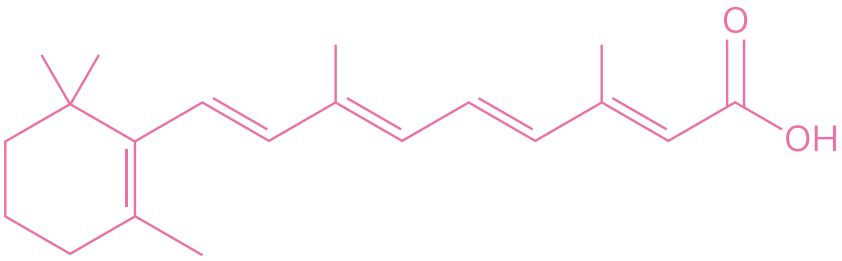
- Dry skin,
- Sensitive skin,
- Senior skin with wrinkles,
- Oily skin,
- Oily skin with large pores.

Benzoyl peroxide, like all peroxides, is not very stable. The bond energy of the –O–O- bond is small (αH~29 kcal/mole). Thermal bond breaking occurs easily and two benzoyl radicals are formed. A multitude of reactions may/will subsequently occur. The benzoyl radicals can directly react with the wall of bacteria, moulds & yeasts, without exhibiting any selectivity. All micro-organisms living on the skin, in symbiosis with the human being, are affected/destroyed. The reactivity is so high that it also will react with skin tissue and the accessible sub-cutaneous tissue. The damage caused by the benzoyl radicals is sincere, also leading to a high degree of cytotoxicity. In the most positive case it will cause skin irritation and/or sensitisation.
Last but not least: the benzoyl radical may lose carbon dioxide and a phenyl radical may be formed. The phenyl radical may abstract a hydrogen atom from a suitable substrate, and benzene is formed. Not the most wanted product indeed in personal care & cosmetic products and medical devices. Benzene is carcinogenic, mutagenic, reprotoxic and teratogenic, and has endocrine disruption properties.

EU Regulation 1223/2009 states that benzoyl peroxide is strictly forbidden in personal care & cosmetic products. As benzoyl peroxide also exhibits dramatic cytotoxic properties it is also forbidden in medical devices. Compared to the EU the legal situation in the USA is quite different: benzoyl peroxide may be used in OTC anti-acne products. However, the FDA is currently evaluating the status of benzoyl peroxide. The forecasts for the survival of benzoyl peroxide in the USA market looks grim, and that would be a more than realistic scenario.

Retinoids

Retinoids are defined as C20-terpenoids. The most important representatives are retinoic acid/tretinoin and retinol (vitamin A). Retinol and its esters may be used in personal care cosmetic products.



Retinoic acid plays an important role in growth and development. Retinoic acid is required in all chordate animals. Retinoic acid is important during early embryonic development. Vitamin A (retinol) plays a role in the maintenance of the immune system and is (as retinaldehyde) indispensable in the chemistry of vision.

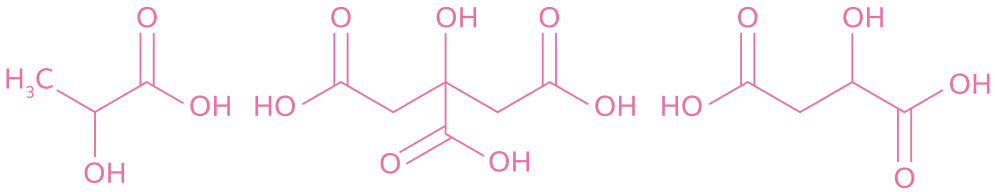
A variety of cis-trans isomers of retinoic acid are known. Retinoic acid (tretinoin; Renova®/Johnson & Johnson) identified as all-trans) and its salts exhibit anti-acne activity. It was developed by Kligman, and is considered to be one of the most powerful anti-ageing agents. Isotretinoin (13-cis-retinoic acid; Roaccutane®/Roche) is more powerful than tretinoin, but the side effects are also more outspoken.

Alitretinoin (9-cis-retinoic acid) is used as an anti-neoplastic ingredient, and is also used for chronic hand eczema.

All these, first generation, retinoids exhibit sincere side effects such dry lips, skin & mucous membranes irritation/sensitisation, reduced tear fluid production (resulting in eye irritation), disturbed liver function, thinning skin, sensitivity to sunlight (direct sunlight shall be avoided and an SPF>50 cream must be used), hair loss (usually reversible) or hirsutism, joint & muscle pain and an increased cholesterol level. Diabetes patients shall be very careful because of potential hyperglycaemia. These retinoids shall never be used during pregnancy or planned pregnancy: retinoids are considered severely teratogenic. For males gynaecomastia and disturbed potency have been reported. Many retinoids exhibit sincere phototoxicity and cytotoxicity.
The mechanism for the activity of retinoids for the treatment of acne is unknown. On a cellular level there is evidence that it decreases the ability of epithelial cells in hair follicles to stick together, leading to fewer blackheads; it also seems to make the epithelial cells divide faster, causing the blackheads to be pushed out.

α-Hydroxycarboxylic acids

α-Hydroxycarboxylic acids, usually abbreviated as α-hydroxy acids or AHA's and frequently named fruit acids, are characterised as carboxylic acids from the carbon atom in the 2-position carries a hydroxyl group. Well-known members of this group are glycolic acid, lactic acid, pyruvic acid, malic acid, tartaric acid, citric acid, and others. These are usually relatively strong acids that are also effective solvents for the cement between the cells of the epidermis. This cement is composed of ceramides, triglycerides and some sterols, mostly cholesterol. Elimination of the cement between the dead skin cells of the stratum corneum enables easy exfoliation.

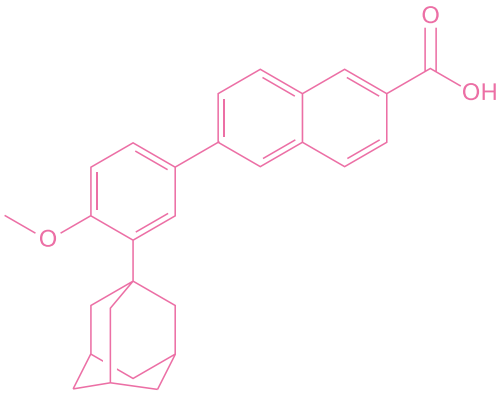


α-Hydroxy carboxylic acids are not true anti-acne products. Because of their exfoliating qualities the tallow glands are opened up to enable the sebum to flow out and distributes on the skin. This is best identified as the keratolytic activity of α-hydroxycarboxylic acids, but there is no activity against Propionibacterium acnes, the organism that is considered the main culprit.

α-Hydroxy carboxylic acids, usually applied as a combination of the free acids and their conjugated bases, are suitable for both personal care & cosmetic application, for medical devices and pharmaceutical preparations. Many of these products are body-own products or occur in nature, without CMR properties, no serious side effects (except when used in extreme concentration), inducing only limited phototoxic properties and no cytotoxicity.

Adapalene

Adapalene is frequently identified as a third generation retinoid. However, the structure of adapalene does not at all compare to retinoids such as vitamin A (retinoic acid; vitamin A), retinaldehyde or retinol. The structure of adapalene compares more to quinine. It is also used for the treatment of malaria and similar protozoal infections. Adapalene is a pharmaceutical ingredient that shall not be used in personal care & cosmetic products and medical devices.

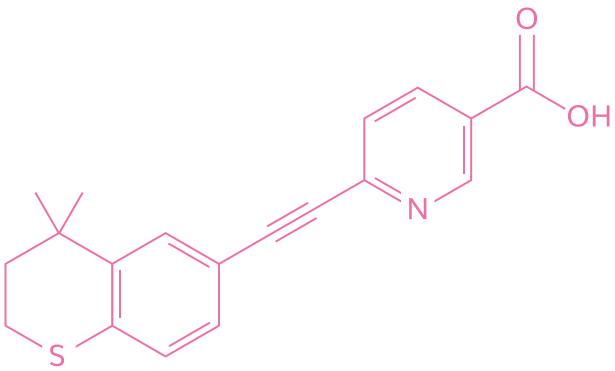


Adapalene, commercially available as Differin® Gel [0,1-1,0% adapalene) is used for the treatment of acne vulgaris, by means of shedding dead skin cells and promoting the formation of new skin cells. It also helps to unclog pores and reduces inflammation. When using an acne treatment with the active ingredient of adapalene, acne may worsen temporarily at first but should eventually improve. Side effects can include skin irritation, stinging and burning sensations, and sensitivity to UV light.

The functionality of adapalene is improved when using the product in conjunction with clindamycin, an antibiotic used for the treatment of bacterial infections. Clindamycin is also used for the treatment of otitis media, pneumonia and endocarditis, and is sometimes used to handle MRSA (Methicillin Resistant Staphylococcus Aureus).

Major side effects of adapalene are skin irritation (or burning or stinging sensation), dryness and peeling of the skin, itching and redness of the skin. Adapalene shall not be used if the patients suffer from eczema, in case of sunburn or pregnancy. It may take considerable time before the functionality of adapalene becomes obvious (8-10 weeks).

Another pharmaceutical anti-acne ingredient is taratozene, also defined as a third generation retinoid.



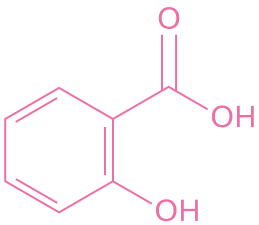
It is used for the treatment of acne, psoriasis and photo-damaged skin. The mechanism of action is still unknown. Common side effects include worsening of acne, increased sensitivity to sunlight, dry skin, itchiness, redness and in some cases extreme drying and cracking of skin. For most patients these side effects are uncomfortable but mild and decrease markedly after the first 2–4 weeks of use, except for increased sensitivity to sunlight.

Taratozene is not allowed in personal care & cosmetic products and medical devices, and must be prescribed by a medical professional. Despite the undesired side effects of taratozene it is frequently preferred better than tretinoin, that has even more serious side effects.

Salicylic acid

Salicylic acid is chemically described as 2-hydroxybenzoic acid. It is also considered to be a β-hydroxy acid. Salicylic is used as a preservative in personal care & cosmetic products with a maximum concentration of 0,5% (not to be used in products for children younger than three years of age). Salicylic acid may be used in excess of 0,5% for purposes other than inhibiting the development of micro-organisms in the product. This purpose has to be apparent from the presentation of the product.

Salicylic acid is poorly soluble in water (2,5 g/l; 25°C). The sodium salt is easily soluble in water but is subject to decarboxylation phenol being the primary reaction product.



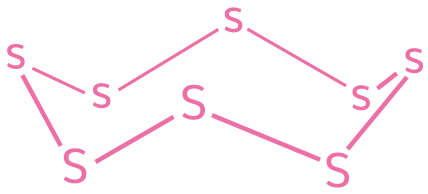
Salicylic acid is frequently used in personal care & cosmetic products as exfoliant to shed off dead skin cells (keratolyticum) to avoid dead cells to block the pores allowing the sebum to pass through. EU Regulation allows a maximum of 2% in stay-on products.

Salicylic acid may exhibit multiple side effects: skin irritation (eventually quite serious), dry skin, itching & stinging, unusually warm skin and swelling of the face, lips and tongue (potentially leading to suffocation). Possible suffocation may also be induced by salicylic acid derivatives such as some fragrance compounds (e.g. benzyl salicylate, methyl salicylate) and salicylic based UV filters. Furthermore salicylic acid may exhibit side effects that are potentially life threatening.

The FDA is currently evaluating the status of salicylic acid as the product may eventually not be safe to use in personal care & cosmetic products and medical devices.

Sulphur

Sulphur is probably one of the oldest anti-acne ingredients. At present it is rarely used, and if it is used it is always in combination with other anti-acne ingredients. Sulphur is a bright yellow crystalline solid found in free form in Nature, and is mostly from volcanic origin. It melts at 115°C and has a typical, unpleasant smell. Sulphur occurs as an eight-membered ring structure



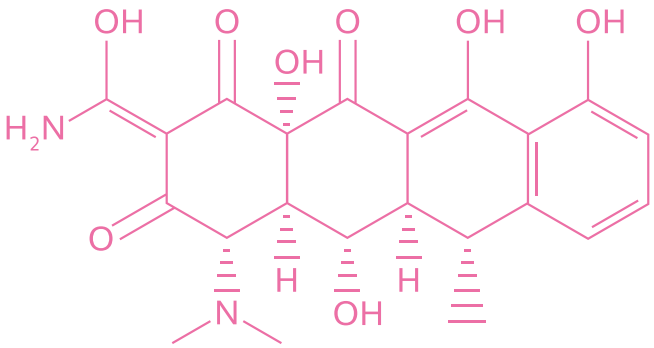
Sulphur is able to remove dead skin cells and eliminate excess oil from the skin's surface. This property may help in the prevention of acne, but sulphur is also known to exhibit adverse side effects. Redness is a common side effect when using products containing sulphur. Acne may begin to subside at first but the skin quality can become worse if sensitive to sulphur. Soreness is also accredited to the use of acne products containing sulphur.

Sulphur has germicidal, fungicidal, parasitical, and keratolytic properties.. The germicidal activity may be the result of its conversion to pentathionic acid (H2S5O6) by particular microorganisms. Also the formation of hydrogen sulphide and polysulphides, as well as (di)methyl (poly)sulphides will occur. Polysulphides generally have the formulae RSnR). These substances have a particular odour: hydrogen sulphide (H2S) smells after rotten eggs, methylmercaptan (CH3SH) has a distinctive putrid odour while the odour of dimethyl sulphide is commonly described as cabbage-like. Dimethyl disulphide has the characteristic odour of onions. The odour threshold value for these products is very low, usually < 1 ppm. Creams and ointments containing elementary sulphur always have the typical odour of these sulphides and are usually impossible to fragrance. Apart from the poor odour sulphides are usually toxic. The LD50-value of hydrogen sulphide is 800 ppm; H2S acts in a similar fashion as carbon monoxide and is considered to be a sincere CMR ingredient.

Antibiotics

The application of antibiotics for the treatment of acne is exclusively reserved for medical professionals. Antibiotics are not allowed in personal care & cosmetic products and medical devices. Antibiotics can be taken orally, but also administered via the skin using a cream. Frequently the use of antibiotics is combined with the use of benzoyl peroxide to avoid antibiotic resistance. Topically applied antibiotics are clindamycin and erythromycin. Orally taken antibiotics are doxycycline & minocycline (tetracyclines) and also erythromycin.

The side effects of these antibiotics are numerous: skin rash, upset of the stomach and intestine and fungal infections. Sometimes the side effects can quite serious indeed, such as severe allergic reactions (difficult breathing, facial swelling), destruction of the intestinal flora (bloody diarrhoea), vaginal candidiasis and mouth sores. Combined with potential antibiotic resistance the use of antibiotics for the treatment of (juvenile) acne should only be considered if there are no other options left.



Virtually all antibiotics used for the very severe cases of acne also have cytotoxic properties and have distinct CMR and hormone disrupting properties. Antibiotics also should not be used during pregnancy, unless unavoidable.

2.2 Azelaic acid for anti-rosacea products

Azelaic acid has been demonstrated to be effective for the treatment of rosacea. It reduces inflammatory lesions and erythema in rosacea patients. The major advantage of azelaic acid is that it lacks the side effects of the pharmaceutical ingredients.

2.2.1 Products used for the treatment of rosacea

Rosacea is a common, chronic and incurable condition that shows up as an acne-like skin condition. Rosacea affects mostly the central part of the face, especially the nose. To some degree outbreaks of rosacea are predictable.

The symptoms of rosacea include facial redness, tiny red pimples and fine red lines (telangiectasia [spider veins]) on the facial skin. Spider veins are small dilated blood vessels near the surface of the skin. These spider veins may also show up on other parts of the body such as the lower & upper extremities. An extreme example of rosacea is rhinophyma (an enlarged, bulbous red nose). There are not too many medications for rosacea, and except for azelaic acid and particular flavonoids, all of these are pharmaceutical by nature.

APPLICABILITY

PRODUCTS FOR TREATMENT OF ROSACEA	COSMETIC USE	MEDICAL DEVICE USE	PHARMACEUTICAL USE
AZELAIC ACID	++	++	+
BRIMODINE	-	-	++
METRONIDAZOLE	-	-	+
α-HYDROXY ACIDS	+	+/-	+/-
ORAL ANTIBIOTICS	-	-	+
ISOTRETINOIN	-	-	++
ALTERNATIVE THERAPIES	+/-	+/-	+

Legend: (++ Strongly recommended / Very suitable) (+ Limited recommended / Suitable) (+/- Limited allowed / Limited suitable) (- Forbidden)

FUNCTIONALITY

PRODUCTS FOR TREATMENT OF ROSACEA	COSMETIC FUNCTIONALITY	MEDICAL DEVICE FUNCTIONALITY	PHARMACEUTICAL FUNCTIONALITY
AZELAIC ACID	++	++	+
BRIMODINE	-	-	+
METRONIDAZOLE	-	-	+
α-HYDROXY ACIDS	+	+	+/-
ORAL ANTIBIOTICS	-	-	+/-
ISOTRETINOIN	-	-	++
ALTERNATIVE THERAPIES	+	+/-	-

Legend: (++ Strongly recommended / Very suitable) (+ Limited recommended / Suitable) (+/- Limited allowed / Limited suitable) (- Forbidden)

ADVERSE EFFECTS

PRODUCTS FOR TREATMENT OF ROSACEA	CMR PROPERTIES	SKIN IRRITATION	SIDE EFFECTS	EXFOLIATION	PHOTO ACTIVITY	CYTOTOXI-CITY
AZELAIC ACID	-	+	-	+	-	-
BRIMODINE &	+	+	+	-	-	+
METRONIDAZOLE	+	+	+	-	-	+
α-HYDROXY ACIDS	-	+	-	++	+	-
ORAL ANTIBIOTICS	++	++	++	-	+	++
ISOTRETINOIN	++	++	++	-	++	++
ALTERNATIVE THERAPIES	+/-	+/-	+/-	+/-	-	+/-

Legend: (++ Very strong effects) (+ Noticable effects) (+/- Hardly noticable) (- Not noticable)

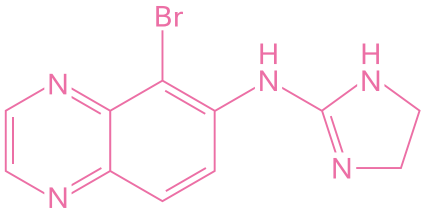
2.2.2 General ingrediënt characteristics

Azelaic acid

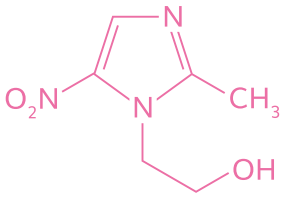
Azelaic acid has been demonstrated to be effective for the treatment of rosacea. It is available as a 20% cream or a 15% hydrogel. It reduces inflammatory lesions and erythema in rosacea patients and also inhibits neutrophilic ROS (Reactive Oxygen Species). In the neutrophil system azelaic acid inhibits the ROS formation in a dose-dependent manner, markedly decreasing the number of free radicals. In the xanthine-xanthine oxidase system, none of the ROS generated was decreased by any dose of azelaic acid, indicating that azelaic acid does not scavenge generated ROS, but rather inhibits cell metabolism, possibly by decreasing enzymatic activity within the cell membrane. Azelaic acid is probably the only non-pharmaceutical ingredient that has been demonstrated to exhibit good activity for the treatment of rosacea, without side effects.

Brimondine & Metronidazole

These pharmaceutical ingredients are not allowed to be used in personal care & cosmetic products as well as in medical devices. Brimonidine, applied as a gel or as a stick, is reasonably effective for redness reduction in mild cases of rosacea. It functions by vasoconstriction of the small blood vessels. Brimonidine binds to the cellular α-2-adrenergic receptors of the small veins, leading to vasoconstriction. Consequently the transport of blood through these small blood vessels is reduced resulting in a reduced facial redness. The effects become visible after 6-12 hours and are fully reversible. Brimonidine is not a cure for rosacea, and that is also the case metronidazole. Brimonidine is also used to lower the intraocular pressure.



Brimonidine



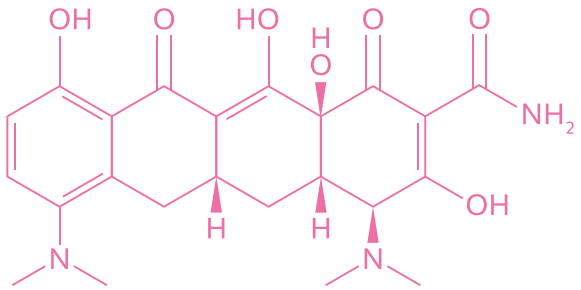
Metronidazole

Metronidazole is considered to an antibiotic, which is also used for the treatment of bacterial infections. It is ineffective for yeast infections such as vaginal yeast infections caused by e.g. Candida albicans.

Oral antibiotics

The application of antibiotics, mostly tetrecyclines, for the treatment of rosacea is exclusively reserved for medical professionals. Antibiotics are not allowed in personal care & cosmetic products and medical devices. Antibiotics for the treatment of rosacea are mostly taken orally. Orally taken antibiotics are doxycycline & minocycline (tetracyclines).

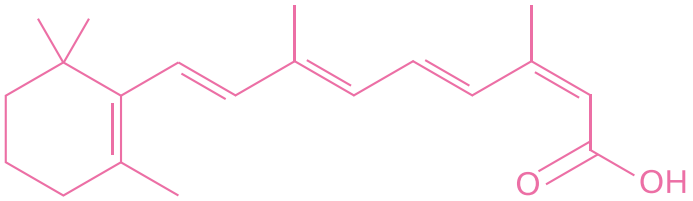
The side effects of these antibiotics are numerous: skin rash, upset of the stomach and intestine and fungal infections. Sometimes the side effects can quite serious indeed, such as severe allergic reactions (difficult breathing, facial swelling), destruction of the intestinal flora (bloody diarrhoea), vaginal candidiasis and mouth sores. Combined with potential antibiotic resistance the use of antibiotics for the treatment of rosacea should only be considered if there are no other options left, having said that the efficacy of antibiotics for the treatment of rosacea are not well proven.



Virtually all antibiotics have cytotoxic properties and have distinct CMR & hormone disrupting properties. Antibiotics should not be used during pregnancy, unless unavoidable. In actual fact, the use of antibiotics for the treatment of rosacea is sincerely discouraged.

Isotretinoin

In case of severe rosacea that does not respond to antibiotics isotretinoin may be helpful. Isotretinoin is also a powerful oral acne drug that also helps to clear up acne-like lesions of rosacea. Isotretinoin has severe side effects and should not be used during pregnancy or planned pregnancy as it causes serious birth defects (teratogenic activity).



Isotretinoin is not compatible with oral antibiotics, oral contraceptives and particular botanicals such as St.John's Wort. This botanical product has been reported to deactivate oral contraceptives.

Alternative therapies

A number of alternative therapies have been proposed for the treatment of rosacea. Examples are colloidal silver, emu oil and oregano oil. No conclusive evidence supports the idea that any of these substances are effective.

Chrysanthellum indicum contains phenylpropenoic acids and flavonoids, and has a well-documented effect on vascular wall permeability and increase of the mechanical resistance of capillaries. Particular flavonoids such as apigenin, rutin, silymarin and naringenin have been reported to strengthen the capillaries. The combination of flavonoids with azelaic acid is considered challenging because of the absence of side reactions, but much more information must be gathered on the functionality of flavonoids.

2.3 Azelaic acid for skin-lightening products

Azelaic acid is advantageously used for skin lightening processes. It can be used both for integral skin lightening to obtain a more radiant complexion, but also to fight "old-age spots". One of the major advantages of using azelaic acid for skin lightening is the fact that it not interfere with any of the bodily processes. This is contrary to virtually all other skin lightening products that exhibit sincerely side reactions that are detrimental for human health, or are insufficiently selective.

2.3.1 General ingrediënt characteristics

Azelaic acid is known the enzyme tyrosinase, the enzyme behind the tan. Azelaic acid is also used for the treatment of melasma, lentigo maligna and other disorders of hyperpigmention. Azelaic acid has been reported to be effective for hypermelanosis caused by physical or photochemical agents, and lentigo maligna melanoma as well as other disorders characterized by abnormal proliferation of melanocytes. Its mechanism of action is to inhibit DNA synthesis and mitochondrial enzymes, thereby inducing direct cytotoxic effects toward the melanocyte.

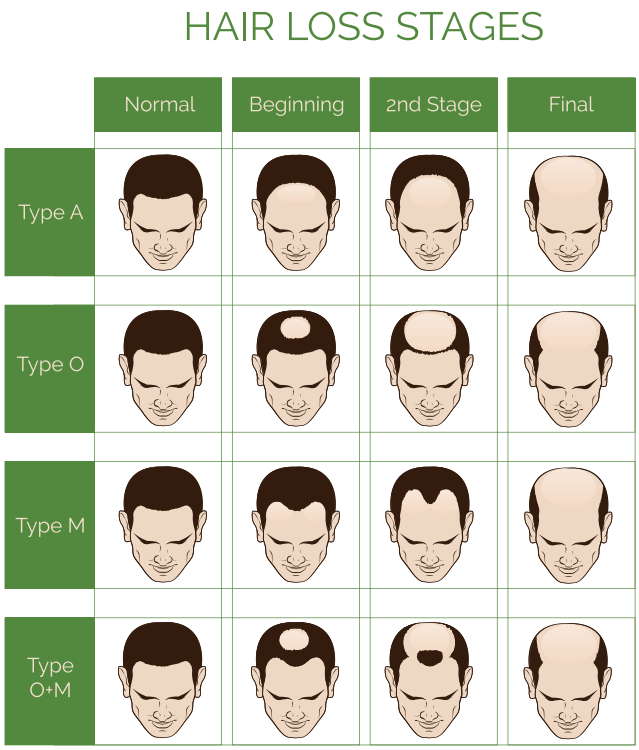
Acne lesions are frequently darker coloured compared to the surrounding skin. Azelaic acid can effectively be used for this post-inflammatory hyperpigmentation, believed to be caused by reactive oxygen species. Free radicals are believed to contribute to hyperpigmentation, and azelaic acid acts by reduction of the free radical production. Azelaic acid 20% is currently available in the US and is only indicated for the treatment of acne, although it has off-label use for hyperpigmentation.

2.4 Azelaic acid for hair-growth & regrowth products

Hair grows everywhere on our body except on the palms of our hands and the soles of our feet. An average human adult is the proud owner of approximately 150,000 hairs on her/his head, but also loses up to 100 of them per day. A lot of people, however, own a rather broad hair line, that even may spread over the complete skull. Virtually all individuals will face sooner or later involutional alopecia (old age hair loss) and that can only be delayed by providing the hair follicles with a frequent shot of essential nutrients (B vitamins and some metal ions). A low-protein diet or severely calorie-restricted diet frequently causes temporary hair loss. Alopecia areata (spot baldness) and alopecia universalis (total body hair fall-out, including eye-brows & eye lashes) are auto-immune disorders for which no general treatment is available.

Azelaic acid is a well-known inhibitor for 5-α-reductase, and is therefore able to inhibit the conversion of testosterone into dihydrotestosterone. Inhibition of the formation of dihydrotestosterone enables to wake up the dormant hair follicle, and if the follicle has not completely destroyed hair growth/regrowth is possible.

The most frequently observed cause of hair loss is genetic: androgenetic alopecia. Common types of hair loss Hair loss may furthermore be caused by hair diseases such as alopecia diffusa (effluvium) whereby the scalp becomes visible due to hair loss, shortage of iron, malfunctioning of thyroid gland, cancer or the use of particular medicines (some oral contraceptives or chemotherapeutic agents), and also psychological artefacts such as trichotillomania, also known as “hair pulling disorder”.



Hair loss is a common problem. Pattern hair loss by age 50 affects about half of all males and a quarter of females. About 2% of people develop alopecia areata at some point in time.

2.4.1 Products used for hair-growth & regrowth

APPLICABILITY

PRODUCTS FOR REACTIVATE HAIR GROWTH	COSMETIC USE	MEDICAL DEVICE USE	PHARMACEUTICAL USE
AZELAIC ACID	++	++	+
ANTHRALIN	-	-	+
FINASTERIDE	-	-	++
DUTASTERIDE	-	-	++
MINOXIDIL	-	-	++
SPIRONOLACTON	-	-	+
CAFEINE	++	++	+
BOTANICAL PRODUCTS	+	+	-

Legend: (++ Strongly recommended / Very suitable) (+ Limited recommended / Suitable) (+/- Limited allowed / Limited suitable) (- Forbidden)

FUNCTIONALITY

PRODUCTS FOR REACTIVATE HAIR GROWTH	COSMETIC USE	MEDICAL DEVICE USE	PHARMACEUTICAL USE
AZELAIC ACID	++	++	++
ANTHRALIN	-	-	+
FINASTERIDE	-	-	++
DUTASTERIDE	-	-	++
MINOXIDIL	-	-	++
SPIRONOLACTON	-	-	+
CAFEINE	+	+	+
BOTANICAL PRODUCTS	+	+	-

Legend: (++ Strongly recommended / Very suitable) (+ Limited recommended / Suitable) (+/- Limited allowed / Limited suitable) (- Forbidden)

ADVERSE EFFECTS

PRODUCTS FOR REACTIVATE HAIR GROWTH	CMR PROPERTIES	SKIN IRRITATION	SIDE EFFECTS	EXFOLIATION	PHOTO ACTIVITY	CYTOTOXI-CITY
AZELAIC ACID	-	+/-	-	+	-	-
ANTHRALIN	++	+	+	-	+	+
FINASTERIDE	++	+/-	+	-	-	+
DUTASTERIDE	++	+/-	++	-	-	+
MINOXIDIL	+	+	++	-	+/-	++
SPIRONOLACTON	++	-	+	-	+/-	+
CAFEINE	-	-	-	-	+/-	-
BOTANICAL PRODUCTS	+/-	-	+/-	-	+/-	-

Legend: (++ Very strong effects) (+ Noticable effects) (+/- Hardly noticable) (- Not noticable)

2.4.2 General ingrediënt characteristics

Azelaic acid

Azelaic acid is a very potent 5-α-reductase inhibitor, type 1. According to Stamatiadis 5-α-reductase inhibition is already detectable at an azelaic acid concentration as low as 0,2 mMol/l. Inhibition is complete at a concentration of 3 mMol/l, equivalent to ~0,6 mg/l. Stamatiadis also studied the inhibitory effects of zinc sulphate (3-9 mMol/l) using an in vitro assay with 1,2[3H]-testosterone as substrate; also zinc sulphate showed to be a potent 5-α-reductase inhibitor. An additive effect of these two inhibitors was observed. Pyridoxine (vitamin B6) potentiated the inhibitory effect of zinc sulphate, but not of azelaic acid. This observation suggests that different mechanisms are involved. Simultaneous use of the three products showed to be already effective for the treatment of androgenic alopecia, indicative for a powerful synergy.

The powerful combination {azelaic acid + zinc sulphate + vitamin B6} for the treatment of androgenic alopecia is cosmetically suitable contrary to the steroidal and non-steroidal pharmaceutical preparations. In addition, azelaic acid has a superior toxicological profile. Side effects of azelaic acid boil down to the particular cosmetic properties: skin lightening at the site of application, a slight risk of hypertrichosis, and [seldom] slight skin irritation.

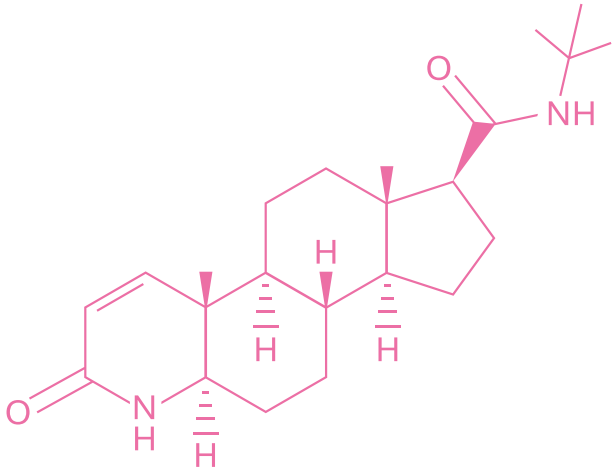
Combinations of minoxidil and azelaic acid are commercially available, despite the unwanted side effects of minoxidil. Both products work on the basis of different mechanisms of action in preventing baldness. The combination of the two would work more effectively than either alone. Commercial products contain up to 15% azelaic acid and 5% minoxidil. These high concentrations are explained because of the poor bioavailability of especially minoxidil. Lower but equally effective preparations can be made using transdermal preparations based on phosphatidylcholine-based organogels, to be mentioned organogels containing azelaic acid and caffeine.

Anthralin

Anthralin is used for the treatment of long-term psoriasis. It is chemically described as 1,8-dihydroxyanthron and is found in goa powder. Goa powder, also named Bahia powder, comes from the araroba tree (Andira araroba). At present anthralin is produced artificially. Anthralin is also used to promote hair growth, but there are sincere concerns on the safety of the product. Insufficient toxicological information is available, both for application against psoriasis and for hair growth stimulation.

Finasteride & Dutasteride

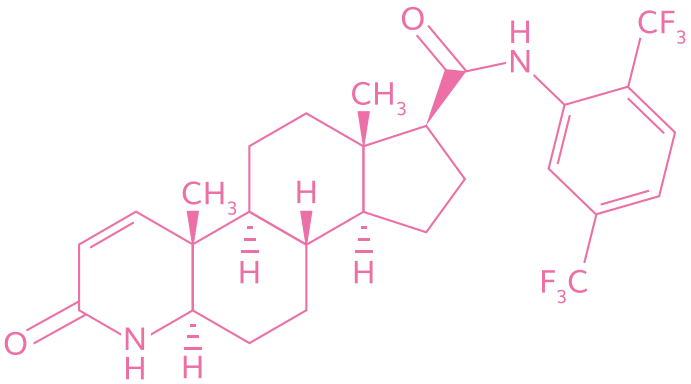
Finasteride is probably the most effective medication proven for the treatment of androgenic alopecia. It is prescribed for males with a genetic predisposition of male-pattern baldness. Finasteride is a 5-α-reductase type II inhibitor, approved by the FDA, for the treatment of enlarged prostate glands.



A side effect of the medication with finasteride was decreased hair loss and often also hair re-growth. In 1998 finasteride was also approved for anti-baldness treatment. Finasteride is marketed by Merck as Proscar for prostate treatment and Propecia for hair loss treatment.

The enzyme 5-α-reductase is responsible for the conversion of testosterone into dihydrotestosterone (DHT). For males that are subject to genetic predisposition for hair loss DHT assumes responsibility for the hair follicle to enter the telogen state. Finasteride inhibits 5-α-reductase, so many of the follicles that would have quit instead continue to produce new hairs. The limitation is that the treatment must be continued to be used; if treatment is discontinued baldness returns, although this may take considerable time. Finasteride is exclusively approved for males only; it is not suitable for (pregnant) females and may cause male foetus to develop ambiguous genitals; female foetuses are not affected. Finasteride may lead to multiple sexual disorders, eventually impotence.

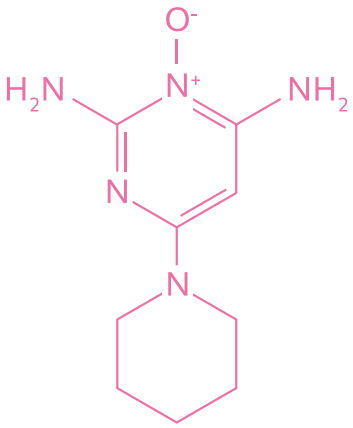
As an extension of finasteride dutasteride has been developed. Like finasteride it is also an anti-androgen and is also used to treat an enlarged prostate; it also inhibits 5-α-reductase. Dutasteride is expected to be effective for the treatment of androgenic alopecia. However, the side effects are more sincere than in the case of finasteride.



Both finasteride and dutasteride are pharmaceutical products and shall by no means be used in personal care & cosmetic products and medical devices.

Minoxidil

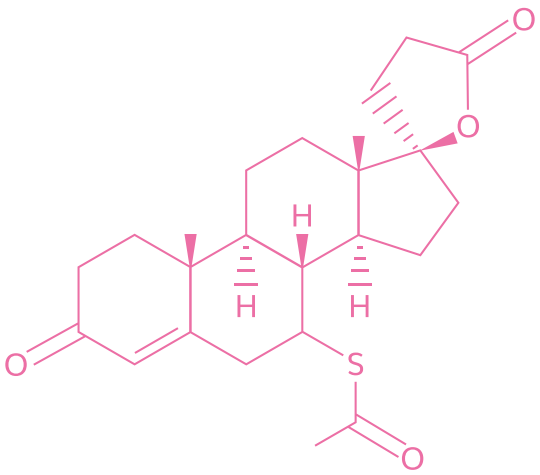
Minoxidil was originally developed for the treatment of high blood pressure, but it was also observed that it affected hair growth. Contrary to finasteride & dutasteride minoxidil has no hormonal activity. Minoxidil is, however, not allowed in personal care & cosmetic preparations as well as in medical devices; minoxidil is considered to be a pharmaceutical product. A disadvantage of minoxidil is the fact that newly formed hairs frequently stay in the "vellus" phase: short and fine, soft and usually not pigmented hairs.



Minoxidil has a number of side effects: acne, headache/migraine, heart palpitations and irregular heart beat and (unwanted) blood pressure lowering. Minoxidil shall not be used by lactating females. The mode of action of minoxidil is yet unknown.

Spironolactone

Spironolactone is a potassium-sparing diuretic that prevents from absorbing too much salt and keeps the potassium levels from getting too low. It is also used for the treatment of acne, hirsutism and androgenic alopecia. Spironolactone is for females what finasteride for males is.

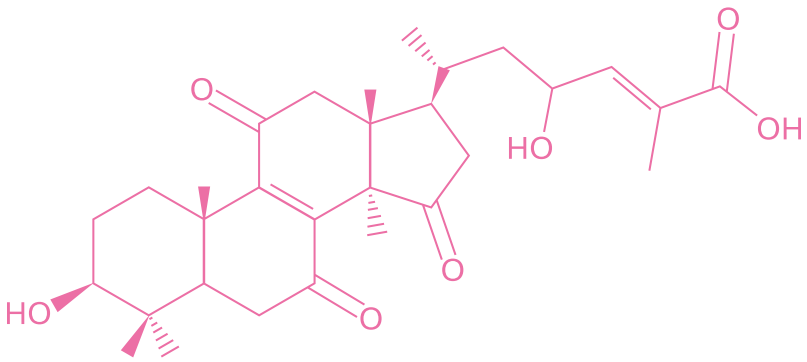


The efficacy of spironolactone is rather limited indeed, and hair regrowth is merely a side effect of the diuretic activity. The side effects may be quite sincere indeed. The product shall by no means be part of personal care & cosmetic products and medical devices.

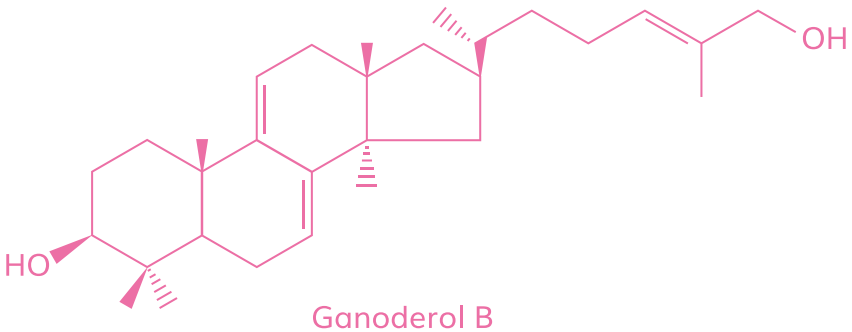
Botanical products

There are not to many cosmetically allowed products that inhibit 5-α-reductase; saw palmetto (INCI: Sabal Serrulata/Serenoa Repens) is an example. The applicable part of saw palmetto is the ripe fruit. The lipid fraction of the volatile oil and fatty oils contains constituents active in treating benign prostatic hyperplasia (BPH), for which saw palmetto is recommended. Saw palmetto has a proven positive track record for hair (re)growth preparations because of its potential to inhibit 5-α-reductase. Saw palmetto also hides a significant content of phytosterols (ß-sitosterol, stigmasterol, lupeol, lupenone & cycloartenol).

Some other botanical products are also claimed to inhibit 5-α-reductase, but there is insufficient proof of their activity. Examples are Ganoderma lucidum (reishi mushroom), that lives on the oil palm (Elaeis guineensis); ganoderic acid & ganoderol B are believed to be the active species.



Ganoderic Acid



Ganoderol B

Ganoderol B has been described as a potent anti-androgen. Ganoderol B has recently also received quite a bit of attention for the treatment of diabetes mellitus type II. It is a α-glucosidase inhibitor that prevents digestion of carbohydrates.

Also alfalfa (Medicago sativa), the Japanese pagoda tree (Sophora japonica), red clover (Trifolium pratense) and the often praised Indian mulberry (noni fruit; Morinda citrifolia) have been reported to exhibit 5-α-reductase inhibition properties. Although the inhibitory effect has been clearly demonstrated its efficacy is quite variable indeed due to seasonal variation and frequently a high degree of adulteration of the extracts. Furthermore, many of those extracts also contain isoflavones (genistein, daidzein, biochanin, formonometin, etc., either as the glycosides or the aglycons) that exhibit estrogenic properties.

2.4.3 Androgenetic alopecia

Androgenetic alopecia is hereditary and androgen-dependent. Currently only oral finasteride and topical minoxidil are approved for pharmaceutical treatment of androgenetic alopecia. Recently caffeine has also been shown to have beneficial effects in patients suffering from androgenetic alopecia. The proposed mechanism includes phosphodiesterase inhibition rather than inhibition of 5-α-reductase thereby increasing cAMP levels in cells and promoting cell proliferation by stimulating cell metabolism (T.W.Fischer, U.C.Hipler, P.Elsner, Effect of caffeine and testosterone on the proliferation of human hair follicles in vitro. Int.J.Dermatol., 46,27,(2007)).

The combination of caffeine with azelaic acid shall be mentioned as a powerful method to treat androgenic alopecia, with the advantage that both caffeine and azelaic acid are recognised personal care &cosmetic ingredients that also may be used in medical devices.

3. Technical info and declarations

Source

Open Library : Free accessible at www.azelaic.com

Closed Library : With Pass Word at www.azelaic.com

On request : Contact Customer Service at service@azelaic.com

Source	Code	Subject
Open Library	AA-001	Aflatoxin Statement
Open Library	AA-002	Allergen Statement
On request	AA-003	Certificate of manufacture
On request	AA-004	DMF : Open Part
On request	AA-005	FDA Certificate
On request	AA-006	Free sale document
On request	AA-007	GMP Certificate
Open Library	AA-008	Halal Statement
Open Library	AA-009	Genotoxicity
Open Library	AA-010	HALAL Statement
On request	AA-011	Impurity Declaration
On request	AA-012	Justification of the specification
On request	AA-013	Manufacturing license
Open Library	AA-014	Methanol Statement
On request	AA-015	Methods of analysis
Open Library	AA-024	Material safety data sheet
Open Library	AA-016	Non GMO Declaration
Open Library	AA-022	Product data sheet Azepur99 ; pharma grade
Open Library	AA-023	Product data sheet Azepur99 ; cosmetic grade
On request	AA-017	SMF ; Site Master File
Open Library	AA-018	Solvents and Catalysts Statement
On request	AA-019	Stability Study Protocol
Open Library	AA-020	TSE – BSE Statement
On request	AA-021	Validation report
On request	AA-025	Written Confirmation

Questions and requests : service@azelaic.com

Azepur99®

www.azelaic.com