

PENTAPHARM SERVICE CENTER COSMETICS

Formulation Guidelines for SYN[®]-AKE (Code no 800628)

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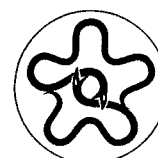
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SUMMARY

SYN[®]-AKE was tested with different groups of raw materials like preservatives, hydrocolloids, sunscreens, detergents, commonly used water-soluble substances and various PENTAPHARM actives.

INTRODUCTION

SYN[®]-AKE is a glycerine solution of a synthetic ingredient, which is water-soluble, clear and ready to use. SYN[®]-AKE is a small peptide that mimics the activity of Waglerin-1, a polypeptide that is found in the venom of the Temple Viper. Clinical trials have shown that SYN[®]-AKE is capable of reducing mimic wrinkles by inhibiting muscle contractions.

PENTAPHARM has screened a wide range of common ingredients to test their compatibility with SYN[®]-AKE.

The following guideline gives an overview of those raw materials tested and found to be either compatible or incompatible with SYN[®]-AKE.

GENERAL RECOMMENDATIONS

- Dosage:** For skin care preparations, concentrations of 1 to 4% SYN[®]-AKE are recommended.
- Processing:** SYN[®]-AKE can be processed either cold or warm (up to 2 hours at 70°C) and is incorporated into the aqueous phase of a cosmetic formulation.
- pH:** The optimal pH for the formulation with SYN[®]-AKE ranges between 3.0 and 5.5.
- Ethanol:** SYN[®]-AKE is compatible with ethanol at concentrations up to 50% (highest concentration tested).
- Storage:** between 15 and 25°C in the original sealed container, protected from light and in a clean place.



TEST PROCEDURE

The different raw materials were tested with 4% SYN[®]-AKE in aqueous solutions.

The raw materials to be tested were used in concentrations according to the manufacturer's indications. **Should these raw materials be used at other concentrations, we recommend to eventually re-test their stability with SYN[®]-AKE.**

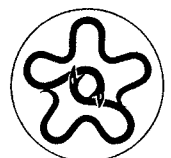
The compatibility test was not performed for raw materials whose optimal pH-ranges were too divergent.

The samples were stored at 4°C, room temperature and 40°C. The samples were judged after 1 month and again after 3 months according to the following criteria: pH value, odour, colour, appearance, viscosity.

The results of these compatibility tests are split into three groups:

- **Recommended substances:** without or with very slight turbidity, stable pH value, no odour or colour development, stable viscosity.
- **Compatible substances:** with slight turbidity, stable pH value or slight variation, no odour or colour development, stable viscosity.
- **Substances with limited compatibility:** high turbidity, and/or unstable pH value, and/or odour or colour development, and/or unstable viscosity.

However, if these substances with limited compatibility are used with SYN[®]-AKE in an emulsion or/and in lower concentration, improved compatibility might result.



PRESERVATIVES

RECOMMENDED PRESERVATIVES

Product Name / Supplier	% Wt.	INCI Name
Nipastat Sodium / Nipa	0.1	Methylparaben, Butylparaben, Ethylparaben, Propylparaben
Phenoxetol / Nipa	1.0	Phenoxyethanol
Nipaguard PDU / Nipa	0.5	Diazolidinyl Urea
Glydant 2000 / Lonza	0.4	DMDM Hydantoin
Isocil PC / Lonza	0.1	Methylchloroisothiazolinone, Methylisothiazolinone
Spectradyne / Lonza	0.3	Chlorhexidine Digluconate
Benzyl Alcohol / VWR	1.0	Benzyl Alcohol
Benzoic Acid / VWR	0.2	Benzoic Acid
Irgasan DP300 / Ciba	0.3	Triclosan

With SYN[®]-AKE, these preservatives formed stable aqueous solutions without turbidity.

COMPATIBLE PRESERVATIVES

Product Name / Supplier	% Wt.	INCI Name	Observations
Unicide U-13 / Lipo	0.6	Imidazolidinyl Urea	Slight pH variations
Glycacil 2000 / Lonza	0.8	Iodopropynyl Butylcarbamate	Slight pH decrease

PRESERVATIVES WITH LIMITED COMPATIBILITY

Product Name / Supplier	% Wt.	INCI Name	Observations
Potassium Sorbate / CFS-Schweizerhall	0.5	Potassium Sorbate	Coloration
Geogard 221 / Lonza	0.8	Dehydroacetic Acid (and) Benzyl Alcohol	Coloration



HYDROCOLLOIDS

RECOMMENDED HYDROCOLLOIDS

Product Name / Supplier	% Wt.	INCI Name
Carbopol Ultrez 10 / Noveon	0.5	Carbomer
Natrosol 250 HHX / Hercules	2.5	Hydroxyethyl Cellulose
Sepigel 305 / Seppic	3.0	Polyacrylamide (and) C13-14 Isoparaffin (and) Laureth-7
Aristoflex AVC / Clariant	1.0	Ammonium Acryloyldimethyltaurate / VP Copolymer

These hydrocolloids formed stable gels with SYN[®]-AKE.

COMPATIBLE HYDROCOLLOIDS

Product Name / Supplier	% Wt.	INCI Name	Observations
Pemulen TR-1 / Noveon	1.0	Acrylates / C10-30 Alkyl Acrylate Crosspolymer	Slight pH decrease at 40°C
Keltrol RD / Kelco	3.0	Xanthan Gum	Slight pH decrease
Stabileze QM / ISP	0.5	PVM/MA Decadiene Crosspolymer	Slight pH decrease
Structure XL / National Starch	5.0	Hydroxypropyl Starch Phosphate	Slight pH decrease

With SYN[®]-AKE, these hydrocolloids formed gels that showed a slight pH variation during the stability tests, but kept a stable appearance (colour, consistency).



UV FILTERS

RECOMMENDED UV FILTERS

Product Name / Supplier	% Wt.	INCI Name
Parsol HS / DSM	5.0	Phenylbenzimidazole Sulfonic Acid
Uvinul MS 40/ BASF	5.0	Benzophenone-4

With SYN[®]-AKE, these UV filters formed stable solutions, without turbidity.

DETERGENTS

RECOMMENDED DETERGENTS

Product Name / Supplier	% Wt.	INCI Name
Tego Betain F / Degussa	20.0	Cocamidopropyl Betain
Rewoteric AMCAS / Rewo	20.0	Cocamidopropyl Hydroxysultaine

With SYN[®]-AKE, these detergents formed stable solutions, without turbidity.

COMPATIBLE DETERGENTS

Product Name / Supplier	% Wt.	INCI Name	Observations
Genapol LRO liquid / Clariant	20.0	Sodium Laureth Sulfate	Slight pH decrease
Rewopol SB FA 30 / Rewo	20.0	Disodium Laureth Sulfosuccinate	Slight pH decrease at 40°C
Plantacare 2000 UP / Cognis	20.0	Decyl Glucoside	Slight pH rise

DETERGENTS WITH LIMITED COMPATIBILITY

Product Name / Supplier	% Wt.	INCI Name	Observations
Rewoteric AM2CNM / Rewo	20.0	Disodium Cocoamphodiacetate	Precipitate



MISCELLANEOUS SUBSTANCES

RECOMMENDED MISCELLANEOUS SUBSTANCES

Product Name / Supplier	% Wt.	INCI Name
D-Panthenol 50P	2.0	Panthenol
EDTA	0.1	EDTA
Glycerin 86.5%	20.0	Glycerin
1,3-Butandiol	20.0	Butylene Glycol
Glycine	2.0	Glycine
L-Lysin	2.0	Lysine
L-Glutamic Acid	2.0	Glutamic Acid
Lactic Acid	2.0	Lactic Acid
Citric Acid	2.0	Citric acid
Glycolic Acid	2.0	Glycolic Acid

With SYN[®]-AKE, these miscellaneous substances formed stable solutions, without turbidity.

COMPATIBLE MISCELLANEOUS SUBSTANCES

Product Name / Supplier	% Wt.	INCI Name	Observations
EDG Plus	5.0	Ethoxydiglycol	Slight pH decrease

MISCELLANEOUS SUBSTANCES WITH LIMITED COMPATIBILITY

Product Name / Supplier	% Wt.	INCI Name	Observations
Sodium Metabisulfite	0.1	Sodium Metabisulfite	pH decrease
Propylene Glycol	20.0	Propylene Glycol	Filamentous precipitate
Cremophor RH 410	5.0	PEG-40 Hydrogenated Castor Oil	pH decrease at 40°C

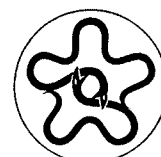


PENTAPHARM ACTIVES

RECOMMENDED PENTAPHARM ACTIVES

Product Name	Product Code	% Wt.	INCI Name
CEPHALIPIN	293-01	5.0	Cephalins, Disodium Cocoamphodiacetate
COLHIBIN	800616	5.0	Hydrolyzed Rice Protein
DISMUTIN [®] -BT	313-01	1.0	Superoxide Dismutase
EASHAVE	316-01	5.0	Water, Wheat (Triticum Vulgare) Germ Extract, Saccharomyces Cerevisiae Extract, Sodium Hyaluronate
ELHIBIN [®]	301-02	5.0	Soybean (Glycine Soja) Protein
HYASOL-BT	296-04	5.0	Sodium Hyaluronate
IMMUCELL [®]	302-01	5.0	Glycoproteins
IRICALMIN	316-02	5.0	Water, Wheat (Triticum Vulgare) Germ Extract, Saccharomyces Cerevisiae Extract, Sodium Hyaluronate
MARISCAN [®]	284-01	5.0	Glycosaminoglycans
MELAWHITE [®]	282-01	5.0	Leukocyte Extract, Water
PENTACARE-HP	305-02	5.0	Water, Ceratonia Siliqua Gum, Hydrolyzed Casein
PENTACARE-NA	319-01	5.0	Hydrolyzed Wheat Gluten, Ceratonia Siliqua Gum
PENTAGLYCAN	181-01	5.0	Glycosaminoglycans
PENTAVITIN [®]	180-01	5.0	Saccharide Isomerate
PEPHA [®] -CTIVE	800545	5.0	Algae Extract
PEPHA [®] -NUTRIX	800272	5.0	Colostrum Whey
PEPHA [®] -PROTECT	800464)	5.0	Melon Extract, Glycerol, Water, Sodium Benzoate, Potassium Sorbate, Phenoxyethanol
PEPHA [®] -TIGHT	800356	5.0	Algae Extract, Pullulan
PEPHA [®] -TIMP	800420	5.0	Human Oligopeptides-20
PHYTALURONATE [®]	298-01	5.0	Ceratonia Siliqua Gum
REGU [®] -AGE	800131	5.0	Hydrolyzed Rice Bran Protein, Glycine Soja (Soybean) Protein, Oxido Reductases
REVITALIN [®] -BT	291-01	5.0	Glycoproteins
SERICIN	303-02	5.0	Sericin
SETAKOL [®]	320-01	5.0	Hydrolyzed Sericin

These water-soluble PENTAPHARM actives formed stable, clear to very slightly turbid solutions with SYN[®]-AKE.



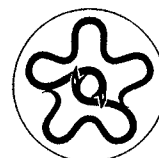
COMPATIBLE PENTAPHARM ACTIVES

Product Name	Product Code	% Wt.	INCI Name	Observations
ALPAFLOR [®] EDELWEISS GC	900-01	5.0	Leontopodium Alpinum Extract	Slight coloration at 40°C
ALPAFLOR [®] GIGAWHITE™	910-02	5.0	Water, Glycerin, Malva Sylvestris (Mallow) Extract, Mentha Piperita (Peppermint) Leaf Extract, Primula Veris Extract, Alchemilla Vulgaris Extract, Veronica Officinalis Extract, Melissa Officinalis Leaf Extract, Achillea Millefolium Extract	Slight turbidity at 25°C
ALPHA-ARBUTIN	336-01	2.0	Alpha-Arbutin	Slight coloration and pH decrease at 40°C
ERYTHRULOSE	307-01	5.0	Erythrulose	Slight pH decrease
FITOBROSIDE	292-01	5.0	Triticum Vulgare (Wheat) Germ Extract	Slight pH decrease at 40°C
LACTOMIDE	309-01	5.0	Milk lipids, Ceramide 3	Slight pH decrease at 40°C
MELFADE [®] -J	308-02	5.0	Water, Arctostaphylos Uva Ursi Leaf Extract, Glycerin, Magnesium Ascorbyl Phosphate	Slight coloration at 40°C
PREREGEN [®]	315-01	5.0	Glycine Soja (Soybean) Protein, Oxido Reductases	Slight pH decrease
SYN [®] -COLL	800421	5.0	Palmitoyl Tripeptide-5, Glycerin	Slight precipitate at 40°C*

* SYN[®]-COLL usually precipitates if diluted with excess of water. This precipitate does not have any influence on the activity of SYN[®]-COLL and disappears by adding an oil phase.

PENTAPHARM ACTIVES WITH LIMITED COMPATIBILITY

Product Name	Product Code	% Wt.	INCI Name	Observations
ALPAFLOR [®] NECTAPURE	911-02	5.0	Glycerin, Water, Buddleja davidii Extract, Thymus vulgaris (Thyme) Extract	pH decrease



DISCUSSION


SYN[®]-AKE is easy to formulate in gels, cream gels and emulsions.

Some of the tested substances showed a limited compatibility in aqueous solution with SYN[®]-AKE. This does not necessarily mean that they cannot be used in combination with SYN[®]-AKE in emulsions: the formula and/or the concentrations have to be carefully evaluated in detail to ensure the stability of the product.

We are open to discuss any questions connected with the formulation of SYN[®]-AKE and any additional information to these guidelines would be welcome.

April 19, 2006

PENTAPHARM LTD.



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Cosmetic Application

AGE KILLING EFFECT DAY CREAM (SYN®-AKE)

Description This soft cream is formulated with PENTAPHARM's new active SYN®-AKE, which has excellent smoothing and anti-wrinkle properties. It is particularly effective against expression lines.

Item	Ingredients	INCI Name	% w/w	Suppl.
1	A) Abil Care 85	Bis-PEG/PPG-16/16 PEG/PPG Dimethicone (and) Caprylic/Capric Triglyceride	1.50	6
2	Teginacid C	Ceteareth-20	1.00	6
3	Tego Alkanol 1618	Cetearyl Alcohol	2.00	6
4	Cetyl Alcohol	Cetyl Alcohol	2.00	
5	Pristerene 9559	Stearic Acid	1.00	64
6	Tegosoft MM	Myristyl Myristate	2.00	6
7	Dragoxat EH	Ethylhexyl Ethylhexanoate	4.00	105
8	Myritol 331	Cocoglycerides	4.00	7
9	B) Water	Aqua	73.50	
10	Structure XL	Hydroxypropyl Starch Phosphate	1.00	103
11	C) Glycerin	Glycerin	4.00	
12	Preservative	q.s.		
13	SYN®-AKE	Water, Glycerin, Dipeptide Diaminobutyroyl Benzylamide Diacetate	4.00	1

Procedure

Heat phases A) and B) to 80°C separately.
 Under stirring add phase A) to phase B), then homogenize.
 Cool down to 35°C, then add components of phase C) one after the other.
 If necessary, adjust the pH at approx. 5.5.

Suppliers

- 1) PENTAPHARM, CH 103 National Starch, USA
- 6) Degussa / Goldschmidt 105 Symrise, GER
- 7) Cognis, GER
- 64) Uniqema, B

We recommend to adjust the formulation and manufacture to the local conditions, to the raw materials available and to the current patent situation. Although this formulation has been designed with utmost care, we cannot assume any responsibility.

**Cosmetic Application****WRINKLE KILLING MOISTURIZER FOR MEN (PENTAVITIN® / SYN®-AKE)**

Description This quickly penetrating day cream for men is formulated with PENTAPHARM's new active SYN®-AKE, which is very effective against expression lines and with PENTAVITIN®, which has excellent moisturizing properties.

Item	Ingredients	INCI Name	% w/w	Suppl.
1	A) Cetyl Alcohol	Cetyl Alcohol	1.00	
2	Tegosoft DEC	Diethylhexyl Carbonate	6.00	6
3	Tegosoft OP	Ethylhexyl Palmitate	4.00	6
4	Tegosoft TN	C 12-15 Alkyl Benzoate	4.00	6
5	B) Water	Aqua	70.20	
6	Keltrol RD	Xanthan Gum	0.20	65
7	Arlatone LC	Sorbitan Stearate (and) Sorbityl Laurate	4.50	64
8	C) Glycerin	Glycerin	4.00	
9	Preservative	q.s.		
10	D) SYN®-AKE	Water, Glycerin, Dipeptide Diaminobutyroyl Benzylamide Diacetate	4.00	1
11	PENTAVITIN®	Saccharide Isomerate	2.00	1
12	Timid DC10357	Fragrance	0.10	105

Procedure

Let item 6 (Keltrol RD) swell in item 5 (water), then add item 7 (Arlatone LC).
Heat phase B) to 80°C, then homogenize shortly.
Heat phase A) to 80°C. Add phase A) to phase B), then homogenize.
Cool down to 40°C, then add phase C).
At 25°C, add components of phase D) one after the other.
If necessary, adjust the pH at 5.5 - 6.0.

ATTENTION: stability not guaranteed. Tests are still ongoing.

Suppliers

- | | |
|--------------------------|------------------|
| 1) PENTAPHARM, CH | 105 Symrise, GER |
| 6) Degussa / Goldschmidt | |
| 64) Uniqema, B | |
| 65) Kelco, USA | |

We recommend to adjust the formulation and manufacture to the local conditions, to the raw materials available and to the current patent situation. Although this formulation has been designed with utmost care, we cannot assume any responsibility.