RISK PROFILE

Melanotan I

CAS No. 75921-69-6

and

Melanotan II

CAS No. 121062-08-6

Date of reporting 15.01.2013

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1. Identification of substance

Chemical name (IUPAC):	Melanotan –I	Melanotan -II
INCI	[Nle4-D-Phe7]α-Melanocyte Stimulating Hormone = [Nle4, D-Phe7]α-MSH	Ac-NIe-c[Asp-His-D-Phe-Arg-Trp- Lys]-NH ₂
CAS No.	MT-I: 75921-69-6	MT-II: 121062-08-6
EINECS No.		
Synonyms	MT-I: "afamelanotide", Melanotan, Melanotan-1, Melanotan 1, Melanotan I,	MT-II: Ac-[Nle4Asp5D- Phe7Lys10] α-MSH-(4-10)-NH2

	Melanotan-I, NDP-MSH, CUV1647, EPT1647	
Molecular formula	MT-I: C ₇₈ H ₁₁₁ N ₂₁ O ₁₉	MT-II: C ₅₀ H ₆₉ N ₁₅ O ₉
Chemical structure	Ac-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH2 α-Melanotropin (α-MSH) Ac-Ser-Tyr-Ser-Nle-Glu-His-DPhe-Arg-Trp-Gly-Lys-Pro-Val-NH2 Melanotan I (MTI) Ac-Nle-c[Asp,His,DPhe,Arg,Trp,Lys]-NH2 Melanotan II (MTII)	
	(see Annex 1)	
Molecular weight	MT-I: 1646.9 g /mol	MT-II: 1024.2 g /mol
Contents (if relevant))		1
Physiochemical properties	No data retrieved	

References: a-MSH [online]

2. Uses and Origin

Uses	
Uses	Cosmetic products:
	Functions according to
	Cosing database:
	No matching results found (February 16, 2012)
	Other:
	Concentrations of Melanotan being applied
	No data retrieved (February 16, 2012).
	Frequency of use
	No data retrieved (February 16, 2012).
	> Food
	No data retrieved (February 16, 2012).
	Medicinal products

	To our knowledge these peptides currently find no therapeutic usage. They were invented for cosmetic purposes ("sunless tanning") – see below. As of today there is no registered drug anywhere in Europe. ¹ MHRA [online]; CIEH.org [online]).
	> Other products
	Melanotan was initially (and continues to be) popular with bodybuilders, models, actresses, and others seeking an instant tan, but has now reached a larger "audience". Melanotan –II (nicknamed "the Barbie drug"), the most potent α -MSH analogue, exhibits more side effects compared to MT-I, promising to make users "tanned, thin and turned on" (Wired Science [online]; CIEH.org [online]). One way by which MT-II intake causes weight loss in laboratory animals is by appetite reduction and fat burning (Li et al. 2004; Zhang et al., 2010).
	Currently the only efficient administration is sub cutaneous injection. Therefore, for the time being, "tanning" products relying on these peptides fall outside the scoop of the cosmetic products legislation.
	The effects of the melanotan preparations are not documented. Melanotan has not been tested for safety, quality or effectiveness, and it is not known what the possible side effects are or how serious they could be (MHRA [online]).
	Melanotan can be purchased from the internet as formulations for subcutaneous injection or nasal spray. The drug is also administered in tanning salons, beauty parlors, fitness studios, and hairdressers (Wired Science [online]). An internet search, using "Melanotan –I", "Melanotan –II" or "Melanotan" as search phrases, revealed that a wide range of products are marketed and sold on the internet.
	The prevalence of the use of melanotan is unknown. In Norway, a survey by the branch organization The Norwegian Pharmacy Association "Apotekforeningen", suggests that around 10000 syringe/needles are sold each year at Norwegian pharmacies for the purpose of self-injecting melanotan (Statens Legemiddelverk [online]; VG [online]).
Origin (natural/synthesis)	Developed at Arizona University in the 1980s as a protection against sunburn, melanotan is a synthetic hormone that, when injected, stimulates the naturally occurring melanin in the body by mimicking the naturally occurring hormone α -melanocyte stimulating hormone (α -MSH) (CIEH.org [online]; α -MSH [online]).
	Melanotan peptides consist of two primary products: Melanotan One (MT-I) and Melanotan 2 (MT-II), the first being a more natural amino acid, and the second being a super potent analogue ((Hadley & Dorr, 2006). The primary peptide structures of α -MSH and MT-I/MT-II are shown below (Hadley, 2005).

¹ The regulated α-MSH analogue "afamelanotide" i.e. MT-I (Clinuvel), available as depot formulation, is undergoing clinical trials as a method of photoprotection in patients with photosensitive disorders (e.g. erythropoietic protoporphyria, polymorphous light eruption, actinic keratosis), those susceptible to non-melanoma skin cancer (e.g. squamous cell carcinoma) and hypopigmentary disorders such as Vitiligo (Melanotan – I [online]).

Ac-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH ₂ α-Melanotropin (α-MSH)
Ac-Ser-Tyr-Ser-Nle-Glu-His-DPhe-Arg-Trp-Gly-Lys-Pro-Val-NH ₂ Melanotan I (MTI)
Ac-Nle-c[Asp,His,DPhe,Arg,Trp,Lys]-NH ₂ Melanotan II (MTII)
More details are provided in Annex1.

3. Regulation

Norway	No regulation (cf. Annex 2)
EU	No regulation (cf. Annex 2)
Rest of the world	No regulation (cf. Annex 2)

4. Relevant toxicity studies

Absorption Skin / GI tractus	 Transdermal penetration of MT-I through mammalian skin seems to be rather inefficient (e.g. < 0.05 % in intact rodent skin) (Dorr et al., 1988; Hadley & Dorr, 2006) - possibly related to a general refractoriness of the dermis /epidermis to uptake of peptides with molecular mass > 500 (in the absence of vehicle). ² Dorr et al. (1988) suggested that even low doses of topically applied MT-I (10 ⁻⁴ M) might be capable of increasing melanotropin levels in the skin <i>in vivo</i>, given that MT-I is biologically active at concentrations as low as 10 ⁻¹⁰ to 10 ⁻¹¹ M in experimental models.
Distribution	No data retrieved.
Metabolism	
Excretion	
Local toxic effects Irritation Sensitivity	No data retrieved.
Systemic toxic effects	Approximately 100 human subjects treated with MT-I over a 5-year period achieved consistent pigmentation without toxic side-effects (Hadley & Dorr, 2006). Three Phase I clinical trials determined that the licensed MT-I (i.e. afamelanotide) can be safely combined with UV-B light or sunlight (Dorr et al., 2004).
Acute	No acute toxic effects of MT-I were observed in rodents by subcutaneous injection at doses of 2 mg/kg /day for 12 weeks

 $^{^2}$ The molecular masses of MT-I and MT-II are 1646.9 g /mol and 1024.2 g /mol, respectively.

	(Hadley & Dorr, 2006).
Repeated dose	Repeated daily subcutaneous doses of 0.6 mg/kg/day MT-I in rats over a period of 30-days was well tolerated with no change in lethality, no effect on weight gain, no serum chemistry changes, except for a slight increase (30 %) in lactic dehydrogenase levels (Hadley & Dorr, 2006).
Mutagenicity /genotoxicity	No data retrieved – no evidence for genotoxicity.
Carcinogenicity	Paurobally et al. (2011) raised concerns about the safety of melanotan (MT-I and MT-II), in particular to the effects on melanocytic naevi. However, there is still no clear relationship between the development of melanoma and the use of melanotan. The authors caution that the question of carcinogenesis has not been adequately addressed, and that the harmlessness of melanotan should not be promoted. Another danger in this respect comes from the long-lasting stimulating potential of MT-I/MT-II, related to their resistance to enzymatic breakdown (Langan et al., 2010).
	Carcinogenic toxicity has not been consistently demonstrated for MT-I <i>in vitro</i> and <i>in vivo</i> (Hadley & Dorr, 2006). In a series of preclinical studies, melanoma tumor colony formation in a clonogenic assay system using melanoma cells isolated from patients was not enhanced (or slightly inhibited) by MT-I (Meyskens 1980, cited in Hadley & Dorr, 2006). Similar results were found in cultured melanoma cell lines. Moreover, no effect of MT-I was observed on primary tumor size or metastatic spread to the lungs in DBA/2J mice carrying melanoma cells (Gehlsen et al., 1992, cited in Hadley & Dorr, 2006). MT-I also did not influence melanoma invasiveness in the human amniotic basement membrane model <i>in vitro</i> .
	MT-I (2 and 10 mg/kg) did not increase the incidence of tumor development of subsequent growth rate of human melanomas in SCID (immunodeficient) mice. Nor did malignant transformation of normal human melanocytes occur after implantation in the SCID mice.
	MT-I treated normal human melanocytes were not able to grow after implantation in the SCID mice, suggesting that no malignant transformations had occurred (Hadley & Dorr, 2006).
Reproductive toxicity /teratogenicity	No developmental / teratogenic effects of MT-I (or α-MSH) were observed in rats, as seen by lack of fetal malformations and timing of parturition, following MT-I pumped directly into the gravid uterus over days 5-19 (the period of organogenesis in fetal development) (Dawson et al., 1993, and cited in Hadley & Dorr, 2006). Similarly, no toxic effects of MT-I were observed in Yucatan pigs (pig skin similar to that of humans), when administered subcutaneously at a dose of 0.16 mg /kg /day for 30 days.
Other effects	

5. Exposure estimates and critical NOAEL /NOEL

NOAEL /NOEL critical	not determined - insufficient data.
Exposure cosmetic products	not determined - hitherto, melanotan has not been found in cosmetic products.
Margin of safety (MoS)	not determined

6. Other sources of exposure than cosmetic products

Food stuffs	Data not retrieved
Pharmaceuticals	Data not retrieved
Other sources	It is currently illegal to sell subcutaneous self-injected tanning products such as melanotan (MHRA [online]).
Adverse side effects – from uses other than cosmetics	Recently, serious concerns have been raised concerning the safety of illegally advertised melanotan peptides sold from unregulated sources for subcutaneous self-injection. Untested MT-I is offered for tanning, whereas MT-II peptides is also used for its other effects on satiety and penile erection – the so called Barbie drug (Langan et al., 2009, 2010).
	Melanotan has been banned throughout Europe after reported side effects including nausea, flushing, the darkening of freckles, high blood pressure, scarring, suppressed appetite, spontaneous erections and increased libido (MHRA [online]; TV2 [online]; CIEH.org [online]).
	Adverse effects from short term subcutaneous administration of MT-I in small clinical trials seem to be limited to transient facial, neck and upper trunk flushing (40% subjects), nausea (10%) and lethargy (3%), and at doses greater than that needed for pigmentation, nausea and vomiting (Hadley & Dorr, 2006). These authors claim that <i>tanning effects</i> could be differentiated from <i>gastrointestinal effects</i> as regards the dose of MT-I required for activity. At the <i>maximally effective daily dose for tanning (0.16 mg /kg /day)</i> , administered <i>subcutaneously by a depot formulation</i> , they found that pigmentation is induced with minimal, if any, side effects.
	Being a shorter truncated cyclic version of MT-I, MT-II is capable of enhancing melanin pigmentation of the skin as efficiently as MT-I, and shares the same adverse effects. Nausea and "stretching and yawning complex" is frequently reported side-effects of MT-II at doses as low as 0.025 mg /kg body weight.
	A clinical study of 20 men with psychogenic and organic erectile dysfunction concluded that MT-II is a potent initiator of penile erection in men with erectile dysfunction (Wessells et al., 2000).
	Frequently reported adverse effects of Melanotan in the general population include increased size and darkening of naevi, as well as an "unnormal" skin tan (Cousen et al., 2009; melanotan.org [online]).
	Paurobally et al. (2011) present a case report on melanotan- associated melanoma in a 42-year-old woman, following a 3-month

period after subcutaneous injections of MT-II (100 mg daily for 2 days, and 50 mg daily for 5 days) in the abdomen. The woman stopped further injections due to nausea. The authors caution that the <i>harmlessness of melanotan should not be promoted because the potential risk for skin cancer has not been adequately addressed</i> . Malignant melanoma in a MT-I user has also been suspected (Ellis et al., 2009; Evans-Brown et al., 2009).
Although the association between melanotan and malignant melanoma is not scientifically documented there is concern that long term use might lead to increased risk for malignant melanoma <u>(Kreftforeningen</u> [online]; Langan et al., 2010; Thestrup-Pedersen, 2011).
Langan et al. (2009) also warned that use of melanotan may <i>confuse clinical presentation</i> and diagnosis of patients with pigmented lesions. The use of these peptides may be suspected in unexpectedly tanned individuals with rapidly pigmenting naevi.
MHRA has raised concerns about <i>transmission of blood-borne</i> <i>viruses</i> (HIV, hepatitis) from needle sharing as well as potential impurity of melanotan products (due to contaminated water) and from subcutaneous injection (the preferred delivery method) (MHRA [online]).
The Danish Medicinal Agency issued a renewed warning last summer after reports that the uncontrolled and unlicensed use of melanotan is <u>ever expanding</u> , despite earlier warnings regarding concerns about the safety of these substances (2008).
Similarly, in a newspaper article by TV2, the Norwegian Medicinal Agency strongly warns against the potentially fatal and ever-lasting adverse effects of melanotan. Moreover, there is increasing concern that melanotan usage is increasing even in young age groups; i.e. adolescents down to 13-14 years of age.
An incidence of brain hemorrhage, with suspected link to melanotan usage, although not proven, was recently reported in the Norwegian newspaper (Romerikes Blad [online]).

7. Assessment

Media has since 2002 reported a high demand for subcutaneously self-injected melanotropic peptides sold as "melanotan" (melanotan I and II) in the general population, mainly for their ability to tan the skin without UV light and sunburns. The cyclic peptide MT-II increases skin pigmentation at lower cumulative doses than MT-I, but has been found in clinical trials to result in more side effects, including nausea, appetite suppression, and increased libido (Langan et al., 2010).

The extent by which these peptides are used is not known, but unlicensed and untested powders sold as "melanotan" are found on the internet, tanning salons and gyms, and are reported to be used by thousands of members of the general public³. The Norwegian Pharmacy Association estimated that 10000 syringes are sold annually to Norwegian users of MT-I and MT-II (VG [online]).

There is growing concerns regarding the health risks of these unregulated agents, which have not been approved by medicinal agencies in any country, as their effect and safety have not been demonstrated.

Recent alerts continue to be issued from medicines and healthcare products regulatory authorities throughout Europe and worldwide (MHRA [online]; Evans-Brown et al., 2009), including Norway (Statens Legemiddelverk [online], TV2 [online], VG [online]). The concerns are based on numerous reports about adverse effects (see e.g. section 6), some of which might be related to potential impurity of chemicals from unregulated sources and infective complications, including transmission of blood-borne viruses from needle sharing.

The regulated α -MSH analogue afamelanotide (i.e MT-I), is undergoing clinical trials as a protective agent in photosensitivity skin disorders⁴. Although and preclinical toxicity studies indicate that the *licensed* MT-I is non-toxic, caution must still be exercised, because the biological effect of melanotan on the development of atypical and even malignant pigmented neoplasms is not yet well understood (Cardones & Grichnik, 2009; Cousen et al., 2009; Langan et al., 2010).

We have not found evidence (by internet search) for cosmetic products containing melanotan.

³ An internet community of users (>5000 members as of February 2009) has discussed their experiences and has been publishing information about the Melanotan peptides since June 14, 1999 at http://melanotan.org.

⁴ Potentially useful applications of MT-I (a.k.a. afamelanotide under the marketing trade name "SCENESSE") as protective agents in photosensitive disorders and for use in prevention of non-melanoma skin cancer are being pursued by Clinuvel Pharmaceuticals Ltd. (currently undergoing phase II and III clinical trials). The Italian Medicines Agency is the first to authorize afamelanotide for therapeutic treatment of erythropoietic protoporphyria (EPP), http://clinuvel.com/resources/cmsfiles/pdf/20100517ITAnnouncement.pdf.

8. Conclusion

Illegal melanotan products for subcutaneous self-injection or nasal spray are proliferating on the internet, mainly for the purpose of obtaining a tan – which is a cosmetic purpose. To our knowledge no authority has subjected concrete products based on these pepetides to a formal qualification procedure in accordance with European legislation. So far different medicinal products agencies around Europe have, however, considered Melanotan a drug falling within the scoop of the medicinal products legislation. This is mainly because of the physiological effects and because Melanotan, this far, is injected only. Melanotan is not licensed anywhere in the world as a medicine and we don't know what the short- or long-term effects are" (CIEH.org [online]).

We have hitherto not found evidence that melanotan agents are used in cosmetic products.

However, proof of principle exists that topical administration of melanotan elicits a significant biological response with regard to melanocyte stimulation and skin pigmentation (Dorr et al., 1988). It is therefore not inconceivable that melanotan products designed for topical administration might appear on the market in the future.

Regulatory authorities worldwide are concerned about the effects and health risks of unregulated melanotan agents. Especially worrisome is the trend of increasing usage of melanotan among teenagers, given the potential for causing lifelong serious health effects.

Thus, we propose to ban all forms and formulations of melanotan peptides in cosmetic products.

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10. Annexes

Annex 1: Structure and properties of MSH-peptides

 α -MSH is produced in keratinocytes as a cleavage product from a large precursor peptide called proopiomelanocortin (POMC).

proopiomelanocortin derivatives						
POMC						
γ-MSH	ACTH	β-lipotropin				
	i					
[α-MSH CLIP	y-lipotropin	β-endorphin			
		β-MSH				

http://en.wikipedia.org/wiki/Melanocyte-stimulating_hormone#Structure_of_MSH

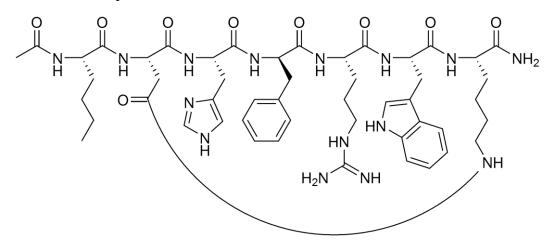
Ac-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH₂ α-Melanotropin (α-MSH)

Ac-Ser-Tyr-Ser-Nle-Glu-His-DPhe-Arg-Trp-Gly-Lys-Pro-Val-NH₂ Melanotan I (MTI)

> Ac-Nle-c[Asp,His,DPhe,Arg,Trp,Lys]-NH₂ Melanotan II (MTII)

Fig. 2 – Comparative primary sequences of α -MSH and two superpotent analogs, MTI and MTII.

Melanotan II – cyclic chemical structure



http://www.health-res.com/polymorphous-light-eruption-pmle/

<u>Melanotan I (MT-I)</u> is a *linear* 13 amino acids [Nle4-D-Phe7] α -MSH peptide with 10-1000 times the potency of the endogenous α -MSH, depending on the assay system. Unregulated MT-I is injected subcutaneously for the purpose of obtaining a tan, and this effect is mediated by activated melanocortin 1 receptors (MC1R) (Hadley et al., 1993; Annex 1; Langan et al., 2010 and references therein).

The regulated Melanotan –I product is known as **afamelanotide** (international non-proprietary name) with the marketing trade name "**SCENESSE®**" (Clinuvel Pharmaceuticals Ltd., Melbourne, Australia).

Melanotan II (MT-II) is a shorter *cyclic* variant, which enhances tanning of the skin in humans at lower cumulative doses than MT-I, but also is used for its other wanted "side-effects" of satiety and penile erections – the so called Barbie drug: a pill or nasal spray than can make you thin, tan, pain-free, and sexually aroused all at once, without effort (McCarthy, 2002; Hadley, 2005; Langan et al., 2009). A wider range of side-effects such as nausea, somnolence and penile erections is thought to result from interaction with melanocortin receptors in the gut (MC2R) and brain (MC3R), respectively.

PT-141 (CAS No. 189691-06-3):

Bremelanotide (formerly PT-141; Palatin Technologies, N.J., USA) is originating from MT-II (C-terminal NH₂ group replaced with –OH) and exhibits aphrodisiac effects in both males and females, mediated by actions in the hypothalamus – the brains emotional switchboard - on neurons that express MC3R and MC4R receptors (Hadley & Dorr, 2006; Ze & Li, 2011). It is under drug development by Palatin Technologies as a treatment for hemorrhagic shock and reperfusion injury, using a new subcutaneous drug delivery system that appears to have little effect on blood pressure

(<u>http://en.wikipedia.org/wiki/Bremelanotide</u>). It was originally developed for use in treating sexual dysfunction, but temporally discontinued in 2008 because concerns were raised over adverse side effects of increased blood pressure.

Annex 2: Regulatory status of melanotan as a medicinal agent

Norway:

The Norwegian Medicinal Products Agency considers Melanotan a pharmaceutical drug. However, no concrete ready to use product has been subjected to an ordinary classification procedure whereby all aspects are evaluated. (cf. Statens Legemiddelverk). http://www.slk.no/templates/InterPage____65110.aspx?filterBy=CopyToGeneral

Norwegian Medicines Agency ("Legemiddelverket") warns against use of Melanotan (2008). <u>www.legemiddelverket.no/templates/InterPage___65110.aspx</u>.

EU:

Warnings over the sale and use of unregulated Melanotans have been issued by drug regulatory authorities in Europe and in the United States:

Ireland:

Microbial contamination: The Irish Medicines Board (IMB) detected the presence of microbial contamination in the water vial supplied with a pack of MT-II. Microbial contamination of an injectable product exposes any recipient to the risk of serious infection.

Melanotan (I and II) is not authorized for use in Ireland, or anywhere throughout the EU, so there can be no guarantees as to its quality, safety or effectiveness. <u>http://www.imb.ie/EN/Safety--Quality/Advisory-Warning--Recall-Notices/Human-Medicines/Melanotan-Powder-for-Injection-.aspx</u>

<u>UK</u>:

In November 2008 the UK Medicines and Healthcare products Regulatory Agency (MHRA) warned people not to use Melanotan (I and II) as it is an unlicensed medicine and may not be safe. It also warned eighteen different companies in relation to their selling or advertising of the product. http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON031009

Medicines and Healthcare Products Regulatory Agency. "Tan jab" is an unlicensed medicine and may not be safe—warns medicines regulator. 2008.

 $\underline{www.mhra.gov.uk/NewsCentre/Pressreleases/CON031009}$

Denmark:

Melanotan is a medicinal product for injection, but its effect and side effects have not been investigated, and we therefore warn against using it.

http://laegemiddelstyrelsen.dk/en/service-menu/news/warnings/warning-against-the-productmelanotan

Danish Medicines Authority. Warning against the product Melanotan. 2008. www.dkma.dk/1024/visUKLSArtikel.asp?artikeIID=13865

Sweden:

In late July 2010 the Swedish Medical Products Agency issued a warning against the usage of melanotan II.

"Läkemedelsverket varnar för användning av Melanotan II". Medical Products Agency. Retrieved 2010-07-26. (Swedish)

Austria and Germany:

The Austrian Bundesamt für Sicherheit im Gesundheitswesen has issued a Warning (reply #8 - 05/19/09):

Warning - Austria - <u>**BASG</u>** May 18, 2009: <u>**Melanotan II**</u> (Appears to only be available in German) This warning consists primarily of links to the FDA's Melanotan II warning and the MHRA's warnings.</u>

<u>ltaly</u>:

SCENESSE® can now be prescribed for patients diagnosed with EPP in Italy under Law 648/96 (innovative new treatments to be prescribed for patients with no other effective therapy), while marketing authorization for the European Community is being prepared.

Melanotan-1 ([NIe4, D-Phe7]α-MSH - under its generic name "afamelanotide") was approved on May 5, 2010 by the Italian Medicines Agency (AIFA - Agenzia Italiana del Farmaco) as a medication for those afflicted with the orphan disease erythropoietic protoporphyria (EPP). The drug is used to induce photoprotective dermal eumelanin pigmentation and thereby reduce the effects of painful, burning dermal photosensitivity caused by the disease (Melanotan.org [online]).

12/5/2011: EMA acknowledges Clinuvel filing afamelanotide in Europe `11. http://asx.netquote.com.au/search-announcements.asp?S=CUV

US:

In September 2007, the US Food and Drug Administration (FDA) advised consumers to stop using unregulated MT-II as it was an unapproved drug and that there was no evidence that it was safe or effective for its labeled uses. The FDA also issued a Warning Letter to the owner of the company that was illegally selling and marketing the product on its website.

US Food and Drug Administration. FDA warns about unapproved product, Melanotan II. 2007. www.fda.gov/consumer/updates/melanotan090507.html

MT-I (under the name afamelanotide or "SCENESSE") as a protective agent in photosensitive disorders and in the prevention of non-melanoma skin cancer are pursued by Clinuvel Pharmaceuticals Ltd. (Melbourne, Australia).

3/3/2011: FDA allows Clinuvel's innovative Vitiligo trial; Vitiligo affects 1-2 % of the human population. 12/5/2011: EMA acknowledges Clinuvel filing afamelanotide in Europe `11. http://asx.netquote.com.au/search-announcements.asp?S=CUV

Annex 3: Examples of proposed uses for melanotan agents

Product Name	Distributor /Manufacturer	Markets –retail trade	Cosmetic category (intended use)	References /internet links
Melanotan-II (MT-II)	Qingdao Liyuan Trading Co., Ltd, China	International http://bit.ly/imxxXE	Synthetic tanning agent	1)
Melanotan II - 3 PACK 3-4 Vial Packs	GenX Chemicals, U.S.A	http://bit.ly/kl7VEb	melanogenesis (tanning) and aphrodisiac effects	2)
Melanotan I-II	Alishot international trade co ltd, China	http://bit.ly/jbM7QU	melanogenesis (tanning) and aphrodisiac effects	3)
MELANOTAN II (MT2)	RhoidsPharm.com, U.S.A	http://bit.ly/IMDwxi	 -Induces tanning at low doses -Increases sexual desire and function for men and women - Minimal or no undesirable side effects. - Decrease body fat mass and reduce food intake - Potent self- tanner applications. 	4)

Internet image search (bing.com): ca. 500 hits http://www.bing.com/images/search?q=melanotan&go=&form=QBIL&qs=n#x0y1100

Links accessed February 17, 2012:

- http://liyuan.en.ec21.com/Melanotan_II--2754506_2755651.html
 <u>http://www.genxchemicals.com/search-results.html</u> (search for melanotan)
 <u>http://www.tradekey.com/product_view/id/1494994.htm</u>
 Dead link