



Office for Product
Safety & Standards

Prostaglandin analogues in cosmetics – Literature review, market survey, analytical method development and testing.

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Prostaglandin analogues in cosmetics – Literature review, market survey, analytical method development and testing.

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Executive Summary

Introduction

1. Cosmetic products and their ingredients are regulated in the UK by EU retained law Regulation (EC) No. 1223/2009. Any substance can be used as an ingredient in a cosmetic product provided it has been assessed as safe for human health under normal or reasonably foreseeable conditions of use, and not subject to prohibition, restriction or control (on function) which applies to specified substances listed in the annexes to Regulation (EC) No. 1223/2009.
2. Prostaglandin analogues are used to promote eyelash growth and can be listed as an ingredient in eyelash growth serums.
3. Prostaglandin analogues are not listed in the annexes to Regulation (EC) No. 1223/2009 and therefore only subject to the conditions required for all cosmetic products.
4. OPSS asked LGC to review the science and use of prostaglandin analogues recorded in the literature and to assess the availability of prostaglandin analogue ingredients in eyelash growth products available on the UK market.
5. Based on the literature review, LGC was required to develop and verify a suitable method with the intention of analysing eyelash growth serums containing prostaglandin analogues purchased from the UK market.
6. A report to be provided to OPSS with a review of the literature, the availability of eyelash growth serums containing prostaglandin analogues on the UK market, verification of a suitable method, the results of testing applying the verified method to purchased products and a discussion.

Literature Review

7. The literature search identified four synthetic prostaglandin analogues bimatoprost, latanoprost, travoprost, and tafluprost being used in topical treatment for the eye disease glaucoma having the side-effect of increased eyelash growth.
8. Some manufacturers of cosmetic products have identified use of synthetic prostaglandin analogues and their derivatives as active eyelash growth ingredients for use in cosmetic products.
9. The four most common synthetic prostaglandin analogue ingredients identified in eyelash growth serums are isopropyl cloprostenate (a travoprost derivative), bimatoprost, ethyl tafluprostamide [tafluprost derivative] and 17-phenyl trinor prostaglandin E2 serinol amide [not a PGF2 α analogue]. Three less commonly reported synthetic prostaglandin analogue ingredients include norbimatoprost (bimatoprost derivative), methylamido dihydro noralfaprostal (a bimatoprost derivative) and dechloro dehydroxydifluoro ethylcloprostenolamide (a tafluprost derivative).

UK Market Survey

10. One hundred and ten eyelash growth serums were available from UK accessible websites. Twenty-three eyelash growth serums were identified as having a prostaglandin ingredient with nineteen eyelash growth serums identifying a synthetic prostaglandin analogue ingredient and four eyelash growth serums containing a natural prostaglandin ingredient.
11. Isopropyl cloprostenate is the most commonly listed synthetic prostaglandin analogue ingredient declared in ten eyelash growth serums followed by ethyl tafluprostamide declared in five eyelash growth serums, with norbimatoprost declared in two eyelash growth serums and methylamido dihydro noralfaprostal declared in one eyelash growth serum.
12. Black sea rod oil as an ingredient was listed in four products. This ingredient contains a naturally occurring prostaglandin produced by the sea coral and has similar properties to prostaglandin analogues encouraging eyelash growth. Naturally occurring prostaglandin eyelash growth ingredients appears not to have been considered by authorities.

Testing

13. Based on the literature review and market survey, LGC proposed to OPSS to obtain and analyse eye lash serums for three target prostaglandin analogues; isopropyl cloprostenate, ethyl tafluprostamide and bimatoprost using a method involving liquid/liquid extraction and determination using reverse phase liquid chromatography (RP-HPLC) coupled to two mass spectrometers in tandem (RP-HPLC/MS-MS).
14. A suitable RP-HPLC/MS-MS analytical method was verified for determining isopropyl cloprostenate, ethyl tafluprostamide and bimatoprost in eyelash growth serums having a limit of quantification of 1 mg/kg (0.0001 %). The verified method was applied to twenty-one eyelash serums identified in the market survey either containing prostaglandin or prostaglandin analogue ingredient.
15. Eight samples were found not to contain measurable levels of the three target prostaglandin analogue compounds. Eight samples were found to contain isopropyl cloprostenate in the range 8 - 72 mg/kg (0.0008 - 0.0072 %). Four samples were found to contain ethyl tafluprostamide in the range 18 - 176 mg/kg (0.0018 - 0.0176 %). One sample was found to contain bimatoprost at 270 mg/kg (0.0270 %).

Discussion

16. The LC/MS method verified in this project was shown to be repeatable and accurate requiring minimal sample preparation for determining the three target prostaglandin analogues isopropyl cloprostenate, ethyl tafluprostamide and bimatoprost in commercial eyelash growth serums.
17. The range of values for isopropyl cloprostenate, ethyl tafluprostamide and bimatoprost found in this project appears to correspond to earlier analytical results reported in published studies. These values are also consistent with an application made by cosmetic manufacturers to the EU Commission in seeking approval for permitted maximum concentrations of 0.007 % for isopropyl cloprostenate and 0.018 % for ethyl tafluprostamide in cosmetic products.

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18. The EU scientific committee on consumer safety (SCCS) in considering the application for the use of isopropyl cloprostenate and ethyl tafluprostamide in cosmetic products concluded in opinion SCCS/1635/21: *'In view of the potential for causing effects at very low concentrations, and the intended use in the proximity of the eye, the SCCS has noted concerns over the safety of prostaglandin analogues when used in cosmetic products.'*

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1. Introduction

1.2 Background

Prostaglandin analogues are listed ingredients in cosmetic products sold on the UK market with the function of promoting eyelash growth. These ingredients have pharmacological properties and prostaglandin analogues are used as active ingredients in medicinal products requiring a doctor's prescription in the UK.

To investigate the use of prostaglandin analogues in cosmetic products, the OPSS invited LGC to review their use and analyse eye lash growth products available to the UK consumer.

OPSS Research Objectives

1. Literature review and market analysis – A literature review covering both the safety and use of prostaglandins in cosmetic products as well the currently available test methods for their detection and quantification. An analysis of the cosmetic market, utilising the information identified in the literature review to provide a comprehensive market analysis as to the prevalence of prostaglandin analogues in eyelash growth products.
2. Method development – The development of a method suitable for the detection and quantification of prostaglandin analogues.
3. Product procurement and testing – working with OPSS, products are identified from online and high street vendors for testing. The contractor will then undertake testing using the developed methods to produce data tables, which will be captured in the draft report.
4. Draft and final report – The contractor will capture all the other outputs in a final report to identify evidence gaps for future research.

1.3 LGC Approach

LGC identified a series of tasks elaborated in the bid submission to ensure the successful outcome of the project to meet OPSS research objectives as described in Table 1.

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Table 1 LGC Tasks to Meet OPSS Research Objectives

	OPSS Research Objective	LGC Tasks
1	Identification and development of analytical methods for the detection of prostaglandins	<ul style="list-style-type: none"> ➤ Literature review for the detection and quantification of prostaglandins in eyelash growth products. ➤ Market analysis to understand the prominence of prostaglandins analogues in eyelash growth products. ➤ Liaise with OPSS officials.
2	Product Procurement & Sampling	<ul style="list-style-type: none"> ➤ In conjunction with OPSS, obtain representative samples of agreed cosmetic products from commercial suppliers (online & high street) – up to 40 samples.
3	Method Development	<ul style="list-style-type: none"> ➤ Development of a method suitable for the detection and quantification of the prostaglandin chemical/chemicals of interest.
4	Method performance verification	<ul style="list-style-type: none"> ➤ Validate method performance (limit of detection, limit of quantification, linearity, range, spiked sample recovery, reference material recovery).
5	Testing	<ul style="list-style-type: none"> ➤ Analysis of samples agreed with OPSS using validated method.
6	Data interpretation	<ul style="list-style-type: none"> ➤ Analysis of LC-MS data ➤ Preparation of findings
7	Project report	<ul style="list-style-type: none"> ➤ Prepare a draft report identifying key findings.

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2. Literature Review

A search of public databases was made using combinations of keywords. Titles and abstracts of the publications found in the literature search were assessed to eliminate duplicates and screened to identify a subset of “key” sources that meet criteria for relevance and usefulness for the report or issue papers. Key sources were “tagged” to assist in identifying the most relevant sources for topics covered in the report.

The following databases were searched for relevant peer-reviewed literature using the key words ‘eyelash’ ‘growth,’ ‘serum,’ ‘prost,’ ‘prostaglandin’ ‘analogue’ and ‘chromatography’ for the period 2010 to 2022 with the number of references found indicated in the square brackets:

- Google Scholar: Google Scholar provides a simple way to broadly search for scholarly literature. From one place, you can search across many disciplines and sources: articles, theses, books, abstracts and opinions, from academic publishers, professional societies, online repositories, universities and other web sites [437].
- ScienceDirect: ScienceDirect is Elsevier's platform of peer-reviewed scholarly literature. It includes thousands of books, journal articles, and other reference materials [64].
- Pubchem: US National Library of Medicine National Institutes of Health. PubChem provides a collection of freely accessible chemical information. Search chemicals by name, molecular formula, structure, and other identifiers [18].
- EU SCIENCE HUB: The European Commission's science and knowledge service [0].

Considering the literature the following review was compiled.

2.1 Eyelashes

The primary role of eyelashes is to protect and maintain the health of the eyelid which produces the tear film lipid layer that protects the eye from external trauma. The lower eyelid has 75-80 lashes dispersed in three to four rows, and the upper eye lid has 90-160 lashes scattered on five to six rows (Aumond & Bitton, 2018).

The eyelash is made up of three layers, the innermost layer, the medulla, consisting of loose cells, a second layer of a thicker cortex surrounding the medulla ensuring strength and stability and the third layer, the cuticle, consisting of several cell layers and forming the outermost impermeable layer providing protection.

Eyelash growth is a three-phase cycle; with the anagen, catagen and telogen phases regulated by the body’s hormones (Severson, 2018) described as follows:

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Anagen (Growth) Phase

The anagen phase (also known as the growth phase) occurs when lashes are actively continually growing between 30 and 45 days. Only about 40 percent of the upper lashes and 15 percent of the lower lashes are in the anagen phase at any one time. Each lash will grow to a certain length and then stops growing.

Catagen (Transition) Phase

The catagen phase (also known as the transition phase) occurs when the lash stops growing and the hair follicle shrinks. If an eyelash falls out or is plucked out during this phase, the lash will not grow back right away as the follicle needs to complete the catagen phase before the next phase. The catagen phase lasts between two and three weeks.

Telogen (Resting) Phase

The telogen phase (also referred to as the resting phase) can last more than 100 days before the eyelash falls out and a new one begins to grow. As each individual lash is in a different phase of the growing cycle, then a few lashes will fall out most days. Typically, it takes between four and eight weeks to fully replace an eyelash.

Using biochemically active compounds the phase of eyelash growth can be influenced to promote the anagen phase over the catagen phase to cause the eyelash to continue growing.

Prostaglandin and prostaglandin analogues are biochemically active compounds that can be applied to eyelashes to enhance growth.

2.2 Nomenclature and Biochemistry of Prostaglandins

Prostaglandins are a group of endogenously produced substances that play essential roles in regulating human physiology. All prostaglandins are composed of a cyclopentanone nucleus with two side chains. Primary prostaglandins contain a 15-hydroxyl group with a 13,14-trans double bond. Each type of prostaglandin is also allocated a group letter (e.g., A, B, C, D, E, F, G, H), in agreement with the functional substitutions in the cyclopentanone nucleus. For example, in prostaglandin F₂α (PGF₂α), 'F' indicates that the prostaglandin has two hydroxyl groups in the cyclopentanone ring (F series), the '2' indicates that it has two double bonds, and the 'α' indicates that its hydroxyl grouping at carbon 9 is in the α configuration (Zreik & Behrman, 2008).

Prostaglandins are highly lipophilic molecules that enter cells via a prostaglandin transporter called PGT (prostaglandin transporter). There they bind to prostaglandin receptors to exert their effect. There are currently nine known prostaglandin receptors in the body. All prostaglandin receptors are members of the G-protein which are specialised proteins with the ability to bind the nucleotides guanosine triphosphate (GTP) and guanosine diphosphate (GDP). The G-protein coupled receptors (GPCRs) mediate the majority of cellular responses to external stimuli activating a cascade of further signalling events that results in a change in cell function. As members of the G-protein signalling family, prostaglandins can activate secondary signalling pathways by activating or inhibiting enzymes such as adenylyl cyclase and phospholipase C, causing downstream physiological effects (Malik & Dua, Updated 2022 May 2015).

These properties of prostaglandins have been used by medical science (Xue, 2022) to treat diseases where synthetic prostaglandin analogues, derivatives of prostaglandin that do not occur naturally in the body, such as prostaglandin F₂ (PGF₂α) and E₂ (PGE₂) are used to target prostaglandin receptors in the eye to treat elevated intraocular pressure (IOP) which

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is the most prevalent risk factor for the eye disease glaucoma. Whilst these prostaglandin analogues are effective in treating glaucoma, there are potential side effects including eyelash growth, peri-ocular skin discoloration and iris pigmentation. It is the side effect of eyelash growth which has been used to develop eyelash growth products.

In addition to the use of synthetic prostaglandin analogues in the treatment of glaucoma and subsequent use in cosmetic products, it is also known that the prostanoid derivative (15S)-PGF₂α has been found naturally present in the Caribbean coral species *Plaxaura homomalla* (Valmsen, et al., 2001) listed as a cosmetic ingredient in some eyelash growth serums.

2.3 Prostaglandin Analogues in Pharmaceutical and Cosmetic Products

As previously described, the emergence of prostaglandin analogues is due to the development of medical treatments to reduce elevated intraocular pressure for patients with glaucoma.

Although the use of a prostaglandin analogue to treat IOP in patients affected by glaucoma was first reported in Japan in 1993, it was only with the approval of the prostanoid; latanoprost (an isopropyl analogue of PGF₂α) by the US FDA in 1996 which saw wider commercial use. The US FDA also approved two other prostanoids travoprost in 2001, tafluprost in 2012 and the prostamide bimatoprost in 2011. All these substances are commonly referenced in treating the effects of glaucoma.

Bimatoprost, latanoprost, travoprost, and tafluprost are identified by the National Institute for Health and Care (NICE) as topical treatments for glaucoma and ocular hypertension in the UK (National Care for Health and Care Excellence, 2022).

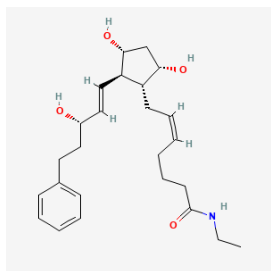
NICE and the US National Institutes of Health (NIH, 2022) both provide information on structures, formulas, guidance etc. on bimatoprost, latanoprost, travoprost, and tafluprost in pharmaceutical products.

Bimatoprost

- IUPAC name: (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(E,3S)-3-hydroxy-5-phenylpent-1-enyl]cyclopentyl]-N-ethylhept-5-enamide.
- Molecular Formula: C₂₅H₃₇NO₄.
- Common or very common side effects: Dry eye; eye discolouration; eye discomfort; eye disorders; eye inflammation; headache; hypertension; hypertrichosis; skin reactions; vision disorders.
- Warnings: For women who are pregnant the manufacturer advises avoid unless potential benefit outweighs risk and for women who are breastfeeding the manufacturer advises avoid.

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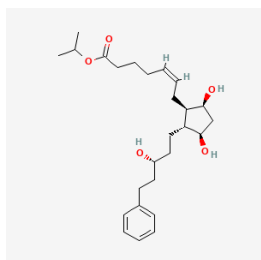
Figure 1: Chemical structure of (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(E,3S)-3-hydroxy-5-phenylpent-1-enyl]cyclopentyl]-N-ethylhept-5-enamide.



Latanoprost

- IUPAC Name: Propan-2-yl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]hept-5-enoate.
- Molecular Formula: $C_{26}H_{40}O_5$
- Common or very common side effects: Eye discolouration; eye discomfort; eye disorders; eye inflammation; vision disorders.
- Warnings: For women who are pregnant or subsequently breastfeeding the manufacturer advises to avoid.

Figure 2: Chemical structure of propan-2-yl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]hept-5-enoate.

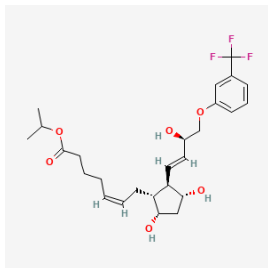


Travoprost

- IUPAC Name: Propan-2-yl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(E,3R)-3-hydroxy-4-[3-(trifluoromethyl)phenoxy]but-1-enyl]cyclopentyl]hept-5-enoate.
- Molecular Formula: $C_{26}H_{35}F_3O_6$
- Common or very common side effects: Dry eye; eye discolouration; eye discomfort; eye disorders.
- Warnings: For women who are pregnant the manufacturer advises avoid unless potential benefit outweighs risk. For women who are breastfeeding the manufacturer advises avoid.

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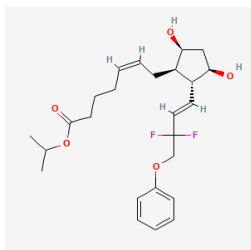
Figure 3: Chemical structure of propan-2-yl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(E,3R)-3-hydroxy-4-[3-(trifluoromethyl)phenoxy]but-1-enyl]cyclopentyl]hept-5-enoate.



Tafluprost

- IUPAC Name: Propan-2-yl (Z)-7-[(1R,2R,3R,5S)-2-[(E)-3,3-difluoro-4-phenoxybut-1-enyl]-3,5-dihydroxycyclopentyl]hept-5-enoate.
- Molecular Formula: C₂₅H₃₄F₂O₅
- Common or very common side effects: Dry eye; eye discolouration; eye discomfort; eye disorders; eye inflammation; headache; vision disorders.
- Warnings: For women who are pregnant the manufacturer advises avoid unless potential benefit outweighs risk and for women who are breastfeeding the manufacturer advises avoid.
- NICE also identify misoprostol (National Care for Health and Care Excellence, 2022) as another pharmaceutical prostaglandin analogue used in treating gastric and duodenal ulcers highlighting its unlicensed use in terminating pregnancies.

Figure 4. Chemical structure of propan-2-yl (Z)-7-[(1R,2R,3R,5S)-2-[(E)-3,3-difluoro-4-phenoxybut-1-enyl]-3,5-dihydroxycyclopentyl]hept-5-enoate.



Medical Treatments

Uses of prostaglandin analogues in medical treatments are described in a number of papers including (Lee & McCluskey, 2010) and (Winkler & Fautsch, 2014). Winkler & Fautsch identified bimatoprost as being more potent than latanoprost in generating eyelash growth. Lee & McCluskey provided information on concentrations of prostaglandin analogues typically used in glaucoma treatment products including 0.005% latanoprost, 0.004% tafluprost and 0.03% bimatoprost.

Whilst pharmaceutical products containing prostaglandin analogues are mainly used in treating IOP in glaucoma affected patients, there are references (Jones, 2011) and (Barron-Hernandez & Tosti, 2017) in using ophthalmic solutions containing prostaglandin analogues to treat hair loss (alopecia or hypotrichosis) of eyelashes or eyebrows. This use of prostaglandin analogues to treat a medical condition appears to have influenced cosmetic companies to consider non-medical use for improving poorly developed eyelashes.

2.4 Eyelash Growth Serums in the USA

Examining the use of ophthalmic solutions containing prostaglandin analogues to treat hypotrichosis a paper (Jones, 2011) describes the use of an ophthalmic solution under the trade name 'Latisse' containing 0.03% bimatoprost to treat hypotrichosis of eyelashes. In a more recent paper (Barron-Hernandez & Tosti, 2017) there is also information regarding an ophthalmic solution containing 0.03% bimatoprost to treat scalp alopecia as well as to restore missing eyelashes and eyebrows.

The use of ophthalmic solutions containing prostaglandin analogues to treat eyelash loss can be considered a medical condition but this appears also to have prompted companies to consider using prostaglandin analogues for cosmetic purposes.

This use of prostaglandin analogues in cosmetic products in the US has been highlighted in articles on US websites including HBW Insight (HBW, 13 March 2022). HBW Insight reported on court cases in the USA concerning the status of eyelash growth serums containing prostaglandin analogues considered to impart drug-like structure and/or function effects on the human body.

These reports have prompted the US Cosmetic Ingredient Review (CIR), who provide advice to industry and the FDA on cosmetic ingredients, to issue a memorandum on eyelash growth serums (Cosmetic Ingredient Review, 2022).

The CIR memorandum considers recent judicial cases identifying an eyelash growth product as either a drug or cosmetic has largely depended on the claims being made for the product. Where claims identify the product as a drug (pharmaceutical product) then requirements for marketing as drugs apply but in the absence of such claims, these may be considered as a cosmetic product.

2.5 Eyelash Growth Serums in Europe

Information on eyelash growth serums in Europe have been mainly reported EU and national government institutions.

EU Commission

National competent authorities and manufacturers in the EU apply the Cosmetic Products Regulation (EC) No 1223/2009 and accompanying guidance documents in considering whether products are appropriate to the cosmetics legislation or other product safety legislation.

The EU Manual on Borderline Products for Cosmetic Products Version 5.2 (EU Commission - Manual on Borderline Products, 2017) provides guidance on eyelash growth products in Section 3.3.5 under the title 'Products that make eyelashes grow.'

Section 3.3.5 considers identification of an eyelash growth product as a cosmetic should be based on certain characteristics including presentation, promotional literature, composition, specific pharmacological, immunological or metabolic properties, the mode of application under normal and reasonably foreseeable conditions of use, the frequency of application, the application site, the degree of penetration, and the risk in using the product.

Section 3.3.5 specifically highlights

“...a substance is used in medicinal products as an active ingredient [e.g. prostaglandins and their analogues] is not decisive. However, this may be an indicator for a pharmacological, immunological or metabolic action of the product.”

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No prostaglandin analogue is currently listed in the Cosmetic Products Regulation. In addition, sixteen synthetic prostaglandin analogues are currently listed in the EU Cosmetic Ingredients (CosIng) Database (EU Commission - CosIng Database, 2022) as cosmetic ingredients identified with the function as a 'hair conditioner.'

Swedish Medical Products Agency

The Swedish Medical Agency (Lakemedalsverket) first identified eyelash growth serums on the European market in 2011. In 2013, the Swedish Medical Products Agency conducted a survey identifying twenty-six eyelash growth products available to consumers on the Swedish market. An analysis of the twenty-six eyelash growth products found nine products listing a prostaglandin analogue as an ingredient confirmed by analysis with a further three products not listing a prostaglandin analogue ingredient but later shown by analysis to be present. In the press release (Swedish Medical Products Agency, 15 April 2013) it was stated eyelash growth serums containing prostaglandin analogues are banned in Sweden.

The Swedish Medical Products Agency identified five different prostaglandin analogues in nine eyelash growth products namely:

- Isopropyl closprostenate (travoprost derivative) in five products.
- Dechloro dehydroxydifluoro ethylcloprostenolamide (tafluprost derivative) in one product.
- Bimatoprost in one product.
- Methyamido dihydro noralfaprostal (bimatoprost derivative) in one product and
- 17-Phenyl trinor prostaglandin E2 serinol amide (not a PGF2 α analogue) in one product.

Details of the analytical method used by the Swedish Medical Products Agency to identify prostaglandin analogues in eyelash growth serums were not given in the press release and subsequent efforts to locate the original report proved unsuccessful.

German Federal Institute of Risk Assessment

In 2018, the German Federal Institute of Risk (Bundesinstitut für Risikobewertung - BfR) published a report (BfR, July 2018) considering a health assessment of prostaglandins, prostaglandin analogues and prostamides in eyelash growth treatments.

The BfR report described an investigation by German regional authorities into eyelash growth treatments sold as cosmetic products. The authorities had surveyed the market and identified four prostaglandin analogues with concentrations ranging from 0.0006 % to 0.03 % (6-300 mg/ml) in eyelash growth products. The prostaglandin analogues identified in the eyelash growth products were derivatives of existing pharmaceutical compounds used in medical treatments namely:

- Norbimatoprost (bimatoprost derivative),
- Cloprostenol isopropyl ester (travoprost derivative),
- Ethyl tafluprostamide (tafluprost derivative) and
- Bimatoprost.

The BfR report further considered the chemistry and toxicology of prostaglandin analogues identifying other prostaglandin analogue derivatives based on the four pharmacologically active compounds bimatoprost, tafluprost, travoprost and latanoprost to identify fourteen

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different compounds that could potentially be used in eyelash growth products as shown in Table 2.

Table 2 List of pharmacological prostaglandin analogues and corresponding derivatives.

Pharmacological prostaglandin analogue	Derivative of pharmacological prostaglandin analogue
Bimatoprost	Cyclopropyl bimatoprost
	Cyclopropylmethyl bimatoprost
	Dechloropropylmethyl cloprostenolamide
	Norbimatoprost/Methylamido Dihydro noralfaprostol
Tafluprost	Nortafluprost
	Ethyl tafluprostamide
Travoprost	Isopropyl cloprostenate.
	Ethyl travoprostamide
	Keto travoprost
	Methyl travoprost
Latanoprost	Benzothiophenyl dephenethylatanoprost
	Dihydroxypropyl dehydrolatanoprostamide
	Dehydrolatanoprost
	Trifluoromethyl dehydrolatanoprost

In considering the chemistry, toxicology and use of prostaglandin analogues, the BfR report concluded with the following observation:

“...no data that can be used to derive a safe application concentration with respect to the observed adverse side effects of PGF₂α analogues in eyelash growth treatments.”

EU Scientific Committee on Consumer Safety (SCCS)

The health assessment made by BfR in 2018 prompted the EU commission in 2019 to ask EU countries to survey their markets for eyelash growth products containing prostaglandins and their analogues in their respective markets. This survey helped identify an uneven situation in terms of applicable regulatory framework (e.g. cosmetic products or medicinal products). This was followed by the EU commission considering the SCCS should make an evaluation of prostaglandins and their analogues making a call for data in 2020.

The call for data asked for contributions on the safety of the following substances:

- Ethyl Tafluprostamide (CAS 1185851-52-8)
- Ethylcloprostenolamide and
- Isopropyl cloprostenate (CAS 157283-66-4).

In January 2021, the EU Commission mandated the SCCS to investigate the use of prostaglandins and prostaglandin analogues in cosmetic products. The terms of reference for the SCCS in the mandate asked three questions:

1. In light of the data provided, does the SCCS consider Isopropyl cloprostenate (CAS 157283-66-4) and Ethyl Tafluprostamide or DDDE (CAS 1185851-52-8) safe when

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use up to the concentrations provided in the respective dossiers (0.006% and 0.007% for Isopropyl cloprostenate and 0.018% for Ethyl Tafluprostanamide)

2. Does the SCCS have any further scientific concerns with regard to the use of Isopropyl cloprostenate (CAS 157283-66-4) and Ethyl Tafluprostanamide/DDDE (CAS 1185851-52-8) in cosmetic products?
3. In light of the available data, does the SCCS consider that the use in cosmetic products of prostaglandins analogues (listed in Table 1) raises safety concerns and might pose a risk to human health?

The Final Opinion SCCS/1635/21 titled "Prostaglandins and prostaglandin-analogues used in cosmetic products" was published on the 4 February 2022 (Ulrike, et al., 2022).

The SCCS identified twenty prostaglandin analogues including the fourteen prostaglandin analogues already listed in EU CosIng database described by their chemical or International Nomenclature Cosmetic Ingredient (INCI) name and corresponding chemical abstracts (CAS) identifying number shown in Table 3.

Table 3. List of prostaglandin analogues identified by the SCCS.

Prostaglandin analogue	CAS No.
Isopropyl cloprostenate	157283-66-4
Ethyl tafluprostanamide	1185851-52-8
Benzothiophenyl dephenethylatanoprost	Not listed
Cyclopropyl bimatoprost	1138395-12-6
Cyclopropyl methylbimatoprost	1138395-10-4
Dechloro ethylcloprostenolamide	1138395-11-5
Dechloro cyclopropylmethylcloprostenolamide	1138395-09-1
Dechloro ethylcloprostenolamide	951319-59-8
Dehydrolatanoprost	130209-76-6
Dihydroxypropyl dehydrolatanoprostamide	Not listed
Dihydroxypropyl didehydrolatanoprostamide	1193782-16-9
Ethyl Travoprostamide	1005193-64-5
Ketotravoprost	404830-45-1
Methyl bimatoprost acidate	38315-47-8
Norbimatoprost	155206-01-2
Nortafluprost	209860-89-9
Tafluprost	209860-87-7
Trifluoromethyl dechloro ethylcloprostenolamide	1005193-64-5
Travoprost	157283-68-6
Methyl travoprost	Not listed

The list of prostaglandin analogues made by the SCCS does not identify latanoprost or bimatoprost but does include tafluprost and travoprost. Also, three of the four pharmacologically active compounds latanoprost, travoprost and bimatoprost are not included in the EU CosIng database. Tafluprost is included in the EU CosIng database and identified as a 'hair conditioner.' The EU CosIng database and corresponding glossary of

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cosmetic ingredients includes a disclaimer that listed ingredients are not an indication of authorised use in cosmetic products.

The SCCS in reviewing prostaglandin analogues, and in particular isopropyl cloprostenate and ethyl tafluprostamide, at the maximum concentration indicated in the mandate observed:

“In view of the potential for causing effects at very low concentrations, and the intended use in the proximity of the eye, the SCCS has noted concerns over the safety of prostaglandin analogues when used in cosmetic products”

There are no further known comments or actions made by the SCCS or EU commission at the time this report is made although there appears to be continuing discussions between EU member states and commission as well actions by competent authorities. In May 2022, the Austrian authorities (EU Commission [Austria], 2022) took enforcement action on an eyelash growth serum containing the prostaglandin analogue cloprostenol isopropyl ester at a concentration of 0.0012 %, considering the product prohibited under the EU Cosmetic Products Regulation.

2.6 Analysis of Prostaglandin Analogues in Pharmaceutical Products

The literature search found three papers describing analytical methods for determining prostaglandin analogues in pharmaceutical solutions using liquid chromatography coupled to an ultraviolet/visible (UV/vis) wavelength detector.

An analytical method (Mehta, et al., 2010) for determining latanoprost in ophthalmic solutions uses reverse-phase high performance liquid chromatography (RP-HPLC) coupled to a UV-vis detector. Chromatographic separation was achieved on a reverse phase cyano column (Hypersil BDS CN 250 x 4.6 mm, particle size 5 mm) under gradient elution conditions. A mixture of phosphate buffer at pH 3.2, acetonitrile and methanol are used as the mobile phase. The determination was carried out at 295 nm and 210 nm and the flow rate 1mL/min. The method was considered to be precise and linear throughout the range and with the lowest level of quantification for latanoprost given as 0.018 mg/mL.

The second paper (Kumar, et al., 2011) similarly describes an analytical method for determining bimatoprost in pharmaceutical solutions using RP-HPLC coupled to a UV-vis detector. Chromatographic separation was achieved on a reverse phase C18 column (BDS Hypersil C18, 150 mm x 4.6 mm ID, particle size 5µm). The mobile phase used phosphate buffer (pH 2.8) and acetonitrile (55:45 v/v). The wavelength used for detection of bimatoprost was 210 nm and flow rate 1 mL/min. Limits of detection (LOD) and quantification (LOQ) for bimatoprost were found to be 0.137 µg/mL and 0.416 µg/mL, respectively. The method was considered to be precise and linear.

More recently a third paper (Zezula, et al., 2019) describes a reverse phase ultra-high-performance liquid chromatographic (RP-UHPLC) analytical method with a UV detection for the determination of the chemical purity and assay of bimatoprost in pharmaceutical solutions. Chromatographic separation was achieved using a C8 column (BEH C8, 150 × 2.1 mm, particle size 1.7 µm) under gradient elution conditions. The mobile phase consisted of 0.01% phosphoric acid: acetonitrile (initial conditions 80: 20 v/v) with a flow rate of 0.7 mL/min. An additional LC/MS method was used for the identification of the unknown impurities in bimatoprost as well as the degradation impurities generated during the forced degradation studies.

The three papers show that reverse phase liquid chromatography coupled to a UV-vis detector using readily available chromatography columns and chemicals can be used to identify and quantify individual synthetic prostaglandin analogues such as bimatoprost and latanoprost at low concentrations in pharmaceutical solutions. Whether multiple prostaglandin analogues could be determined at the same time using a UV-vis detector would require further investigation.

2.7 Analysis of Prostaglandin Analogues in Cosmetic Products

More relevant to this project are methods described for determining prostaglandin analogues in cosmetic products where multiple prostaglandin analogues may be present and where extraction from the cosmetic product may cause interferences from other ingredients present in the cosmetic product compared to cleaner pharmaceutical solutions.

The literature search found two papers identifying analytical methods for determining prostaglandin analogues in cosmetic products.

In the first paper (Wittenberg, et al., 2014) a QuEChERS (Quick, Easy Cheap, Efficient, Rugged, Safe) method is validated using liquid-liquid extraction with reverse phase liquid chromatography coupled to two mass spectrometers in tandem (RP-HPLC-MS/MS) to determine sixteen prostaglandin analogues in thirty one aqueous cosmetic samples and three pharmaceutical products.

Chromatographic separation was achieved using a C18 column (XB-C18, 100 mm × 2.1 mm) under gradient elution conditions. The mobile phases consisted of 0.1% formic acid in water: methanol (95:5 v/v) and 0.1% formic acid in water: methanol (5:95 v/v) and passed through the column at the flow rate of 0.5 mL/min into the ion source. The mass spectrometer was operated in selected reaction monitoring (SRM) mode with the following instrument conditions shown in Table 4.

Table 4 Conditions Used for the RP-HPLC-MS/MS System in SRM mode.

RP-HPLC-MS/MS System	Operating conditions
Ion spray voltage	5000 V
Turbo heater	400 °C
Entrance potential	10 V for all transitions
Curtain gas	30 psi
Ion source gas 1	40 psi
Ion source gas 2	50 psi

- Nitrogen was used as the curtain gas and collision gas.
- Other conditions including declustering potential, collision energy, and cell exit potential were optimised for each compound. Positive ionization mode was used for all compounds except the four free acids, which were optimised using negative ionization mode.

Multiple reaction monitoring (MRM) parameters for quantitation and confirmation transitions are provided in the paper but MRM-transitions can vary between different instruments.

Wittenberg et al provides further details of the validation process but for the purposes of this project the details of sample preparation and analysis are described as this will be

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important in developing a suitable method in conduct a survey in the second part of this project.

To analyse the cosmetic samples, calibration curves were prepared for sixteen prostaglandin analogue calibration solutions in methanol: water (50:50 v/v) with the addition of a known aliquot of the 10 ng/mL internal standard solution containing deuterated bimatoprost (Bima-d4), latanoprost (Lat-d4), bimatoprost free acid (Bima FA-d4) and latanoprost free acid (Lat FA-d4) also in methanol: water mix (50:50 v/v).

Calibration solutions were prepared for sixteen prostaglandin analogues grouped into three sets of calibration standards, based on differing sensitivities where the lowest concentration corresponds to the limit of detection (LoD) for the prostaglandin analogue shown in each range of calibration solutions shown in Table 5.

Table 5 Range of prostaglandin analogue calibration solutions

Range of prostaglandin analogue calibration solutions (ng/mL)	Prostaglandin analogue
0.25 – 50	Bimatoprost
	Tafluprost ethyl amide
	17-Phenyl trinor prostaglandin F2 α methyl amide
0.50 – 100	Bimatoprost isopropyl ester
	Bimatoprost serinol amide
	Cloprostenol isopropyl ester
	Latanoprost
	Travoprost
	16-Phenoxyprostaglandin F2 α ethyl amide
1 – 200	Tafluprost
	Tafluprost ethyl ester
	17- Phenyl trinor prostaglandin E2 serinol amide
	Bimatoprost Free Acid
	Latanoprost Free Acid
	Cloprostenol free acid

The cosmetic samples were prepared by weighing approximately 50-100 mg of the sample and dissolving in water: acetonitrile (50:50) and adding 100 μ L of the internal deuterated standard solution. The solution was mixed and centrifuged to obtain a 2 phase solution where an aliquot from the organic layer is taken and diluted with water before injection onto the RP-HPLC-MS/MS.

Triplicate analysis was made on thirty-one commercial cosmetic products using the method as previously described and thirteen cosmetic products were found to contain a prostaglandin analogue with the following concentrations (converted from μ g/g to % to enable comparison):

- Six cosmetic products were found to contain cloprostenol isopropyl ester in the range 0.0027 - 0.0090%.
- Three cosmetic products were found to contain tafluprost ethyl amide in the range 0.0092 - 0.0141%.

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- Two cosmetic products were found to contain bimatoprost isopropyl ester at 0.0172 and 0.0206% .
- Two cosmetic products were found to contain 17-phenyl trinor prostaglandin F2 α methyl amide at 0.0132 and 0.0297%.

Wittenberg et al, also analysed three pharmaceutical products containing a prostaglandin analogue of known concentration using the method as previously described giving the following results with the declared assay value in brackets:

- Bimatoprost found at a concentration of 0.0293% (assay value 0.030%).
- Latanoprost found at a concentration of 0.0050% (assay value 0.0050%).
- Travoprost found at a concentration of 0.0037% (assay value 0.0040%).

The results for the pharmaceutical products are calculated to be within 9% of the labelled assay concentrations.

The second paper (Marchei, et al., 2016) similarly describes a validated analytical method for determining bimatoprost, latanoprost and travoprost in eyelash enhancing cosmetic serums also using liquid-liquid extraction and using RP-HPLC-MS/MS.

Chromatographic separation was achieved using a biphenyl column (biphenyl 100A, 2.1 mm \times 100 mm, 2.6 μ m) under gradient elution conditions. The mobile phases consisted of 5 mM ammonium acetate with 0.02% formic acid and 5 mM ammonium acetate in acetonitrile: water (95/5 v/v) with 0.02% formic acid and passed through the column at the flow rate of 0.25 mL/min into the ion source.

The mass spectrometer was operated in MRM mode via positive electrospray ionization (ESI) with the following instrument conditions shown in Table 6.

Table 6 Conditions Used for the RP-HPLC-MS/MS System in MRM mode.

RP-HPLC-MS/MS System	Operating conditions
Capillary voltage	3.0 kV
Desolvation temperature	550 °C
Source temperature	150 °C
Cone gas flow rate	50 L/h
Desolvation gas flow rate	600 L/h

Cone energy voltages, collision energy voltages and MRM transitions were established for each analyte as provided in the paper but MRM-transitions can vary between different instruments.

Marchei et al also provides details of the validation process including sample preparation and analysis. To analyse the samples a calibration curve is first prepared for a series of standards containing 1, 5, 10, 50, 100, and 500 μ g/g of bimatoprost, latanoprost and travoprost in methanol including 5 μ g of the internal standard (0.5 mg/mL) reserpine in methanol added to each calibration standard.

For the extraction of prostaglandin analogues from the cosmetic serums 100 mg of the sample is weighed into a glass tube with 5 μ L of the internal standard solution and made to 1 mL volume using the mobile phase solution. The extract solution is sonicated and centrifuged, and a clear portion of the solution analysed.

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The results of analyses showed two of the seven samples analysed contained a prostaglandin analogue ingredient where one sample contained tafluprost ethylamide and another bimatoprost.

Tentative identification of tafluprost ethylamide in the sample was also made based on fragment ion spectrum showing peaks at m/z 438 > 306 and 438 > 232 but in the absence of a calibration standard for tafluprost ethylamide could not be quantified. Quantification of bimatoprost in the sample was reported as 629.3 $\mu\text{g/g}$ equivalent to 0.069 % which is twice the level reported in the literature for bimatoprost in pharmaceutical products.

The two papers by Wittenberg and Marchei both show how simple liquid/liquid extraction of prostaglandin analogues from the cosmetic matrix is possible without incurring interferences from other ingredients using reverse phase high performance liquid chromatography (RP-HPLC). Combining RP-HPLC with two mass spectrometers (MS-MS) it is possible have a system RP-HPLC/MS-MS that can specifically identify and quantify prostaglandin analogues in cosmetic products at low concentrations.

Whilst a liquid chromatography system coupled to mass spectrometers in tandem can be used to determine prostaglandin analogues in cosmetic products, it is important that specificity and accuracy is assured. Consequently, it is important reference prostaglandin analogue materials of known purity are used to enable accurate identification as well as internal standards to compensate for potential losses during extraction and analysis stages preferably using a deuterated compound matching the target prostaglandin analogue.

2.8 Evaluation of the Literature Search

The literature search identified four synthetic prostaglandin analogues bimatoprost, latanoprost, travoprost, and tafluprost are used in topical treatment for the eye disease glaucoma where a side-effect of increased eyelash growth was identified.

The discovery of prostaglandin analogues causing increased growth of eyelashes enabled the use of these prostaglandin analogues, particularly bimatoprost in treatment alopecia or hypotrichosis of eyelashes or eyebrows.

Manufacturers of cosmetic products seeing the potential use of prostaglandin analogues in improving eyelashes have included prostaglandin analogues as ingredients into cosmetic products. These prostaglandin analogue ingredients have included bimatoprost and has also seen the use of derivatives of bimatoprost, travoprost and tafluprost. In addition, other prostaglandin analogues based on the functional substitution E2 such as 17-Phenyl trinor prostaglandin E2 serinol amide have been identified.

The use of pharmaceutical ingredients in cosmetic products are not prohibited by legislation unless prohibited by Annex 2 to the Cosmetic Products Regulations, the concentration of the ingredient in the cosmetic product is harmful to health or the concentration of the ingredient has physiological effects such that the product is considered outside the scope of the definition of a cosmetic product and more applicable to a medicinal product.

The four most commonly reported synthetic prostaglandin analogue ingredients in eyelash growth serums found in the literature in order of prevalence are:

- Isopropyl closprostenate (travoprost derivative).
- Bimatoprost.
- Ethyl tafluprostamide (tafluprost derivative).

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- 17-Phenyl trinor prostaglandin E2 serinol amide (not a PGF2 α analogue).

Less commonly reported synthetic prostaglandin analogue ingredients identified include:

- Norbimatoprost (bimatoprost derivative).
- Methylamido dihydro noralfaprostal (bimatoprost derivative).
- Dechloro dehydroxydifluoro ethylcloprostenolamide (tafluprost derivative).

The SCCS identified potentially twenty different prostaglandin analogues that may exist but the literature search only identified seven prostaglandin analogues being used in eyelash growth products. Whilst the scope of any future study may need to consider the twenty different prostaglandin analogues, it is suggested to initially target those prostaglandin analogue compounds identified in the literature search.

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3. Market Survey

An initial search for information on eyelash growth serums in the UK was made using the Microsoft Bing search engine applying key terms 'eyelash growth,' 'serum' and 'UK'.

Supplementing the internet search were visits to the local high street determining the availability of eyelash growth products, where younger consumers without access to purchasing on-line may be able to obtain these products.

3.1 Internet Search

A search of the internet identified a large number of eyelash products available to the UK consumer and required further filtering to specifically identify 'eyelash growth' products. The search identified products are available from a range of on-line sources and shown in Tables A1-A5 in Annex 1.

Companies Offering Eyelash Growth Products Available on UK Accessible Internet Sites

The search for companies specifically offering 'eyelash growth' products on the internet identified twenty websites. By searching the company's website it was possible to identify specific eyelash growth products of interest without producing results but even with a limited search term such as 'eyelash growth' there were hundreds of results with false eyelashes and mascaras often displayed requiring individual checks on the product being displayed.

The twenty websites specifically offering 'eyelash growth' products shown in Table A1 are considered representative of the UK market in July 2022.

UK Supermarket and Cosmetic Products Retailer Websites

To reflect the UK's unique trading landscape, an additional search was also made of UK supermarket, cosmetic and retail websites using terms 'lash' 'eyelash' 'growth' and 'serum' the results are shown in Table A2. These results are likely to indicate the most commonly available eyelash growth serums available to UK consumers in July 2022 whether purchased in-store or on-line. There are relatively low numbers of eyelash growth serums being sold reflecting the specialised nature of these products.

A search was also made on the major cosmetic brands websites to capture eyelash growth serums sold by the major cosmetics companies and shown in Table A3. Again, there are a relatively low numbers of eyelash growth serums reflecting the specialised nature of these products.

Comparison/media Websites

A search was made of comparison/media websites shown in Table A4, and identified the most 'popular' or 'effective' eyelash growth serums. The search was considered providing useful confirmation of eyelash growth products available to UK consumers.

The comparison sites invariably identified the same products but whether this reflects a true selection or influenced by marketing activity is difficult to know, but it did provide a useful check on whether most eyelash growth serums available on the market had been captured. One comparison site did identify the use of prostaglandin-analogue ingredient being present in the eyelash serum (marked in bold).

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Listing of Eyelash Growth Products on Websites

Using the information obtained in Tables A1-A4, a comprehensive list of eyelash growth serums was compiled and shown in Table A5 identifying the eyelash growth serum, brand and the list of ingredients where shown. The prostaglandin analogue compound in the list of ingredients has been identified in bold.

3.2 High Street Search

A search of high street retailers selling eyelash serums was made in Teddington and in Kingston-on-Thames in Southwest London corresponding to eyelash growth products widely available on websites.

3.3 Assessment of the UK Market Survey

One hundred and ten different eyelash growth serums were found on websites accessible to UK consumers and shown in Table A5 in Annex 1 .

Eight-four eyelash growth serums listed on a webpage contained a full listing of ingredients to be able to identify eyelash growth ingredients including prostaglandin analogues.

Sixteen eyelash growth serums listed on a webpage had incomplete ingredients listing and ten eyelash growth serums did not provide details of ingredients (at time of writing) on the webpage.

The UK Cosmetic Product Regulations requires:

“cosmetic products shall be made available on the market only where the container and packaging of cosmetic products bear the following...(g) a list of ingredients. This information may be indicated on the packaging alone. The list shall be preceded by the term ‘ingredients.’”

Consequently, to be able to determine ingredients for which are only partially visible or missing on the webpage will require purchasing the product to determine whether the full list of ingredients is included on the product or packaging as required.

Reviewing the sixteen eyelash growth serums whose webpages appear to have incomplete ingredients list, there were two eyelash growth serums identified as having possible prostaglandin analogues present as an ingredient. One eyelash growth serum was identified black sea rod/Caribbean sea whip extract as an ingredient. Black sea rod/Caribbean sea whip extract is a source for naturally occurring prostaglandin compounds. The remaining thirteen eyelash serums indicated polypeptides/peptides or natural ingredients were present as eyelash conditioning ingredients.

Reviewing the ten eyelash growth serums whose webpages did not show ingredients, it is difficult to form a view as to whether an eyelash growth serum contained prostaglandin analogues or not without obtaining the product, examining the product, and packaging. It is, however, considered likely that with the costs in producing synthetic prostaglandin analogues being relatively high compared to other ingredients, this will be reflected in a higher price for the eyelash growth serum.

Examining the range of eyelash growth serums containing prostaglandin analogue ingredients, the median price in the region of £15/mL where most serums contained around 3-5 mL. Consequently, it was considered seven eyelash growth serums whose ingredients were not apparent on the webpage and retailing at around £7/mL were unlikely to contain a prostaglandin analogue ingredient.

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Reviewing the list of ingredients for eyelash growth serums, it is possible to identify seven prostaglandin analogues or a natural prostaglandin ingredient in twenty-three eyelash growth serums shown below and identified by the corresponding number listed in Table A5 in Annex 1 shown in brackets.

- Norbimatoprost/Bimatoprost: (60) & (76).
- Ethyl tafluprostamide: (18), (62), (70), (74) & (90).
- Isopropyl closprostenate: (5), (21), (32), (61), (63), (66), (67), (68) & (69).
- Methylamido dihydro noralfaprostal: (76).
- Prostaglandin analogue present but not identified: (101) & (105).
- Black sea rod oil or Caribbean sea whip: (72), (77), (79) & (95)

Identifying prostaglandin ingredients requires further consideration as manufacturers use different naming conventions and the following listing provides information on the nomenclature of the prostaglandin ingredients as listed.

Bimatoprost & Norbimatoprost

Bimatoprost is not a chemical or International Nomenclature Cosmetic Ingredient (INCI) name but a generic name for possibly one of five synthetic prostaglandin analogues having the following INCI/chemical names:

- 1) Cyclopropylbimatoprost
- 2) Cyclopropylmethylbimatoprost
- 3) Dihydroxypropyl Didehydrolatanoprostamide
- 4) Methyl Bimatoprost Acidate
- 5) Norbimatoprost.

Norbimatoprost is the only bimatoprost derivative identified in the literature as an ingredient in eyelash serums and has the identifier CAS No. CAS No. 155205-89-3.

Dihydroxydifluoro ethylcloprostenolamide & Ethyl tafluprostamide

Dechloro dihydroxy difluoro ethylcloprostenolamide (DDDE) and ethyl tafluprostamide (its alternative INCI name) are the same synthetic prostaglandin analogue with the identifier CAS No. 1185851-52-8.

Ethyl tafluprostamide is a derivative of tafluprost.

Isopropyl closprostenate

Isopropyl closprostenate is a recognised prostaglandin analogue compound and is the INCI name with the identifier CAS No. 157283-66-4.

Isopropyl closprostenate is a derivative of travoprost.

Methylamido dihydro noralfaprostal

Methylamido dihydro noralfaprostal (MDN). Chemical name 17- phenyl trinor prostaglandin F2 α methyl amide with the identifier CAS No. 155206-01-2. It is a synthetic prostaglandin analogue compound but does not have an INCI name.

There are four main prostaglandin analogues norbimatoprost, ethyl tafluprostamide, isopropyl cloprostenate and methylamido dihydro noralfaprostal and one naturally occurring prostaglandin compound black sea rod oil identified in eyelash serums.

3.4 Summary

There are twenty-three eyelash growth serums identified having a prostaglandin ingredient out of the hundred eyelash growth serums found on the internet where ingredients are fully or partially shown. This is a significant proportion of eyelash growth serums being sold and suggests eyelash growth serums containing a prostaglandin ingredient can be readily obtained by the UK consumer.

Of the twenty-three eyelash growth serums declaring a prostaglandin ingredient, nineteen contained a synthetic prostaglandin analogue ingredient, with four eyelash growth serums containing a natural prostaglandin ingredient.

Isopropyl cloprostenate is the most commonly listed synthetic prostaglandin analogue ingredient, being declared in ten eyelash growth serums followed by ethyl tafluprostamide declared in five eyelash growth serums, with norbimatoprost declared in two eyelash growth serums and methylamido dihydro noralfaprostal declared in one eyelash growth serum.

One eyelash growth serum declared two synthetic prostaglandin analogue ingredients. It is not known whether this is a mistake or the serum does contain two types of prostaglandin analogue. The manufacturers website only declares norbimatoprost whereas the retailer additionally declares methylamido dihydro noralfaprostal.

The presence of isopropyl cloprostenate and ethyl tafluprostamide declared in eyelash growth serums is not surprising given these two synthetic prostaglandin analogue ingredients are featured in the SCCS call for data and opinion SCCS/1635/21.

The presence of norbimatoprost and methylamido dihydro noralfaprostal (MDN) in eyelash growth serums is not addressed by the SCCS opinion (see Section 3.4) although norbimatoprost was identified.

The identification of the ingredient 'black sea rod oil' containing a naturally produced prostaglandin present in sea coral, has similar properties to the prostaglandin analogues encouraging eyelash growth and was declared in four samples. Naturally occurring prostaglandin eyelash growth ingredients had not previously been discussed.

3.5 Next Steps

Based on the literature review and market survey, LGC proposed to obtain and analyse eyelash growth serums containing prostaglandin analogues and to analyse for three target prostaglandin analogues; isopropyl cloprostenate, ethyl tafluprostamide and bimatoprost validating a method using liquid/liquid extraction and determination using reverse phase liquid chromatography coupled to two mass spectrometers in tandem (RP-HPLC/MS-MS).

4. Testing

Based on the literature survey, liquid chromatography coupled to mass spectrometers in tandem was considered most appropriate technique to identify and quantify the main synthetic prostaglandin analogues and naturally occurring prostaglandins listed as ingredients in eyelash growth serums. Having identified the appropriate analytical technique, LGC began the process of verifying a suitable method and obtaining calibration and reference standards to accurately identify and measure the target compounds in eyelash growth serums for three target compounds (isopropyl cloprostenate) ethyl tafluprostamide and bimatoprost.

In parallel, the purchase of eyelash growth serums for testing was started. The market survey identified twenty-three eyelash growth serums available from the internet (Table A5) containing a prostaglandin or prostaglandin analogue ingredient and therefore can be purchased by the UK consumer. As many as possible of the twenty three eyelash growth serums identified as containing prostaglandin and/or prostaglandin analogue were obtained.

4.1 Sampling

Twenty-one eyelash growth serums were purchased from the market based on the market survey selecting products listed in Annex A - Table A5 containing a natural prostaglandin or prostaglandin analogue. Each eyelash growth serum was given a unique laboratory reference number with prefix OA/22.

4.2 Analysis

The instrument chosen for the analysis was a quadrupole-time-of-flight mass spectrometer (Q-TOF) to allow untargeted quantitative data. These are high resolution instruments which record a full mass spectrum per scan. Typically a triple quadrupole (QQQ) in multi-reaction monitoring (MRM) mode would be used for quantitative analysis but can only be used for targeted analyses based on specific mass transitions. Using a Q-tof in an untargeted quantitation mode would allow retrospective analysis of the data to look for other suspected prostaglandins if standards are available. The HPLC method would still be applicable to transfer to an LC-QQQ as this would potentially give a lower LOQ if needed.

The following MRM transitions were determined during method development before untargeted analysis was subsequently used for the analysis:

Bimatoprost 398>362 and 398>196

Ethyl tafluprostamide 438>418 and 438>288

Isopropyl cloprostenate 467>321 and 467>249.

4.3 Preparation of Standards and Samples

Chemicals and Reagents

Formic acid was obtained from LGC standards (Teddington UK). Acetonitrile, isopropyl alcohol and methanol were obtained from Honeywell and ultrapure water at 18mΩ obtained in-house from an Elga water system. Tafluprost ethyl amide and cloprostenol isopropyl ester were obtained from Cambridge Bioscience, Cambridge UK. Bimatoprost was obtained from LGC Standards, Luchenwalde Germany.

Preparation of Standards

The calibration curve was prepared volumetrically using solvent standards at the following nominal concentrations: 5, 50, 100, 150, 200 and 250 ng/mL.

1000 µL of each calibration standard was mixed with 10µL of reserpine at 10µg/mL as an internal standard.

Preparation of Samples

The samples were prepared gravimetrically at 10mg/mL in methanol/water (50:50). The samples were then diluted to 1 mg/mL in methanol/water.

(Sample OA/22/4286 was diluted to 0.5 mg/mL as the initial concentration was above the higher limit of quantification.)

1000 µL of each sample was mixed with 10µL of reserpine at 10µg/mL as an internal standard.

4.4 LC-MS Method

The LC/MS system used a Waters G2-XS QTOF instrument with operating conditions shown in Table 7 and a gradient elution programme for the solvents as shown in Table 8.

Table 7. Conditions used for the LC/MS system in MRM mode.

LC/MS system	Operating conditions
Polarity	Positive ion; 200-800 Da
Column	Kinetex XB-C18 2.6µm, 100 x 2.1 mm
Column temperature	30°C
Flow rate	300µL/min
Injection volume	10µL
Solvent A	Water containing 0.1% formic acid
Solvent B	Methanol containing 0.1% formic acid
Solvent B	Acetonitrile/isopropyl alcohol (50:50)

Table 8. Solvent gradient elution programme for LC/MS system.

Time (min)	Solvent A (%)	Solvent B (%)	Solvent C (%)
0.0	80	20	0
1.0	80	20	0
3.0	40	60	0
8.0	20	80	0
10.0	0	100	0
12.0	0	100	0
12.1	0	0	100
17.0	0	0	100
17.1	80	20	0
20.0	80	20	0

4.5 Method Verification

An eyelash growth serum not containing a prostaglandin analogue ingredient was used as a blank for method verification. Samples were prepared at three levels in 1 and 5 mg/mL

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serum samples. These were analysed against a solvent standard calibration line with six injections at each level.

At 1 mg/mL all results were within 5% of the expected value with CV for replicate measurements <4% and at 5mg/mL replicate measurements gave a CV <6%. Accuracy was -23.5 to 7.4 %.

Based on this the maximum concentration of serum analysed was 1mg/mL and this gives a LLOQ of 5mg/kg.

4.6 Acceptance Criteria

For the sample batch to pass the following acceptance criteria was applied.

- Calibration $R^2 > 0.99$
- All standards within 15% on calibration line
- QCs within 15%
- Signal-to-noise > 10 at LOQ, >3LOD
- Retention time within 0.1 minute

4.7 Results

The results of analysis are shown in Table 9.

Table 9. Quantification of isopropyl cloprostenate, ethyl tafluprostamide and bimatoprost.

LGC Sample No.	#	Isopropyl Cloprostenate (mg/kg)	Ethyl Tafluprostamide (mg/kg)	Bimatoprost (mg/kg)
OA/22/4270	105	ND	ND	ND
OA/22/4271	69	70*	ND	ND
OA/22/4272	96	ND	ND	ND
OA/22/4273	66	64*	ND	ND
OA/22/4274	74	ND	18*	ND
OA/22/4275	5	31*	ND	ND
OA/22/4276	77	72	ND	ND
OA/22/4277	77	32	ND	ND
OA/22/4278	21	31*	ND	ND
OA/22/4279	61	ND	ND	ND
OA/22/4280	63	<LOQ*	ND	ND
OA/22/4281	90	ND	176*	ND
OA/22/4282	60	8*	ND	ND
OA/22/4283	70	ND	145*	ND
OA/22/4284	68	57*	ND	ND
OA/22/4285	-	<LOQ	ND	ND
OA/22/4286	101	ND	ND	270*
OA/22/4287	62	ND	ND	ND
OA/22/4288	18	ND	176*	ND
OA/22/4289	67	ND	ND	ND
OA/22/4290	79	ND	ND	ND

Number of eyelash growth product shown in Annex A Table A5.

* The target prostaglandin analogue is listed as an ingredient on the packaging.

<LOQ Detected but below the limit of quantification.

ND Not Detected.

4.8 Assessment of Results

Of the twenty-one samples analysed eight samples OA/22/4270, 4272, 4279, 4280, 4285, 4287, 4289 and 4290 were found not to contain measurable levels of the three target prostaglandin analogue compounds.

- Sample OA/22/4280 had included isopropyl cloprostenate as a listed ingredient but although detected was below the limit of quantification (≤ 1 mg/kg).
- Samples OA/22/4279, 4280 and 4289 had isopropyl cloprostenate listed as an ingredient when identified on the internet search but was not listed on the packaging when purchased. Analysis confirmed the absence of isopropyl cloprostenate.
- Sample OA/22/4287 had ethyl tafluprostamide listed as an ingredient when identified on the internet search but was not listed on the packaging when purchased. Analysis confirmed the absence of ethyl tafluprostamide.

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- Sample OA/22/4270 had listed 'water soluble prostaglandin derivative' when identified in the internet search but analysis did not detect the presence of the three target prostaglandin analogues.
- Sample OA/22/4290 listed 'Black Sea Rod Oil' a naturally occurring source for prostaglandin obtained from coral. Analysis did not detect the three target prostaglandin analogue compounds which is to be expected.
- Samples OA/22/4272 and 4285 did not list any prostaglandin or prostaglandin analogue ingredient which was confirmed by analysis.

A further eight samples OA/22/4271, 4273, 4275-78, 4282 and 4284 were found to contain isopropyl cloprostenate.

- Six samples OA/22/4271, 4273, 4275, 4278, 4282, and 4284 had isopropyl cloprostenate listed as an ingredient identified in the internet search and were listed on the packaging when purchased.

The concentration of isopropyl cloprostenate found in each sample was 70, 64, 31, 31, 8 and 54 mg/kg, respectively.

- Two samples OA/22/4276 and 4277 are packaged as the same brand of eyelash growth serum but have different ingredients listing on the packaging. Sample OA/22/4276 has black sea rod oil listed as an ingredient on the packaging consistent with the internet listing. Whereas Sample OA/22/4277 does not list black sea rod oil or any prostaglandin analogue as ingredient on the packaging.

The concentration of isopropyl cloprostenate found in each sample was 72 and 32 mg/kg, respectively.

Four samples OA/22/4274, 4281, 4283, and 4288 were found to contain ethyl tafluprostamide.

- All four samples had ethyl tafluprostamide listed as an ingredient identified in the internet search and listed on the packaging when purchased.
- The concentration of ethyl tafluprostamide found in each sample was 18, 176, 145 and 176 mg/kg, respectively.

One sample OA/22/4286 was found to contain bimatoprost.

- Sample OA/22/4286 had bimatoprost listed as an ingredient identified in the internet search and listed on the packaging when purchased.
- The concentration of bimatoprost found in the sample was 270 mg/kg .

5. Discussion

The LC/MS method verified for this project was shown to be repeatable and accurate requiring minimal sample preparation for determining the three target prostaglandin analogues isopropyl cloprostenate, ethyl tafluprostamide and bimatoprost in commercial eyelash growth serums.

It is considered likely that the LC/MS method can be applied to other prostaglandin analogues in eyelash growth serums, provided suitable calibration/reference materials for the prostaglandin analogues are available.

The lowest limit of quantification (LLOQ) for all three target prostaglandin analogues in eyelash growth serums using the LC/MS method was 1 mg/kg (0.0001%).

The LC/MS method may be applied to other matrices than serums but would likely require further sample preparation as well as verification to assess the LLOQ. There is, however, no evidence in the market survey to indicate other matrices other than serums are used to apply prostaglandin analogues to eyelashes.

The results of analyses provided the following range of values for the target prostaglandin analogues in eyelash growth serums: isopropyl cloprostenate 8 – 72 mg/kg (0.0008 - 0.0072 %), ethyl tafluprostamide 18 - 176 mg/kg (0.0018 - 0.0176 %) and bimatoprost 270 mg/kg (0.0270 %). These values compare favourably with other analytical results identified in the literature search. Moreover these values appear to correspond with industry's intention to seek approval for use of isopropyl cloprostenate and ethyl tafluprostamide in cosmetic products in the EU, as revealed in a call for data by the SCCS in 2020 where applicants were seeking permitted maximum concentrations of 0.007 % for isopropyl cloprostenate and 0.018 % for ethyl tafluprostamide.

It should be noted the subsequent opinion SCCS/1635/21 made the following statement:

“In view of the potential for causing effects at very low concentrations, and the intended use in the proximity of the eye, the SCCS has noted concerns over the safety of prostaglandin analogues when used in cosmetic products.”

The SCCS statement is not explicit in considering the use of these prostaglandin analogues are ‘unsafe’ only that there are ‘concerns’ and therefore this is still a subject for further consideration. This does not provide the usual assurance given by the SCCS that the use of a particular ingredient is safe at a specified maximum concentration.

It is noted that bimatoprost is more often identified as a pharmaceutical ingredient where it is present in ophthalmic solutions at 0.03% for patients suffering from glaucoma and the treatment of hypotrichosis of eyelashes. The concentration 0.03% bimatoprost corresponds to values generally found in analytical studies eyelash growth serums for cosmetic use.

The use of pharmaceutical/medicinal ingredients in cosmetic products needs to be considered in the context of EU retained law Regulation (EC) No. 1223/2009 where the definition of a cosmetic product is:

“cosmetic product’ means any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition or correcting body odours.”

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The EU Commission elaborated guidance on eyelash growth products in the EU Manual on Borderline Products for Cosmetic Products (version 5.2) in Section 3.3.5 but also needs to be considered with Section 3.3.3 'Product containing substances which restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action.'

Although only guidance and not legally binding in the EU, the EU Manual has influenced manufacturers and enforcement agencies as to whether eyelash growth products should be considered as cosmetic products with the following information:

Section 3.3.3:

"If a product is a medicinal product, it falls exclusively within the regulatory framework of medicinal products. A product can be a medicinal product 'by virtue of its presentation' or 'by virtue of function'. The latter is the case, if the product is a substance or a combination of substances which are used in or administered to human beings inter alia with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action. However, not any minor modification of physiological function suffices to render a product a medicinal product by virtue of function."

Section 3.3.3:

"...The fact that a substance is used in medicinal products as an active ingredient [e.g. prostaglandins and their analogues] is not decisive. However, this may be an indicator for a pharmacological, immunological or metabolic action of the product."

The use of bimatoprost or any other prostaglandin analogue to actively promote or maintain eyelash growth for longer of existing healthy eyelashes may be considered a cosmetic rather than pharmacological action which has caused uncertainty for Competent Authorities as to whether prostaglandin analogues at the concentrations generally found in eyelash growth products are cosmetic products. Bimatoprost at a concentration of 0.03% is generally used topical treatments for the treatment of glaucoma and ocular hypertension in the UK requiring a prescription and identified as having potential side effects such as dry eye; eye discolouration; eye discomfort; eye disorders; eye inflammation; headache; hypertension; hypertrichosis; skin reactions; vision disorders as well as requiring warnings for women who are pregnant.

The literature search and market survey identified bimatoprost, isopropyl cloprostenate, ethyl tafluprostamide, norbimatoprost (a derivative of bimatoprost), methylamido dihydro noralfaprostal and black rod oil (a source of naturally occurring prostaglandins listed in eyelash growth products available to UK consumers. It was possible to identify and quantify the three target prostaglandin analogues isopropyl cloprostenate, ethyl tafluprostamide and bimatoprost in thirteen out of twenty-one eyelash growth products obtained from the UK market.

Glossary

Bima-d ₄	Deuterated bimatoprost
Bima FA-d ₄	Deuterated bimatoprost free acid
BfR	German Federal Institute of Risk Assessment
CosIng	EU Cosmetic Ingredients database
CIR	Cosmetic Ingredient Review
EU	European Union
GDP	Guanosine diphosphate
GPCRs	G-protein coupled receptors
GTP	Guanosine triphosphate
INCI	International Nomenclature of Cosmetic Ingredients
IUPAC	International Union of pure and Applied Chemistry
Lat-d ₄	Deuterated latanoprost
Lat FA-d ₄	Deuterated latanoprost free acid
LC/MS	Liquid chromatography/mass spectroscopy
LOD	Limit of detection
LOQ	Limit of quantification
LLOQ	Lowest limit of quantification
mg/kg	milligrams per kilogram
MRM	Multiple reaction monitoring
ND	Not detected
OPSS	Office of Product Safety and Standards
OTC	Over-the-counter
PGF ₂ α	Prostaglandin F ₂ α
PGT	Prostaglandin transporter
RP-HPLC	Reverse phase high performance liquid chromatography
RP-UHPLC	Reverse phase ultra-high-performance liquid chromatography
RP-HPLC-MS/MS	Reverse phase high performance liquid chromatography coupled to two mass spectrometers in tandem.
SCCS	EU Scientific Committee on Consumer Safety
US FDA	USA Food and Drugs Administration.

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Annex A

Table A1. UK Websites Offering Eyelash Growth Products

Website	Hits for Eyelash Growth Products
Redacted	3
Redacted	246
Redacted	3
Redacted	692
Redacted	343
Redacted	7
Redacted	340
Redacted	5
Redacted	2
Redacted	13
Redacted	25
Redacted	1
Redacted	440
Redacted	83
Redacted	9
Redacted	4
Redacted	2
Redacted	2
Redacted	6
Redacted	3

Table A2. UK Supermarkets and Retailers Websites

Website	Hits for Eyelash Growth Products
Redacted	0
Redacted	13
Redacted	3
Redacted	2
Redacted	1
Redacted	3
Redacted	0
Redacted	2
Redacted	3
Redacted	1
Redacted	7

Table A3 Cosmetic Brands UK Websites.

Website	Hits for Eyelash Growth Products
Redacted	1
Redacted	0
Redacted	1
Redacted	0
Redacted	1
Redacted	0
Redacted	0
Redacted	1
Redacted	0
Redacted	0

Table A4 Eyelash Growth Serums Identified by Comparison/Magazine Websites

Website	Eyelash Growth Serums
Redacted	Redacted
	Redacted
	Redacted
	Redacted
	Redacted
	Redacted
	Redacted
	Redacted
	Redacted
	Redacted
Redacted	Redacted
	Redacted
	Redacted
	Redacted
	Redacted
Redacted	Redacted
	Redacted
	Redacted
	Redacted
	Redacted
	Redacted
	Redacted
Redacted	Redacted
	Redacted
	Redacted
	Redacted
	Redacted

Table A4 Eyelash Growth Serums Identified by Comparison/Magazine Websites

Website	Eyelash Growth Serums
Redacted	Redacted
	Redacted
	Redacted
	Redacted
	Redacted
	Redacted
	Redacted
Redacted	Redacted
	Redacted
	Redacted
	Redacted
	Redacted
	Redacted
	Redacted
	Redacted
	Redacted

Table A5 List of Eyelash Growth Serums & Ingredients

#	Product name	Brand	Ingredients Listing
1	Redacted	Redacted	Aqua (Water), Glycerin, Butylene glycol, Disodium phosphate, Phenoxyethanol, Betaine, Xanthan gum, Tocopheryl acetate, Sodium PCA, Panthenol, Methylparaben, Sorbitol, Cystine, Hydrolyzed keratin, Sodium hyaluronate, Retinyl palmitate, Ascorbyl glucoside, Serine, Glycine, Glutamic acid, Lysine, Sodium phosphate, Alanine, Arginine, Threonine, Tetrapeptide-21, Sorbic acid, Proline, Biotinoyl tripeptide-1, Tocopherol, Propylparaben.
2	Redacted	Redacted	Aqua (Water), Pvp, Butylene Glycol, Polyquaternium-37, Caprylyl Glycol, Glycerin, Caprylhydroxamic Acid, Disodium Edta, Lecithin, Aminomethyl Propanol, Ppg-26-Buteth-26, Gluconolactone, Laminaria Digitata Extract, Pelvetia Canaliculata Extract, Xanthan Gum, Peg-40 Hydrogenated Castor Oil, Sodium Benzoate, Isopropyl Alcohol, Apigenin, Tetrasodium Edta, Oleanolic Acid, Biotinoyl tripeptide-1.
3	Redacted	Redacted	Aqua/water, Alcohol Denat, Hydroxyethylcellulose, Pentylene glycol, Aminopropyl triethoxysilane, PEG-40 hydrogenated castor oil, Madecassoside, Phenoxyethanol, Polysorbate 21. Lactic acid, Methylparaben, Ricinus communis seed oil/castor seed oil, Sodium hyaluronate, Arginine, Serine, Citric acid, Panthenol, Glutamic acid, Threonine, Proline, Alanine, Cysteine.
4	Redacted	Redacted	Glycerin, Hydroxyethylcellulose, Pentylene Glycol, Sodium Hyaluronate, Madecassoside, Rosa Centifolia Extract / Rosa Centifolia Flower Extract, Rosa Meichibon/Delgramaue Callus, Safflower Glucoside, Threonine, Sodium Citrate, Arginine, Serine, 2-Oleamido-1,3-Octadecanediol, Proline, Alanine, Aminopropyl Triethoxysilane, Ascorbyl Glucoside, Propanediol, Propylene Glycol, Hydroxypropyl Tetrahydropyrantriol, Citric Acid, Xanthan Gum, Panthenol, Biotin, Glutamic Acid, Polysorbate 21, Tocopherol, Tocopheryl Acetate, Phenoxyethanol.

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5	Redacted	Redacted	Water (Aqua), Butylene Glycol, Hydroxyethylcellulose, Octapeptide-2, Copper Tripeptide-1, Biotin, Panthenol, sh-Polypeptide-1, Glycine Soja (Soybean) Oil, Cucurbita Pepo (Pumpkin) Seed Extract Sodium Hyaluronate, Hydrolyzed, Glycosaminoglycans, Allantoin, Dipotassium Glycyrrhizate, Pantethine, Hydrogenated Lecithin, Sea Water (Maris Aqua), Glycerin, Rhizobian Gum, Disodium Phosphate, Polysorbate 60, Sodium Phosphate, Ethyl Acetate, Sodium Oleate, Sodium Hydroxide, Citric Acid, Alcohol Denat., Isopropyl Cloprostenate , Phenoxyethanol, Chlorphenesin, Sorbic Acid, Potassium, Sorbate, Disodium EDTA.
6	Redacted	Redacted	Aqua, Biotin, Glycerin, Hyaluronic acid,, Hydrolyzed keratin, Panthenol (Vitamin 85), Octapeptide 2, Biotinoyl tripeptide-1, Myristoyl pentapeptide-16, Myristoyl pentapeptide-17, Pumpkin seed oil, Larix Europaea wood extract , glycine max (soybean) polypeptide.
7	Redacted	Redacted	Aqua/Water, Rhamnose, Glycerin, Alcohol Denat., Dimethicone, Hydroxyethylpiperazine Ethane Sulfonic Acid, Peg-20 Methyl Glucose Sesquistearate, Ci 77891 / Titanium Dioxide, Mica, Triethanolamine, Sodium Hyaluronate, Salicyloyl Phytosphingosine, Phenoxyethanol, Adenosine, Ammonium Polyacryldimethyltauramide/Ammonium, Polyacryloyldimethyl Taurate, Chlorphenesin, Disodium Edta, Xanthan Gum, Octyldodecanol, Acrylates/C10-30 Alkyl Acrylate Crosspolymer.
8	Redacted	Redacted	Water/Eau/Aqua, Betaine, Red Ginseng Extract, Panax Notoginseng Extract, Helichrysum Extract, Phenoxyethanol, Citric Acid, Laurocapram.
9	Redacted	Redacted	Aqua/Water/Eau, Butylene Glycol, Glycerin, Sodium Chloride, Hydroxyethylcellulose, 1,2-Hexanediol, Hydroxyacetophenone, Sodium Levulinate, Sodium Benzoate, Disodium EDTA, Sodium Nitrate, Potassium Hydroxide, Benzoic Acid, Myristoyl Pentapeptide-17, Dextran, Disodium Phosphate, Polysorbate 60, Acetyl Tetrapeptide-3, Trifolium Pratense (Clover) Flower Extract, Sodium Phosphate, Glyoxal.

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10	Redacted	Redacted	Aqua (Water), Alcohol Denat, Glycerin, Pvp, Carbomer, Disodium Edta, Phenoxyethanol, Sodium Hydroxide, Ricinus Communis Seed Oil, Centella Asiatica Extract, Acrylates/C10-30 Alkyl Acrylate Crosspolymer, Panthenol, Arginine, Citric Acid, Potassium Sorbate, Sodium Benzoate, Biotinoyl Tripeptide-1.
11	Redacted	Redacted	Water (aqua / Eau), Glycerin, Caprylyl Glycol, Malus Domestica Fruit Cell Culture Extract, Myristoyl Pentapeptide-17, Biotinoyl Tripeptide-1, N-prolyl Palmitoyl Tripeptide-56 Acetate, 1,2-hexanediol, Polysorbate 20, Lactitol, Xylitol, Troxerutin, Pentylene Glycol, Panthenol, Disodium Edta, Phenoxyethanol, Xanthan Gum, Sodium Hydroxide, Lecithin, Sodium Benzoate, Benzoic Acid.
12	Redacted	Redacted	Aqua, Alcohol Denat, Cellulose, Pvp, Butylene Glycol, Panthenol, Carbomer, Aminomethyl Propanol, Dextran, Disodium Edta, Acetyl Tetrapeptide-3, Trifolium Pratense (clover) Flower Extract.
13	Redacted	Redacted	Aqua, Magnesium Aluminum Silicate, Butylene Glycol, Propylene Glycol, Alcohol Denat., Xanthan Gum, Lactococcus Ferment, Glycosaminoglycans, Pronline, Riboflavin, Methylparaben, Propylparaben, Hexamidine Diisethionate, 2-Bromo-2-Nitropropane-1, 3-Diol.
14	Redacted	Redacted	Water (Aqua), Snail Secretion Filtrate, Magnesium Aluminum Silicate, Butylene Glycol, Phenoxyethanol, Xanthan Gum, Propylene Glycol, Chlorphenesin, Disodium EDTA, Ethylhexylglycerin, Gluconolactone, Sodium Cocoyl Glutamate, Caprylyl Glycol, Sodium Benzoate, Lactococcus Ferment, Lactic Acid, Glucose, Calcium Gluconate, Urea.
15	Redacted	Redacted	Vitamin B5, Phyto-Peptides and Clover Flower Extract.

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16	Redacted	Redacted	Water/Aqua/Eau, Butylene Glycol, Glycerin, Acrylates/C10-30 Alkyl Acrylate Crosspolymer, Aloe Barbadensis Leaf Extract, Ascorbyl Palmitate, BHT, Camellia Oleifera Leaf Extract, Camellia Sinesis Leaf Extract, Caprylic/Capric Triglyceride, Chamomilla Recutita (Matricaria) Flower Extract, Cucumis Sativus (Cucumber) Fruit Extract, Cyclohexasiloxane, Disodium EDTA, Disodium Phosphate, Ethylhexylglycerin, Hydrogenated Leicithin, Leicithin, Myristoyl Hexapeptide-16, Myristol Octapeptide-1, Myristol Pentapeptide-17, Panthenol, Propylene Glycol, Retinyl Palmitate, Sodium Hyaluronate, Sodium Phosphate, Tocopheryl acetate, Triethanolamine, Chlorphenesin, Phenoxyethanol.
17	Redacted	Redacted	Water(Aqua/Eau), Dipropylene Glycol, Butylene Glycol, Sorbitol, Alcohol, Polyvinyl Acetate, Glycerin, Carbomer, Phenoxyethanol, Ethylhexylglycerin, Methylparaben, Polyvinyl Alcohol, Potassium Hydroxide, Arginine, Xanthan Gum, Zizyphus Jujuba Fruit Extract, Dimethicone, Trisodium EDTA, Tocopherol.
18	Redacted	Redacted	Aqua, Glycerin, Biotin, Cellulose Gum, Phenoxyethanol, Chlorphenesin, Disodium Phosphate, Phosphoric Acid, Decloro Dihydroxy Difluoro Ethycloprostenolamide , Butylene Glycol, Calendula Officinalis Extract, Panax Ginseng Extract, Serenoa Serrulata Extract, Camellia Sinensis Extract, Swertia Japonica Extract, Triticum Vulgare Germ Protein, Pentylene Glycol, Biotinoyl Tripeptide-1, Octapeptide-2.
19	Redacted	Redacted	Purified Water (Aqua), Cucurbita Pepo (Pumpkin) Seed Extract, Vitis Vinifera (Grape) Seed Extract, Panax Ginseng Extract, Swertia Japonica Extract, Pentapeptide-17, Hyaluronic Acid (HA), Vitamin E (Tocopherol), Vitamin B7 (Biotin), Vitamin B5 (Panthenol).
20	Redacted	Redacted	Purified Water (Aqua), Disodium Phosphate, Citric Acid, Cellulose Gum, Swertia Japonica Extract, Panax Ginseng Extract, Biotin, Sodium Chloride, Vitamin B2 (Riboflavin), Benzalkonium Chloride.

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21	Redacted	Redacted	Water/Aqua/Eau, Panthenol, Glycerin, Sodium Citrate, Leuconostoc/Radish Root Ferment Filtrate, Alanine, Alcohol, Aloe Barbadensis Leaf Juice, Arctostaphylos Uva URSI Leaf Extract, Arginine, Aspartic Acid, Calcium Gluconate, Caprylyl Glycol, Chamomilla Recutita (Metricaria) Flower Extract, Ethylhexylglycerin, Gluconolactone, Glycine, Hexylene Glycol, Histidine, Honey Extract/Mel/Extrait de Miel, Hydrolyzed Glycosaminoglycans, Hydrolyzed Yeast Extract, Hydroxyethylcellulose, Isoleucine, Isopropyl Cloprostenate , Magnesium Ascorbyl Phosphate, Panax Ginseng Root Extract, PCA, Phenylalanine, Polysorbate 20, Proline, Propylene Glycol, Serine, Sodium Hyaluronate, Sodium Lactate, Sodium PCA, Threonine, Tocopheryl Acetate, Triethanolamine, Tussilago Farfara (Coltsfoot) Leaf Extract, Valine, Vitis Vinifera (Grape) Seed Extract, Phenoxyethanol, Sodium Benzoate, Sodium Metabisulfite.
22	Redacted	Redacted	Vitamins, peptides and amino acids.
23	Redacted	Redacted	Ingredients not shown on website.
24	Redacted	Redacted	Aloe Barbadensis Leaf Juice, Aqua, Lactobacillus / Quinoa Ferment Extract Filtrate, Argania Spinosa Kernel Oil, Adansonia Digitata Oil, Brassicyl Isoleucinate Esylate, Phospholipids, Brassica Alcohol, Ricinus Communis Seed Oil, Biotin, Leuconostoc Radish Root Ferment, Tocopherol, Capryloyl Glycerin / Sebacic Acid Copolymer, Lysolecithin, Sclerotium Gum, Benzyl Alcohol (0.85%), Xanthan Gum, Pullulan, Caffeine, Salicylic Acid, Silica, Sorbic Acid, Glycerin.
25	Redacted	Redacted	Purified Water, Folium Isatidis Extract, Cacumen Platycladi Extract, Black Cumin, Fructus Chebulae Extract, Polygonum Multiflorum Root Extract, Coral Powder.
26	Redacted	Redacted	Ingredients not shown reference to angelica sinensis for eyelash growth.
27	Redacted	Redacted	Ingredients not shown on website references to peptides, biotin & other natural extracts.

Prostaglandin analogues in cosmetics – Literature review, market survey, analytical method development and testing

28	Redacted	Redacted	Aqua, Paraffin wax, Bis-diglyceryl polyacyladipate-2, Carnauba wax, Stearic acid, Bis-PEG-12 dimethicone beeswax , Propylene glycol, Triethanolamine, Glyceryl dibehenate, Tribehenin, Cetearyl alcohol, Ceteareth-20 , Hyaluronic acid, Hydroxyethylcellulose, Phenoxyethanol, Methylparaben, Ethylparaben, Butylparaben, Propylparaben, Hydrolised soya extract, DMDM Hydantoin, Argania spinosa kernal oil, Panthenol, EDTA.
29	Redacted	Redacted	Aqua (water), Paraffin wax, Bis-diglyceryl Polyacyladipate-2, Camauba wax, Stearic Acid, Bis-PEG-12 Dimethicone beeswax , Propylene glycol, Triethanolamine , Glyceryl dibehenate/tribeheinin/glyceryl behenate, Cetearyl alcohol, Ceteareth-20, Hyaluronic acid, Hydroxyethylcellulose, Phenoxyethanol, Methylparaben, Ethylparaben, Butylparaben, Propylparaben, Hydroxysed soy protein, DMDM Hydantoin, Panthenol, EDTAL, Ceteareth-20, Hyaluronic acid.
30	Redacted	Redacted	Aqua (Water), Paraffin, Bis-Diglyceryl Polyacyladipate-2, Copernicia Cerifera Cera, Stearic Acid, Bis-PEG-12 Dimethicone Beeswax, Propylene Glycol, Glyceryl Behenate, Cetearyl Alcohol, Triethanolamine, Phenoxyethanol, Hydroxyethylcellulose, Ceteareth-20, DMDM Hydantoin, Argania Spinosa Kernel Oil, Panthenol, Hydrolyzed Soy Protein, Methylparaben, Ethylparaben, Butylparaben, Butylene Glycol, Propylparaben, Sodium Nitrate, Hydrated Silica, Potassium Sorbate, Trisodium EDTA, Disodium EDTA, Sodium Hyaluronate.
31	Redacted	Redacted	Ingredients not shown on website.
32	Redacted	Redacted	Aqua, Glycerin, Pentylene Glycol, Prunus Amygdalus Dulcis Oil, Oryza Sativa Bran Oil, Myristoyl Pentapeptide-17, Myristoyl Hexapeptide-16, Panthenol, Sodium Hyaluronate, Allantoin, Acrylates/C10-30 Alkyl Acrylate Crosspolymer, Disodium Phosphate, Sodium Hydroxide, Isopropyl Cloprostenate , Phenoxyethanol, Alcohol, Decylene Glycol, 1,2-Hexanediol.

Prostaglandin analogues in cosmetics – Literature review, market survey, analytical method development and testing

33	Redacted	Redacted	Aqua/Water, Acetyl Tetrapeptide-3, Glycerin, 1,3-Butanediol, Alteromonas ferment extract, Phenoxyethanol, Cetearyl olivate/Sorbitan Oliviate, Lecithin, Hyaluronic acid.
34	Redacted	Redacted	Purified water, Hyaluronic acid, Phyto-Collagen, Cucurbita Pepo (pumpkin seed extract), Myriatoyl Pentapeptide–17, Sphingolipid, Arginine.
35	Redacted	Redacted	Aqua (water), pvp, butylene glycol, polyquaternium-37, caprylyl glycol, glycerin, caprylhydroxamic acid, disodium edta, lecithin, aminomethyl propanol, ppg-26-buteth-26, gluconolactone, laminaria digitata extract, pelvetia canaliculata extract, xanthan gum, peg-40 hydrogenated castor oil, sodium benzoate, isopropyl alcohol, apigenin, tetrasodium edta, oleanolic acid, biotinoyl tripeptide-1.
36	Redacted	Redacted	Ingredients not shown on website.
37	Redacted	Redacted	Ingredients not shown on website.
38	Redacted	Redacted	Ingredients not fully shown with references to peptides, biotin & other natural extracts.
39	Redacted	Redacted	Ingredients not shown on website.
40	Redacted	Redacted	Aqua, glycerin, myristoyl pentapeptide-17, Sweet Almond Oil, hyaluronic acid, phenoxyethanol
41	Redacted	Redacted	Ingredients not fully shown references to natural ingredients, biotin and hyaluronic acid.
42	Redacted	Redacted	Ingredients not fully shown references to myristoyl pentapeptide-4.
43	Redacted	Redacted	Ingredients not shown on website.

Prostaglandin analogues in cosmetics – Literature review, market survey, analytical method development and testing

44	Redacted	Redacted	Ingredients not fully shown references to woad oil containing linoleic (omega-6), oleic (omega-9), palmitic (omega-7), arachidic, erucic, lignoceric acids, alkaloids, flavonoids, nitrogen compounds and polysaccharides.
45	Redacted	Redacted	Purified water, disodium phosphate, citric acid, cellulose gum, myristoyl pentapeptide-4, EPM biological enzyme, sodium chloride, benzalkonium chloride.
46	Redacted	Redacted	Ingredients not shown on website.
47	Redacted	Redacted	Ingredients not shown on website.
48	Redacted	Redacted	Ingredients not shown on website.
49	Redacted	Redacted	Purified water, Hyaluronic acid, Phyto-Collagen, Cucurbita Pepo (pumpkin seed extract), Myristoyl Pentapeptide-17, Sphingolipid, Arginine.
50	Redacted	Redacted	Deionized Water, Lactobacillus, Cocos Nucifera (Coconut) Fruit Extract, Glycerin, Propanediol, Polysorbate 80, Xanthan Gum, Bacillus Ferment, Saccharomyces Ferment Filtrate, Wheat Amino Acids, Soy Amino Acids, Propylene Glycol, Diazolidinyl Urea, Disodium EDTA, Sodium Citrate, Panthenol, Arginine HCl, Serine, Threonine, Myristoyl Pentapeptide-17, Iodopropynyl Butylcarbamate, Biotinoyl Tripeptide-1.
51	Redacted	Redacted	Ingredients not fully shown with references to castor oil, vitamin E and sweet almond oil.
52	Redacted	Redacted	Water/aqua, caprylyl glycol, ethylhexylglycerin, hydroxyethylcellulose, glycerin, chlorphenesin, panthenol, hydrolyzed lupine protein, prunus amygdalus dulcis fruit extract, silica, phenoxyethanol, citric acid, isopropyl phenylhydroxypentene dihydroxycyclopentylheptanate.
53	Redacted	Redacted	Aqua, Magnesium Aluminum Silicate, Faex, Propylene Glycol, Horse Tissue Extract, Hydrolyzed Glycosaminoglycans, Serum Protein, Vitulus, Methylparaben, Propylparaben, 2-Bromo-2-Nitropropane-1, 3-Diol, Hexamidine Diisethionate.

Prostaglandin analogues in cosmetics – Literature review, market survey, analytical method development and testing

54	Redacted	Redacted	Purified water, sodium chloride, benzalkonium chloride, citric acid, disodium phosphate, cellulose gum, EPM enzyme.
55	Redacted	Redacted	Aqua (Water), Butylene Glycol, Glycerin, PEG-40 Hydrogenated Castor Oil, Phenoxyethanol, Carbomer, Benzyl Alcohol, Hydrolyzed Wheat Protein/PVP Crosspolymer, Panthenol, Sodium Hyaluronate, Sodium Hydroxide, Dehydroacetic Acid, Phytic Acid, Dextran, EDTA, Potassium Sorbate, Acetyl Tetrapeptide-3, Trifolium Pratense (Clover) Flower Extract, Ethylhexylglycerin.
56	Redacted	Redacted	Ingredients not shown on website.
57	Redacted	Redacted	Water, Butanediol, Octyl hydroxamic acid, Glyceryl octanoate, Propylene glycol, Hydroxyethyl cellulose, P-hydroxyacetophenone, Helichrysum stoechas extract, Polygonum multiflorum root extract, Nymphaea coerulea flower extract, hydrolyzed silk, Oligopeptide-1, Methyl hydroxybenzoate.
58	Redacted	Redacted	Ingredients not fully shown with references to Myristol Pentapeptide-17 and Myristol Hexapeptide-16.
59	Redacted	Redacted	Ingredients not fully shown with references to Myristoyl Pentapeptide-17.
60	Redacted	Redacted	Aqua, Pentylene Glycol, Pentaerythrityl Tetraisostearate, Propanediol, Butylene Glycol, Arginine, Phenoxyethanol, Alcohol, Panthenol, Glycerin, Lactic Acid, Acrylates/C10-30 Alkyl Acrylate Crosspolymer, Allantoin, Sodium Hyaluronate, Decylene Glycol, Disodium Phosphate, Glycine Soja Germ Extract, Triticum Vulgare Germ Extract, 1,2-Hexanediol, Urea, Norbimatoprost , Gluconolactone, Scutellaria Baicalensis Root Extract, Panax Ginseng Root Extract, Biotin, Sodium Benzoate, Cucurbita Pepo Seed Extract, Undaria Pinnatifida Extract, Dextran, Citric Acid, Potassium Sorbate, Acetyl Tetrapeptide-3, Trifolium Pratense Flower Extract, Calcium Gluconate.

Prostaglandin analogues in cosmetics – Literature review, market survey, analytical method development and testing

61	Redacted	Redacted	Deionized Water, Glycerin, BETA-GLUCAN, Sodium Hyaluronate, Dexpanthenol Vitis Vinifera Seed Oil, Sodium Lactate, Sodium PCA, Panax Ginseng Root Extract Proline, Hydrolyzed Yeast Extract, Phenoxyethanol, Chamomilla Recutita Flower Extract Arctostaphylos UVA R Ursileaf Extract, Magnesium Ascorbyl Phosphate Tocopheryl Acetate, Polysorbate 20, Isopropyl Cloprostenate , Sorbitol Carbomer, Biotin, Silk Amino Acid Blend (Sodium L-Pyrrolidone Carboxylate, Sodium Lactate, L-Aspartic Acid, L-Arginine, L-Pyrrolidonecarboxylic Acid, Glycine, L-Valine, L-Serine, L-Proline, L-Alanine, L-Threonine, L-Isoleucine, L-Histidine, L-Phenylalanine).
62	Redacted	Redacted	Aqua, Propanediol, Panthenol, Glycerin, Biotinoyl Tripeptide-1, Acorus Calamus Root Extract, Acrylates/C10-30 Alkyl Acrylate Crosspolymer, Calendula Officinalis Flower Extract, Dechloro Dihydroxy Difluoro Ethylcloprostenolamide , Disodium EDTA, Ethylhexylglycerin, Equisetum Arvense Leaf Extract, Hydrolyzed Silk, Linum Usitatissimum Seed Extract, Phenoxyethanol, Propylene Glycol, Serenoa Serrulata Fruit Extract, Sodium Hyaluronate, Sodium Hydroxide.
63	Redacted	Redacted	Water, Butylene Glycol, Hydroxyethylcellulose, Glycerin, Rhizobian Gum, Sodium Hyaluronate, Biotin, Panthenol, Pantethine, Hydrolyzed Glycosaminoglycans, Allantoin, Cucurbita Pepo (Pumpkin) Seed Extract, Sea Water, Dipotassium Glycyrrhizate, Octapeptide-2, Copper Tripeptide-1, SH-Polypeptide-1, Alcohol, Isopropyl Cloprostenate , Glycine Soja (Soybean) Oil, Phenoxyethanol, Chlorphenesin, Sorbic Acid, Potassium Sorbate, Sodium Oleate, Disodium EDTA, Citric Acid, Hydrogenated Lecithin.
64	Redacted	Redacted	Ingredients not fully shown but references to peptides.

Prostaglandin analogues in cosmetics – Literature review, market survey, analytical method development and testing

65	Redacted	Redacted	Aqua (Water), Glycerin, Alcohol denat., Panthenol, Curcuma Longa (Turmeric) Callus Culture Conditioned Media, Myristoyl Pentapeptide-17, Biotinoyl Tripeptide-1, Niacinamide, Soluble Collagen, Arginine, Proline, Alanine, Glutamic Acid, Aleuritic Acid, Sodium Hyaluronate, Bisabolol, Allantoin, Lactic Acid, Gluconolactone, Carbomer, Sodium Lactate, Phenethyl Alcohol, Phenoxyethanol, Sodium Benzoate.
66	Redacted	Redacted	Water (Aqua), Butylene Glycol, Hydroxyethylcellulose, Sodium Hyaluronate, Octapeptide-2, Copper Tripeptide-1, sh-Polypeptide-1, Cucurbita Pepo (Pumpkin) Seed Extract, Glycine Soja (Soybean) Oil, Glycerin, Hydrogenated Lecithin, Hydrolyzed Glycosaminoglycans, Rhizobian Gum, Biotin, Dicalcium Phosphate, Panthenol, Pantethine, Dipotassium Glycyrrhizate, Allantoin, Sea Water, Alcohol, Isopropyl Cloprostenate , Polysorbate 60, Disodium Phosphate, Sodium Phosphate, Phenoxyethanol, Disodium EDTA, Citric Acid, Chlorphenesin, Sorbic Acid, Sodium Oleate, Potassium Sorbate.
67	Redacted	Redacted	Water. Butylene glycol, hydroxyethmicellulose, keratin, hydrolysed keratin, biotin, sodium hyaluronate, isopropyl cloprostenate , octapepetide-2, allatonin, panthenol, copper tripeptide-1, pantethine, polypeptide-23, cucurbita pepe (pumpkin) seed extract, glycerin, sea water, malus domestica fruit cell culture extract, hydrolysed glycosaminoglycans, prunus amygdalus fruit extract, backhousia citriodora leaf oil, dipotassium glycyrrhizate, rhizobian gum, styrene/acrylates/ammonium methacrylate copolymer, xanthan gum, PVP, lecithin, PEG-12 demithicaone, alchol denat, chlorphensin, phenoxyethanol, sorbic acid, sodium hydroxide.
68	Redacted	Redacted	Water/Aqua/Eau, Butylene Glycol, Hydroxyethylcellulose, Rhizoblan gum, Sodium Hyaluronate, Biotin, Panthenol, Pantethine, Hydrolyzed Glycosaminoglycans, Alantoin, Cucurbita pepo (pumpkin) seed extract, Dipotassium glycyrrhizate, Sea water, Octapeptide-2, copper tripeptide-1, Polypeptide-23, Glycine soja (soybean) oil, glycerin, Phosphidylcholine, Alcohol denat, Isopropyl cloprostenate , phenoxyethanol, chlorphenesin, sorbic acid.

Prostaglandin analogues in cosmetics – Literature review, market survey, analytical method development and testing

69	Redacted	Redacted	Water (Aqua), Glycerin, Panthenol, Sodium Citrate, Leuconostoc / Radish Root Ferment Filtrate, Alanine, Alcohol, Arbutin, Arginine, Aspartic Acid, Biotin, Calcium Gluconate, Caprylyl Glycol, Chamomilla Recutita (Matricaria) Flower Extract, Ethylhexylglycerin, Gluconolactone, Glycine, Hexylene Glycol, Histidine, Hydrolyzed Glycosaminoglycans, Hydroxyethylcellulose, Isoleucine, Sodium Lactate, Magnesium Ascorbyl Extract, PCA, Valine, Phenylalanine, Polydextrose, Polysorbate Phosphate, Panax Ginseng Root 20, Proline, Propylene Glycol, Serine, Vitis Vinifera (Grape) Seed Extract, Sodium Hyaluronate, Isopropyl Cloprostenate , YeaExtract, Sodium PCA, Threonine, Tocopheryl Acetate, Triethanolamine, Phenoxyethanol, Sodium Benzoate, Sodium Metabisulfite.
70	Redacted	Redacted	Aqua, Ethyl Tafluprostamide , Euphrasia Officinalis Extract, Propylene Glycol, Sodium Chloride, Alcohol, Sodium Hydroxymethylglycinate, Citric Acid, Triethanolamine.
71	Redacted	Redacted	Ingredients not fully shown with references to keratin stimulating peptides, rhodiola rosea root, and biotin.
72	Redacted	Redacted	Ingredients not fully shown with references to Black Sea Rod/Caribbean Sea Whip Extract.
73	Redacted	Redacted	Organic Aloe Barbadensis Leaf Juice, Organic Ricinus Communis (Castor) Seed Oil, Tussilago Farfara (Coltsfoot) Flower Extract, Achillea Millefolium (Yarrow) Extract, Cinchona Succirubra Bark Extract, Water, Tocopheryl Acetate (Vitamin E), Glycerin, Honey Extract, Prunus Amygdalus (Sweet Almond) Oil, Sucrose Laurate, Sodium Stearoyl Lactylate, Nasturtium Officinale (Watercress) Extract, Tropaeolium Majus (Indian Cress) Extract, Xanthan Gum, Coleus Forskohlii Root Oil, Carya Ovata (Hickory) Bark Extract.
74	Redacted	Redacted	Aqua, Pentylene Glycol, Propanediol, Glycerin, Butylene Glycol, Magnolia Officinalis Bark Extract, Gellan Gum, Xanthan Gum, Alcohol Denat, Trifolium Pratense (Clover) Sprout Extract, Vigna Radiata Sprout Extract,

Prostaglandin analogues in cosmetics – Literature review, market survey, analytical method development and testing

			Acetyl Tetrapeptide-3, Trifolium Pratense (Clover) Flower Extract, Dextran, Ethyl Tafluprostamide .
75	Redacted	Redacted	Aqua; (Pisum Sativum (Pea) Sprout Extract (and) Alcohol (and) Aqua/Water); (Lysolecithin (and) Sclerotium Gum (and) Xanthan Gum (and) Pullulan); Panthenol; Plunkenetia volubilis seed oil; Ricinus communis Oil; Glycerol; Mangifera Indica Seed Butter; Sodium hyaluronate; Tocopherol ; Benzyl Alcohol, Ethylhexylglycerin.
76	Redacted	Redacted	Aqua, Caprylyl glycol, Hydrolyzed glycosaminoglycans, Triethanolamine, C12-15 alkyl benzoate, Acrylates/C10-30 alkyl acrylate crosspolymer, Panthenol, Sodium lactate, Sodium pca, Sodium chloride, Biotin, Alcohol, Hyaluronic acid, Sodium phosphate, Phenoxyethanol, Methylamido dihydro noralfaprostal , Arginine, Sodium hyaluronate, Aspartic acid, Glycine, Alanine, Serine, Valine, Isoleucine, Threonine, Histidine, Phenylalanine, Norbimatoprost , PCA.
77	Redacted	Redacted	Aqua (water), Glycerin, Polysorbate 20, Panthenol, Black sea rod oil, Myristoyl pentapeptide-17, Sodium hyaluronate, Chamomilla recutita extract, Panax ginseng root extract, Sodium pca, Gluconolactone, Arctostaphylos uva ursi extract, Vitis vinifera leaf extract, Pisum sativum sprout extract, Tocopheryl acetate, Sodium ascorbyl phosphate, Faex extract, Leucine, Hydroxyethylcellulose, Propylene glycol, Triethanolamine, Citric acid, O-cymen-5ol, Hydrogenated starch hydrolysate, Hydrolyzed glycosaminoglycans, Sodium benzoate, Lactic acid, Phenoxyethanol, Alcohol.
78	Redacted	Redacted	Aqua Vp/Methacrylamide/Vinyl Imidazole Copolymer, Glycerin, Sodium Carbomer, Butylene Glycol, Glycogen, Caprylyl Glycol, Hexylene Glycol, Potassium Sorbate, Glycine, Larix, Europaea Wood Extract, Sodium Metabisulfite, Dextran, Camelia, Sinensis Leaf Extract, Zink Chloride, Acetyl Tetrapeptide-3, Trifolium Pratense Extract.

Prostaglandin analogues in cosmetics – Literature review, market survey, analytical method development and testing

79	Redacted	Redacted	Water, Glycerin, Phenoxyethanol, C12-15 Alkyl Benzoate, Caprylyl Glycol, Panthenol, Acrylates/C10-30 Alkyl Acrylate Crosspolymer, Alcohol, Biotin, Sodium Hydroxide, 1,2-Hexanediol, Black Sea Rod Oil, Sodium Hyaluronate, Benzoic Acid, Myristoyl Pentapeptide-17, Sodium Benzoate, Phenethyl Caffeaate.
80	Redacted	Redacted	Raspberry seed oil, Pomegranate oil, Baobab oil, Argan oil, Olive squalene, Castor oil, Rosemary leaf extract, Candlenut oil, Borage oil, Jojoba oil, Tamanu oil, Sunflower seed oil.
81	Redacted	Redacted	Aqua (Deionized Water), Glycerin, Complex: Myristoyl Pentapeptide-17, Cyclomethicone, Bis-Vinyl Dimethicone copolymer, PEG-12 Dimethicone, Biotin (vitamin B7), dl-Panthenol, Cucurbita Pepo (Pumpkin) Seed Extract, Cyanocobalamin (Vitamin B-12), Allantoin, Pyridoxine HCl (Vitamin B6), Hesperidin Methyl Chalcone, Steareth-20, Dipeptide-2, Palmitoyl (tetrapeptide-7), Polysorbate-20, Xanthan Gum, Sodium Hyaluronate (Hyaluronic Acid), Retinyl Palmitate (Vitamin-A), Punica Granatum (Pomegranate) Extract, Cucumis Sativus (cucumber) Fruit Extract, Camellia Sinensis Leaf (White Tea) Extract, Phenoxyethanol.
82	Redacted	Redacted	Purified water, Sodium chloride, Benzalkonium chloride, Citric acid, Disodium phosphate, Cellulose gum.
83	Redacted	Redacted	Vitamin E, oatstraw, sage, marshmallow root, rosemary, nettle leaf, nettle root, horsetail, castor oil, sweet almond oil
84	Redacted	Redacted	Ingredients not fully shown with references to Biotinoyl Tripeptide-1, Myristoyl Peptides (Oleanolic Acid, Biotinoyl Tripeptide-1, Apigenin), Malus Domestica.
85	Redacted	Redacted	Ingredients not shown on website.
86	Redacted	Redacted	Ingredients not shown on website.

Prostaglandin analogues in cosmetics – Literature review, market survey, analytical method development and testing

87	Redacted	Redacted	Ingredients not shown on website.
88	Redacted	Redacted	Water, Glycerin, Myristoyl Pentapeptide-17, Biotinoyl Tripeptide-1, D-Panthenol, Camellia Sinensis Leaf Extract, Urtica Dioica (Nettle) Root Extract, Serenoa Serrulata Fruit Extract, Hydroxyacetophenone, 1,2-Hexanediol, Sodium PCA, Hydroxyethylcellulose.
89	Redacted	Redacted	Ingredients not fully shown with references to witch hazel, apple, nettle, horse chestnut and St. John's wort.
90	Redacted	Redacted	Aqua, Myristoyl Pentapeptide-17, Myristoyl Hexapeptide-16, Propanediol, Arginine, Lactic Acid, Glycine Soja Germ Extract, Triticum Vulgare Germ Extract, Scutellaria Baicalensis Root Extract, Sodium Benzoate, Gluconolactone, Calcium Gluconate, Sodium Chloride, Alcohol, Sodium Hydroxymethylglycinate, Ethyl Tafluprostamide , Citric Acid, Triethanolamine.
91	Redacted	Redacted	Purified water, sodium chloride, benzalkonium chloride, citric acid, disodium phosphate, Myrostoylexyl hexapeptide-17, complex hydroxyethylcellulose, Panax ginseng extract, Swertia japonica extract, Phenoxyethanol, Capryl glycol, Imadazolidnyl urea, Potassium sorbate, EDTA, Hyaluronic acid, Biotin.
92	Redacted	Redacted	Aqua, Glycerin, Panthenol, Propanediol, Myristoyl Pentapeptide-17, Arginine, Glycine Soja Germ Extract, Triticum Vulgare Germ Extract, Scutellaria Baicalensis Root Extract, Sodium Hyaluronate, Hydrolyzed Keratin, Saccharide Isomerate, Acrylates/C10-30 Alkyl Acrylate Crosspolymer, Lactic Acid, Triethanolamine, Phenoxyethanol, Ethylhexylglycerin.
93	Redacted	Redacted	Ingredients not fully shown with references to peptide complex, amino acids, ginseng root, sodium hyaluronate, chamomile, radish root ferment.

Prostaglandin analogues in cosmetics – Literature review, market survey, analytical method development and testing

94	Redacted	Redacted	Aqua (Water/Eau), Glycerin, Butylene glycol, Disodium phosphate, Betaine, Xanthan gum, Tocopheryl acetate, Panthenol, Sodium PCA, Sodium hyaluronate, Hydrolyzed keratin, Cystine, Sorbitol, Retinyl palmitate, Ascorbyl glucoside, Serine, Glycine, Glutamic acid, Sodium phosphate, Alanine, Lysine, Arginine, Pantolactone, Threonine, Tripeptide-21, Proline, Tocopherol, Biotinoyl tripeptide-1, Phenoxyethanol, Methylparaben, Sorbic acid, Propylparaben.
95	Redacted	Redacted	Aqua, Phenoxyethanol, C12-15 Alkyl Benzoate, Caprylyl Glycol, Panthenol, Acrylates / C10-30 Alkyl Acrylate Crosspolymer, Biotin, Alcohol, Sodium Hydroxide, Black Sea Rod Oil, Sodium Hyaluronate, Phenethyl Caffeate, Hydrolyzed Glycosaminoglycans.
96	Redacted	Redacted	Aqua, PEG-40 Hydrogenated Castor Oil, Helianthus Annuus Seed Oil, Panicum miliaceum (millet) seed extract, Sodium Hyaluronate, Caprylyl Glycol, Panthenol, Hydrolyzed Wheat Protein, Aloe Barbadensis Leaf Juice, Sodium Benzoate, Rosmarinus Officinalis Leaf Extract, Triticum aestivum (wheat) seed extract, Potassium Sorbate, Citric Acid.
97	Redacted	Redacted	Aqua, Alcohol, denat., Urea, Hydrolyzed Lupine Protein, Sodium Lactate, Laureth - 7 Citrate, Caffeine, Di-Sodium Hydrogen Phosphate, Carbomer, Panthenol, Sodium Hydroxide, Biotin, Phenoxyethanol, Caprylyl Glycol, Sodium Hyaluronate, Ethylhexylglycerine,
98	Redacted	Redacted	Ingredients not shown on website.
99	Redacted	Redacted	Aqua, Curcuma Longa Callus Conditioned Media, Pentylene Glycol, Phytic Acid, Myristoyl Pentapeptide-17, Glyceryl Glucoside, Biotinoyl Tripeptide-1, Sodium PCA, Sodium Lactate, Arginine, Aspartic Acid, PCA, Glycine, Alanine, Serine, Valine, Proline, Threonine, Isoleucine, Histidine, Phenylalanine, Amaranthus Caudatus Seed Extract, Biotin, Panthenol, Sodium Benzoate, Potassium Sorbate, Sodium Hydroxide, Citric Acid.

Prostaglandin analogues in cosmetics – Literature review, market survey, analytical method development and testing

100	Redacted	Redacted	Aqua (Water), Propanediol, Glycerin, Panthenol, Sodium Hyaluronate, Carbomer, Sodium Phytate, Ethylhexylglycerin, Tilia Tomentosa Extract, Biotinoyl Tripeptide-1, Sodium Hydroxide, Citric Acid, Phenoxyethanol, Potassium Sorbate, Sodium Benzoate.
101	Redacted	Redacted	Ingredients not shown but references to bimatoprost .
102	Redacted	Redacted	Aqua, Aloe Barbadensis Extract, Glycerin, Myristoyl Pentapeptide-17, 1,2-Hexanediol, Butylene Glycol, Caprylyl Glycol, Dextran, Acetyl Tetrapeptide-3, Trifolium Pretense Flower Extract, Pisum Sativum Sprout Extract, Larix Europaea Wood Extract, Glycine, Sodium Metabisulfite, Zinc Chloride, Camellia Sinensis Leaf Extract, Malus Domestica Fruit Cell Culture Extract, Lecithin, Xanthan Gum, Panthenol, Hydrolyzed Collagen, Sorbitol, Polysorbate 20, Hydroxyethylcellulose, Allantoin, Sodium Benzoate, Phenoxyethanol, Tocopheryl Acetate, Biotin, Sodium Hyaluronate, Niacin, Benzoic Acid.
103	Redacted	Redacted	Aqua (Water), Glycerin, PEG-40 Hydrogenated Castor Oil, Butylene Glycol, Phenoxyethanol, Carbomer, Sodium Hydroxymethylglycinate, Hydrolyzed Wheat Protein/PVP Crosspolymer, Panthenol, 1, 2-Hexanediol, Caprylyl Glycol, Benzoic Acid, Sodium Benzoate, Sodium Hyaluronate, Disodium EDTA, Myristoyl Pentapeptide-17, Sodium Hydroxide, Phenoxyethanol, Potassium Sorbate, EDTA, Ethylhexylglycerin.
104	Redacted	Redacted	Aqua, Hyaluronate, Pentylene glycol, Panax ginseng extract, Japonica extract, Pumpkin seed extract, Acorus calamus extract, Panthenol, Sirenoa fruit extract, Biotinoyl tripeptide-1, Myristoyl pentapeptide-17, Oligopeptide-10, Tocophenol, Biotin.
105	Redacted	Redacted	Buffer solution (aqua, sodium chloride, potassium phosphate, disodium phosphate), sodium hyaluronate, phenoxyethanol, water soluble prostaglandin derivative .

Prostaglandin analogues in cosmetics – Literature review, market survey, analytical method development and testing

106	Redacted	Redacted	Ingredients not fully shown. References to peptides, including Capixyl (red clover extract & acetyl tetrapeptide-3).
107	Redacted	Redacted	Aqua (Water), Glycerin, Propylene Glycol, Phenoxyethanol, Hydroxyethylcellulose, Biotinoyl Tripeptide-1, Simmondsia Chinensis (Jojoba) Seed Oil, Panthenol, Tetrasodium EDTA, Triethylene Glycol.
108	Redacted	Redacted	Aqua (Water, Eau), PEG-40 Hydrogenated Castor Oil, Glycerin, Phenoxyethanol, Hydrolyzed Wheat Protein/PVP Crosspolymer, Carbomer, Disodium EDTA, Panthenol, Ethylhexylglycerin, Lycium Barbarum Fruit Extract, Tocopherol, Sodium Hydroxide, Helianthus Annuus (Sunflower) Seed Oil, Potassium Sorbate, Rubus Idaeus (Raspberry) Fruit Extract, Sodium Benzoate, Pantolactone, EDTA, Myristoyl Pentapeptide-17, Benzoic Acid, Sorbic Acid.

Prostaglandin analogues in cosmetics – Literature review, market survey, analytical method development and testing

109	Redacted	Redacted	<p>'Water\Aqua\Eau, Dimethicone, Butylene Glycol, Methyl Trimethicone, Vinyl Dimethicone/Methicone Silsesquioxane Crosspolymer, Polysorbate 20, Glycerin, Bis-Peg-18 Methyl Ether Dimethyl Silane, Silica, Polymethylsilsesquioxane, Lauryl Peg-9 Polydimethylsiloxyethyl Dimethicone, Peg-60 Almond Glycerides, Methyl Gluceth-20, Polysilicone-11, Curcuma Longa (Turmeric) Root Extract, Panax Ginseng Root Extract, Polygonum Cuspidatum Root Extract, Creatine, Camellia Sinensis (Green Tea) Leaf Extract, Acetyl Carnitine Hcl, Galactoarabinan, Trifolium Pratense (Clover) Extract, Phyllanthus Emblica Fruit Extract, Caffeine, Cholesterol, Glycine Soja (Soybean) Seed Extract, Yeast Extract\Faex\Extrait De Levure, Disodium NADH, Sodium Hyaluronate, Palmitoyl Tripeptide-1, Adenosine Phosphate, Arginine, Palmitoyl Tetrapeptide-7, Acetyl Tetrapeptide-3, Dipotassium Glycyrrhizate, Laurdimonium Hydroxypropyl Hydrolyzed Soy Protein, Sodium Hydroxide, Ethylhexylglycerin, Caprylyl Glycol, Tocopheryl Acetate, Lecithin, Hexylene Glycol, Carbomer, Xanthan Gum, Disodium Edta, Tocopherol, BHT, Phenoxyethanol, Sodium Dehydroacetate.</p>
110	Redacted	Redacted	<p>Aqua/Water/Eau, Cera Alba/Beeswax/Cire D'Abeille, Ammonium Acrylates Copolymer, Propylene Glycol, Vp/Eicosene Copolymer, Copernicia Cerifera Cera/Copernicia Cerifera (Carnauba) Wax/Cire De Carnauba, Cetyl Alcohol, Polysorbate 20, Ethylene/Acrylic Acid Copolymer, Alcohol Denat., Potassium Cetyl Phosphate, Hydrogenated Palm Glycerides, Styrene/Acrylates Copolymer, Stearic Acid, Phenoxyethanol, Disodium Deceth-6 Sulfosuccinate, Panthenol, Aminomethyl Propanediol, Hectorite, Laureth-30, C11-15 Pareth-40, C11-15 Pareth-7, Hydroxyethylcellulose, Tocopheryl Acetate, Argania Spinosa Kernel Oil, Disodium EDTA, Sodium Dehydroacetate, Caprylyl Glycol,</p>

Prostaglandin analogues in cosmetics – Literature review, market survey, analytical method development and testing

			Sodium Laureth-12 Sulfate, Hydrolyzed Collagen (Derived from Fish), Silica, Pantolactone, Hydrolyzed Keratin, Sodium Sulfate, Potassium Sorbate, Sodium Benzoate, [May contain +/-: Mica, Iron Oxides (CI 77491, CI 77492, CI 77499), Titanium Dioxide (CI 77891), Ferric Ferrocyanide (CI 77510), Carmine (CI 75470), Chromium Hydroxide Green (CI 77289), Chromium Oxide Greens (CI 77288), Ultramarines (CI 77007)].
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