NEW ZEALAND DATA SHEET

1. PRODUCT NAME

LATISSE® (bimatoprost) 0.3 mg/mL topical solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LATISSE ® topical solution contains bimatoprost 0.3 mg/mL

For full list of excipients, see section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

A sterile topical solution.

LATISSE® (bimatoprost) topical solution is clear, sterile, isotonic and colourless.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LATISSE® topical solution is indicated to treat hypotrichosis of the eyelashes by increasing their growth including length, thickness, and darkness.

4.2 Dose and method of administration

The recommended use of LATISSE® topical solution is once nightly. Apply to clean face, ensure makeup and contact lenses are removed prior to application. Carefully apply one drop of LATISSE® topical solution to the disposable sterile applicator supplied with the package and apply evenly along the skin of the upper eyelid margin at the base of the eyelashes. Apply evenly and lightly to minimise runoff. Blot any excess solution runoff outside the upper eyelid margin with a tissue or other absorbent cloth. Dispose of the applicator after one use and then repeat for the opposite eyelid margin using a new sterile applicator. Do not reuse applicators and do not use any other brush/applicator to apply LATISSE® topical solution. Do not apply to the lower eyelash line.

To avoid contamination of the solution, keep the container tightly closed. Do not touch the dropper tip to any surface. Discard contents 4 weeks after opening the bottle. Contents are sterile if seal is intact.

Paediatric Use

Safety and effectiveness in patients below 18 years of age have not been established.

Use in Elderly

No dosage adjustment in elderly patients is necessary.

4.3 Contraindications

LATISSE® topical solution is contraindicated in patients with hypersensitivity to bimatoprost or to any component of the medication.

4.4 special warnings and precautions for use

General:

Iris and Eyelid Pigmentation:
LATISSE® topical solution should only be applied to the upper eyelid margin. Bimatoprost ophthalmic solution has been reported to cause changes to pigmented tissues. When bimatoprost ophthalmic solution 0.3 mg/mL (LUMIGAN® eye drops) was instilled directly into the eye (for treatment of elevated IOP) the most frequently reported pigmentary changes have been increased pigmentation of periorbital tissue (eyelid), eyelashes and the iris. Periorbital tissue pigmentation has been reported to be reversible in most patients. In a pivotal clinical trial with LATISSE® topical solution, pigmentation of the periorbital tissue (eyelid margin) has been seen.

Post-marketing reports of perceived colour changes of the iris have been received. In the pivotal clinical trial with LATISSE® topical solution no sustained change to iridial pigmentation was reported. Patients should be advised about the potential for increased brown iris pigmentation which is likely to be permanent. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes.

Increased iris pigmentation has occurred when bimatoprost solution has been administered. The long term effects of increased iridial pigmentation are not known. Iris colour changes seen with ophthalmic administration of bimatoprost may not be noticeable for several months to years. Neither nevi nor freckles of the iris appear to be affected by treatment.

Effects on IOP:
Bimatoprost ophthalmic solution (LUMIGAN® eye drops) lowers intraocular pressure (IOP) when instilled directly to the eye in patients with elevated IOP. If LATISSE® topical solution gets into the eye there is the potential for a reduction in IOP.In clinical trials in patients without elevated IOP, statistically significant differences in mean IOP reduction were observed between LATISSE® topical solution vs. vehicle treated groups, however, the magnitude of the reduction was not cause for clinical concern.

Co-administration of LATISSE® topical solution on the skin at the base of the upper lid margin along with prostaglandin analogues, including LUMIGAN® eye drops, instilled on the eye for elevated intraocular pressure (IOP) has not been studied. In LUMIGAN® eye drops studies in patients with glaucoma or ocular hypertension, it has been shown that more frequent exposure of the eye to more than one dose of bimatoprost daily may decrease the intraocular pressure lowering effect. Patients using these products concomitantly should be monitored for changes to their intraocular pressure.

Growth of hair outside the treatment area:
There is the potential for hair growth to occur in areas where LATISSE® topical solution comes repeatedly in contact with the skin surface. Thus, it is important to apply LATISSE® topical solution, using the accompanying sterile applicators, only to the skin of the upper eyelid margin at the base of the eyelashes and to carefully blot any excess LATISSE® topical solution from the eyelid margin to avoid it running onto the cheek or other skin areas.

Macular oedema and uveitis:
Macular oedema, including cystoid macular oedema, has been reported during treatment with bimatoprost 0.3 mg/mL ophthalmic solution for elevated IOP. LATISSE® topical solution should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular oedema (e.g. intraocular surgery, retinal vein occlusions, ocular inflammatory disease and diabetic retinopathy). LATISSE® topical solution should be used with caution in patients with active intraocular inflammation (e.g. uveitis) because inflammation may be exacerbated.

Contamination of solution or applicators:
The LATISSE® topical solution bottle must be kept intact during use. It is important to use LATISSE® topical solution as instructed, by applying one drop to the single-use-per eye applicator. The bottle tip should not be allowed to contact any other surface since it could become contaminated. The accompanying sterile applicators should only be used on one eye each and then discarded, since reuse of applicators increases the potential for contamination and infection.

There have been reports of bacterial keratitis associated with the use of multiple dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent ocular disease. Patients with a disruption of the ocular epithelial surface are at greater risk of developing bacterial keratitis.

Use with contact lenses:

LATISSE® topical solution contains the preservative benzalkonium chloride, which may be absorbed and cause discolouration of soft contact lenses. Patients wearing soft (hydrophilic) contact lenses should remove them prior to administration of LATISSE® topical solution and wait at least15 minutes before reinserting soft lenses.

The tip of the bottle should not be allowed to contact the eye, surrounding structures, fingers or any other surface in order to avoid eye injury and contamination of the solution.

Hepatic Impairment

In patients enrolled in the long-term bimatoprost 0.3 mg/mL studies who had a history of mild liver disease or abnormal ALT, AST and/or bilirubin at baseline, LUMIGAN® eye drops had no adverse effect on liver function over 48 months.

Renal Impairment

There are no data specific for renal impairment and therefore the product should therefore be used with caution in such patients.

No clinically relevant, treatment-related effects on heart rate and blood pressure have been observed in clinical trials.

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed.

No drug-drug interactions are anticipated in humans since systemic concentrations of bimatoprost are extremely low (less than 0.2 ng/mL) following ocular dosing.

There is a potential for the IOP-lowering effect of the prostaglandin analog LUMIGAN® eye drops to be reduced in patients with glaucoma or ocular hypertension when used in conjunction with LATISSE® topical solution (see 4.4 Special warnings and precautions for use).

4.6 Fertility, pregnancy and lactation

Impairment of Fertility:

Bimatoprost did not affect fertility in male or female rats at oral doses up to 0.6 mg/kg/day (approximately 103 times the intended human exposure).

Use in Pregnancy:

Pregnancy Category B3

In embryofoetal development studies in pregnant mice and rats, abortion but no developmental effects were observed at oral doses that were at least 33 or 97 times higher, respectively, than the intended human exposure. In peri/postnatal studies in rats, reduced gestation time, foetal death and decreased pup body weights were observed in dams given $\geq$ 0.3 mg/kg/day (a rodent-specific pharmacological effect; systemic exposure estimated to be at least 41 times the intended human exposure). This maternal toxicity likely resulted in decreased mating performance and gestational body weight gain in the offspring, but neurobehavioural functions were not affected.

There are no adequate and well-controlled studies in pregnant women. LATISSE® topical solution should not be used during pregnancy unless clearly necessary.

Use in Lactation:

Bimatoprost was excreted in rat milk following PO administration. Increased pup mortality and depressed pup growth occurred when dams were treated PO with bimatoprost from gestation day 7 to lactation day 20 at $\geq$ 0.3 mg/kg/day, corresponding to exposures approximately 41 times the expected human exposure.

There are no data on the excretion of bimatoprost into human milk or on the safety of bimatoprost exposure in infants. Because many drugs are excreted in human milk, nursing women who use LATISSE® topical solution should stop breast feeding.

4.7 Effects on ability to drive and use machines

LATISSE® topical solution is not expected to affect the ability to drive and use machines.

4.8 Undesirable effects

The following information is based on clinical trial results from a multicenter, double-masked, randomised, vehicle-controlled, parallel group study including 278 patients who were dissatisfied with their overall eyelid prominence. Patients underwent four months of treatment followed by a one month post-treatment evaluation period.

The following events were considered treatment related and were reported in >1% of patients during the treatment phase of clinical trials with LATISSE® topical solution.
The frequency is defined as follows: Very Common (≥10%); Common (≥1% to <10%); Uncommon (≥0.1% to <1%); Rare (≥0.01% to <0.1%); Very Rare (<0.01%).

Eye disorders:
Common: eye pruritus, conjunctival hyperaemia, eye irritation, erythema of eyelid

Skin and subcutaneous tissue disorders:
Common: skin hyperpigmentation

Post-marketing Experience

In addition to what has been observed in clinical trials, the following adverse reactions have been identified during post-marketing use of LATISSE® topical solution. Because post-marketing reporting is voluntary and from a population of uncertain size, it is not possible to reliably estimate the frequency of these reactions.

Eye disorders:
Blepharitis, Deepened lid sulcus (enophthalmos), dry eye, eye discharge, eye pain, eye swelling, eyelid irritation, eyelid oedema, eyelid pain, eyelids pruritus, iris hyperpigmentation, lacrimation increased, foreign body sensation, dry skin of the eyelid and/or periocular area and vision blurred.

Immune system disorder:
Hypersensitivity (local allergic reactions)

Nervous system disorders:
Headache

Skin and subcutaneous tissue disorders:
Hair growth abnormal, burning sensation (eyelid), erythema periorbital, madarosis and trichorrhexis (temporary loss of a few eyelashes to the loss of sections of eyelashes, and temporary eyelash breakage respectively), rash (including macular, erythematous, and pruritic limited to the eyelids and periorbital region), skin discolouration (periorbital), hordeolum and trichiasis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

No information is available on overdose in humans. If overdose occurs, treatment should be symptomatic and supportive.

Ophthalmic overdose: No case of overdose has been reported, and is unlikely to occur after ocular administration.

In short term oral (by gavage) mouse and rat studies, doses up to 100 mg/kg/day did not produce any toxicity. This dose, expressed as mg/m^2, is at least 165 times higher than the amount of bimatoprost to which a 10 kg child would be exposed were it to accidentally ingest one 3 mL bottle of LATISSE® topical solution.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

Bimatoprost is a white to off-white powder and is very soluble in ethyl alcohol and methyl alcohol and slightly soluble in water.

5.1 Pharmacodynamic properties

Mechanism of action

Bimatoprost is a synthetic prostamide, structurally related to prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$).

The mechanism of action through which bimatoprost causes eyelash growth is currently unknown. Human hair growth is a cyclic process whereby the hair follicle undergoes periods of growth (anagen), transition (catagen) and rest (telogen). In response to a stimulus of unknown origin from the dermal papilla, the anagen growth phase of the hair follicle is initiated. When anagen is triggered, a new hair shaft is formed during early anagen. The dermal papilla is necessary to both induce and maintain the hair shaft. It is possible that dormant hair follicles are stimulated to enter the anagen phase of the hair cycle, and this may result in eyelash growth. An eyelash enhancing effect of bimatoprost has been demonstrated in mice. Hair growth stimulation has also been reported in mice with prostamides, $PGF_{2\alpha}$ latanoprost and isopropyl unoprost, which are structurally and functionally related to bimatoprost in mouse and/or monkey models. These three agents were shown to stimulate hair growth in the telogen and anagen phases.

Clinical efficacy and safety

LATISSE® topical solution was evaluated for its effect on overall eyelash prominence in a multicentre double-masked, randomised, vehicle-controlled, parallel group study including 278 adult patients for 4 months of treatment. LATISSE® topical solution was applied once daily in the evening to the right and left upper eyelid margins using a disposable single-use-per-eye applicator. Treatment was followed by a one-month, post-treatment, evaluation period.

The primary efficacy endpoint in this study was an increase in overall eyelash prominence as measured by at least a 1-grade increase on the 4-point Global Eyelash Assessment (GEA) scale, from baseline to the end of the treatment period (week 16). The primary efficacy measurement collected during this study was overall eyelash prominence measured using the Global Eyelash Assessment (GEA) scale with photonumeric guide (1 [minimal], 2 [moderate], 3 [marked], 4 [very marked], corresponding to frontal and superior eyelash views). Secondary efficacy measurements included upper eyelash length, upper eyelash thickness/fullness, and upper eyelash darkness (intensity) based on digital image analysis.

A statistically significantly higher percentage of subjects in the LATISSE® topical solution group (78.1%, 107/137) compared with the vehicle group (18.4%, 26/141) experienced at least a 1-grade increase from baseline in overall eyelash prominence as rated by the GEA scale at week 16 ($p < 0.0001$) (See Table 1). This difference between the 2 treatment groups became pronounced by week 4, with the LATISSE® topical solution group having a higher percentage of subjects with increased eyelash prominence compared with the vehicle group. By week 8, a statistically significant difference in favour of LATISSE® topical solution was detected ($p < 0.0001$) and this difference was maintained throughout the remainder of the treatment and post-treatment periods.

Table 1: Number (%) of subjects with at least a 1-grade increase from baseline in GEA score on the 4-point GEA scale

Visit[a]	LATISSE® N = 137 N (%)	Vehicle N = 141 N (%)	p- value[b]
Week 1	7/137 (5%)	3/137 (2%)	0.2124[c]

Week 4	20/137 (15%)	11/137 (8%)	0.0719
Week 8	69/137 (50%)	21/137 (15%)	<0.0001
Week12	95/137 (69%)	28/137 (20%)	<0.0001
Week 16 (primary endpoint)	107/137 (78%)	26/137 (18%)	<0.0001
Week 20	103/131 (79%)	27/131 (21%)	<0.0001

[a] LOCF performed on weeks 1 to 16 and week 20 analysis was based only on observed cases.
[b] p values are based on Pearson's chi-square test or Fisher's exact test if at least 25% of the cells have expected cell sizes of < 5.
[c] Fisher's exact test was performed.

An additional, more stringent analysis was performed for those subjects who experienced at least a 2-grade increase on the 4-point GEA Scale. By week 12, a statistically significantly higher percentage of subjects in the LATISSE® topical solution group compared with the vehicle group experienced a 2-grade increase from baseline in GEA score. At the end of the treatment period (week 16), 32.8% of subjects in the LATISSE® topical solution group compared with 1.4% of subjects in the vehicle group experienced at least a 2-grade increase from baseline, a difference that was statistically significant ($p < 0.0001$, Table 2). This statistically significant difference was maintained for the 1-month post-treatment period.

Table 2: Number (%) of subjects with at least a 2-grade increase from baseline in GEA score on the 4-point GEA scale: Treatment and post-treatment periods

Visit[a]	LATISSE® (N = 137)	Vehicle (N = 141)	P-value[b]
Week 1	0/137 (0%)	0/141 (0%)	N/A
Week 4	0/137 (0%)	0/141 (0%)	N/A
Week 8	5/137 (4%)	1/141 (1%)	0.1164[c]
Week 12	28/137 (20%)	1/141 (1%)	< 0.0001
Week 16 (primary endpoint)	45/137 (33%)	2/141 (1%)	< 0.0001
Week 20	49/131 (37%)	4/126 (3%)	< 0.0001

[a] LOCF performed on weeks 1 to 16 and week 20 analysis was based only on observed cases.
[b] p values are based on Pearson's chi-square test or Fisher's exact test if at least 25% of the cells have expected cell sizes of < 5.
[c] Fisher's exact test was performed.

In this study, the secondary analysis of the effect of LATISSE® topical solution on the length, thickness and darkness of the eyelashes was measured using digital image analysis. Improvements from baseline in eyelash growth as measured by increased eyelash length, thickness/fullness, and darkness were statistically significantly more pronounced in the LATISSE® topical solution group compared with the vehicle group, starting at week 4 for eyelash length ($p = 0.0006$), week 8 for progressive eyelash thickness/fullness ($p < 0.0001$), and week 8 for eyelash darkness ($p < 0.0001$).

Table 3: Mean change from baseline at week 16

Efficacy endpoint at Week 16 (Mean Change from Baseline)	LATISSE® (N = No. of patients)	Vehicle (N = No. of patients)	p-value[a]
Eyelash growth (length) (mm; % increase)	N=137 1.4; 25%	N=141 0.1; 2%	< 0.0001
Eyelash fullness/thickness (mm^2; % increase)	N=136 0.7; 106%	N=140 0.1; 12%	< 0.0001
Eyelash darkness (intensity*; % increase in darkness)	N=135 -20.2; -18%	N=138 -3.6; -3%	< 0.0001

[a] p–values are based on the Wilcoxon rank-sum test, * a negative value is representative of eyelash darkening

A statistically significant difference between the LATISSE® topical solution and vehicle groups for all three parameters (eyelash length, thickness/fullness, and darkness) was maintained through the 1-month post-treatment follow-up period ($p < 0.0001$ for all).

After the 16-week treatment period, a 4-week post-treatment period followed during which the effects of LATISSE® topical solution started to return toward baseline. The effect on eyelash growth is expected to abate following longer term discontinuation.

5.2 Pharmacokinetic properties

Absorption

Bimatoprost penetrates the human cornea and sclera *in vitro*.

After once daily ocular administration of one drop of 0.03% bimatoprost to both eyes of 15 healthy subjects for two weeks, blood concentrations peaked within 10 minutes after dosing and declined to below the lower limit of detection (0.025 ng/mL) within 1.5 hours after dosing. Mean bimatoprost C_{max} values were similar on days 7 and 14 at 0.0721 and 0.0822 ng/mL respectively. The mean $AUC_{0\text{-}24hr}$ values were also similar on days 7 and 14 at 0.0742 and 0.096ng.hr/mL respectively, indicating that a steady systemic exposure to bimatoprost was reached during the first week of ocular dosing. The systemic exposure of bimatoprost is very low with no accumulation over time.

Distribution

Bimatoprost is moderately distributed into body tissues with a steady state systemic volume of distribution in humans of 0.67 L/kg. In human blood, bimatoprost resides mainly in the plasma. The plasma protein binding of bimatoprost is approximately 90%.

Data from *in vitro* studies showed that the overall extent of melanin binding was not dependent on concentration and the binding was reversible.

Metabolism

Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing in humans. Bimatoprost then undergoes oxidation, N-deethylation and glucuronidation to form a diverse variety of metabolites.

Excretion

Bimatoprost is eliminated primarily by renal excretion. Up to 67% of an intravenous dose of radiolabelled bimatoprost administered to healthy volunteers was excreted in the urine, 25% of the dose was excreted via the faeces. The elimination half-life, determined after intravenous administration, was approximately 45 minutes, the total blood clearance of unchanged bimatoprost was 1.5 L/hr/kg.

After twice daily dosing, the mean $AUC_{0\text{-}24hr}$ value of 0.0634 ng.hr/mL for bimatoprost in the elderly (subjects 65 years or older) was statistically significantly higher than that of 0.0218 ng.hr/mL in young healthy adults, suggesting the existence of an age effect. However, this finding is not clinically relevant as systemic exposure for elderly and young subjects remained very low from ocular dosing. There was no accumulation of bimatoprost in the blood over time and the safety profile was similar in elderly and young patients.

5.3 Preclinical safety data

Ocular administration of bimatoprost in monkeys at concentrations of 0.03% or 0.1% once or twice daily for 6 months to 1 year caused an increase in iris pigmentation and reversible dose-related periocular effects characterised by a prominent upper and/or lower sulcus and widening of the palpebral fissure. No associated increase in melanocyte number was observed with the pigmentation. It appears that the mechanism of increased iris pigmentation is due to increased stimulation of melanin production in melanocytes and not to an increase in melanocyte number.

Periocular effects were also observed in an intravenous toxicity study at systemic exposures at least 235-fold higher than that observed in humans after ocular administration. No functional or microscopic changes related to the periocular effects were observed. The mechanism of action for the observed periocular changes is unknown.

The systemic exposure after dermal application of bimatoprost 0.3 mg/mL on the upper eyelid margin is not expected to exceed that obtained after ocular dosing in humans.

Carcinogenicity

The carcinogenic potential of orally administered (gavage) bimatoprost was evaluated in mice given 0.3, 1.0 or 2.0 mg/kg/day and in rats given 0.1, 0.3 or 1.0 mg/kg/day for 104 weeks. There was no evidence of tumorigenic potential at any of the administered dosages in either species. In the rat carcinogenicity study, a dose-related increase in vacuolated corpora lutea was observed. The ovarian effects in rats is believed to be species specific.

Mutagenicity

Bimatoprost was not mutagenic or clastogenic in a bacterial mutation assay, in a mouse lymphoma test *in vitro* or in a mouse micronucleus test.

6. PHARMACEUTICAL PRECAUTIONSPARTICULARS

6.1 List of excipients

Preservative: benzalkonium chloride
Inactives: dibasic sodium phosphate heptahydrate; citric acid monohydrate; sodium chloride; and purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

6.2 Incompatibilities

Not applicable

6.3 Shelf life:

2 years

6.4 Special precautions for storage

Store below 25°C

To avoid contamination of the solution, keep container tightly closed. Do not touch dropper tip to any surface. Contents are sterile if seal is intact.

6.5 Nature and contents of container

LATISSE® (bimatoprost) 0.3 mg/mL sterile topical solution is supplied in plastic dropper bottles with a plastic screw cap, accompanied by 60 sterile, disposable applicators. Each bottle has a fill volume of 3 mL.

6.6 Special precautions for disposal

Discard contents 4 weeks after opening the bottle.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Allergan New Zealand Ltd,
Cnr Manu Tapu Drive & Joseph Hammond Place,
Auckland International Airport, Mangere
Auckland, NEW ZEALAND
Toll free telephone: 0800 659 912

9. DATE OF FIRST APPROVAL

15 December 2011

10. DATE OF REVISION OF TEXT

June 2018

SUMMARY TABLE OF CHANGE

Sections changed	Summary of new information
All headings amended to align to Medsafe's updated DS requirements and sections within the Data Sheet have been moved under the appropriate headings in line with Medsafe's updated DS requirements.	
Minor editorial changes, including typographical and grammatical amendments, implemented throughout the DS to ensure legibility of this document.	
4.8	Additional Post-marketing Adverse Events have been included under the sub-heading"Skin and subcutaneous tissue disorders", in line with CCDS v11.0. Addition of information relating to "Reporting of suspected adverse reactions" in line with Medsafe's updated DS requirements.
4.9	Addition of information relating to the management of overdose in line with Medsafe's updated DS requirements.
6.1	Excipient names have been amended to align to Medsafe's Product Detail
6.2	Additional information included in line with Medsafe's updated DS requirements.
6.6	Additional information included in line with Medsafe's updated DS requirements.
9	Addition of Date of First Approval of LUMIGAN® eye drops