



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for brimonidine (as tartrate)

Proprietary Product Name: Mirvaso

Sponsor: Galderma Australia Pty Ltd

January 2015

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<http://www.tga.gov.au>>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
AE	adverse event
ASA	Australian specific annex (to the RMP)
AUC	area under the concentration time curve
BA	bioavailability
b.i.d.	twice daily
BP	British Pharmacopeia
BSA	body surface area
CEA	clinician erythema assessment
CER	clinical evaluation report
C _{max}	maximum serum concentration
CNS	central nervous system
COL-118	Previous sponsor development code for brimonidine tartrate
CRC	child-resistant cap
DP	drug product
EP	European pharmacopeia
ER _{AUC}	exposure ratio based on AUC
ER _{local}	exposure ratio based on local dose of brimonidine
ETR	erythematotelangiectatic rosacea
EU	European Union
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IGA	Investigators' global assessment
IOP	intraocular pressure
ISS	integrated summary of safety

Abbreviation	Meaning
ITT	intent-to-treat
LOQ	limit of quantification
LTS	long term safety
MCII	mean cumulative irritancy index
MedDRA	Medical Dictionary for Regulatory Activities
NMT	not more than
NOEL	no observable effect level
OTE	overall treatment effect
PAA	patient assessment of appearance
PAW	patient assessment of whitening
PK	Pharmacokinetic/s
PCS	Pharmaceutical Chemistry Section (of TGA)
PSA	patient self-assessment
PSUR	periodic safety update reports
PT	preferred term
q.d.	once daily (latin: quaque die)
QoL	quality of life
QTc	QT interval corrected for heart rate
QTcB	Bazett-Corrected QT interval
QTcF	Fridericia-corrected QT interval
QTcI	QT interval, individual-based correction factor
RMP	risk management plan
SAE	serious adverse event
SCS	summary of clinical safety
SD	standard deviation
SOC	system organ class

Abbreviation	Meaning
TEAE	treatment-emergent adverse event
TGA	Therapeutic Goods Administration
TeGA	telangiectasia grading assessment
Tmax	time when maximum drug concentration occurs
TTC	threshold of toxicological concern
USA	United States of America
UV	ultra violet

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New Indication, new dosage form, new formulation, new strength
<i>Decision:</i>	Approved
<i>Date of decision:</i>	1 August 2014
<i>Active ingredient:</i>	Brimonidine Tartrate
<i>Product name:</i>	Mirvaso
<i>Sponsor's name and address:</i>	Galderma Australia Pty Ltd PO Box 502 Frenchs Forrest NSW 2086
<i>Dose form:</i>	Gel
<i>Strength:</i>	3.3 mg/g
<i>Container:</i>	Tube
<i>Pack sizes:</i>	2g physician's sample pack, 10g, 30g
<i>Approved therapeutic use:</i>	<i>For the treatment of facial erythema of rosacea in adult patients</i>
<i>Route of administration:</i>	Topical
<i>Dosage:</i>	Once daily application. Further details regarding dosage are provided in the PI (attachment 1)
<i>ARTG number:</i>	212325

Product background

Rosacea is one of the most common chronic dermatological diseases. It is classified into 4 different subtypes: erythematotelangiectatic rosacea (ETR) (subtype 1), papulopustular rosacea (subtype 2), phymatous rosacea (subtype 3), ocular rosacea (subtype 4), and the variant granulomatous rosacea. The most defining characteristic of the disease for both subtypes 1 and 2 is the presence of persistent erythema of the central portion of the face lasting for at least 3 months (Crawford 2004).

The pathophysiology of rosacea is poorly understood and may be multifactorial, involving abnormal vascular reactivity, immune system responses, and follicular microorganisms (Crawford 2004¹, Nally 2006², Pelle 2008³, Wolf 2005⁴).

¹ Crawford GH et al., Rosacea: I. Etiology, pathogenesis, and subtype classification. *J Am Acad Dermatol.* 2004;51:327-41.

² Nally JB, and Berson DS. Topical therapies for rosacea. *J Drugs Dermatol.* 2006;5:23-6.

³ Pelle MT. Rosacea. In Wolff K, et al, editors: *Fitzpatrick's Dermatology in General Medicine, 7th Ed.* McGraw-Hill. 2008:704-9.

⁴ Wolf JE Jr. Present and future rosacea therapy. *Cutis.* 2005;75:4-7.

The currently available pharmaceutical treatments for rosacea primarily target subtype 2 of the disease, reducing rosacea lesions through anti-inflammatory/antiparasitic mechanisms. There are currently no approved pharmaceutical agents that directly target the persistent facial erythema of rosacea common to both subtype 1 and 2. Treatments that stabilize the contractile state of the cutaneous facial blood vessels are expected to have the most beneficial effect in addressing this unmet need.

Brimonidine tartrate is a selective α_2 -adrenoceptor agonist that is 1000 fold more selective for the α_2 -adrenoceptor than the α_1 -adrenoceptor (Burke 1996⁵). The α_2 -adrenoceptor plays a role in the vasoconstriction of cutaneous arteries (Chotani, 2000⁶). Brimonidine tartrate, as a α_2 -adrenoceptor agonist applied directly to the face, is anticipated to have a subcutaneous vasoconstrictive effect, thereby reducing facial erythema in rosacea patients.

Brimonidine tartrate (0.15%) and brimonidine (0.2%) are currently registered in eye drops formulations for the treatment of glaucoma.

Currently there are no products registered in Australia for acne rosacea and no gel products containing brimonidine tartrate.

This AusPAR describes the application by Galderma Australia Pty Ltd (the sponsor) to register Mirvaso gel containing brimonidine (as tartrate) 3.3 mg/g for the following indication:

Mirvaso is indicated for the treatment of facial erythema of rosacea in adult patients.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 4 August 2014.

At the time the TGA considered this application, a similar application had been approved in the USA (23 August 2013); European Union (EU) (21 February 2014); Canada (26 February 2014); Chile, (9 December 2013) Mexico (31 January 2014); and Puerto Rico (15 October 2013) and was under consideration in 5 additional countries.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

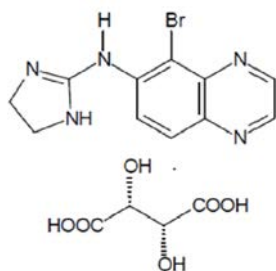
II. Quality findings

Introduction

The structure of brimonidine tartrate is shown in Figure 1. The proposed product is a solution of brimonidine tartrate in a water based gel at a concentration of 5 mg/mL (0.5 % w/w). However in line with best practice the product will be labelled in terms of the active brimonidine: 3.3 mg/g (0.33 % w/w).

⁵ Burke J, Schwartz M. Preclinical evaluation of brimonidine. *Surv Ophthalmol.* 1996;41:S9-18.

⁶ Chotani, MA et al., Silent α_2 -adrenergic receptors enable cold-induced vasoconstriction in cutaneous arteries. *Am. J. Physiol. Heart Circ. Physiol.* 2000;278:1075-83

Figure 1. Chemical structure of brimonidine tartrate.

Drug substance (active ingredient)

A European Pharmacopoeia (EP) monograph for brimonidine tartrate will come into effect on 1 July 2014 and the material will meet these requirements. There is also an additional test for residual solvents with limits that meet International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) requirements. However lower limits are required for two of the impurities (see *First round recommendation*, below).

Drug product

The product contains no unusual excipients for this dosage form: water is used as the base, and the other components include a gelling agent; preservatives; humectants; an opacifier; and sodium hydroxide to adjust pH.

Manufacture is typical for a topical formulation and involves the dissolution and suspension of the active and excipients to form a homogeneous gel before filling into tubes. The 10 g and 30 g presentations are closed with a child resistant polypropylene closure.

There are no compendial monographs for the product, but the specifications for the product ensure the British Pharmacopoeia (BP)/EP general requirements for gels are met. The expiry limits for the chemistry and physical tests are mostly acceptable and justified, and, where required, the release limits are tighter than the expiry limits to allow for change on storage. However, the proposed limits for two of the three specified impurities are unacceptable (see *First round recommendation*, below).

Biopharmaceutics

This product is for topical use and is intended to act without systemic absorption. As a consequence no bioavailability (BA) data were required to be submitted.

Consideration by the Pharmaceutical Subcommittee of ACPM (PSC)

As there were no issues relating to BA, details of this submission have not been presented to PSC.

First round recommendation

Following the first round evaluation approval of the registration of the proposed product could not be recommended on quality / safety grounds because:

- The proposed expiry limit for two impurities is above the threshold of toxicological concern (TTC)⁷ and the Toxicology section of TGA has advised that as these impurities are potentially genotoxic and no data were provided to demonstrate they are not genotoxic, the proposed expiry limit is unacceptable.
- However, the sensitivity of the test method is insufficient to determine the actual levels of these impurities in the gel and whether the recommended expiry limit is met.
- As a consequence of this advice the release limit for the two impurities is also unacceptable. Given that the levels increase on storage, the release limit must be lowered.
- Finally, the limits for the two impurities in the drug substance specifications must also be lowered.

If this issue could be resolved approval could be recommended.

Second round evaluation and recommendation

In response to the first round recommendation, the sponsor proposed to the TGA that in accordance with ICH guideline M7, the initially requested limit for potentially genotoxic impurities would pose negligible risk over long term use (< 10 years) and that these limits had been approved in other jurisdictions, that the initially requested limit for potentially genotoxic impurities stand for 4 months after which time the sponsor will have developed a test method sensitive enough to determine the levels of these impurities in batches of the product over the life time of the product.

After this time the sponsor would submit a variation application to the TGA to change the test method and to tighten the expiry limit for these impurities.

The sponsor estimated that following such a path would mean that patients could theoretically be administered product containing the initially requested level of each of these impurities for a maximum of 10 months and that this was substantially below the TTC. The advice of the Toxicology section is that this would be acceptable for short duration use (< 3 years).

Given the toxicological advice, the Pharmaceutical Chemistry Section (PCS) can in principal agree to the proposal, however it would be very preferable that the lower expiry limit be adopted now, not in four months.

The PCS recommends that it should be made a condition of registration that the company submit a variation application within 4 months (company estimate) with the improved test method and appropriate release limits for these impurities, and, limits for these impurities in the drug substance specifications.

III. Nonclinical findings

Pharmacology

Primary pharmacology

No animal data were provided to support the proposed indication. There are no widely used animal models for rosacea. A mouse model for rosacea has been used previously

⁷ The TTC represents a dose for which a genotoxic impurity is considered to pose negligible carcinogenic risk.

(Yamasaki et al., 2007⁸; Zhang et al., 2011⁹), but the validity of this model is unknown. Assessment of the efficacy of brimonidine tartrate gel for the proposed indication needs to rely solely on clinical data.

Pharmacokinetics

The plasma kinetics of brimonidine following dermal administration of brimonidine tartrate gel was assessed in rats, minipigs and human subjects. There were no consistent or significant sex differences in systemic exposure in any species. On Day 1, brimonidine was detectable in the plasma of most treated animals at the first sampling point (0.5 to 1 hours); suggesting brimonidine is readily absorbed from the skin. However, time when maximum drug concentration occurs (T_{max}) values were highly variable in rats (1 to 12 hours) and systemic exposure was fairly constant in minipigs over a 24 hour period, suggesting prolonged absorption. Systemic exposure (plasma area under the concentration time curve (AUC)) was generally dose proportional in rats but this should be considered in the context of high inter individual variability.

Rats showed significantly higher systemic exposure following dermal application compared to either minipigs or humans at equivalent mg/kg doses (approximately 20 times higher than in minipigs and approximately 6 times higher than in humans using data for approximately 1 mg/kg doses in animals and the maximum recommended clinical dose in humans). Due to similarities in skin structure and physiology, minipigs are considered a more predictive model of dermal absorption than rats (reviewed in Poet et al., 2002¹⁰; and Bode et al., 2010¹¹). In rats, systemic exposures were lower on Day 1 than on subsequent days, but aside from this, there was no evidence of systemic accumulation.

Accumulation in the skin was not assessed. No studies assessed the effect of co administered dermal products (including cosmetics or sunscreens), or damaged skin, on the systemic absorption of brimonidine.

Systemic exposure to brimonidine in patients treated with Mirvaso gel is comparable to that with use of existing brimonidine tartrate containing eye drop products.

Toxicology

Repeat dose toxicity

Repeat dose toxicity studies by the dermal route were conducted in hairless mice (up to 13 weeks), rats (up to 57 weeks) and minipigs (up to 39 weeks). The choice of species for the pivotal studies (rats and minipigs) is considered appropriate; minipigs are good animal models to assess dermal toxicity. The duration of the pivotal studies is considered acceptable considering the possible chronic use of Mirvaso. The 13 week mouse study was conducted as a dose ranging study prior to conducting a photocarcinogenicity study. As such, examinations were restricted to gross signs of toxicity, while the photocarcinogenicity study focussed primarily on dermal tumour formation. Daily dermal exposure was for the entire 24 hour period in all studies except for the pivotal study in minipigs where the treated area was washed after 6 hours (except on toxicokinetic days).

⁸ Yamasaki K et al., Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. *Nat. Med.* 2007;13: 975–980.

⁹ Zhang J et al., Novel sulfated polysaccharides disrupt cathelicidins, inhibit RAGE and reduce cutaneous inflammation in a mouse model of rosacea. *PLoS ONE* 2011; 6: 16658.

¹⁰ Poet TS and McDougal JN. Skin absorption and human risk assessment. *Chem. Biol. Interactions* 2002; 140:19–34.

¹¹ Bode G et al., The utility of the minipig as an animal model in regulatory toxicology. *J. Pharmacol. Toxicol. Methods* 2010;62:196–220.

Dosing in the mouse study was once daily (q.d.) for 4 or 5 days/week. Both pivotal studies included a water control as well as a vehicle control group.

Two studies compared the dermal toxicity of gel and cream formulations of brimonidine tartrate (in rats and minipigs; 13 weeks duration); these studies are only discussed with reference to local reactions.

The concentration of brimonidine tartrate in the formulations used in the animal studies spanned that to be used clinically (0.18 to 2% compared to 0.5% in the clinical formulation) and the dosing area (relative to body surface area (BSA)) was larger than that expected clinically (10 to 20% BSA compared to approximately 3% BSA clinically).

Relative exposure

Exposure ratios have been calculated based on animal: human plasma AUC values (for consideration of systemic effects) and animal: human doses per unit treatment area (for consideration of local effects). Relative systemic exposures achieved in rats were very high (see Table 1) and the maximum tolerated dose was clearly achieved in mice and rats. Systemic exposures in minipigs were similar to the clinical AUC. Substantial multiples of the clinical local dose (on a $\mu\text{g}/\text{cm}^2$ basis) were obtained in most studies/species at the highest doses tested, although local doses in male rats in the pivotal repeat dose toxicity study and the carcinogenicity study were less than or only a modest multiple of the clinical local dose. Overall, the doses/concentrations used in the toxicity studies are considered appropriate.

Table 1: Relative exposure in repeat dose toxicity and carcinogenicity studies.

Species	Study & duration	Dose mg/kg/day	Local dose $\mu\text{g}/\text{cm}^2$ ^b	AUC _{0-24h} ng·h/mL	Exposure ratio		
					Local	Systemic	
Mouse (CrI:SKH1- <i>hr</i> ; [hairless])	RDS.03.SRE.12627 [13 weeks]	6	7.2	–	0.72	–	
		33	40	–	4	–	
		66	80	–	8	–	
		133	160	–	16	–	
	RDS.03.SRE.12629 [carcinogenicity]	6	7.2	–	0.72	–	
		33	40	–	4	–	
66		80	–	8	–		
Rat (Wistar Han)	RDS.03.SRE.12648 [13 weeks]	5.4	16.2	353	1.6	847	
		30	90	2455	9	5887	
		60	180	2405	18	5767	
	RDS.03.SRE.12626 [57 weeks]	M/ F ^d	1.08/5.4	3.24/16.2	42.6/208	0.3/1.6	102/499
			6/30	18/90	145/964	1.8/9	348/2312
			12/60	36/180	507/2440	3.6/18	1216/5851

Species	Study & duration	Dose mg/kg/day	Local dose µg/cm ^{2b}	AUC _{0-24h} ng·h/mL	Exposure ratio		
					Local	Systemic	
	RDS.03.SPR.12667 [carcinogenicity]	M/ F	0.9/5.4	2.7/1.62	22.5/294	0.3/1. 6	54/705
			1.8/10.8	5.4/32.4	74.6/407	0.5/3. 2	179/976
			5.4/21.6	16.2/64.8	215/1070	1.6/6. 5	516/2566
Minipig (Göttingen)	RDS.03.SRE.12694 [39 weeks]	1.2	42	0.453 ^c	4	1.1	
		3.6	126	0.348 ^c	13	0.83	
		20	700	1.35 ^c	70	3.2	
Human	steady state	[5 mg/day] ^a	10	0.417	–	–	

- 1 g of a 0.5% gel;
- based on treatment areas of 25 cm² in mice and 500 cm² in humans, 20% BSA in rats and 10% BSA in minipigs, and calculated using mg/kg to mg/m² BSA conversion factors of 6 and 35 for rats and minipigs, respectively
- reported AUC_{0-24h} values have been divided by 4 as animals were exposed for 6 h/day only, and the rate of exposure was fairly constant
- M = male, F = female

Systemic toxicity

Deaths were seen at high doses in mice (≥ 66 mg/kg/day) and rats (60 mg/kg/day). Systemic exposure in rats at this dose is > 5800 times the clinical AUC; toxicokinetic data were not obtained in mice. A cause of death was only identified in one case, but the mortality is considered to be drug related. Various systemic clinical signs were observed in mice and rats that received topical dermal applications of brimonidine tartrate gel, and these can largely be attributed to the pharmacological action of brimonidine; sedation and hypo activity, hypersensitivity to touch and hyper reactivity, bradypnoea and tachypnoea and distended abdomen (Angelov et al., 1996a¹²). The no observable effect level (NOEL) for these clinical signs was 6 mg/kg/day for mice and 1.08 mg/kg/day for rats in the pivotal study (exposure ratio based on AUC (ER_{AUC}), approximately 100).

No consistent target organs for toxicity were identified during post mortem analyses. Increased severity of lymphoid depletion was seen in the thymus of treated rats (12 mg/kg/day in males and 60 mg/kg/day in females; ER_{AUC} at the NOEL is > 340). An increased incidence of brown tubular pigment was seen in the kidney of female rats that received ≥ 30 mg/kg/day brimonidine tartrate (ER_{AUC} at the NOEL, approximately 500). The identity of the pigment was not determined but there was no accompanying renal toxicity. There were no signs of systemic toxicity in minipigs (ER_{AUC} at the highest tested dose, approximately 3).

Based on the large exposure margins at the NOELs for systemic effects, none of these findings are predicted to be of relevance in patients with clinical use as directed. Additionally, there is some margin in the event of increased exposure due to co administered ocular products, damaged skin or inadvertent (small levels of) ingestion.

¹² Angelov OV *et al.*, Preclinical safety profile of brimonidine. *Eur. J. Ophthalmol.* 1996a;6:21–25.

However, if significant levels of the gel are ingested, there is a risk for clinical signs of toxicity (for example sedation).

Recommended revisions to warnings related to over dosage with ingestion in the draft PI and CMI are beyond the scope of the AusPAR.

Local dermal effects

Local changes at application sites included a transient reduction in skinfold thickness in mice (at strengths $\geq 0.18\%$; exposure ratio based on local dose of brimonidine (ER_{local}) 0.72), an increased severity of epidermal hyperplasia/hyperkeratosis and hypertrophy/hyperplasia of the sebaceous glands in male rats (at $\geq 0.2\%$; ER_{local} , 24) (in one study only and the severity was, at the most, mild) and greater erythema in minipigs (principally at $\geq 1\%$; ER_{local} , 35). Overall, local skin reactions during clinical use are predicted to be minimal.

Genotoxicity

No new studies assessing the genotoxic potential of brimonidine were submitted. Snyder and Green (2001)¹³ reported that negative results were obtained for brimonidine in assays for mutagenicity (bacterial mutation assay and a dominant lethal test) and clastogenicity (in vitro chromosomal aberration assay and an in vivo micronucleus assay). A positive result for mutagenicity in one *Salmonella typhimurium* strain in the absence of metabolic activation is reported for the drug in the approved Australian PI documents for Alphagan and Combigan (eye drop products containing brimonidine). The weight of evidence supports that brimonidine does not pose a genotoxic hazard.

Potentially genotoxic impurities in the proposed drug product (DP) require appropriate control (see *Impurities* section below).

Carcinogenicity

Carcinogenicity studies consisted of a standard 2 year study in rats and a 40 week photo carcinogenicity study in hairless mice. The dermal route was used in both studies. The choice of species and scope of studies are considered acceptable given the historical use of brimonidine and the expected use of the product on sun exposed skin. The conduct of the studies was as expected according to the relevant EU guidelines. Local exposure ratios were reasonable in mice and female rats but relatively low in male rats (only 1.6 times the clinical local exposure at the highest tested dose). The low local dose in male rats is not considered to compromise the interpretation of the results, given the reasonable exposures in females, and noting also the lack of overall genotoxic concern and the absence of drug related dermal pre neoplastic lesions in the general repeat dose toxicity studies at high local doses in rats and minipigs. Systemic exposures in rats far exceeded the clinical exposure (AUC). Potential systemic carcinogenicity was not assessed in the mouse study.

Brimonidine tartrate gel did not enhance or promote skin tumour formation in mice in the presence of ultra violet (UV) light. There were no tumours either local or systemic in rats that could be attributed to treatment with brimonidine tartrate gel.

Published data indicated there was no evidence of a drug related increase in tumour incidence in mice treated orally with 2.5 mg/kg/day brimonidine for 21 months or rats treated orally with 1 mg/kg/day brimonidine for 2 years (Angelov et al., 1996a). These studies are described in the approved Australian PI documents for Alphagan and Combigan.

¹³ Snyder RD and Green JW. A review of the genotoxicity of marketed pharmaceuticals. *Mutat. Res.* 2001;488:151-169.

Brimonidine tartrate is not considered to pose a carcinogenic hazard to patients.

Reproductive toxicity

No new reproductive toxicity studies were submitted. The clinical systemic exposure following dermal application of brimonidine tartrate gel is similar to that obtained from currently registered brimonidine tartrate eye drop formulations and, when used as directed, similar risks for reproductive toxicity associated with brimonidine exist with both dose forms. The sponsor provided an abstract (with minimal detail) describing the reproductive and developmental toxicity studies with brimonidine tartrate conducted by Allergan Inc (Angelov et al, 1996b¹⁴). It is likely that these studies were evaluated in the application by Allergan Australia Pty Ltd to register Alphagan and are the same studies referred to in the PI documents for Alphagan and Alphagan P. The doses in the abstract likely refer to brimonidine tartrate salt, while the doses in the Alphagan P PI document refer to the base.

Pregnancy classification

The sponsor has proposed Pregnancy Category B1¹⁵. This is the current pregnancy category for the registered product, Alphagan eyedrops (containing 2 mg/mL brimonidine tartrate). However, the subsequently registered Alphagan P eyedrops product containing 0.15% brimonidine tartrate, has been assigned Category B3¹⁶. Findings of post implantation loss and embryotoxicity in brimonidine treated rats and rabbits (albeit at maternotoxic doses) described in the PI documents support Category B3 as the appropriate category, and not B1.

Local tolerance

Brimonidine tartrate gel was not phototoxic when applied dermally to hairless mice, and was not considered an ocular irritant in rabbits or a skin sensitiser in guinea pigs.

Paediatric use

Mirvaso is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Impurities

The sponsor has proposed release and expiry limits for two potentially genotoxic impurities in the DP that result in doses that exceed the threshold of TTC value of 1.5 µg per day without appropriate justification. These limits are not acceptable. Support for registration of Mirvaso gel is conditional on the limits for these impurities being reduced.

¹⁴ Angelov O et al, Reproductive and developmental safety studies with brimonidine. *Invest. Ophthalmol. Visual Sci.* 1996b;S1101

¹⁵ *Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.*

¹⁶ *Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.*

Nonclinical summary

- The scope of nonclinical studies submitted is considered appropriate for this type of application and the conduct of the studies was generally acceptable.
- No nonclinical efficacy studies were submitted to support the proposed indication. Use is rationalised by the drug's vasoconstrictor activity (α_2 -adrenoceptor mediated).
- The drug was readily absorbed following dermal administration of gel in rats, minipigs and humans. Plasma concentration time profiles were highly variable in rats and systemic exposure at equivalent mg/kg doses was significantly higher in this species than in minipigs or humans. Systemic levels were fairly constant over time in minipigs, though, and this species is considered a better model for dermal absorption in humans. There was no evidence of systemic accumulation. Accumulation in the skin was not assessed. No studies assessed the effect of co administered dermal products (including cosmetics or sunscreens), or damaged skin, on the systemic absorption of brimonidine.
- Repeat dose toxicity studies by the dermal route were conducted in hairless mice (up to 13 weeks), rats (up to 57 weeks) and minipigs (up to 39 weeks). Systemic clinical signs were observed at very high exposure levels in mice and rats, and these can largely be attributed to the pharmacological action of brimonidine (such as sedation and bradypnoea). No signs of systemic toxicity were observed in rats at an exposure margin of approximately 100, nor in minipigs up to the highest dose tested (exposure margin of around 3).
- Local dermal reactions were minimal to mild at clinically-relevant concentrations. Greater erythema was seen in minipigs at $\geq 1\%$.
- Brimonidine returned overall negative results for genotoxicity. Two genotoxic impurities require appropriate control.
- In a dermal carcinogenicity study, there were no tumours (either local or systemic) in rats that could be attributed to brimonidine tartrate gel. Brimonidine tartrate gel did not enhance or promote skin tumour formation on hairless mice in the presence of UV light. The drug batches used in these studies did not contain detectable levels of two genotoxic impurities proposed to be specified in the DP; consequently, the studies are unable to support that the impurities do not pose a carcinogenic risk to patients.
- No new reproductive toxicity studies were submitted. Existing data have shown some adverse effects on embryofetal development in rats and rabbits.
- Brimonidine tartrate gel was not phototoxic when applied dermally to hairless mice, and was not considered an ocular irritant in rabbits or a skin sensitiser in guinea pigs.

Conclusions and recommendation

- Support for efficacy in the proposed indication relies on clinical data only.
- The toxicity studies indicate a large safety margin for systemic effects. Therefore, there is some margin in the event of increased exposure due to co administered ocular products, damaged skin or inadvertent (small levels of) ingestion. However, if significant levels of the gel are ingested, there is a risk for clinical signs of toxicity (for example, sedation), warranting appropriate warnings.
- Local skin reactions during clinical use are predicted to be minimal.
- Brimonidine tartrate itself is not considered to pose a genotoxic or carcinogenic hazard to patients.

- Based on the anticipated systemic exposure, the risks for reproductive toxicity are expected to be similar to those with registered brimonidine containing eye drop products. The product should be placed in Pregnancy Category B3 (rather than B1 as the sponsor proposes).
- There are no objections on nonclinical grounds to the registration of Mirvaso gel for the proposed indication provided that two potentially genotoxic impurities are controlled to at or below the TTC value of 1.5 µg/day. Currently proposed limits for these impurities are considered to pose an unacceptable carcinogenic risk to patients.
- The nonclinical evaluator also recommended amendments to the draft PI document. Details of these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Brimonidine is a highly selective α_2 -adrenoceptor agonist that is 1000 fold more selective for the α_2 -adrenergic receptor than the α_1 -adrenergic receptor. Topical facial application of a highly selective α_2 -adrenoceptor agonist reduces erythema through direct cutaneous vasoconstriction.

The submission proposes registration of Mirvaso 0.5% gel for the proposed indication:

Mirvaso is indicated for the treatment of facial erythema of rosacea.

Clinical rationale

Rosacea is one of the most common chronic dermatological diseases, with reports suggesting prevalence between 2% to 10% in both Europe and the United States (Berg 1989¹⁷, Kyriakis 2005¹⁸, Powell 2005¹⁹, van Zuuren 2005²⁰). While there is a disproportionately higher frequency of occurrence in fair-skinned people of European and Celtic origin, it also occurs less frequently in other mixed populations (Kyriakis 2005, Powell 2005, van Zuuren 2005). Onset typically occurs between 30 to 50 years of age, and while women are more commonly affected than men, disease manifestations, especially rhinophyma, are frequently more severe in males than in females (Crawford 2004, Powell 2005, van Zuuren 2007²¹). Because the facial skin is the predominant site of involvement, many patients sense that the disease alters their social and professional interactions, leading to problems in the workplace, in relationships, and in other social interactions (Crawford 2004).

An expert committee assembled by the National Rosacea Society in April 2002 (Wilkin 2002²²) explicitly defined and classified rosacea into 4 different subtypes based upon specific clinical signs and symptoms: ETR (subtype 1), papulopustular rosacea (subtype 2), phymatous rosacea (subtype 3), ocular rosacea (subtype 4), and the variant granulomatous rosacea. Perhaps the most defining characteristic of the disease for both

¹⁷ Berg M and Liden S. An epidemiological study of rosacea. *Acta Derm Venereol.* 1989;69:419-23.

¹⁸ Kyriakis KP et al., Epidemiologic aspects of rosacea. *J Am Acad Dermatol.* 2005;53:918-9.

¹⁹ Powell FC. Rosacea. *N Engl J Med.* 2005;352:793-803.

²⁰ van Zuuren EJ et al., Interventions for rosacea. *Cochrane Database System Rev.* 2005;3:CD003262.

²¹ van Zuuren EJ et al., Systematic review of rosacea treatments. *J Am Acad Dermatol.* 2007;56:107-15.

²² Wilkin J et al., Standard classification of rosacea: Report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. *J Am Acad Dermatol.* 2002;46:584-7.

subtypes 1 and 2 is the presence of persistent erythema of the central portion of the face lasting for at least 3 months (Crawford 2004).

The pathophysiology of rosacea is poorly understood and may be multifactorial, involving abnormal vascular reactivity, immune system responses, and follicular microorganisms (Crawford 2004, Nally 2006, Pelle 2008, Wolf 2005). Many of the most cited pathogenic theories on the aetiology of the persistent facial erythema of rosacea focus on abnormalities in cutaneous vascular homeostasis, or vasomotor instability, the term commonly used to refer to abnormal involuntary dilatation and reactivity of small subcutaneous resistance arteries. The aetiology of vasomotor instability in patients with rosacea is unknown (Crawford 2004, Kyriakis 2005).

Currently, there are no approved pharmaceutical agents in the US or EU that directly target the persistent facial erythema of rosacea. Current pharmaceutical treatments for rosacea available on the US and EU market primarily target the papulopustular rosacea subtype of the disease, reducing rosacea inflammatory lesions through anti-inflammatory/antiparasitic mechanisms. Topical metronidazole targets the papulopustular stage of rosacea, although certain brand products in the US and EU include “erythema” or “acute inflammatory” or “rosacea” statement in the indication²³, it is important to note that topical metronidazole products primarily focus on the papulopustular aspect of the disease, targeting the inflammatory lesion component through anti-inflammatory mechanisms. Metronidazole has no known vasoconstrictive activity, thus, any reduction in general facial erythema, which is not well documented to date, is likely due to focal reductions in transient peri lesional erythema, secondary to the anti-inflammatory action, rather than a true reduction in the persistent generalized erythema of rosacea that is vascular in origin.

Some reported effectiveness of non-pharmaceutical/mechanical treatments for rosacea has been documented in the literature with use of both vascular lasers and intense pulsed light emitters (Pelle 2004, Adamic 2007²⁴). There are no large, well-controlled trials to fully substantiate a claim for the reduction of the persistent facial erythema of rosacea with these devices. In general, these procedures have not gained wide-acceptance as a standard of care for rosacea, which may be in part due to their lack of accessibility and/or availability (for example, they can only be performed by a qualified physician, in an office setting, with multiple treatments often required) and high financial costs to patients (Pelle 2004).

The persistent erythema of rosacea, common to both subtype 1 and 2, represents an unmet medical need that is not adequately addressed by currently approved pharmaceutical treatments, and no products have specifically demonstrated reduction in persistent facial erythema to date. Based on the current etiological theories, treatments that stabilize the contractile state of the cutaneous facial blood vessels are expected to have the most beneficial effect in addressing this unmet need. Brimonidine tartrate is a potent and highly selective α_2 -adrenoceptor agonist that is approximately 1000 fold more selective for the α_2 -adrenoceptor than the α_1 -adrenoceptor (Burke 1996). In consideration of the subcutaneous vasoconstrictive activity of brimonidine tartrate, it was expected to offer a positive effect on reducing cutaneous erythema caused by vasomotor instability through direct cutaneous vasoconstriction and the sponsors have investigated

²³ Noritate 1% Cream (US) is indicated for the topical treatment of inflammatory lesions and erythema of rosacea; Metrogel 0.75% (UK) is indicated for the treatment of acute inflammatory exacerbation of rosacea; Zyomet Gel 0.75% (UK) is indicated for the treatment of acute inflammatory exacerbations of acne rosacea; Rozex cream or gel 0.75% (broad EU brand) is indicated in the treatment of inflammatory papules, pustules and erythema of rosacea; Metronidazole Actavis 1% cream (EU Nordic countries) is indicated for rosacea.

²⁴ Adamic M et al., Vascular lasers and IPLS: guidelines for care from the European Society for Laser Dermatology (ESLD). *J Cosmet Laser Ther.* 2007;9:113–24.

Brimonidine Tartrate 0.5% Gel for topical treatment of facial erythema of rosacea in adults.

Contents of the clinical dossier

Scope of the clinical dossier

The submission contained the following clinical information:

The clinical development program for brimonidine tartrate gel included a total of 18 clinical trials conducted in adult subjects. A total of 10 of the 18 clinical trials were conducted in subjects with rosacea, and brimonidine tartrate 0.5% gel (the proposed to be marketed concentration) was evaluated in 6 of the 10 studies in subjects with rosacea. Brimonidine tartrate 0.5% gel was also evaluated in 4 studies in healthy subjects. These studies were as follows:

- Thirteen clinical pharmacology studies, including 3 that provided pharmacokinetic (PK) data and 11 that provided pharmacodynamics data.
- Two pivotal efficacy/safety studies; 18140 and 18141.
- 3 dose finding studies; ROSE 201, 18144 and 18161.
- A long term efficacy and safety study, 18142.

The dossier also included pooled analyses, meta analyses, Periodic Safety Update Reports (PSURs), Integrated Summary of Efficacy, and Integrated Summary of Safety.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

All studies were conducted in accordance with the ICH E6 Guideline for Good Clinical Practice, the ethical principles originating from the Declaration of Helsinki revised version and local regulatory requirements.

Pharmacokinetics

Studies providing PK data

Table 2 shows the studies relating to each PK topic.

Table 2: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	Primary aim of the study
PK in healthy adults	General PK Single dose	COL-118-BAPK-101	Relative BA of 0.2% Mirvaso gel compared to 0.2% brimonidine ophthalmic solution
PK in special populations	Target population	RD.06.SRE.18126	Relative BA of 0.18% Mirvaso gel and 0.2% brimonidine ophthalmic solution under conditions of maximum use.
		RD.06.SRE.18143	PK of Mirvaso gel (0.07%, 0.18%, and 0.5%) after 4 weeks treatment compared to PK of brimonidine tartrate ophthalmic solution 0.2% after 1 day.

None of the PK studies had deficiencies that excluded their results from consideration.

Evaluator's summary and conclusions on pharmacokinetics

- Mirvaso is a topical aqueous gel, which is absorbed through the epidermis.
- The absolute BA of Mirvaso gel is unknown.
- Dermal BA of 0.18% Mirvaso gel compared to the ophthalmic solution (100 pg/mL) was less than 3%.
- In the target population, quantifiable plasma levels of brimonidine were detected in samples from 74% of the patients following a single application of 0.5% Mirvaso gel and the calculated mean maximum serum concentration (C_{max}) and AUC_{0-24 h} values for brimonidine were 19.44 pg/mL and 262.11 pg.h/mL, respectively.
- Following administration of the 0.18% formulation q.d., plasma levels of brimonidine could only be detected in 32% of treated subjects and the calculated C_{max} and AUC values reported were 13.07 pg/mL and 72.3 pg.h/mL, respectively.
- Following a single administrations of Mirvaso gel containing 0.18% or 0.5% brimonidine the C_{max} of brimonidine increased less than dose-proportionally (ratio = 1.49), whereas, AUC increased greater than dose proportionally (ratio = 3.63).
- Following 29 days of q.d. dosing with formulations of Mirvaso gel containing 0.18% and 0.5% brimonidine a similar pattern was seen and the C_{max} and AUC for the higher dose was 1.35 fold and 3.49 fold higher, respectively, than following the 0.18% dose.
- Following 15 days of treatment with either 0.5% q.d. or 0.18% twice daily (b.i.d.) exposure to brimonidine increased. However, after 29 days of treatment there was little to no drug accumulation and steady state conditions were achieved.
- Following 29 days administration of either the 0.18% facial gel b.i.d. or the 0.5% dose formulation q.d. the C_{max} values were similar (ratio 0.5% q.d./0.18% b.i.d. = 1.07), whereas the AUC was approximately 33% for the 0.5% q.d. dose.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 3 shows the studies relating to pharmacodynamics (PD).

Table 3: Submitted pharmacodynamics studies.

PD Topic	Subtopic	Study ID	Primary aim of the study
Primary Pharmacology	Single-dose	COL-118-ROSE-101	Dose-response, tolerability and duration of effect
		RD.06.SRE.18144	PD profiles of three different concentrations
		COL-118-ROSE-102	Impact of formulation on the PD profile
	Multiple-dose	COL-118-ROSE-201	PD profiles of three different concentrations
Secondary Pharmacology	Effect on QTc ^a	RD.06.SRE.18139	Thorough QT
	Phototoxicity	COL-118-Phototoxicity-104	Phototoxicity of 0.2% gel
		RD.06.SRE.18189	Phototoxicity of 0.07%, 0.18%, and 0.50% gel
		RD.06.SRE.18124	Photosensitisation potential of 0.07%, 0.18%, and 0.50% gel
	Tolerability	RD.06.SRE.18123	Sensitisation and local tolerability of 0.07%, 0.18%, and 0.5% gel
		RD.06.SRE.18125	Cumulative irritancy following repeated dosing with 0.07%, 0.18%, and 0.5% gel

- a. QT interval corrected for heart rate (QTc). The QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death. The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval QTc is often calculated. The standard clinical correction is to use Bazett's formula, named after physiologist Henry Cuthbert Bazett.

Evaluator's conclusions on pharmacodynamics

Brimonidine tartrate is a highly selective α_2 -adrenoceptor agonist with potent vasoconstrictive/ vasostabilising activity.

Primary pharmacodynamics in target population

Single administration

- Fifteen minutes following administration of 0.0125%, 0.025%, 0.10% or 0.20% Mirvaso gel, chromameter values had significantly decreased ($p \leq 0.019$).

- By 2 hours post dose, statistically significant decreases were observed for all Mirvaso gel concentrations, with mean decreases of 1.6, 2.1, 3.0, 3.1 and 4.5 at 0.0125%, 0.025%, 0.05%, 0.1% and 0.2%, respectively.
- Statistically significant decreases continued through 5 hours with all Mirvaso concentrations, and through 8 hours, the last evaluated time point, with 0.05%, 0.1% and 0.2%.
- The magnitude of the change appeared to be dose related.
- Based on the criterion of 1 grade improvement on clinician erythema assessment (CEA) and patient self-assessment (PSA), the response rates were 83.9% (0.50% Mirvaso gel), 80.6% (0.18%), 75% (0.07%) and 28.1% (vehicle).
- The median times to onset of 1 grade improvement on CEA and PSA were 2.98 hours (0.50% Mirvaso gel), 2.08 hours (0.18%) and 2.03 hours (0.07%) post dose.
- Comparisons of the response curves were statistically significant ($p < 0.05$) for the individual CEA and PSA responses in the 0.50% and 0.18% groups. For the combined CEA and PSA, the comparisons of time to 1 grade improvement were significant ($p < 0.05$) for each active group versus vehicle.
- The median duration of effect was more than 7 hours in each of the Mirvaso gel groups and approximately 3 hours in vehicle group.
- For 2 grade improvement on combined CEA and PSA, the response rates were 54.8% (0.50% Mirvaso gel), 32.3% (0.18%), 25% (0.07%) and 12.5% (vehicle).
- The median time to onset of 2 grade improvement was 10.03 hours after dosing for the 0.50% group.
- The median duration of effect was approximately 6 hours in the 0.50% group and 3 to 4 hours in the remaining groups.
- The mean number of time points with CEA ≤ 1 ranged from 0.7 in the vehicle group to 5.0 in the 0.50% group. The mean number of time points with CEA and PSA ≤ 1 ranged from 0.5 in the vehicle group to 2.8 in the 0.50% group.
- Significant reductions in chromameter results were identified for Mirvaso gel (0.50%, 0.18% and 0.07%) versus vehicle gel and 0.50% showed statistically significant reductions versus the 0.18% and 0.07% treatment groups.

Multiple-administrations

- Following administration of 0.18% Mirvaso gel there was a significant improvement in erythema based on the subjective scales of PSA and CEAs up to 8 hours following dosing.
- Following application of 3 concentrations (0.02%, 0.07% and 0.20% Mirvaso gel, no more often than once every 4 hours and no more than 3 times per day for 28 days, the reduction in erythema across all time points (0 to 8 hours) and all visits (Day 0, Day 14, and Day 28), showed a clear dose response relationship as did the reduction in investigator's global assessment (IGA).
- Both the 0.2% and 0.07% dose groups displayed significantly greater changes from baseline than the vehicle group ($p < 0.001$ and $p < 0.05$, respectively).
- In the Day 28 responder analysis, with success defined as an IGA score of 0 or 1 or an improvement of at least 2 points, the differences among the treatment groups were statistically significant at hours 1 through 4 ($p < 0.05$, Mantel-Haenszel Chi-Square statistics). At hour 3, 37.5% of patients in the 0.2% group, 13.6% in the 0.07% group, 15.0% in the 0.02% group and 0% in the vehicle group were successes.

- Telangiectasia and total inflammatory lesion count neither improved nor worsened following treatment.
- Peak efficacy was significantly higher in the 0.2% group than in the vehicle group on Days 0, 14, and 28 when represented by the greatest change from baseline in CEA and on Day 28 when represented by the greatest change from baseline in IGA.
- An onset of effect was seen as early as 15 minutes after study drug application and the duration of effect was about 5 hours.

Secondary pharmacodynamic effects

- Brimonidine does not prolong the QTc interval compared to placebo.
- Overall Mirvaso gel did not possess detectable phototoxicity potential in human skin.
- There was no apparent correlation between increasing concentrations Mirvaso gel and the appearance or intensity of topical erythema/irritation.
- Each active test concentration, the gel vehicle and the white petrolatum produced no reaction in 95% to 96% of test sites on any given evaluation day, mild erythema in 4% to 5% of test sites on any given evaluation day, and only isolated instances of moderate erythema and/or erythema with vesicles or erosion or bullae.
- There were no confirmed cases of contact sensitisation for any of the Mirvaso concentrations, including the vehicle gel.
- Based on the mean cumulative irritancy index (MCII), test sites patched with the higher concentrations of Mirvaso gel (0.5% and 0.18%) exhibited slightly less irritation (MCII = 0.01) than the weakest concentration (0.07%)(MCII = 0.02) and gel vehicle (MCII = 0.02).
- The three concentrations of Mirvaso gel and the gel vehicle produced slightly less irritation than the negative control (MCII = 0.03) and markedly less irritation than the positive control (MCII = 1.69).
- No studies examined race, genetic, gender and age related differences in pharmacodynamic response.
- No studies examined the pharmacodynamic interactions between Mirvaso gel and other drugs.

Dosage selection for the pivotal studies

Table 4 contains a summary of the clinical studies providing data for the dose selection used in the pivotal studies.

Table 4: Summary of relevant clinical studies contributing to dose selection.

Study Number	Study Design	Number of subjects Gender Mean age	Doses and treatment duration	Results
18144	Randomised, double blind, parallel group, vehicle controlled, multicentre, dose finding study.	122 subjects 30 male, 92 female 45.7 years	Brimonidine tartrate (0.5%, 0.18%, 0.07%) gel or vehicle gel Single dose.	Brimonidine tartrate gel was found to be effective in the treatment of facial erythema of rosacea. The effect was superior to vehicle gel and consistently dose dependent with the highest concentration (0.5%) being the most effective. Safety and tolerability were good and comparable between the groups treated the brimonidine tartrate gel and vehicle gel.
18161	Randomised, double blind, parallel group, vehicle controlled, multicentre, efficacy and safety study.	269 subjects 52 male, 217 female 44.3 years	Brimonidine tartrate (0.5% q.d., 0.18% q.d. or b.i.d.) gel or vehicle gel (q.d. or b.i.d.).	Brimonidine tartrate 0.5% gel was statistically superior to vehicle gel for the primary endpoint. No evidence of tachyphylaxis was observed. All brimonidine tartrate gel concentrations/regimens were well-tolerated with an acceptable safety profile during the treatment and follow up phases.
ROSE-201	Outpatient, randomised, double blind, vehicle controlled, parallel group, multicentre study.	110 subjects 27 male 83 female 47.6 years	Brimonidine tartrate 0.2%, 0.07%, 0.02% or vehicle gel Applied each morning and as needed thereafter but no more than once every 4 hours and no more than 3 times per day for 28 days.	This previous study provided supportive data on the efficacy of brimonidine tartrate gel in the treatment of erythema of rosacea. However the interpretation was limited as brimonidine tartrate 0.5% gel was not used and the endpoints evaluated were different to those used in the pivotal studies.

Based on the Phase IIb study results and additional data from previous studies, brimonidine tartrate 0.5% gel applied once daily was an appropriate concentration and dose regimen selected for the Phase III program.

Efficacy

Studies providing efficacy data

Pivotal efficacy studies

- Study 18140, was, a Phase III multicentre, randomised, double blind, parallel group, vehicle controlled pivotal study. The main objective of the study was to demonstrate the efficacy of brimonidine tartrate 0.5% gel, applied topically q.d. for 4 weeks versus vehicle control, in the treatment of moderate to severe facial erythema associated with rosacea.
- Study 18141, was also a Phase III multicentre, randomised, double blind, parallel group vehicle control study. The study design and objectives were identical to those for Study 18140.

Other efficacy studies

- Study 18194, a CEA scale, single centre study, was an independent study conducted by the sponsor to evaluate the inter-rater and intra-rater reliability of the final version of the CEA scale for assessment of the severity of persistent facial erythema in subjects with rosacea. Study subjects were not treated with brimonidine tartrate gel in this study.
- Long term Study 18142 was a Phase III, multicentre, open label, non comparative 52 week study which evaluated the long term safety and efficacy of brimonidine tartrate 0.5% gel applied q.d. in 449 patients with moderate to severe facial erythema of rosacea. Efficacy assessment was a secondary objective of this study. The efficacy measurements included the PSA, CEA, patient assessment of appearance (PAA), and overall treatment effect (OTE).

Evaluator's conclusions on efficacy

Brimonidine tartrate 0.5% gel, applied topically q.d., was selected as the optimal concentration and dose regimen for Phase III because the single (18144) and multiple (18161) dose finding studies had demonstrated that brimonidine tartrate 0.5% gel showed the best potential for achieving the desired treatment objectives of reducing facial erythema in the greatest number of subjects. That is, brimonidine tartrate 0.5% gel q.d. provides significant effectiveness without significant over extended effects, while maintaining a high safety margin with respect to systemic exposure. The treatment objective for the product was to maintain, on a daily basis, at least a 1 grade improvement (that is, a noticeable effect) in CEA and/or PSA for a maximal amount of time (target of 12 hours after dosing), while being able to achieve daily 2 grade improvement in both assessments for a sustained period (Table 5).

Table 5: Summary of relevant clinical studies contributing to dose selection.

Study Number	Study Design	Number of subjects Gender Mean Age	Doses and Treatment Duration	Results
Subjects with Rosacea				
RD.06.SRE.18144	Randomized, double-blind, parallel-group, vehicle-controlled, multicenter, dose-finding study	122 subjects 30M, 92F 45.7 years	Brimonidine Tartrate Gel (0.5%, 0.18%, 0.07%) Gel or Vehicle Gel Single dose	Brimonidine Tartrate Gel was found to be effective in the treatment of facial erythema of rosacea. The effect was superior to Vehicle Gel and consistently dose-dependent with the highest concentration (0.5%) being the most effective. Safety and tolerability were good and comparable between the groups treated with Brimonidine Tartrate Gel and Vehicle Gel.
RD.06.SRE.18161	Randomized, double-blind, parallel-group, vehicle-controlled, multicenter, efficacy and safety study	269 subjects 52M, 217F 44.3 years	Brimonidine Tartrate Gel (0.5%, 0.18% QD or BID) Gel or Vehicle Gel (QD or BID) 29 days	Brimonidine Tartrate 0.5% gel was statistically superior to Vehicle Gel for the primary endpoint. No evidence of tachyphylaxis was observed. All Brimonidine Tartrate Gel concentrations/regimens were well-tolerated with an acceptable safety profile during the treatment and follow-up phases.
RD.06.SRE.18143	Intra-individual, double-blind, randomized, multicenter, comparative, maximal use PK study	102 subjects 40M, 62F 41.6 years	Day 1: 1 drop of brimonidine tartrate 0.2% ophthalmic solution instilled in each eye every 8 hours over a 24-hour period Days 2-3: washout Days 4 to 32 (29 days): Topical administration of Brimonidine Tartrate Gel (0.07% BID, 0.18% QD or BID, and 0.5% QD). For the BID groups, the second application of Brimonidine Tartrate Gel was 6 hours after the first dose	Systemic bioavailability of Brimonidine Tartrate 0.5% Gel administered topically QD for 29 days was lower in comparison to ophthalmic instillation of brimonidine tartrate 0.2% ophthalmic solution administered for a single day (3 times at 8 hour intervals over a 24-hour period)

The two Phase III pivotal studies (18140 and 18141) were designed and conducted as adequate and well controlled trials that satisfied the criteria outlined in the relevant ICH Guidelines and USA Title 21 Code of Federal Regulations Part 314.126. The Phase III pivotal studies were designed in consideration of input from both USA and EU Regulatory Authorities.

The patients included in these pivotal studies were representative of the target patient population for the proposed brimonidine 0.5% gel topical treatment; the majority of the patients were female (75 to 79%), White (98%) with moderate facial erythema (85 to 88% had CEA and PSA scores > 3 at baseline).

The primary endpoint of 2 grade composite success was a composite endpoint based on analyses of independent static evaluations of erythema by the investigators (CEA) and the subjects (PSA). The final version of the PSA that was used in the Phase IIb and Phase III studies was developed and validated in accordance with the 2009 Food and Drug Administration (FDA) USA Guidance titled "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labelling Claims." The Phase IIb study (18161) provided evidence of the appropriateness and sensitivity of the primary endpoint within a 29 day treatment period, in consideration of the anticipated design of the subsequent Phase III pivotal studies, and evaluated the same primary endpoint as the subsequent Phase III pivotal studies.

The 2 grade composite success rate for the brimonidine tartrate 0.5% gel group was statistically significant and clinically meaningful compared to the vehicle gel group at each time point (Days 1, 15, and 29). Two (2) grade composite success ranged from 18.9% to 32.1% on Day 29 compared to the vehicle gel control (3.6% to 7.3%) at Hours 3, 6, 9, and 12. The Phase III pivotal studies met the predefined primary endpoint of 2 grade composite success, demonstrating the superiority of brimonidine tartrate 0.5% gel compared to vehicle gel in reduction of facial erythema in subjects with rosacea. The brimonidine tartrate 0.5% gel q.d. dose regimen showed robust efficacy when compared to the vehicle q.d. regimen, as demonstrated by the analyses of 2 grade composite success over Hours 3, 6, 9 and 12. Because the treatment effect was significant at Day 29 ($p < 0.001$), the successive earlier time points were tested (Day 15 and Day 1), which also showed statistically significant and clinically relevant improvement in erythema of rosacea starting from the first day of treatment.

A statistically significant ($p < 0.001$) rapid onset of action was also demonstrated for the secondary endpoint (30 minute effect) in the Phase III pivotal studies, which was 1 grade improvement on both the CEA and PSA 30 minutes after the first dose on Day 1.

Brimonidine tartrate 0.5% gel was superior to vehicle gel at initiating the onset of a meaningful clinical effect on erythema as assessed independently by the investigator and by the subject within 30 minutes after the very first dose. In each study, approximately 28% of subjects in the brimonidine tartrate 0.5% gel group showed 1 grade improvement on both the CEA and PSA at 30 minutes post dosing on Day 1, compared to 6.9% of vehicle gel subjects in Study 18140 and 4.8% of vehicle gel subjects in Study 18141. The odds of achieving 1 grade composite success on both the CEA and PSA 30 minutes after the first dose on Day 1 were 5 times higher in Study 18140 and 7 times higher in Study 18141 in the brimonidine tartrate 0.5% gel groups relative to the vehicle gel groups.

Both the 2 grade composite success and 30 minute effect in the intent to treat (ITT) populations for the Phase III pivotal studies were confirmed by per protocol (PP) population analyses and sensitivity analyses of success and failure for both studies.

The endpoint of 1 grade composite success (1 grade improvement on both CEA and PSA) was a secondary endpoint in Study 18161 and a tertiary endpoint in the Phase III pivotal studies (18140 and 18141). The endpoint of 1 grade composite success is an apparent and distinguishable improvement from the baseline condition as assessed independently by the investigator and by the subject within the 12 hour post dosing period. Given that each scale is a 5 point scale, a 1 grade change can be considered relevant (for example, severe to moderate or moderate to mild).

The odds of achieving 2 grade and 1 grade composite success in the brimonidine tartrate 0.5% group on Day 29 were 3 to 4 times higher compared to the vehicle gel groups in the pivotal studies (18140 and 18141).

Each of the Phase III pivotal studies demonstrated that the positive effect of brimonidine tartrate 0.5% gel on reducing facial erythema was sustained during the treatment day. On Days 1, 15, and 29, at each of the 4 time points in Studies 18140 and 18141, brimonidine tartrate 0.5% gel showed a consistent and clinically meaningful reduction in erythema. The observed effect tended to be strongest at Hours 3 and 6, and although smaller at Hour 12, was still present. Over the course of each 12 hour measurement period, a single dose of brimonidine tartrate 0.5% gel generally provided at least a 1 grade improvement, as measured by composite success (CEA and PSA combined), CEA Success, and PSA success; this effect was maintained for a maximal amount of time (12 hours) in a majority of subjects.

The use of brimonidine tartrate gel in the treatment of erythema of rosacea did not result in exacerbation of other signs of rosacea (inflammatory lesions and telangiectasia) or unintended effects such as subjects perceiving an overextended pharmacodynamic effect due to the vasoconstrictive effect of the drug (over whitening). In addition, quality of life (QoL) assessments were included. No worsening of lesions was observed in the Phase IIb or Phase III pivotal studies in the brimonidine tartrate 0.5% gel groups relative to the corresponding vehicle gel groups in any of the studies. In addition, no worsening of mean telangiectasia grading assessment (TeGA) scores was observed in the brimonidine tartrate 0.5% gel groups during the studies. As reduction in vascular erythema is the primary effect of brimonidine tartrate 0.5% gel, the drug is not expected to reduce the incidence or severity of inflammatory lesions of rosacea. Although the drug could potentially reduce the transient perilesional erythema of papulopustular lesions of rosacea, thus making them temporarily less visible, this was not specifically investigated by the applicant.

The Phase IIb and the Phase III pivotal studies demonstrated that subjects perceived improvements on both clinic and non clinic days in their erythema and overall facial appearance, and showed minimal unwanted over whitening effects, as measured by the PSA, PAA, and patient assessment of whitening (PAW), respectively. Some subjects in the brimonidine tartrate 0.5% gel q.d. group reported being bothered by unwanted over whitening in each study. There is evidence to suggest that skill in treatment application

technique (smooth, even application across all facial surfaces), which generally improves over time in subjects, may reduce any noticeable contrast between treated and untreated areas, and thus may contribute to the reductions in reports of unwanted over whitening from Day 1 to Day 29 in the brimonidine tartrate 0.5% gel groups in each study. The incidence of unwanted over whitening was similar in the brimonidine tartrate 0.5% and vehicle gel groups by Day 29. Furthermore, no subjects discontinued any of the studies due to any effects of over whitening.

The long term, open label, uncontrolled Study 18142 demonstrated that treatment with brimonidine tartrate 0.5% gel for up to 1 year resulted in reduction in facial erythema in the target patient population, which was clinically meaningful in terms of investigator and subject assessments. The observed efficacy data confirmed the known short term effectiveness of brimonidine tartrate 0.5% gel and also suggested a positive impact on the long term psychosocial function of rosacea. However, interpretation was limited by the open label, uncontrolled nature of the study.

No evidence of tachyphylaxis of the treatment effect was observed in the 29 day vehicle controlled studies or in the 1 year long term study. Furthermore, during the follow up period in the 4 vehicle controlled studies that evaluated potential erythema rebound effect (Studies ROSE-201, 18161, 18140, and 18141), no rebound effect was observed.

The main limitations of the submission regarding demonstration of efficacy were lack of evaluation in patients aged < 18 years of age and lack of a long term, controlled, double blind study (to provide evidence of efficacy beyond 29 days).

Safety

Studies providing safety data

Overall, 18 clinical studies were performed in the program and the safety of brimonidine tartrate gel was assessed in each of the studies; 10 of the 18 studies were conducted in subjects with rosacea and 8 studies were conducted in healthy subjects.

Five safety populations were defined for analysis of safety.

1. Core Studies: Four studies in subjects with rosacea including 2 identically designed double blind, randomised pivotal clinical trials (18140 and 18141), the 4 week double blind, randomised Study 18161 and the 52 week open label, uncontrolled Study 18142.
2. Dose ranging studies population: This included 5 studies in rosacea subjects with each study analysed separately (COL-118-ROSE-101, COL-118-ROSE-102, COL-118-ROSE-201, 18144 and 18161).
3. Dermal safety studies population: This included 6 studies in healthy subjects with each study analysed separately (COL-118-104, 18189, 18123, 18124, 18125 and 18137).
4. PK studies population included 4 studies with each study analysed separately (COL-118-BAPK-101, 18126, 18143 and 18139).
5. Open label, long term safety (LTS) and efficacy Study 18142.

The safety monitoring of brimonidine tartrate gel for each study was performed by collecting treatment emergent adverse events (TEAEs) and routine laboratory data, physical examination, and vital signs and, in some studies, intraocular pressure (IOP) measurements. The Medical Dictionary for Regulatory Activities (MedDRA) classification system by System Organ Class (SOC) and Preferred Term (PT) was employed where appropriate. Regardless of the dictionary version used to code adverse events (AEs) at the

study level, all AEs in the pooled summary of clinical safety (SCS) and the integrated summary of safety (ISS) database were coded/re coded using the MedDRA version 11.0 to ensure consistency.

Patient exposure

There were 1619 subjects who were exposed to brimonidine tartrate active gels out of 2174 participants in the 18 studies in the clinical development program. Of the 1619 subjects, 1210 subjects were exposed to brimonidine tartrate 0.5% gel q.d.

Eight (8) studies of the gel formulation were conducted in healthy subjects; 423 healthy subjects were exposed to active gel formulations (0.07% gel, 0.18% gel, 0.20% gel or 0.50% gel) and 432 subjects received vehicle gel applications.

Nine clinical studies, excluding the LTS study, were conducted in subjects with rosacea; 747 rosacea subjects were exposed to active gel formulations (0.02% gel, 0.07% gel, 0.1% gel, 0.18% gel, 0.20% gel and 0.50% gel) and 462 rosacea subjects received vehicle gel applications. In addition, 120 subjects in Studies 18126 and 18143 were treated with the 0.2% ophthalmic solution.

In the 2 Phase III, well controlled, efficacy and safety studies (18140 and 18141), 277 subjects were exposed to 0.50% gel q.d. If the 53 subjects from the Phase IIb, vehicle controlled, efficacy and safety Study 18161 treated with the 0.50% gel are included in this sum, a total of 330 rosacea subjects received 0.50% gel q.d. under controlled conditions for a 29 day treatment period, which is the concentration and regimen selected for the proposed marketed product.

In the LTS and efficacy Study 18142, a total of 449 subjects were to be exposed to 0.50% gel q.d. up to 365 days; 276 of these subjects were exposed for \geq 365 days. Exposure to brimonidine tartrate gel in all clinical studies are summarised in Table 32 of the CER (see attachment 2).

In the short term studies in rosacea subjects, the average number of treatment days for subjects treated with the 0.50% gel or the vehicle was approximately 26 days. The mean number of treatment days for subjects who received 0.50% gel or vehicle in the controlled core studies was approximately 29 days (that is 28.6 days), while the mean treatment duration of the LTS study was approximately 278 days. The mean daily treatment use for subjects who received 0.50% gel q.d. in Studies.18161, 18140, and 18141 was 0.8 g. In the LTS study, the mean daily treatment use was 0.5 g.

Safety issues with the potential for major regulatory impact

Liver toxicity

None.

Haematological toxicity

None.

Serious skin reactions

There were no serious adverse events (SAEs) related to skin and subcutaneous tissue, although they were the most commonly reported TEAEs (most of these were mild to moderate in severity).

Cardiovascular safety

None.

Unwanted immunological events

Sensitisation to any of the components of the brimonidine tartrate gel was assessed in 12 studies, possible sensitisation reactions were reported in only 2 of these (18123 and 18142). For identification of sensitisation reactions, no specific clinical threshold criteria were predefined.

Sensitization responses could only be determined by an experienced evaluator who was a board certified dermatologist.

In Study 18123, the sensitisation potential of various concentrations of the study drug and vehicle showed no evidence of sensitisation except in 1 subject who exhibited positive sensitisation results at challenge with the 0.07% gel and the vehicle gel. Response was equivocal at re challenge and the subject was unavailable for a second re challenge.

In the long term Study 18142, 24 subjects (5.3%) developed adverse reactions that the investigators considered suspicious enough to require patch testing in order to rule out an allergic sensitisation to the study product (allergic dermatitis). Of these 24 subjects, 17 agreed to undergo diagnostic patch testing and 14 of these subjects had a negative patch test result suggesting no allergy to the study drug, and 3 subjects had a positive patch test result. Of the 3 positive cases, 1 was confirmed as a reaction to brimonidine tartrate, a second was confirmed as a reaction to the phenoxyethanol preservative, and the third was not conclusively confirmed (subject refused further patch testing).

No phototoxicity was observed in Study COL-118-Phototoxicity-104. In Study 18189, 1 subject exhibited contact irritation, not photosensitisation. In photosensitisation Study 18124, no photosensitivity or photo irritancy was observed. A suspected, related, mild "photosensitisation" was reported in 1 subject in Study COL-118-ROSE-201.

Evaluators comments: The rate of sensitisation for the 1619 subjects exposed to brimonidine tartrate gel is estimated at < 1% across the entire clinical development program. This estimate is based upon a conservative calculation, including the 3 subjects with initially positive patch tests in Study 18142, the 7 subjects who refused rechallenge/patch testing in Study 18142, and the 1 subject with suspected but unconfirmed sensitisation in Study 18123.

Evaluator's conclusions on safety

A total of 1619 of the 2174 subjects in the clinical development program were exposed to brimonidine tartrate gel. Of these, 1210 subjects were exposed to the proposed marketing formulation (brimonidine tartrate 0.5% gel) in 10 studies: 377 healthy subjects in 4 studies and 833 subjects with rosacea in 6 studies.

Analysis of TEAEs both overall and those considered related to study drug by the investigator in the dose range finding studies exhibited no dose relationship, were infrequent, mild or moderate in severity, and did not result in discontinuation. Analysis of TEAEs in the dermal safety studies confirmed the safety and local tolerability of brimonidine tartrate topical gels: no phototoxicity, photosensitivity, or irritancy potential and low sensitisation potential were seen in healthy subjects. There was no clear dose relationship and no correlation between TEAEs and plasma concentrations seen in the PK studies performed under maximised conditions of clinical use. The incidences of TEAEs in the controlled core studies were generally equivalent between active gel and vehicle groups (approximately 30% in each group).

The TEAEs considered related to the study drug predominated in the skin and subcutaneous tissue disorders SOC in the controlled core studies, as expected for a topical gel. Flushing, in the SOC vascular disorders, was also more frequently reported in the active gel group. These treatment related local TEAEs, were mostly mild to moderate in severity and transient in duration. Many of these local rosacea related TEAEs were

reported later in the day, consistent with the effect of the study drug wearing off. The vasoconstriction effect of brimonidine tartrate 0.5% gel does diminish several hours after daily application, allowing for progression back towards baseline erythema levels late in the day.

With respect to the LTS study, TEAEs occurred at similar frequencies during the first 29 days when compared to both active and vehicle controlled core study groups. Most TEAEs occurred during that first month and markedly decreased at the second quarter (that is 90 days to 180 days after the first dose). Systemic TEAEs were infrequent and rarely related to study treatment. In particular, treatment related cardiac, metabolic, respiratory, or gastrointestinal disorders were not reported during the first 29 days of the LTS study. As with the controlled core study subjects who received active medication, skin and subcutaneous tissue disorders predominated in the LTS study. Headache incidence was low (3.3% overall; 1.8% treatment related) and did not increase over time. In the LTS study, a minimal, acceptable sensitisation rate (1% to 2.2%) was observed in rosacea subjects exposed to the active gel over 1 year. The presence of inflammatory lesions and the use of concomitant rosacea medications in LTS study subjects did not have a clinically relevant relationship to the incidence of AEs or the seriousness/severity of AEs, overall or related to the study drug. In addition, there were no signals observed from the vital signs or laboratory data collected in this study. The incidence of related AEs and premature discontinuations due to AEs did not increase over time with long term use of the study drug and there was no evidence that long term use of the study drug conveyed an increased risk of occurrence of any specific type of AE.

Across the 18 studies in the development program, SAEs were few and not related to brimonidine tartrate 0.5% gel. One SAE related to study drug, hypotension, was reported in a subject who received 0.2% brimonidine tartrate ophthalmic solution prior to topical treatment (RD.06.SRE.18143). Seven (7) SAEs related to the study drug were reported in 2 children who ingested the 0.50% gel assigned to their mother. The remaining SAEs were systemic events.

Discontinuations due to treatment related TEAE were rare, mostly associated with rosacea pathophysiology, and mainly mild to moderate in severity. Severe TEAEs were also infrequent, and often not related to study drug.

There were no notable, clinically meaningful differences in TEAE incidences with respect to gender, age, or race in the context of subgroup analyses performed on data from the core studies and the full duration of the LTS study. When stratified by age, according to the applicant's data, subjects 65 years of age and older had a similar or lower incidence of TEAEs when compared to those seen in the 18 to 64 years of age group. Those subjects in the older age group reporting TEAEs considered related to the study drug were few. No TEAEs in the geriatric age group were serious, severe, or resulted in study discontinuation.

There were no clinically important effects on laboratory parameters, IOP or vital signs and physical findings seen in any of the 18 studies in the clinical development program. The minor shifts of laboratory parameters or vital signs outside the normal ranges were rare and did not present a safety signal.

Brimonidine tartrate gel showed a good safety profile in the subjects with moderate to severe facial erythema of rosacea enrolled in the dose finding studies. Overall TEAEs and those related to study drug exhibited no dose relationship, were infrequent, generally mild and of short duration, not severe, and did not result in discontinuation. The most common treatment related TEAEs included pruritus, flushing, skin burning sensation, and skin warm, there is no clear dose relationship and no correlation between TEAEs and plasma concentrations in these PK studies, as seen in Study 18143.

In the dermal safety studies, brimonidine tartrate gel is well tolerated locally, with little incidence of application site irritation or treatment related TEAEs observed following

application under patch occlusion. There was only 1 unconfirmed allergic sensitisation in 1 subject out of a total of 407 subjects who were tested under patch occlusion in the dermal safety studies (that is excluding subjects from RD.06.SRE.18137, who were not tested under occlusion).

There was only one death reported in the clinical studies (lung cancer in LTS Study 18142). There were no SAEs reported in the SOC of skin and subcutaneous tissue disorders, cardiac disorders, or nervous system disorders, the SOC with the highest frequencies of TEAEs in the clinical studies of brimonidine tartrate 0.5% gel. Furthermore, no SAE was found to be related to brimonidine tartrate gel in any study subject in any SOC in any of the 18 studies comprising the clinical development program. Two children accidentally ingested the 0.50% gel assigned to their mother in RD.06.SRE.18140²⁵.

TEAEs resulting in discontinuation from any study that were related to treatment with brimonidine tartrate 0.5% gel were typically reports of events common to rosacea (for example, erythema, flushing), which were mild or moderate in intensity and eventually resolved. Other TEAEs that resulted in discontinuation included: skin burning sensation, skin irritation, contact dermatitis, and allergic dermatitis. All of these TEAEs occurred at less than 2% in the LTS study and rarely in the other studies.

In the pivotal short term studies (18140 and 18141), concomitant use of other treatments for rosacea was not permitted (the only topical medications used were emollients and protective). However, concomitant medications for rosacea were permitted in the LT, open label study 18142. In this LTS study, subjects using brimonidine tartrate 0.50% gel concomitantly with other medications for the treatment of rosacea do not appear to be at increased risk for serious, severe, or systemic AEs. There does not appear to be a potentiation or additive effect with respect to AEs above the normal AE profiles anticipated for each drug individually.

Although specific drug interaction studies have not been conducted with brimonidine tartrate gel, the possibility of an additive or potentiating effect with central nervous system (CNS) depressants (alcohol, barbiturates, opiates, sedatives, or anaesthetics) should be considered. No data on the level of circulating catecholamines after brimonidine tartrate gel administration are available. However, caution is advised in patients taking medications that can affect the metabolism and uptake of circulating amines (for example; chlorpromazine, methylphenidate, and reserpine). α -Adrenoceptor agonists should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, thromboangiitis obliterans, scleroderma, or Sjögren's syndrome.

First round benefit-risk assessment

First round assessment of benefits

The benefits of brimonidine tartrate 0.5% gel in the proposed usage are:

- Statistically significant and clinically relevant improvements in facial erythema in adult patients with rosacea, confirmed by the primary endpoint of 2 grade composite success (which was a composite endpoint based on analyses of independent static evaluations of erythema by the investigators (CEA) and the subjects (PSA)).
- Brimonidine tartrate 0.5% gel was significantly better than vehicle gel at initiating the onset of a meaningful clinical effect within 30 minutes after the very first application of study drug and this effect was sustained for up to 12 hours post dose.

²⁵ Sponsor comment: As a result of this, Galderma subsequently designed a Child-Resistant Cap (CRC) for the 10g and 30g tube presentations only. Product in Australia will be supplied with the CRC.

- No evidence of tachyphylaxis of the treatment effect was observed in the 29 day vehicle controlled studies or in the 1 year long term study.
- No rebound effect was observed.
- Brimonidine tartrate 0.5% gel consistently showed a more favourable outcome in PAA and OTE compared to vehicle gel.
- The low incidence of severe local TEAEs confirms that brimonidine tartrate 0.50% gel is safe and well tolerated in the target population.
- Long term treatment (for up to 52 weeks) of subjects with once daily application of brimonidine tartrate 0.5% gel resulted in no new major safety findings or signals, and the safety profile determined during shorter pivotal studies was confirmed. However, interpretation was limited by the open label, uncontrolled study design.

First round assessment of risks

The risks of brimonidine tartrate 0.5% gel in the proposed usage are:

- Rosacea related AEs such as erythema and flushing were most common following treatment with brimonidine tartrate 0.5% gel; however, most of these AEs were mild to moderate in severity and were usually reported later in the day, consistent with the effect of the drug wearing off.
- Unwanted over whitening effects, although there was a reduction in reports of over whitening with continued use, and there was a similar incidence of over whitening between brimonidine tartrate 0.5% gel and vehicle gel treatment groups by Day 29.
- Lack of any drug interaction studies with other medications used in treatment of rosacea in the pivotal short term studies. However, data from the LTS, open label, uncontrolled Study 18142, showed that subjects using brimonidine tartrate 0.50% gel concomitantly with other medications for the treatment of rosacea does not appear to be at increased risk for serious, severe, or systemic AEs.
- Lack of controlled efficacy and safety data beyond 4 weeks.

First round assessment of benefit-risk balance

The PK, efficacy, and safety profile of brimonidine tartrate 0.5% gel was adequately evaluated in adult subjects with erythema of rosacea in a total of 18 clinical trials, including two adequate and well controlled Phase III studies. A total of 1619 of the 2174 subjects in the clinical development program were exposed to brimonidine tartrate gel, with 1210 of the 1619 subjects exposed to proposed marketing formulation of brimonidine tartrate 0.5% gel q.d.

Treatment with brimonidine tartrate 0.5% gel q.d. in vehicle controlled studies for 29 days resulted in statistically significant and clinically meaningful reductions in facial erythema of rosacea, as independently observed by the investigators and the subjects. Furthermore, this onset of effect was rapid (30 minutes after the first dose of study drug on Day 1 in many cases) and was observable and statistically significant relative to subjects who received vehicle gel. This rapid onset of action provides an advantage for proposed brimonidine tartrate gel as the other marketed pharmaceutical treatments for rosacea that target inflammatory lesions require 8 weeks or more of continuous therapy to achieve significant effectiveness on reduction of lesions. Thus, brimonidine tartrate 0.5% gel offers a direct effect on facial erythema of rosacea that is not provided by current pharmaceutical treatments for rosacea and also offers fast onset of effect on reduction in facial erythema of rosacea.

Brimonidine tartrate 0.5% gel was able to maintain, on a daily basis, at least a 1 grade improvement (that is, a noticeable effect) in CEA and/or PSA for a maximal amount of time (target of 12 hours after dosing), while being able to achieve daily 2 grade improvement in both assessments for a sustained period.

The Phase IIb and the Phase III pivotal studies demonstrated that subjects perceived improvements on both clinic and non clinic days in their erythema and overall facial appearance, as measured by the PSA and PAA. The PAW subject self-assessment also showed that few subjects with over whitening were bothered by the effect and, additionally, that the percentage of subjects who were bothered by over whitening decreased over time, which may be due to better application technique with time. Brimonidine tartrate gel should be applied smoothly and evenly across all application areas. A small pea size amount (estimated to be no more than 1 g in total weight) of brimonidine tartrate gel should be applied to each of the five areas of the face (that is, forehead, chin, nose, each cheek) and these facts have been adequately covered in the proposed PI.

No clinically meaningful worsening of lesions was observed in any of the Phase IIb or Phase III pivotal studies in the brimonidine tartrate 0.5% gel groups relative to the corresponding vehicle gel groups. In addition, no worsening of mean TeGA scores was observed during the studies. As, reduction in vascular erythema (that is, vasoconstriction) is the primary target of brimonidine tartrate 0.5% gel, the drug is not expected to reduce the incidence or severity of inflammatory lesions of rosacea.

No clinically meaningful trends with respect to tachyphylaxis or rebound effects (worsening of baseline erythema after cessation of treatment) were observed with use of brimonidine tartrate 0.5% gel for 29 days.

In the long term, open label, 1 year safety and efficacy study, reductions in facial erythema were maintained over the study duration, showing durability of treatment effect with chronic use and a potential for positive impact on the long term psychosocial function of rosacea subjects; however, interpretation was limited by the open label, uncontrolled study design.

The safety of brimonidine tartrate gel in humans was evaluated in 1210 subjects who were exposed to brimonidine tartrate 0.5% gel. The 1 year open label study (18142) provided approximately 345 subject-years of exposure. The subject populations in the applicant's studies were representative of target patient population.

The most commonly reported related TEAEs in subjects treated with brimonidine tartrate 0.5% gel in the controlled core studies were erythema, pruritus, skin burning sensation, and flushing which occurred in 1.2% to 3.3% of subjects. They were usually transient, mild to moderate in severity, and usually did not require discontinuation of treatment. Furthermore, most of these AEs were mild to moderate in severity and were usually reported later in the day consistent with the effect of the drug wearing off.

Clinical local tolerance studies that evaluated brimonidine tartrate 0.5% gel showed no detectable phototoxicity or photosensitisation potential, low contact sensitisation potential, and low cumulative irritancy potential for the active formulations and for the vehicle. This was consistent with the results of the nonclinical local tolerance studies. Furthermore, no cases of allergic dermatitis were reported in rosacea subjects with up to 4 weeks of treatment across all Phase II and Phase III clinical studies. In the 1 year open label study in 449 subjects with rosacea, 17 subjects were patch tested for possible allergic dermatitis. Of these, 3 were confirmed positive and 14 were negative. Seven additional cases of possible allergic dermatitis were reported, but no patch testing was performed for confirmation. All of these events occurred after 4 weeks of exposure, with the onset between 3 and 6 months in the majority of these subjects.

Routine blood chemistry, haematology, and urinalysis were performed in Studies 18143, 18140, 18141, and 18142. No clinically relevant changes in blood chemistry, haematology, or urinalysis were observed for subjects who received brimonidine tartrate gel.

Treatment with brimonidine tartrate 0.5% gel showed reductions in facial erythema that were both statistically significant and clinically meaningful, with a rapid onset of effect in many cases (30 minutes after the first dose on Day 1). Brimonidine tartrate 0.5% gel has been shown to be safe and well tolerated, as evidenced in the data from the development program for brimonidine tartrate 0.5% gel. Furthermore, the long term, open label study showed no attenuation of treatment effect with long term, chronic use, in addition to a positive effect on the social impact of treatment for facial erythema of rosacea with brimonidine tartrate 0.5% gel.

Rosacea is one of the most common chronic dermatological diseases; the prevalence statistics published in EU and the USA are highly variable, ranging from less than 1% to more than 20% of the adult population. Rosacea substantially impacts QoL and can be associated with depressive symptoms. The psychological and social consequences of rosacea are often underestimated as they are not consistently commensurate with the quantitative severity of the facial lesions. Rosacea is significantly associated with depression (Chosidow and Cribier 2011²⁶).

Currently, there are no approved pharmaceutical agents that directly target the persistent facial erythema of rosacea. Current pharmaceutical treatments available for rosacea primarily target the papulopustular rosacea subtype of the disease, reducing rosacea inflammatory lesions through anti-inflammatory/antiparasitic mechanisms.

Topical treatment with brimonidine tartrate 0.5% gel applied q.d. provides a rapid, effective and safe treatment option with potential positive social impact for adult patients with facial erythema of rosacea. However, there are certain limitations of the submission which need to be addressed before recommending authorisation for marketing.

The benefit risk balance of Mirvaso given the proposed usage (for the treatment of facial erythema of rosacea) is unfavourable, but would become favourable if changes recommended in the *First Round Recommendation Regarding Authorisation* (see below) are accepted.

First round recommendation regarding authorisation

It is recommended that approval of the submission be granted subject to the following conditions:

- Approval should be granted for the modified indication of: *“Mirvaso is indicated for the cutaneous symptomatic treatment of facial erythema of rosacea in adult patients.”*
- Approval should be subject to incorporation of changes to PI and CMI²⁷ and adequate responses to the clinical questions (below).

²⁶ Chosidow O and Cribier B. Epidemiology of rosacea: updated data. *Ann Dermatol Venereol.* 2011;138:179-183.

²⁷ Details of these are beyond the scope of the AusPAR.

Clinical questions

Pharmacokinetics

Question 1

Why was the less sensitive analytical method, which had a lower limit of quantification (LLQ) of 25 pg/mL, rather than the method from Study RD.06.SRE.18143, which had a LLQ of 10 pg/mL, used to determine plasma concentrations of brimonidine in the 2 initial BA studies?

Question 2

Why was 0.5% Mirvaso gel (that is, the to be marketed concentration) not examined in the BA studies in healthy subjects, as the higher dose may have been easier to detect in plasma?

Question 3

Have the sponsors conducted a population PK analysis on pooled data which examines the effects of race, age, gender and Fitzgerald's skin types on the PK, PD and safety of Mirvaso Gel?

Question 4

Can the sponsor please justify why drug/drug interaction studies with other pharmaceutical agents used in the treatment of facial rosacea, such as low dose clonidine, long acting beta blockers, antibiotics or retinoids, have not been conducted?

Second round evaluation of clinical data submitted in response to questions

The sponsor provided acceptable responses to Questions 1, 2 and 4. (see CER Extract Attachment 2 for details of the responses). With regards to Question 3, the evaluator accepts that the Mirvaso may have been difficult to detect in plasma. However, due to the small number of participants enrolled in the definitive study, that is Study RD.06.SRE.18143, it is impossible, based on the PK data available, to determine whether gender and age related differences or factors such as hepatic or renal impairment affect the PKs of Mirvaso. The current PI already states that the effects of hepatic and renal impairment have not been studied and that the data relating to subjects older than 65 is limited; however, no statement is included in the PI, which identifies the fact that the effects of gender on the PKs of Mirvaso are unknown and a statement to this effect should be included in the revised PI.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of response to clinical questions, the benefits of Mirvaso in the proposed usage are unchanged from those identified in *First Round Assessment of Benefits*.

Second round assessment of risks

After consideration of response to clinical questions, the risks of Mirvaso in the proposed usage are unchanged from those identified in in *First Round Assessment of Risks*.

Second round recommendation regarding authorisation

It is recommended that approval of the submission be granted for the indication of:

“Mirvaso is indicated for the cutaneous symptomatic treatment of facial erythema of rosacea in adult patients.”

Approval is subject to incorporation of a minor change to the proposed PI details of which are beyond the scope of the AusPAR.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP) EU-RMP Version 1.0 (dated June 2012, data lock point 18/06/2012) and Australian Specific Annex Version (ASA) 1.0 (dated July 2013, data lock point not given) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

Subject to the evaluation of the non clinical aspects of the safety specification (SS) by the Toxicology area of the Office of Scientific Evaluation and the clinical aspects of the SS by the Office of Medicines Authorisation, the summary of the ongoing safety concerns as specified by the sponsor is as follows (Table 6):

Table 6. Ongoing safety concerns provided by the sponsor in their RMP submission.

Ongoing safety concerns	
Important identified risks	Skin and subcutaneous tissue disorders Vascular disorders – flushing Skin sensitisation Accidental oral ingestion
Important potential risks	None identified
Important missing information	Patients with particular severe/complex forms of rosacea Paediatric population Ethnicity other than white Caucasian European patient experience Lactating women Pregnancy Patients with renal and/or hepatic impairment Concurrent significant disease including depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, thrombangiitis obliterans, scleroderma, or Sjögren's syndrome.

OPR reviewer comment

Notwithstanding the evaluation of the non clinical and clinical aspects of the safety specifications, the listed ongoing safety concerns are considered acceptable.

Pharmacovigilance plan

The sponsor proposes routine and additional pharmacovigilance activities (a patient reported outcome study; and a 4 week vehicle controlled study) for important identified and potential risks and missing information.

Risk minimisation activities

The sponsor's conclusion in regard to the need for additional risk minimisation activities is: 'No risk management activities other than labelling through the Summary of Product Characteristics (SmPC) and Patient Information Leaflet²⁸ are proposed for identified risks or for missing information.'

OPR reviewer comment:

The sponsor's conclusion is acceptable.

Risk minimisation plan

No additional risk minimisation activities are proposed for brimonidine tartrate.

Reconciliation of issues outlined in the RMP report

Table 7 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Table 7. Reconciliation of issues outlined in the RMP report.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
Safety considerations may be raised by the nonclinical and clinical evaluators through the TGA consolidated request for further information and/or the nonclinical and clinical evaluation report (CER) respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information	'No safety considerations were raised by nonclinical and clinical evaluators via the TGA consolidated request for further information or the nonclinical or CER reports that impact the RMP. Should such considerations arise, the applicant will provide information relevant and necessary to address such safety issues in the RMP.'	This is considered acceptable.

²⁸ SmPC and PIL are the equivalent of the Australian PI and CMI respectively.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
that is relevant and necessary to address the issue in the RMP.		
It is noted that the sponsor has submitted a RMP in the old EU RMP format. The sponsor is advised to submit the latest version of the EU RMP.	'In compliance with the TGA's request, the applicant provided the RMP using the latest Day 120 EU RMP format. Please note that this RMP version is the same version as the one submitted on the 16 September 2013 as requested by the TGA.	It is noted that the submitted RMP in the new EU-RMP format (version 2) seems to be a draft version, as it does not contain any dates or dates of data lock points and many of the Ongoing Safety Concerns have been removed. It is also noted that the ASA attached to EU-RMP Version 2 (draft) has not been updated to reflect the differing Ongoing Safety Concerns in EU-RMP Version 2. As a result, for the purposes of this submission, the submitted EU-RMP (Version 1) with attached ASA shall apply in conjunction with the agreed changes by the sponsor in the response to TGA's consolidated request for information.
The sponsor is advised to submit protocols or protocol synopses for Studies RD.03.SPR.29107 and RD.03.SPR.40174.	In compliance with the TGA's request, the applicant provided the protocols for European Studies RD.06.SPR.40174 and RD.06.SPR.29107. The former study is a double blind, vehicle controlled evaluation of the efficacy and safety of brimonidine tartrate 0.5% gel applied q.d. for a duration of 29 days in patients with moderate to severe facial erythema of rosacea. The latter study is a double blind, vehicle controlled assessment of patient reported outcomes following treatment of severe facial erythema of rosacea applied q.d. for 8 days. As described in the RMP, the pharmacovigilance plan is based on routine pharmacovigilance activities. Therefore, only routine	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
	pharmacovigilance activities are planned and the conduct of these studies is not part of any additional pharmacovigilance activities.	
The sponsor should make the results of the LTS study available to the TGA.	<p>The applicant has provided the clinical study report for the long term safety study RD.06.SRE.18142 with the initial application. As stated in the RMP, overall, the long term treatment of subjects with a once daily application of brimonidine tartrate 5 mg/g gel resulted in no new major safety findings or signals and the safety profile determined during earlier development was confirmed.</p> <p>Of primary importance was the observation that the incidence of related TEAEs and premature discontinuations due to TEAEs did not increase over time with long term use of the study drug; there was no evidence that long term use of the study drug conveyed an increased risk of occurrence of any specific type of TEAE.</p>	This is considered acceptable.
All the results from any pharmacovigilance activities should inform updates to the RMP, and should also be reported in the periodic safety update reports (PSURs).	As planned in routine pharmacovigilance activities, the applicant agrees to update the RMP if needed and to report in PSURs any safety data collected during post authorisation use of brimonidine tartrate 0.5% gel.'	This is considered acceptable.
The sponsor should present AEs in a table that allows easy visualisation of the AEs according to body system and frequency.	The table of adverse reactions has been reformatted as proposed in the response to the TGA's consolidated request for further information.	This is considered acceptable.

Outstanding issues

It is considered that the sponsor's response to the TGA's request for further information has adequately addressed the issues identified in the RMP evaluation report.

There is an outstanding issue with the draft format of the new version of the submitted EU-RMP (see Table above).

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

Not applicable.

Comments on the safety specifications of the RMP***OMA clinical evaluation report***

The clinical evaluator made the following summary comment in regard to safety specifications in the draft RMP:

'The Safety Specification in the draft Risk Management Plan is satisfactory.'

OSE nonclinical evaluation report

The non clinical evaluator made the following summary comment in regard to safety specifications in the draft RMP:

'Results and conclusions drawn from the nonclinical program for Mirvaso detailed in the sponsor's draft Risk Management Plan (Section 1.1) are in general concordance with those of the Nonclinical Evaluator.'

Recommendation to the delegate

Any changes to the RMP that were agreed to by the sponsor become part of the RMP, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

Once a satisfactory RMP has been submitted, the following is recommended:

- Implement EU-RMP Version 1.0 (dated June 2012, DLP 18/06/2012) and Australian Specific Annex Version 1.0 (dated July 2013, DLP not given), and any future updates (where TGA approved) as a condition of registration

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The Delegate noted the quality findings (see above) and the advice that approval could be recommended if issues relating to two impurities were resolved.

In line with the non clinical evaluator's recommendation, these impurities must be limited to the TTC which for a product with chronic use is 1.5 µg/day. (The TTC represents a dose for which a geno toxic impurity is considered to pose a negligible carcinogenic risk).

The evaluator recommends that the release limit must be set at lower than the TTC and confirms that the limits for the two impurities in the drug substance specifications must also be tightened.

The evaluator also states that the test method used for the determination of these impurities has a LOQ which is above the acceptable expiry limit. Therefore, the test method was not suitable and it was not possible to determine if the stability results meet these limits or not.

The sponsor has agreed to limit the impurities to the TTC and has agreed to develop a test method sensitive enough to detect impurities at the tightened specification²⁹. The sponsor requests time after registration (approximately 4 months) to undertake this.

However, the evaluator has recommended that the expiry limit be set to the TTC prior to registration of the product and is agreeable for an improved test method to be submitted within 4 months of registration.

Nonclinical

The evaluator states that the nonclinical studies were acceptable for this type of application and the conduct was generally satisfactory.

There was no efficacy data submitted for this type of application.

The drug was readily absorbed in rats, pigs and humans following dermal application. The PK was highly variable in rats; it was fairly constant in minipigs; the latter species was a better model for topical absorption in humans. There was no evidence of systemic accumulation. There were no studies on damaged skin.

Repeat dose toxicity studies by the dermal route were conducted in hairless mice (up to 13 weeks), rats (up to 57 weeks) and minipigs (up to 39 weeks). There were exaggerated pharmacological effects at high exposure levels in mice and rats. No signs of systemic toxicity were observed in rats at an exposure margin of approximately 100, nor in minipigs up to the highest dose tested (exposure margin of around 3).

Local dermal reactions were minimal to mild at clinically relevant concentrations.

In a dermal carcinogenicity study, there were no tumours (either local or systemic) in rats that could be attributed to brimonidine tartrate gel. Brimonidine tartrate gel did not enhance or promote skin tumour formation on hairless mice in the presence of UV light.

Brimonidine returned overall negative results for geno toxicity. The evaluator states that two geno toxic impurities require appropriate control. This is dealt with in the quality section, above.

Overall, the evaluator recommends approval from a nonclinical point of view.

Clinical

Pharmacokinetics

There is one single dose PK study, COL-118-BAPK-101, on healthy volunteers and 2 studies on the target population, RD.06.SRE.18126 and RD.06.SRE.18143. The latter 2 studies assessed the relative BA of the gel compared with the ophthalmic solution.

The evaluator states that, "Study COL-118-BAPK-101 aimed to determine the relative BA of 0.2% (2 mg brimonidine) Mirvaso facial gel compared to 0.2% brimonidine ophthalmic solution in 16 healthy subjects. Following facial administration of 0.2% Mirvaso gel,

²⁹ The tightened limit for these impurities was less than the required specifications in the Ph. Eur. Monograph for brimonidine tartrate; however as the importance of ensuring the TTC was recognised, the sponsor complied with the TGA request.

plasma levels of brimonidine, for all subjects, were below LLQ and therefore no PK analysis could be performed.”

Study RD.06.SRE.18126 (a Phase II, double blind randomised placebo controlled study) examined the relative BA of 0.18% Mirvaso facial gel versus 0.2% ophthalmic solution in subjects with moderate to severe erythematous rosacea. Two doses of the gel (1 g each) were applied 4 hours apart whereas the single dose of the eye drop was applied to the eye as a comparison. Systemic exposure to Mirvaso gel (0.18%) was seen in 1 of 18 subjects, whereas, systemic exposure with the eye drops was quantifiable in 11 of 18 subjects. The evaluator states that, “relative BA was calculated using the highest C_{max} obtained with the ophthalmic solution (100 pg/mL) and, as a conservative approach, the LLQ (25 pg/mL) was set as the C_{max} for 0.18% Mirvaso facial gel. Based on this calculation, the dermal BA relative to the ophthalmic route was lower than 3%”.

The evaluator questions the LOQ used in this study (25 pg/ml) compared with 10 pg/mL in the previous study. This has been addressed by the sponsor: this study was conducted by the previous sponsor, which used a different limit. Another deficiency was that the concentration to be marketed (0.5%) was not studied in relation to PK. The sponsor has responded similarly: the proposed strength of 0.5% was developed by Galderma, after the PK studies were completed by the former sponsor, 0.5% was chosen based on dose finding studies. The evaluator accepts this explanation by the sponsor.

Study RD.06.SRE.18143 examined the PK of 0.5% Mirvaso gel following a single application in 23 patients with facial erythema of rosacea. Quantifiable plasma levels of brimonidine were detected in samples from 17 (74%) patients treated. Following statistical analysis of the data, in which the values below the LOQ were replaced by LLQ of 10 pg/mL, the mean C_{max} and AUC_{0-24h} values for brimonidine were 19.44 pg/mL (standard deviation (SD): 11.67) and 262.11 pg.h/mL (209.39) respectively.

The evaluator states that this study reveals that brimonidine is absorbed systemically, “albeit at lower levels” with the AUC and C_{max} at least 2 fold lower than the three times daily administration of 0.2% eye drops (after 1 day).

This study also examined dose proportionality after single dosing of 0.18% and 0.5% strength. The increases in C_{max} and AUC were not shown to be dose proportional. A similar pattern was also seen with multi-dosing (29 days of once daily administration). This study did not reveal accumulation after 29 days of dosing.

Pharmacodynamics

There were 3 single dose and one multidose studies assessing primary pharmacodynamics. Secondary studies also assessed the effect on tolerability, QTc and phototoxicity.

Single dose administration

COL-118-ROSE-101 evaluated the dose response relationship following single administrations of placebo (diluent), 0.0125%, 0.025%, 0.10% or 0.20% Mirvaso gel to a 1 cm² area on the malar region of the face of subjects with rosacea with moderate to severe erythema. Efficacy was evaluated by chromameter measurements and by the CEA score.

Study RD.06.SRE.18144 evaluated the pharmacodynamic profiles of three different concentrations of Mirvaso gel (0.07%, 0.18%, and 0.50%), following a single administration to subjects with stable moderate to severe ETR. With the exception of PSA scores, the baseline scores for all other parameters were comparable between treatment groups.

COL-118-ROSE-102 evaluated the impact of different formulations (cream and gel) on the pharmacodynamic profile of Mirvaso gel applied to a 1 cm² area on the malar region of the face in subjects diagnosed with rosacea with moderate to severe erythema. The chromameter values were similar pre dosing in all facial areas.

Changes in relation the CEA scores were observed within 15 minutes of administration. Statistically significant increases were seen at 2 hours post dose which were maintained at 5 hours. The magnitude of change was dose related. The median duration of effect was greater than 7 hours in each of the Mirvaso gel groups and 3 hours in the vehicle group.

Multiple dose administration

Study COL-118-ROSE-201 evaluated the dose response relationship and pharmacodynamics profile of 3 concentrations (0.02%, 0.07% and 0.20%) of Mirvaso gel applied to the face of subjects with rosacea with moderate to severe erythema and telangiectasia on the malar area. Each patient applied a small amount (approximately 1 g) of the assigned study drug to the affected area of the face each morning and as needed thereafter, but no more often than once every 4 hours and no more than 3 times per day for 28 days. The primary endpoint, reduction in CEA scores across all time points (0 to 8 Hours) and all visits (Day 0, Day 14, and Day 28), showed a clear dose response relationship. The duration of effect was approximately 5 hours. Telangiectasia and total inflammatory lesion count were not significantly affected.

Secondary pharmacodynamics effects

Thorough QTc study: Study RD.06.SRE.18139 evaluated the effect of a single ocular administered dose of brimonidine tartrate (two drops of a 0.2% solution to each eye) on ventricular repolarisation in healthy subjects, compared to placebo and/or 400 mg moxifloxacin. The study also evaluated the change from baseline of QT/QTc interval by: Bazett-corrected QT interval (QTcB), Fridericia-corrected QT interval (QTcF), and QT interval, individual-based correction factor (QTcI, subject specific) at the Tmax using 12 lead electrocardiograms (ECGs). No clinically significant effect was seen with brimonidine.

Three studies examined the potential of Mirvaso gel (0.07% to 0.5%) to produce phototoxicity and sensitisation (COL-118-PT-104, RD.06.SRE.18189, RD. 06.SRE.18124). The evaluator mentions that Mirvaso gel did not possess detectable phototoxicity potential in human skin.

Tolerability and irritancy were assessed in 2 studies. The first, Study RD.06.SRE.18123 examined the sensitisation potential and local tolerability of three concentrations of Mirvaso gel (0.07%, 0.18%, and 0.5%) after applications to the skin of 247 healthy, predominantly Caucasian subjects. Each active test concentration, the gel vehicle, and the white petrolatum produced no reaction in 95% to 96% of test sites on any given evaluation day; mild erythema in 4% to 5% of test sites on any given evaluation day; and only isolated instances of moderate erythema and/or erythema with vesicles or erosion or bullae. There were no confirmed cases of contact sensitisation for any of the Mirvaso concentrations, including the vehicle gel.

The second, Study RD.06.SRE.18125 assessed the cumulative irritancy potential of repeated applications of three concentrations of Mirvaso gel (0.07%, 0.18%, and 0.5%) to the skin of 38 healthy, Caucasian subjects. Based on the MCII, test sites patched with the higher concentrations of Mirvaso gel (0.5% and 0.18%) exhibited slightly less irritation (MCII = 0.01) than the weakest concentration (0.07%; MCII = 0.02) and gel vehicle (MCII = 0.02).

There was no apparent correlation between increasing concentrations of Mirvaso gel and the appearance or intensity of topical erythema/irritation.

Efficacy

Dose response studies

2 studies are submitted.

Study 18144

A Phase IIa, randomized, double blind, parallel group, vehicle controlled, dose finding study investigating the pharmacodynamics and safety of three concentrations of brimonidine tartrate topical gel (0.07%, 0.18%, and 0.50%), applied in subjects with moderate to severe ETR. This was a single dose study which included time to first and second grade improvements on the CEA, PSA or both. Other endpoints are also included.

The ITT population included 122 subjects; 31, 31, 28 and 32 subjects were randomised to brimonidine tartrate 0.5% gel, 0.18% gel, 0.07% gel and vehicle gel, respectively. All completed the study. There was dose response seen in relation to the endpoints assessed. The largest effect observed was with the 0.5% concentration, followed by the 0.18% and 0.07% concentrations. Based on these results, 0.18% and 0.5% were chosen for the next dose finding study, 18161.

Study 18161

A Phase IIb, 4 week, randomised, double blind, parallel group, vehicle controlled, multi-centre study. Brimonidine gel, 0.5% and 0.18% was applied topically in subjects with moderate to severe facial erythema associated with rosacea. Subjects were to be randomised in a 1:1:1:1 ratio to one of the following treatment arms: brimonidine gel 0.5% applied topically q.d.; brimonidine gel 0.18% applied topically b.i.d.; brimonidine gel 0.18% applied topically q.d.; vehicle gel applied b.i.d. or q.d.

The primary efficacy endpoint was 2 grade composite success at Hours 3, 6, 9 and 12 on Day 29, then on Day 15 and lastly on Day 1; a 2 grade composite success was defined as a 2 grade improvement from Baseline (T0 at Day 1) on both CEA and PSA-5 at each time point. Secondary endpoints were also assessed.

269 subjects were randomised to the ITT population. 80% were female and > 95%, were Caucasians. For CAE all baseline scores were in the moderate (CEA = 3) to severe (CEA = 4) range. The baseline demographics and disease characteristics were similar across treatment groups.

On Days 1, 15 and 29, a statistically significantly ($p < 0.001$) greater proportion of subjects treated with brimonidine gel 0.5% q.d. achieved 2 grade composite success, compared to vehicle gel q.d.. The evaluator concludes that the 0.5% gel was significantly more effective than the vehicle; though no direct statistical comparisons are made; it also produced greater efficacy than the 0.18% b.i.d. or q.d. regimens. Based on the results of this study, 0.5% gel (once daily) was chosen for the Phase III studies.

Pivotal studies

2 studies (18140 and 18141) are provided.

Study 18140

A Phase III, multi centre, randomized, double blind, parallel group, vehicle controlled pivotal study. Brimonidine gel 0.5% was to be applied topically once daily for 4 weeks versus vehicle control, in patients with moderate to severe facial erythema associated with rosacea. The main inclusion criteria were: male or female at least 18 years of age or older with a clinical diagnosis of facial rosacea, and CEA score and PSA score of ≥ 3 at screening. Exclusion criteria were comprehensive.

Subject assessments were to be performed at the investigational centre during a 12 hour post dose evaluation period on Day 1, Day 15 and Day 29.

The primary endpoint to compare the active treatment arm with the vehicle control arm was “composite success” at Hours 3, 6, 9 and 12 first on Day 29, then on Day 15 and lastly Day 1. Composite success was defined as 2 grade improvement on both CEA and PSA at each time point.

Secondary endpoints were also assessed.

Randomisation methods, populations analysed, sample size calculations and statistical methods are considered satisfactory.

260 subjects were randomised and included in the ITT and safety analysis. 79% were females and 98.5% were White. 85% had moderate erythema (according to CEA and PSA score). The mean age was 48.8 years. There was no significant difference in baseline characteristics.

Brimonidine gel 0.5% was significantly superior ($p < 0.001$) compared to vehicle gel for the primary endpoint (2 grade Composite Success for CEA and PSA at Hours 3, 6, 9, and 12 on Day 29). The secondary efficacy endpoints showed similar trends. In relation to Patient Assessment of Appearance, brimonidine gel consistently favourable outcome. There were no obvious effect on telegectasiae; there was no evidence of tachyphylaxis.

In regard to rebound phenomenon, the evaluator states that, “after cessation of a 4 week continuous treatment period, no aggravation effect on facial erythema was observed during the follow-up period, in comparison to Baseline/Day 1 (T0) assessments”. Similar incidence of worsening scores in the active and placebo groups were observed in relation to CEA and PSA.

Study 18141

This was a multicentre study which was similar in design and conduct to Study 18140.

293 subjects were randomised to the ITT population. 72% were females and 98% were White. Moderate erythema based on CEA score of 3 was present in 76% of the population and PSA score of 3 was seen in 86%.

Primary efficacy endpoint: Brimonidine tartrate 0.5% gel was significantly superior ($p < 0.001$) compared to vehicle gel for the primary endpoint: 2 grade composite success for CEA and PSA at Hours 3, 6, 9, and 12 on Day 29. Using the observed case data, 2 grade composite success ranged from 17.6% to 25.4% on Day 29 compared to the vehicle gel control (9.2% to 10.6%). The secondary efficacy endpoints showed similar trends.

The evaluator also mentions that brimonidine tartrate 0.5% gel, “consistently showed a more favourable outcome in PAA and OTE compared to vehicle gel. As expected, slightly more subjects in the brimonidine tartrate 0.5% gel group reported unwanted over whitening compared to subjects in the vehicle gel group. Overall, subjects in the active group adapted to the over whitening effect (that is, the incidence decreased from Day 1 to Day 29) and no subjects discontinued from the study due to the effect of over whitening”.

Other studies using Mirvaso

Study 18142

This was a multicentre, open label, non comparative 52 week study which evaluated the long term safety and efficacy of Mirvaso gel 0.5% applied once daily in 449 patients with moderate to severe facial erythema of rosacea. Efficacy was a secondary objective and thus is a supportive study of efficacy. The evaluator mentions that, “the mean change of -1.0 observed at the Baseline (Day 1) Hour 3 assessment improved over the course of the study reaching a level of improvement of -1.6 at the Month 3 visit. For the remaining clinic visits, a mean change in PSA of -1.5 or -1.7 was maintained until the end of the study, which suggested that no tachyphylaxis of treatment effect occurred over time”. Similar observations were made in relation to CEA, PAA, OTE scores and basically confirmed the

short term results. The evaluator also states that there was no evidence of tachyphylaxis with long term chronic use.

Overall efficacy conclusions

The evaluator mentions that the dose finding studies supported 0.5% gel once daily. The objective of the dose finding studies was to produce at least a 1 grade improvement (that is, a noticeable effect) in CEA and/or PSA for a maximal amount of time (target of 12 hours after dosing), while being able to achieve daily 2 grade improvement in both assessments for a sustained period.

The 2 Phase III pivotal studies were vehicle controlled studies. The primary efficacy endpoint was a 2 grade composite success which was a composite endpoint based on analyses of independent static evaluations of erythema by the investigators (CEA) and the subjects (PSA). The Phase III pivotal studies met the predefined primary endpoint of 2 grade composite success, demonstrating the superiority of brimonidine tartrate 0.5% gel compared to vehicle gel in reduction of facial erythema in subjects with rosacea. These studies were 4 week studies.

There was no exacerbation of the condition observed and no unwanted over whitening. There was no evidence of tachyphylaxis.

The treatment effect appeared to be sustained in the long term (52 week) open label study.

The evaluator mentions that the main limitation was that subjects < 18 years were not studied. There are no long term data based on double blind studies.

Safety

The safety data relate to pharmacology, dose finding and efficacy studies.

Study 18142 assessed safety as the primary outcome and was an open label non comparative 52 week study. 449 subjects were enrolled and 279 completed the study. 67 (14.9%) subjects discontinued due to AEs that were related to the study drug. The majority of related AEs that led to study discontinuation were in the skin and subcutaneous tissue disorders SOC and were mild or moderate in severity; AEs ($\geq 4\%$ of subjects) for the entire study were: flushing (10.2%), erythema (7.8%), rosacea (5.3%), nasopharyngitis (4.9%), skin burning sensation (4.2%), increased IOP (4.2%), and headache (4.0%). The cardiovascular events (reported in 6 patients) were assessed by the investigator as unrelated.

In the vehicle controlled pivotal studies, 33% TEAEs were in the brimonidine and 27% in the vehicle group. Frequently reported events were: headache 4.5%, erythema 3.6%, pruritus 2.4% and nasopharyngitis 8%. The events were assessed as severe in 1.2% (one report of contact dermatitis) of the active and 0.3% of the vehicle controlled events. 0.9% (n = 3) versus 0.6% TEAEs led to discontinuation; 2 were due to contact dermatitis and one due to erythema.

Photosensitivity

There were three reports in total; based on this, the rate of sensitisation was < 1% across the clinical development program. It was also well tolerated locally with little incidence of application site irritation or treatment-related TEAEs observed following application under patch occlusion, in the dermal occlusion studies. There was 1 report of unconfirmed allergic sensitisation.

The evaluator states that no specific drug interaction studies have been conducted. Additive effect with CNS depressants should be a consideration as this is an α -adrenoceptor agonist.

Clinical evaluator's recommendation

Overall, the evaluator concludes that the risk/benefit profile is acceptable and recommends approval of the indication: *"Mirvaso is indicated for the cutaneous symptomatic treatment of facial erythema of rosacea in adult patients."*

Risk management plan**OPR evaluation**

There are no outstanding safety concerns that preclude registration.

Risk-benefit analysis**Delegate's considerations**

The Delegate agreed with the chemistry and quality control evaluator that the expiry limit for the two impurities be tightened prior to registration of the product. The Delegate also agreed with the evaluator that the improved test method can be submitted within 4 months of registration.

The Delegate agreed with the clinical evaluator that the indication be restricted to the adult population as the pivotal studies were conducted in adult patients. The sponsor has changed the proposed indication to reflect this.

Short term efficacy from pivotal studies support the treatment of moderate, to severe, persistent (non transient), facial erythema of rosacea. Long term efficacy is based on a 12 month uncontrolled safety study which supports the long term effect of treatment.

There were no reports of local irritation photosensitivity that was clinically significant in the clinical trials; however, these studies were conducted in USA and Canada. No studies were conducted in Australia. This may be of concern relating to the potential UV light exposure in Australia. Is this likely to cause more photosensitivity and local irritation? The sponsor would be requested to address this in the response to this Overview. This may need to be addressed in the draft PI.

Proposed action

The Delegate had no reason to say, at this time, that the application for Mirvaso should not be approved for registration for the following indication:

"Mirvaso gel containing brimonidine: 3.3 mg/g for the cutaneous symptomatic treatment of facial erythema of rosacea in adult patients".

Request for ACPM advice

The Delegate proposed to seek general advice on this application from the Advisory Committee on Prescription Medicines (ACPM) and to request the committee provide advice on the following specific issues:

1. Does the committee agree with the Delegate (and the chemistry and quality evaluator) that that the expiry limit of two impurities be tightened prior to registration of the product?
2. Does the committee agree that the risk/benefit profile is acceptable to approve Mirvaso gel for the treatment of cutaneous symptomatic treatment of facial erythema of rosacea?

3. Does the committee agree to restrict the indication to adults?
4. There is a lack of information on the effect of sun exposure (in Australia) when treating with Mirvaso gel. Does the committee agree with the Delegate that this should be addressed in the PI?

Response from sponsor

Indication and registration

The company agrees with the Delegate to recommend approval of Mirvaso for the following indication:

“Mirvaso is indicated for the cutaneous symptomatic treatment of facial erythema of rosacea in adult patients”.

The company agrees that the risk-benefit profile is acceptable for registration. The company also agrees to the inclusion *“in adult patients”* in the proposed indication.

Impurity limits of two genotoxic impurities

Regarding the Delegate’s comments on the issue of limits for two potentially genotoxic impurities, in the finished product: The company has noted the concerns of the pharmaceutical and chemistry and the nonclinical evaluators and had put forward the following proposal:

“The company agrees to meet the requested limit for the two potentially genotoxic impurities, in the drug substance specification and in the release and shelf life DP specifications. Given the broader limits have been very recently approved in EU and USA, the TGA’s request necessitates further analytical development and impurity controls to be implemented at the manufacturing site, and given the risk associated with the broader limits is only associated with long term treatment (10 years or more), the following is proposed:

Specific condition of approval

Galderma are willing to accept TGA imposing a specific condition of registration for Mirvaso based on an assurance provided by the company that an appropriate variation will be submitted to TGA to tighten the DP release and expiry limits for the two potentially genotoxic substances by no later than four months post approval (following completion of the development and validation of the test method required to quantify the tighter release and expiry limits).

Exemption for the first two batches

Given the minimal exposure of patients to these impurities over the short term, and the carcinogenicity risk being associated with long term use of many years, prior to the implementation of the requested limits, the company seeks an exemption for the first two batches manufactured with the current expiry specifications for the two impurities. This would allow patients to readily access this treatment addressing an unmet medical need in the interim period whilst the test method is being developed. The company refers to the PCS second round recommendation: “Given the toxicological advice, PCS can in principal agree to the proposal; however it would be very preferable that the expiry limit be adopted now, not in four months”.

“PCS believes that it should be made a condition of registration that the company submit a variation application within 4 months (company estimate) with the improved test method and appropriate release limits for these impurities, and, limits for these impurities in the drug substance specifications. An exemption could then be given to allow supply of product with the broader expiry limit for 6 to 10 months.”

The company had previously proposed to PCS that an exemption could then be given to allow supply of product with the broader expiry limit for 6 to 10 months. Consequently, the sponsor understood that the advice from the PCS evaluator (as per the PCS Addendum to the Pharmaceutical Chemistry Summary for the ACPM) was that the sponsor's proposal would be acceptable as would the condition of registration and the exemption (if granted).

The company agrees to tightened limits for the impurities in principal in order to facilitate approval and registration of Mirvaso in the first instance. The company also accepts that a condition of registration be that a variation application would have to be submitted to register the improved test method and release limits for these impurities.

However, the company would like the ACPM and the Delegate to give due consideration of the limited exemption at the time of registration of Mirvaso.

The company requested an exemption to supply two launch batches of Mirvaso with the broader impurity limits of the finished product for the two impurities. It is approximated that these two batches will be sold within 10 months, with a shelf life of 24 months and an in use shelf life of 6 months. The exemption is to allow supply whilst the company will obtain the variation approval and implement the improved test method at the manufacturing site for future Australian batches.

The potential exposure to these impurities has been considered in line with the ICH guideline M7, Step 2, dated 6 February 2013 and for a product with daily exposure of up to 12 months, the acceptable TTC is 20 µg/day for a single impurity and up to 60 µg/day, for total impurities.

The maximum possible patient exposure to the two impurities of was calculated for individual impurity and for total mutagenic impurities when Mirvaso is used in accordance with the maximum recommended dose of 1 g/day. This amount is well within the acceptable exposures and well below the TTC which is accepted to pose negligible carcinogenic risk according to ICH guideline M7.

In addition to the safety assurances as stipulated above, as this issue was not raised by the EMA or the USA FDA prior to the TGA, the global company has already manufactured bulk batches of Mirvaso gel, including batches intended for supply in Australia which meets the broader limits of the two impurities. As such, the company believes that to supply only two launch batches via an exemption will pose no short term safety risk to patients, and will ensure earliest possible patient access to this new product. There are currently no therapeutic alternatives available in Australia to treat erythema associated with rosacea.

Long term efficacy studies conducted in the target population

Delegate comment: "Short term efficacy from pivotal studies support treatment of moderate to severe, persistent (non transient) facial erythema of rosacea. Long term efficacy is based on a 12 month uncontrolled safety study which supports the long term effect of treatment."

Company response: The design of the clinical program to support product registration in the proposed indication included two Phase III pivotal studies (18140 and 18141, 29 day treatment period) and a single open label Phase III study (1 year treatment period). The sponsor asserts that the long term efficacy of the product is primarily supported by the data from these studies.

The efficacy data from the sponsor's clinical trials demonstrated that Mirvaso must be reapplied each day in order to achieve the desired therapeutic effect. This was established in the single day Phase IIa Study 18144, which was conducted to select doses for subsequent studies and also to elucidate the pharmacodynamic profile of the drug. Efficacy data in the study were collected hourly from Hour 0 through Hour 12. The results confirmed that after a single application of the highest dose, Mirvaso achieved a peak level of effectiveness that persisted for several hours, but began to decline after Hour 9. Although a measurable effect on erythema was still present at Hour 12, extrapolation of

these trends over 24 hours indicates a near complete loss of pharmacodynamic effect at the end of a 24 hour post dosing interval.

The PK data from Study 18143 demonstrated an absence of brimonidine systemic accumulation over a 29 day topical treatment and that a single daily dose of Mirvaso is largely eliminated within 24 hours. The terminal half-life for brimonidine tartrate 0.5% gel could not be precisely calculated due to the flat PK profile observed with 29 days of dosing and also due to the low systemic exposures (in the pg/mL range, LOQ 10 pg/mL). Nevertheless, the terminal half-life is longer than the terminal half-life for the ophthalmic product (2 to 3 hours), but shorter than 12 hours as evidenced by (1) the flat PK profile and (2) the absence of systemic accumulation. As such, the sponsor can reasonably conclude that 75% to 88% of brimonidine (from 2 to 3 terminal half-lives) has been completely eliminated from the plasma over a 24 hour dosing interval. In addition, the absence of brimonidine systemic accumulation suggests that the amount of brimonidine remaining in the plasma 24 hours after a single dose of the highest concentration (0.5%) is insignificant. Accumulation in the skin would likely result in accumulation in the plasma; as plasma accumulation was not observed, the sponsor can make the same assertion about the amount of drug remaining in the skin 24 hours after a single dose. These observations further substantiate the position that efficacy over time with Mirvaso is not dependent upon cumulative effect or drug accumulation.

Based on the PD and PK observations described above, the sponsor can conclude that one day of treatment with Mirvaso represents one complete treatment cycle, and thus, a treatment period of 29 days (as implemented in Studies 18161, 18140, and 18141) represents 29 complete treatment cycles. Data from 29 complete and consecutive treatment cycles is sufficient to inform on the long term efficacy and durability of response for an investigational topical product. In addition, based on the sponsor's understanding of adrenoceptor physiology with respect to the temporal pattern for agonist induced desensitisation and down regulation, 29 days of treatment is more than adequate to inform on the presence of tachyphylaxis/tolerance with long term use. As such, data from the 29 day pivotal trials clearly establish that Mirvaso is an effective long term treatment and without significant tachyphylaxis/tolerance. Data from the long term, open label study (18142) provide further corroborative evidence of this observation.

Efficacy and safety in the Australian context of ultraviolet sun exposure

Delegate comment: "There were no [reports of] local irritation, photosensitivity that was clinically significant in the clinical trials; however, these studies were conducted in USA and Canada. No studies were conducted in Australia. This may be of concern relating to the potential ultra violet light exposure in Australia. Is this likely to cause more photosensitivity and local irritation? The sponsor should address this in the response to this Overview. This may need to be addressed in the draft PI."

Company response: As mentioned in the Delegate's Overview, the company performed three phototoxicity and sensitivity studies and Mirvaso did not possess detectable phototoxicity potential in healthy human skin. These studies followed standard protocols for evaluation of the phototoxicity and photosensitivity potential of a topical product, and use directed UV irradiation of application sites to mimic high enough UV exposure conditions to insure that the results of these studies allow for generalization of the photosafety potential of the product regardless of the variations in normal UV exposure experienced by most people in different geographic regions. The conduct of these trials in the USA and Canada has no impact on these study results as the UV is administered by the sites using solar simulators given in specified doses. As such, the sponsor takes the position that these studies have sufficiently ruled out the potential for significant UV toxicity with use of the product, irrespective of geographic location. In addition, only one case of a suspected, related, mild "photosensitisation" was reported in one participant in Study COL-118- ROSE-201. This participant had been treated with 0.02% gel no more than

three times daily and the reaction was observed on Day 28 (last treatment day). No patch testing was specified in the protocol. The subject returned on Day 56 and the condition had resolved.

In addition, the brimonidine tartrate gel formulation was not photo(co)carcinogenic in hairless mice at concentrations up to 2% and was rather protective delaying the appearance of UV induced cutaneous tumours (Study RDS.03.SRE.12629).

Given that the product did not cause any photosensitivity and phototoxicity in the three specific clinical studies on healthy skin using UV radiation and given that there was only one case of a suspected photosensitivity reaction in a patient with rosacea across the entire clinical program, the sponsor believes it would not be appropriate to include a precautionary statement in the PI based on the fact that Phase III clinical studies were not conducted in areas of UV exposure comparable to Australia.

Proposed changes to the Product Information

Details of the proposed changes to the PI are beyond the scope of the AusPAR.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register an extension of indications (and a new dose form) for a currently registered product.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Mirvaso gel containing 5 mg/g of brimonidine tartrate to have an overall positive benefit risk profile for the Delegate's amended indication;

For the treatment of facial erythema associated with rosacea in adult patients.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed PI/CMI amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

A statement in the *Precautions* section of the PI and the relevant sections of the CMI to reflect the lack of information on the effect of sun exposure when treating with Mirvaso gel.

Specific advice

The ACPM advised the following in response to the specific Delegate's questions on this submission:

1. Does the committee agree with the Delegate (and evaluator) that that the expiry limit of the impurities be tightened prior to registration of the product?

Given the Mirvaso gel is intended for chronic use and it is unlikely that there will be serious consequence for patients in awaiting the resolution of the impurities issue prior to registration, therefore the ACPM advised that approval of Mirvaso gel should be delayed

until the improved test method becomes available and the limits for the two specified impurities can be set.³⁰

2. Does the committee agree that the risk benefit profile is acceptable to approve Mirvaso gel for the treatment of cutaneous symptomatic treatment of facial erythema of rosacea?

The ACPM noted that the indication proposed by the Delegate (*for the cutaneous symptomatic treatment of facial erythema of rosacea in adult patients*) was more expansive than what was proposed by the sponsor (for the treatment of facial erythema of rosacea). The ACPM preferred a simpler indication;

For the treatment of facial erythema associated with rosacea in adult patients.

3. Does the committee agree to restrict the indication to adults?

ACPM agreed that Mirvaso for the treatment of facial erythema associated with rosacea could be approved on the basis that an acceptable benefit risk profile had been established in adequate studies, provided registration was delayed until the issues regarding impurities were resolved. Studies were performed in adult patients and therefore approval should be restricted to patients aged 18 years or over.

4. There is a lack of information on the effect of sun exposure (in Australia) when treating with Mirvaso gel. Does the committee agree with the Delegate that this should be addressed in the draft PI?

There were no studies investigating the efficacy and safety of Mirvaso gel in the context of Australian ultraviolet sun exposure. The ACPM noted the lack of evidence for concern over phototoxicity in clinical trials which were conducted in the USA and Canada. While differences in exposure to ultraviolet light between countries were acknowledged, the ACPM advised there was no material evidence to suggest that these differences would alter the benefit risk profile when used in Australia. Nevertheless, the ACPM considered the lack of information on the effect of sun exposure when treating with Mirvaso gel should be stated in the PI. Post market reporting on this issue should be encouraged.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Mirvaso brimonidine 3.3 mg/g (as tartrate) gel tube for topical once daily application, indicated for:

Mirvaso is indicated for the treatment of facial erythema of rosacea in adult patients.

Specific conditions of registration applying to these goods

The Mirvaso (brimonidine tartrate) EU Risk Management Plan (RMP), version 1.0 dated June 2012 datalock point (DLP) 18 June 2012¹ and Australian Specific Annex version 1.0 dated July 2013 (DLP not given), and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Details of additional specific conditions of registration applying to these goods including batch release conditions are beyond the scope of the AusPAR.

³⁰ The sponsor advised that the limits for the potentially genotoxic impurities have been tightened in accordance with the TGA request.

Attachment 1. Product Information

The Product Information approved for Mirvaso at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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