Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for dapsone

Proprietary Product Name: Aczone

Sponsor: Allergan Australia Pty Ltd

December 2017

TGA Health Safety Regulation

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 <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (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; it provides 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.

Contents

Common abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
ADR	adverse drug reaction
AE	adverse event
ANCOVA	analysis of covariance
ASIS	Acne Symptom and Impact Scale
AUC_{0-x}	area under the concentration time curve from time 0 to x hours post dose
AUC_{0-24}	area under the concentration-time curve from 0 to 24 hours
BD	twice daily
CI	confidence interval
Cmax	maximum concentration in plasma
CMI	Consumer Medicine Information
BID/BD	twice daily
BSA	body surface area
CMH	Cochran-Mantel-Haenszel
CSR	clinical study report
DGME	diethylene glycol monoethyl ether
DHA	dapsone hydroxylamine
ECG	electrocardiogram
EP	European Pharmacopeia
FDA	Food and Drug Administration (US)
G6PD	glucose 6-phosphate dehydrogenase
GAAS	Global Acne Assessment Score
GCP	Good Clinical Practice
QTc	corrected QT interval

Abbreviation	Meaning
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
IVRS/IWRS	interactive voice/web response system
ITT	intent-to-treat (analysis population)
LDH	lactate dehydrogenase
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LDPE	low density polyethylene
LOCF	last observation carried forward
LS	least-squares
MCII	mean cumulative irritancy index
MED	minimal erythemal dose
MedDRA	Medical Dictionary for Regulatory Activities
NAD	n-acetyl dapsone
NFD	N-formyl dapsone
PI	Product Information
PP	per protocol
PT	preferred term
QD	once daily
QTc	corrected QT interval
QTcB	QTc Bazett's formula
QTcF	QTc Fridericia-correction
RIPT	repeat insult patch test
RMP	Risk Management Plan
SE	standard error
SLS	sodium lauryl sulphate
SOC	system organ class

Abbreviation	Meaning
TEAE	treatment-emergent adverse event
TMP/SMX	trimethoprim/sulfamethoxazole
SD	standard deviation
UPT	urine pregnancy test
w/w	weight per weight

I. Introduction to product submission

Submission details

Type of submission:	New dose form, new route of administration, and extension of indication
Decision:	Approved
Date of decision:	4 January 2017
Date of entry onto ARTG	10 January 2017
Active ingredient:	Dapsone
Product name:	Aczone
Sponsor's name and address:	Allergan Australia Pty Ltd 810 Pacific Hwy Gordon NSW 2072
Dose form:	Topical gel
Strength:	7.5% w/w
Container:	Bottle with a HDPE piston, polypropylene / polyethylene / polyolefin elastomer pump and a polypropylene cap
Pack sizes:	30 g, 60 g and 90 g bottles + 3 g sample pack tube
Approved therapeutic use:	For the topical treatment of acne vulgaris in patients 12 years of age and older
Route of administration:	Topical
Dosage:	After the skin is gently washed and patted dry, approximately a pea-sized amount of Aczone 7.5% w/w gel should be applied in a thin layer to the entire face once daily. In addition, a thin layer may be applied to other affected areas once daily. Aczone 7.5% w/w gel should be rubbed in gently and completely.
ARTG number:	266267

Product background

This AusPAR describes the application by Allergan Australia Pty Ltd for a new dose form, new route of administration, and extension of indication for dapsone (tradename: Aczone) for the treatment of acne. Acne is a common, non-life threatening disorder. Mild to moderate cases often resolve spontaneously. Dapsone is an anti-inflammatory and anti-infective agent. It is a synthetic sulfone with antibacterial and anti-inflammatory properties.

The submission proposes registration of the following new dosage form and strength:

- Dapsone gel 7.5% w/w dapsone gel formulation is packaged in an airless pump container closure system, and provided in 30 g, 60 g, 90 g and 100 g fill sizes and 3 g professional sample tube.

The proposed new indication is:

> *For the topical treatment of acne vulgaris in patients 12 years of age and older.*

Dapsone is currently approved in Australia (to other sponsors) in a tablet dosage form for the following indications:

- ARTG 17608, Alphapharm Dapsone: 100 mg tablet for leprosy, dermatitis herpetiformis, actinomycotic mycetoma
- ARTG 104482, Link Medical Products Dapsone: 25 mg tablet for dermatitis herpetiformis, leprosy, actinomycotic mycetoma.
- ARTG 104483, Link Medical Products Dapsone: 100 mg tablet for dermatitis herpetiformis, leprosy, actinomycotic mycetoma.

The Dosage and Administration section of the new PI includes the following:

- *For dermatological (topical) use only.*
- *Aczone 7.5% w/w gel should only be applied to affected areas. For external use only. Not for oral, ophthalmic or intravaginal use. If contact with eyes occurs, rinse thoroughly with water.*
- *After the skin is gently washed and patted dry, approximately a pea-sized amount of Aczone 7.5% w/w gel, should be applied in a thin layer to the entire face once daily. In addition, a thin layer may be applied to other affected areas once daily. Aczone 7.5% w/w gel should be rubbed in gently and completely.*
- *Patients should be instructed to wash their hands after application of Aczone 7.5% w/w gel.*
- *If there is no improvement after 12 weeks, treatment with Aczone 7.5% w/w gel should be reassessed.*

A 5% topical gel for twice daily use has been available in the US since 2008 and Canada since 2011. The 7.5% gel has been approved for use in the US since February 2016. The sponsor states that this 7.5% gel is advantageous over the 5% gel as it as it is applied once daily.

Table 1: Currently approved topical therapies for acne.

Active Ingredient	**action**		
	keratinolytic	**antibacterial**	**retinoid**
Triclosan wash		X	
Azelaic acid	X	X	
clindamycin		X	
Salicyclic acid	X		
tazarotene			X
adapalene			X
tretinoin			X
Clindamycin-benzylperoxide		X	X
Adapalene-benzylperoxide	X		X

The anti-inflammatory properties of dapsone result from the inhibition of the cytotoxic system in granulocytes. Inhibition of neutrophil myeloperoxidase and oeosinophil peroxidase by dapsone suppresses the production of hypochlorous acid that kills bacteria but also damages adjacent tissue. Dapsone also scavenges reactive oxygen species and minimises inflammation associated with the generation of these highly reactive species.

Dapsone suppresses neutrophil recruitment and local production of toxic respiratory and secretory products through the inhibition of chemoattractant induced signal transduction. Dapsone competitively inhibits dihydropteroate synthase, which is the enzyme required for the synthesis of folic acid. Therefore, microorganisms that need to synthesise folic acid are sensitive to this class of compounds (sulfones).

In Australia, topical dapsone is not mentioned in the treatment algorithm for acne (Table 2).

Table 2: Treatment algorithm for acne.

	Mild		Moderate	Moderate to severe	Severe
	Comedonal	Papular/pustular			
First line therapy	Topical retinoid	Topical retinoid + BPO or BPO/topical AB	BPO/topical AB or Topical retinoid + BPO	Topical AB + BPO + topical retinoid or Oral AB + BPO + topical retinoid	Oral isotretinoin
Alternatives	Salicylic acid			Oral isotretinoin	Oral AB + topical retinoid + BPO or BPO/topical AB
Alternatives for female patients			Hormonal therapy ± BPO/topical AB or Topical retinoid	Hormonal therapy ± BPO/topical AB or Topical retinoid	Hormonal therapy + oral AB + topical retinoid ± BPO or BPO/topical AB
Maintenance therapy	Topical retinoid ± BPO or BPO/topical AB		Topical retinoid ± BPO or BPO/topical AB	Topical retinoid ± BPO or BPO/topical AB	Topical retinoid ± BPO or BPO/AB

BPO = benzoyl peroxide; AB = antibiotic

2010. Australian Family Physician

In the US, 5% dapsone is recommended as a topical treatment option for patients with acne.[1]

Regulatory status

Dapsone 5%, as Aczone (dapsone) Gel 5%, was approved by the US Food and Drug Administration (US FDA) on 7 July 2005 for the twice daily topical treatment of acne vulgaris in patients 12 years of age and older. It has been marketed in the US by Allergan, Inc. since July 2008 following the acquisition of the product from the original manufacturer (QLT USA Inc). Dapsone 5% gel has been marketed in Canada since 2011.

At the time of the submission to TGA, the 7.5% gel had only been submitted for approval to the FDA in the US. The US FDA approved the 7.5% gel in February 2016 for the requested indication.

The international regulatory status of dapsone 7.5% gel at the time of submission to TGA is listed in Table 3.

[1] Zaenglein AL, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol.* 74: 945-73.e33 (2016).

Table 3: International regulatory status of Aczone (dapsone) Gel 7.5% at time of submission to TGA.

Country/Region	Date submitted or intended to submit	Approval Status	Indication
US	28 April 2015	Pending evaluation	For the topical treatment of acne vulgaris in patients 12 years of age and older
New Zealand	31 March 2016	To be submitted	For the topical treatment of acne vulgaris in patients 12 years of age and older

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 PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

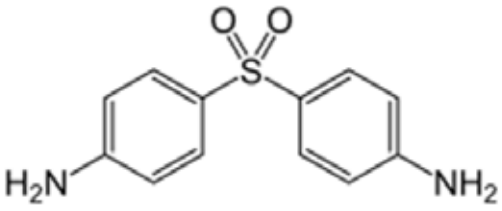
Introduction

Aczone dapsone 7.5 %w/w topical gel is an off-white to yellow suspension of dapsone in an aqueous gel base and is packaged in polypropylene/polyethylene airless pump containers in 30 g, 60 g, and 90 g pack sizes. A 3 g aluminium tube pack size is also intended for use as a professional sample. Three dapsone tablet drug products (25 mg and 100 mg) are currently registered on the Australian Register of Therapeutic Goods (ARTG) by different sponsors for the treatment of leprosy, dermatitis herpetiformis, and actinomycotic mycetoma. However, there are no topical dapsone drug products and no dapsone containing products indicated for treatment of acne vulgaris.

The clinician had no objections to the proposed trade name of Aczone.

The structure of dapsone is as shown below.

Figure 1: Chemical structure of dapsone.



$C_{12}H_{12}N_2O_2S$ MW: 248.30 CAS: 80-08-0 pKa = 13.0

The anti-inflammatory properties of dapsone result from inhibition of granulocyte cytotoxicity via inhibition of peroxidases and scavenging of reactive oxygen species. The antimicrobial properties of dapsone result from competitive inhibition of dihydropteroate synthase, a bacterial enzyme necessary for the synthesis of folic acid.

No maximum daily dose is stated in the proposed PI, although the instructions for use refer to a 'pea-sized quantity' for the face and a thin layer for other areas of the body to be applied once a day. The average daily use of the product in the clinical studies is stated to

be ~0.6 g and the maximum topical use is stated to be 2 g/day, giving a maximum topical dapsone exposure of 150 mg/day.

The product is intended to primarily act topically. The PI states that the systemic exposure from the proposed gel used as directed, is expected to be about 1% of that from a 100 mg oral dose.

The drug substance is the subject of monographs in the British Pharmacopoeia (BP/Ph). European Pharmacopoeia (Ph. Eur.), and the US Pharmacopeia (USP). The finished product is not the subject of a pharmacopoeial monograph, however, there are monographs for Dapsone Tablets in the BP/Ph. Eur. and the USP and for Dapsone Oral Suspension in the USP. The proposed product is subject to the requirements of the general BP/Ph. Eur. monograph for Topical Semi-Solid Preparations.

Drug substance (active ingredient)

Dapsone is a white or slightly yellow-white crystalline powder, which is very slightly soluble in water, freely soluble in acetone and dilute mineral acids, and is sparingly soluble in alcohol.

The drug substance specification complies with the USP monograph for dapsone and includes additional in-house tests and limits for:

- related substances (by HPLC) with a tighter limit of ≤0.15% consistent with the relevant qualification threshold from ICH Q3A;
- residual solvents: with proposed limits tighter than ICH limits; and
- crystallinity characterisation performed using microscopic examination to ensure the polymorph remains the same between batches.

The particle size distribution is assessed internally by the drug substance manufacturer but control limits are applied in the drug product manufacturer's drug product specification, which was considered appropriate.

The manufacturing and quality control of the drug substance (including the drug substance specification) is acceptable.

Drug product

Aczone dapsone 7.5 %w/w topical gel is an off-white to yellow suspension of dapsone in an aqueous gel base and is packaged in polypropylene/polyethylene airless pump containers in 30 g, 60 g, and 90 g pack sizes. A 3 g aluminium tube pack size is also intended for use as a professional sample.

The development and manufacture of the Aczone dapsone 7.5% w/w topical gel was based on an existing dapsone 5%w/w topical gel currently marketed in the US. Quantities of the solubiliser, diethylene glycol monoethyl ether (DGME) were increased, and a new thickener was chosen. No further changes were made, and the proposed commercial formulation is identical to that used in the toxicology and clinical studies.

The Aczone dapsone 7.5% w/w topical gel is to be manufactured in the US. GMP clearances for the drug product manufacturing sites are all currently valid past the expected decision date.

The quality of the drug products is controlled by a specification that includes tests and limits for Appearance, Identification, pH, Viscosity, Assay, Related Substances, Methyl Hydroxybenzoate (preservative) content, Within container Uniformity, Particle size,

Minimum fill, Microbiological quality, and Pump functionality (number of actuations to prime, Amount dispensed per actuation and total amount of drug product dispensed).

The drug product specifications include limits for the particle size distribution of the drug substance suspended in the gel, which were found to be satisfactorily justified.

The analytical methods used to analyse the product were adequately described and validated.

The proposed container closure system is a bottle with a HDPE piston, polypropylene / polyethylene / polyolefin elastomer pump and a polypropylene cap. The sponsor terms this an airless pump container. A 3 g sample pack in an aluminium tube is also proposed, with a distribution pack size of 8 x 3 g tubes proposed for marketing.

A shelf life of 24 months when stored below 25°C has been assigned for the unopened product in the PP bottle with a HDPE piston, PP/PE/polyolefin elastomer pump and PP cap. The additional storage conditions of 'Do not refrigerate or freeze' are also supported. This shelf life is also appropriate for the sample pack 3 g aluminium tube.

An in-use shelf life of 100 days (or 14 weeks) has been assigned to the drug product once opened with all remaining contents to be discarded after this time.

Biopharmaceutics

As the drug product has been formulated as a topical gel for dermal administration only, no bioavailability or bioequivalence studies were evaluated by PCS. In fact none were performed.

The drug product used in the Phase III clinical studies (CSR 225678-006 and -007) was the same as proposed for marketing.

Quality summary and conclusions

Approval is recommended from a chemistry and quality control perspective.

III. Nonclinical findings

Introduction

Dapsone is currently registered on the ARTG for the oral treatment of leprosy, dermatitis herpetiformis and actinomycotic mycetoma. The maximum recommended human dose for these indications is 300 mg/day PO, with dose reductions in children for the treatment of leprosy. Dapsone gel containing 5% dapsone and 25% diethylene glycol monoethyl ether (DGME)[2] is currently registered in the US and Canada for the treatment of acne vulgaris using a twice daily dermal application. Aczone (7.5% dapsone in 30% DGME) was recently approved in the US for once daily dermal use to treat acne vulgaris (February 2016).

The current submission comprised studies conducted to support the topical use of 5% dapsone gel, as well as additional studies to investigate the pharmacokinetic and toxicological profile of 7.5% dapsone gel containing 30% DGME. No pharmacology studies were submitted which is acceptable for this application type. The pharmacokinetics and toxicity studies submitted were of high quality, with all pivotal safety studies being GLP compliant. One combination study was submitted in which dapsone was formulated with

[2] DGME is also known as diethylene glycol ethyl ether, 2-(2-Ethoxyethoxy)ethanol, and as Transcutol.

adapalene, a retinoid like compound indicated for treating acne vulgaris. This study was not formally evaluated as the dapsone concentration was only 5%, and the combination of the compounds is not proposed in this submission.

Pharmacology

Primary pharmacology

Dapsone is generally accepted to have two mechanisms of action that would support the proposed clinical use in acne vulgaris.[3] First, dapsone has antimicrobial action achieved through inhibition of bacterial growth by disrupting folic acid synthesis. Secondly, dapsone reduces inflammation by decreasing oxidative stress, cytokine production and activity, and decreased neutrophil adherence. The sponsor cited data that dapsone also inhibits chemotaxis. However, this effect has recently been reviewed and shown to be inconsistent across species and also in response to different stimuli.[4]

Safety pharmacology

Specialised safety pharmacology studies were not submitted which is acceptable for a locally applied agent with well characterised pharmacology.[5]

Pharmacokinetics

The absorption of dapsone was slow following dermal application (T_{max} of 4-12 h), and its plasma half-life was long (>30 h) in rats, rabbits and humans. Bioavailability was low following a single dermal application in rats and rabbits (10-25%). Percutaneous absorption of dapsone was enhanced by DGME in the dermal formulation. Exposure was generally less than dose proportional following dermal application. In rats, exposure was higher in females compared to males. Exposure to dapsone increased with repeated dosing in rats, rabbits and humans. Accumulation of dapsone in the dermis was also shown *in vitro* and *in vivo*.

After dermal application, the volume of distribution was greater than total body water indicating extensive tissue distribution. Distribution into specific tissues was not investigated. The plasma protein binding of dapsone was reported to be 74% in humans, 72% in rats and 76% in mice in published studies.[6]

The metabolism of dapsone was not fully investigated in animals. In humans, N-acetyl dapsone (NAD) is a major metabolite (~50% the level of dapsone), with dapsone hydroxylamine (DHA) also present in plasma at ~9% the level of the parent. The DHA metabolite is reported to be responsible for many of the toxic effects of dapsone.[7] NAD and DHA were also observed in rats and rabbits. In rats, NAD was present at ~20% and ~40% the level of dapsone in males and females, respectively. Metabolism of dapsone to DHA was markedly higher in male compared to female rats (14% compared to 2% the level of dapsone). In rabbits, the levels of NAD were ~2x higher than dapsone, whereas DHA was present in plasma at ~8% of the level of dapsone. Metabolism of dapsone was limited in

[3] Wozel G, Blasum C. Dapsone in dermatology and beyond. *Arch Dermatol Res.* 306: 103-24 (2014).
[4] Wozel G, Blasum C. Dapsone in dermatology and beyond. *Arch Dermatol Res.* 306: 103-24 (2014).
[5] International Conference on Harmonisation, "ICH Harmonised Tripartite Guideline: Safety Pharmacology Studies for Human Pharmaceuticals (S7A)", 8 November 2000.
[6] Ahmad RA, Rogers HJ. Plasma and salivary pharmacokinetics of dapsone estimated by a thin layer chromatographic method. *Eur J Clin Pharmacol.* 17: 129-133 (1980); Gordon GR, et al. Disposition of dapsone and monoacetyldapsone in rats. *Proc Soc Exp Biol Med.* 150: 485-492 (1975); Levy L, et al. Disposition of the antileprosy drug, dapsone, in the mouse. *Proc Soc Exp Biol Med.* 140: 937-943 (1972).
[7] Wozel G, Blasum C. Dapsone in dermatology and beyond. *Arch Dermatol Res.* 306: 103-24 (2014).

pigs, with NAD the main metabolite and levels of DHA generally bellow the limit of detection. Similarly, published data indicate minimal formation of DHA in mice.[8]

Dapsone is predominantly excreted in the urine in humans. Limited excretion data are available in animals. In rats, biliary excretion has been demonstrated, with low levels of urinary excretion.[9] However, the investigation of excretion was limited.

The absorption, distribution and metabolism of dapsone appear sufficiently similar between rats, rabbits and humans to make the animal models used adequate for predicting the toxicity profile of dapsone. The limited metabolism of dapsone in mice and mini-pigs may reduce their usefulness for investigating systemic toxicity of dapsone.

Pharmacokinetic drug interactions

No new nonclinical studies examining the potential for dapsone to cause drug-drug interactions were submitted.

Toxicology

Acute toxicity

In acute toxicity studies, topical dapsone gels were administered by the oral route to rats, or were applied dermally to rabbits. The rabbit studies only achieved low doses of dapsone (20 mg/kg), and were not considered to be informative. A single dose of 250 mg/kg dapsone and 1250 mg/kg DGME was well tolerated in rats. This dose of dapsone is 15x the Maximum Recommended Human Dose (MRHD) based on body surface area, with an anticipated relative exposure of >200x based on Cmax.[10] Together, the data indicate that dapsone has a low order of acute toxicity at the doses and anticipated exposures associated with dermal application.

Repeat dose toxicity

Studies of up to four weeks duration were conducted in mice, six months in rats, nine months in rabbits and three months in mini-pigs. All of the studies used dermal application, except for one three month duration oral study in rats. The dermal studies applied varying concentrations of dapsone in varying concentrations of DGME. Daily application was generally used, with occlusive dressings used in the pivotal dermal studies in rats and rabbits. Overall, the design and conduct of repeat dose toxicity studies was consistent with the relevant international guidelines.[11]

Relative exposure

Exposure ratios have been calculated based on animal: human plasma total AUC0-24 h. Human reference values are from Clinical Study CSR 225678-004. Combined male and female values were used for the human data as there was no significant effect of gender on exposure. This differs from the approach taken in the Toxicology Written Summary in which exposure ratios were calculated for males and females separately. However, the gender specific human values could not be verified for Study CSR 225678-004. Because of

[8] Tingle et al. Comparison of the metabolism and toxicity of dapsone in rat, mouse and man. *J Pharmacol Exp Ther.* 283: 817-823 (1997).
[9] Tingle et al. Comparison of the metabolism and toxicity of dapsone in rat, mouse and man. *J Pharmacol Exp Ther.* 283: 817-823 (1997).
[10] C_{max} exposure extrapolated from the C_{max} values on day 1 in rats that received 100 mg/kg dapsone PO in Study ATLS-117.
[11] European Medicines Agency, "Committee for Human Medicinal Products (CHMP): Guideline on repeated dose toxicity (CPMP/SWP/1042/99 Rev 1 Corr*)", 18 March 2010.

the marked gender difference in rats, exposure ratios were calculated for both genders in animals. Toxicokinetic data collected from last sampling occasion was used as there was significant accumulation of dapsone with repeated dosing. High relative exposures were achieved in rats and rabbits, but the relative exposures in mice were only low. Relative exposures for the toxic metabolite, DHA, were also very high in rats following dermal dosing with or without possible oral ingestion.

Table 4: Relative exposure in repeat dose toxicity studies.

Species	Study duration; dose route [Study no.]	Dapsone dose		AUC_{0-24h} ^ (ng·h/mL)		Exposure ratio#	
		%	mg/kg/day	♂	♀	♂	♀
Dapsone							
Mouse (FVB/N*)	4 weeks; dermal [Carcinogenicity pilot; Study ATLS-150]	3	150	336	391	1.2	1.4
		5	250	456	528	1.6	1.9
		10	500	753	955	2.7	3.4
Rat (SD)	3 months; oral [Pivotal; Study ATLS-117]	–	3 (PO)	6250	20,800	22	74
		–	30 (PO)	132,000	252,000	468	894
		–	100 (PO)	431,000	529,000	1528	1876
	3 months; dermal with likely ingestion [Study TX14006-TX]	3.75	75	99,400	335,000	352	1,188
		7.5	150	362,000	455,000	1,284	1,613
		15%	150	277,000	545,000	982	1,933
	6 months; dermal [Pivotal; Study ATLS-114]	5	50	1837	6676	6.5	24
		10	100	11,294	11,102	40	39
Rabbit (NZW)	9 months; dermal [Pivotal; ATLS-113]	5	50	3240	2293	11	8.1
		10	100	7671	5470	27	19
Human (Acne vulgaris patients)	steady state; dermal [Study CSR 225678-004]	7.5	[150 mg]	282		–	
Dapsone hydroxylamine metabolite							
Rat (SD)	4 weeks; dermal [Study ATLS-181]	5	50	7584	9086	303	363
	3 months; dermal with likely ingestion [Study TX14006-TX]	3.75	75	9170	3540	367	142
		7.5	150	13,200	4160	528	166
		15	150	11,900	4470	476	179
Human (Acne vulgaris patients)	steady state [Study CSR 225678-004]	7.5	[150 mg]	25		–	

= animal:human plasma total AUC_{0-24h}; ^ = data are from the last sampling occasion; * = FVB/N is the genetic background strain for the transgenic Tg.AC mice used in the 6 month carcinogenicity study.

Major toxicities

The known dapsone toxicities on the haematopoietic system, spleen, liver and kidney were observed at high relative exposures. These included:

- methaemoglobinaemia, including clinical signs of cyanosis, in rats with oral dosing or non-occluded dermal dosing associated with relative exposures >140x that anticipated clinically for both dapsone and DHA;
- anaemia and associated spleen changes (splenomegaly, increased iron content, extramedullary haematopoiesis) in rats following dermal dosing in males rats (Relative Exposure [RE] ≥6.5 for dapsone, and >300 for DHA), and oral dosing in rats of both genders (≥30 mg/kg/day; RE >140 for both dapsone and DHA);
- modest elevations in liver enzymes (ALT, AST, GGT and/or ALP) at high oral doses in rats (RE >1500). Small increases in ALT and AST were also observed in the pivotal rat dermal study, but this effect was not clearly treatment related;
- renal injury (pigmentation, iron accumulation, vacuolation, increased relative weight and/or increased blood urea nitrogen and albumin) following dosing with ≥30 mg/kg/day PO (RE >460 for dapsone).

These effects have previously been reported with oral dosing of dapsone in humans. However, the systemic exposure to dapsone and DHA are relatively low following dermal application. Therefore, while these effects are considered to be of toxicological concern, they are of limited clinical relevance to the proposed indication.

In addition to the effects listed above, the CNS, thyroid, uterus, heart, skin and adipose tissue were target organs for dapsone toxicity in animal studies.

Effects on the CNS were evident in the clinical signs in rodents. Hyperactivity and hyper-reactivity were frequently observed in mice following dermal dosing despite only low relative systemic exposures. Ataxia, prostration and lethargy were also observed in mice. Hyperactivity was also observed in rats with high systemic exposure to dapsone, but not in rats or rabbits with low systemic exposure following dermal dosing.

Enlargement of the thyroid due to hyperplasia and/or hypertrophy were observed in mice (≥250 mg/kg/day, dermal; RE ~2) and rats (≥75 mg/kg/day dermally without occlusion; RE >350). In rats, the gross and microscopic changes in the thyroid were reversed after a short (2 week) recovery period. This effect is likely a class effect of sulphonamides, which decreased circulating T3 and T4, thereby stimulating TSH production.[12] Thyroid hyperplasia was not observed in rats following oral dosing for the same duration (3 months), despite similar systemic exposure. Overall, it is unlikely that adverse thyroid effects would occur clinically with the proposed dosing regimen.

Enlargement of the uterus associated with dilatation was observed in rats with high systemic dapsone exposures following repeated oral and dermal dosing (RE >350x). These effects were reversible. In addition, no adverse effect was seen on female fertility at similar oral doses (see Reproductive toxicity, below). Together, the lack of adverse effects on fertility coupled with the reversibility and occurrence at high relative exposures indicate little clinical concern for effects of dermally applied dapsone on the uterus.

Heart weight was increased in wildtype mice following dermal application of dapsone, but no microscopic examination was performed. In transgenic mice, heart weight was increased with left ventricle hypertrophy present at all dose levels without a clear dose relationship. Left ventricular myocyte degeneration and thrombi were observed in a dose dependent pattern in mice that received daily dermal applications of ≥150 mg/kg/day (RE ≥1). However, it should be noted that the majority of these mice were sacrificed moribund or found dead. There was no histological evidence of cardiac injury in rats or rabbits, even at markedly higher systemic exposures.

[12] Capen, CC. Mechanistic data and risk assessment of selected toxic end points of the thyroid gland. *Toxicol Pathol.* 25: 39-48 (1997).

In transgenic mice, hyperkeratosis was observed at the site of administration and also in untreated skin following dermal application of up to 10% dapsone (RE 1-3). The incidence was higher in premature decedents, and in untreated skin. Hyperkeratosis was not observed in rats, rabbits or mini-pigs following repeated dermal administration. As this finding was only reported in moribund mice and not other species it is considered unlikely to be clinically relevant.

Mild subacute inflammation of the mesenteric adipose tissue was observed in female rats that received 100 mg/kg/day dermally as 5% dapsone (RE 39). Atrophy of the mesenteric adipose was also reported in female rats treated dermally with dapsone with higher systemic dapsone exposures (RE >1100). Mesenteric adipose tissue was normal in rabbits and male rats.

Overall, the repeat dose toxicity studies did not identify any new target organs of toxicity that would have clinical relevance at the systemic exposures anticipated for the proposed indication. Moreover, the known haematological and hepatic toxicities of dapsone were only observed at very high relative exposures.

Genotoxicity

The genotoxic potential of dapsone was assessed in a standard battery of validated studies conducted in compliance with ICH guideline S2 (R1).[13] Dapsone was not mutagenic in bacteria (Ames test). *In vitro*, dapsone induced both structural and numerical chromosomal aberrations in the absence of metabolic activation in mammalian cells. In contrast, dapsone did not cause chromosomal aberrations in a mouse micronucleus test with demonstrated dapsone exposure in bone marrow as indicated by a reduction in the proportion of immature compared to total erythrocytes. Similarly, negative results were obtained in a rat bone marrow micronucleus assay and a skin comet assay following dermal application of N-formyl dapsone which resulted in systemic exposure to dapsone.[14] The exposure to dapsone in skin was unclear. However, the overall weight of evidence indicates little genotoxic concern for the proposed indication.

Carcinogenicity

Three carcinogenicity studies were submitted: a two year oral study in rats, a 6 month dermal study in transgenic Tg.AC mice and a 12 month photocarcinogenicity study in hairless mice. The high dose in the rat study was associated with adverse clinical signs and very high relative exposure (see below), but there was no effect on mortality or body weight. Overall, the high dose was considered adequate, and the study design and conduct was consistent with the relevant ICH guidelines (S1B[15] and S1C(R2)[16]). The strain of transgenic mice used was appropriate for a dermally applied product. However, the doses used in this study exceeded the maximum tolerated dose with no mice in the mid dose female group or either high dose group surviving to the end of the study. The investigation of photocarcinogenicity in hairless mice is generally not recommended for pharmaceuticals (ICH guideline M3(R2)).[17] In addition, this study used dapsone

[13] International Conference on Harmonisation, "ICH Harmonised Tripartite Guideline: Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use [S2(R1)]", 9 November 2011.
[14] Dapsone exposure as AUC at the highest dose was 24,300 and 121,000 ng·h/mL.
[15] International Conference on Harmonisation, "ICH Harmonised Tripartite Guideline: Testing for Carcinogenicity of Pharmaceuticals (S1B)", 16 July 1997.
[16] International Conference on Harmonisation, "ICH Harmonised Tripartite Guideline: Dose Selection for Carcinogenicity Studies of Pharmaceuticals [S1C(R2)]", 11 March 2008.
[17] International Conference on Harmonisation, "ICH Harmonised Tripartite Guideline: Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorisation for Pharmaceuticals [M3(R2)]", 11 June 2009.

concentrations less than the proposed formulation (≤5% compared with 7.5%). The submitted studies therefore do not fully address the requirements of ICH guideline S1B. However, a number of published studies have also investigated the carcinogenic potential of dapsone in long term rodent studies. The available body of evidence was adequate for assessing the carcinogenic potential of dapsone.

Dapsone was not carcinogenic in rats that received daily oral doses of up to 15 mg/kg/day dapsone for 92 weeks in females and 100 weeks in males (RE >110).[18] Mesenchymal tumours of the spleen and peritoneum and thyroid tumours have been reported in rats at higher doses[19] (≥30 mg/kg/day; estimated RE of >460).[20] The carcinogenic potential was also investigated in mice in these published studies. No increase in tumour incidence was reported.

There was no increase in papilloma formation at the site of administration following dermal application of dapsone to Tg.AC mice. The high mortality and low dapsone concentrations used in surviving groups limit the predictive value of this study.

Dapsone did not enhance tumour formation in hairless mice exposed to UV irradiation before or after dosing. In contrast, dapsone appeared to reduce the incidence of tumours which was associated with attenuation of skin reactions (erythema and oedema). Increased residue was also observed at the test site, which may have decreased exposure of the skin to UVR. However, the effect could also be in part due to the pharmacological activity of dapsone, which includes attenuation of inflammation and ROS production. The clinical significance of these findings is unknown.

Together these data indicate that dapsone is carcinogenic in rats. However, these findings are unlikely to be of clinical relevance for the proposed indication due to relatively low systemic exposures.

Reproductive toxicity

The effects of oral dapsone on male and female fertility, embryofetal development and pre/postnatal development were investigated in SD rats, with embryofoetal development studies also conducted in NZW rabbits. Dapsone was administered to male rats for 9 weeks prior to mating which is appropriate. Female rats received dapsone from 2 weeks prior to mating through to GD17 in a combined fertility and embryofoetal development study; this approach is consistent with international guidelines for drugs in which the exposure changes with time. Rabbits were dosed during the period of organogenesis (GD6-18). In the pre/postnatal development study rats were dosed from implantation through to the end of lactation, which was extended from the standard 21 days to 28 days due to reduced weight in the high dose offspring. Overall, the range, design and conduct of studies were consistent with the relevant ICH guideline (S5(R2)).[21]

Relative exposure

See Table 5.

[18] Relative exposure extrapolated from Study ATLS-117 in which rats received oral doses of 3, 30 or 100 mg/kg/day dapsone. AUC_{0-24h} values were estimated based on 5x the 3 mg/kg/day dose and half the 30 mg/kg/day dose which gave values ranging from 31,250-126,000 ng·h/mL.
[19] Griciute L, Tomatis L. Carcinogenicity of dapsone of mice and rats. *Int J Cancer.* 25: 123-129 (1980); National Toxicology Program. Bioassay of dapsone for possible carcinogenicity. *Natl Cancer Inst Carcinog Tech Rep Ser.* 20: 1-97 (1977).
[20] In the NTP study, dapsone was administered at ≥600 ppm in the diet, which gives an approximate daily dose of 30-60 mg/kg/day PO.
[21] International Conference on Harmonisation, "ICH Harmonised Tripartite Guideline: Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility [S5(R2)]", 9 November 2000.

Table 5: Relative exposure in reproductive toxicity studies

Species	Study [Study no.]	Dose (mg/kg/day)	AUC_{0-24h} (ng·h/mL)	Exposure ratio#
Rat (SD)	Male fertility [Study ATLS-183]	0.25	551	2.0
		0.5	1,061	3.8
		1	2,303	8.2
		2	4,469	16
Rabbit (NZW)	Embryofetal development [Study ATLS-116^]	3	1720	6.1
		30	30,600	109
		100	80,200	284
		300	252,000	894
Human (Acne vulgaris patients)	steady state; dermal [Study CSR 225678-004]	[150 mg]	282	–

= animal:human plasma AUC_{0-24h}; ^ = this was a pilot study, the pivotal study used doses of 6, 30 and 150 mg/kg/day

Maximum relative exposures were high in the reproductive toxicity studies using pregnant rabbits. Low to moderate exposures were achieved in the male fertility studies. Toxicokinetic data were not reported for pregnant rats. However, the doses used in the combined fertility and embryofoetal development study (12, 30 and 75 mg/kg/day PO) were associated with very high exposures in non-pregnant rats. Studies of placental transfer and excretion into milk of dapsone were not submitted. Case reports indicate that dapsone crosses the placenta and is also excreted into milk in humans.[22]

Dapsone decreased the number of corpora lutea and implantations in female rats (≥30 mg/kg/day PO; RE 894).[23] The no effect level for effects on corpora lutea and implantations was 12 mg/kg/day (RE ~350).[24] In male rats, 9 weeks oral treatment with dapsone decreased sperm motility at doses of ≥2 mg/kg/day, and also sperm count and density at doses of ≥3 mg/kg/day (RE values of 16 and 24, respectively). These effects were reversible, and did not affect the mating performance or fertility index of male rats at lower doses. At higher doses, the reduced sperm numbers and motility led to a reduction in implantations and viable embryos (≥12 mg/kg/day; RE 95).[25]

Dapsone was not teratogenic in rats or rabbits that were dosed daily during the period of organogenesis with up to 75 or 150 mg/kg/day PO, respectively (RE ~1400 in rats and >400 in rabbits). At the highest doses tested, dapsone decreased live litter size due to an increase in early resorptions in both species. Maternal toxicity was also evident at these doses (decreased weight gain and/or adverse clinical signs). No other adverse effects were observed in the embryofoetal development studies. The no effect levels for embryocidal effects were 30 mg/kg/day in both species (RE of 894 in rats and 109 in rabbits).

Increased still births occurred in rats that received daily oral doses of ≥12 mg/kg/day dapsone from implantation through to the end of lactation (RE ~350).[26] The rate of stillbirths in rats that received 30 mg/kg/day exceeded the level expected based on

[22] Hocking, DR. Neonatal haemolytic disease due to dapsone. *Med J Aust.* 1: 1130-1131 (1968); Sanders SW, et al. Hemolytic anemia induced by dapsone transmitted through breast milk. *Annals of Internal Medicine* 96: 465-466 (1982).
[23] Based on AUC_{0-24h} values in female rats that received 30 mg/kg/day dapsone PO for 3 months in Study ATLS-117.
[24] Extrapolated from AUC_{0-24h} values in female rats that received 30 mg/kg/day dapsone PO for 3 months in Study ATLS-117.
[25] Extrapolated from AUC_{0-24h} values in male rats that received 2 mg/kg/day dapsone PO for ~3 months in Study ATLS-183.
[26] Based on AUC_{0-24h} values in female rats that received 30 mg/kg/day dapsone PO for 3 months in Study ATLS-117.

historical data (2.9% compared with 0-1.5%).[27] An increased rate of stillbirths (1.8%) was also observed in rats that received the excipient, DGME (see DGME excipient). In addition, pup weight at birth and during lactation were decreased in the offspring of rats that received 30 mg/kg/day dapsone PO, which also decreased maternal weight gain during gestation and in the early stages of lactation (to LD4). Maternal exposure to dapsone did not have any other effects on pup growth after weaning, or on sexual development and reproductive performance, or on learning.

Pregnancy classification

The sponsor has proposed Pregnancy Category B3.[28] This category is consistent with the adverse effects observed in animals and the limited human data. However, the Pregnancy Category requires the consideration of the Clinical Delegate based on reported adverse effects in humans such as neonatal anaemia.[29]

Local tolerance

Local tolerance was assessed in repeat dose toxicity studies as well as in specialised local tolerance studies. Repeated dermal application of up to 10% dapsone in up to 40% DGME was well tolerated in mini-pigs, rats and rabbits in studies of 1, ≤6 and ≤9 months duration, respectively. Similarly, dapsone was not a primary skin irritant in rabbits following a single application of 1 or 5% dapsone to intact or abraded skin. The only study that used the clinical formulation of 7.5% dapsone was a 3 month dermal study in rats. There were no clear signs of dermal irritation. However, the site of application was not occluded and the systemic exposure indicated oral ingestion of the test substance. Therefore, dermal contact with the clinical formulation may have been limited due to grooming. Overall, the available data do not indicate any significant concern for dermal irritation.

Ocular irritation was investigated in one *in vitro* study (bovine cornea opacity and permeability [BCOP]), and in two in vivo studies in rabbits. Administration of 1 and 5% dapsone into the eye of rabbits did not produce ocular irritation. However, as the dapsone concentration and excipients differed from the proposed formulation these studies have significant limitations. In the BCOP assay, application of the proposed clinical formulation of dapsone did not adversely affect the permeability or opacity of the cornea. The results identified that dapsone did not require classification as an ocular irritant. However, the irritation induced by the positive control was less than expected, suggesting reduced sensitivity of the assay. The excipient, 30% DGME, was a mild ocular irritant (see DGME excipient). Overall, the available evidence indicates a potential for the proposed clinical formulation of dapsone to cause mild ocular irritation.

Antigenicity

Dapsone did not induce immediate or delayed hypersensitivity reactions following dermal application of 1 or 5% topical gels to guinea pigs. However, the clinical formulation was not tested.

[27] Lang, PL. Historical Control Data for Development and Reproductive Toxicity Studies using the Crl:CD®BR Rat (1993).
[28] 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.
[29] Hocking, DR. Neonatal haemolytic disease due to dapsone. *Med J Aust.* 1: 1130-1131 (1968).

Phototoxicity

Skin irritation was not observed following single or repeated dermal administration of up to 10% dapsone in combination with UV irradiation in guinea pigs and rats. Similarly, 5% dapsone in 25% DGME did not induce a photoallergic reaction in guinea pigs. These data indicate a low phototoxicity potential for dapsone.

DGME excipient

The proposed formulation of 7.5% dapsone contains 30% DGME. The predicted daily dermal DGME dose in humans is 600 mg/day (15 mg/kg/day),[30] assuming application of 2 g dapsone gel. Studies were submitted which investigated the pharmacokinetics and toxicity of DGME to support the proposed formulation. In addition, DGME was included in the dapsone formulation used in many of the repeat dose toxicity studies using dermal administration (2 and 4 week studies in mice, 3 and 6 months in rats, 3 and 9 months in rabbits and 1 and 3 months in mini-pigs). As clinical exposure to DGME following Aczone use was not provided, all relative exposure estimates below are based on body surface area.[31]

DGME had high oral bioavailability. Metabolism was extensive, with ethoxyethoxyacetic acid being the major metabolite which is excreted mainly in the urine. Published data indicate that the dermal bioavailability is ~50%.[32]

DGME had a very low order of acute oral toxicity (LD50 >5 g/kg). Similarly, DGME was well tolerated in rabbits that received daily dermal application of 1000 mg/kg/day for 4 weeks (RE 26). However, there were limitations in the extent of the histopathology investigations. In repeat-dose toxicity studies of dapsone that included DGME in the control article there were no signs of DGME toxicity in rats or rabbits (400 mg/kg/day; REs of 5 and 10). Published data indicate that the kidney is a target organ for DGME toxicity in mice, rats and dogs at high oral doses.[33] DGME was not mutagenic in bacteria and was also negative in two *in vivo* genotoxicity assays (mouse micronucleus and rat liver unscheduled DNA synthesis). In addition, there was no increase in tumour formation in rats that received 540 mg/kg/day PO DGME for 92 weeks (RE 7).

In reproductive toxicity studies, DGME had no clear effect on male of female fertility at doses up to 2000 mg/kg/day PO (RE 26). DGME was not teratogenic at ≤2000 mg/kg/day PO, but this dose level was associated with decreased maternal weight gain. There was a dose related increased in skeletal variations in the offspring of rats that received ≥1000 mg/kg/day PO (RE 13; incomplete ossification of cranial, facial and mandibular bones, asymmetric sternebrae and extra ribs). There was an increase in stillbirths in a rat pre/postnatal development study in dams that received 180 mg/kg/day dermal DGME from implantation through to the end of lactation (RE 2).

Local tolerance studies demonstrated that DGME was a mild ocular irritant. DGME did not induce acute dermal irritation in rabbits. However, very slight dermal reactions were observed at the site of administration in the repeat dose toxicity study conducted in rabbits.

[30] Assuming a 40 kg body weight in patient aged ≥12 years.
[31] The following conversion factors were used to convert GDME dose from mg/kg to mg/m^2: 31 for humans (assuming a 40 kg 12 year old); 6 for rats; 12 for rabbits; 20 for dogs.
[32] Osborne DW. Diethylene glycol monoethyl ether: an emerging solvent in topical dermatology products. *J Cosmet Dermatol.* 10: 324-329 (2011); Sullivan DW Jr, et al. A review of the nonclinical safety of Transcutol, a highly purified form of the diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient. *Food Chem Toxicol.* 72: 40-50 (2014).
[33] Sullivan DW Jr, et al. A review of the nonclinical safety of Transcutol, a highly purified form of the diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient. *Food Chem Toxicol.* 72: 40-50 (2014).

Together these data indicate little overall concern regarding the use of DGME at 30% in dapsone topical gel. However, the increased incidence in stillbirths at relatively low estimated DGME exposure and mild ocular irritation are of toxicological concern.

Paediatric use

Dapsone is proposed for use in patients aged 12 years or over. No specific studies in juvenile animals were submitted. As oral dapsone is indicated for use in children, the lack of juvenile animal studies is not considered a deficiency.

Impurities

The proposed specifications for two impurities in the drug substance are below the ICH qualification thresholds. However, they have not been assessed for potential mutagenicity and therefore do not meet the requirements of published guidelines.[34] One degradant in the drug substance was adequately qualified.

Nonclinical summary and conclusions

Summary

- The submitted dossier was in accordance with the relevant ICH guideline for the nonclinical assessment of pharmaceutical medicines (ICH M3(R2)).[35] The overall quality of the nonclinical dossier was high, with all pivotal safety related studies being GLP compliant.
- Pharmacology studies were not submitted, which is acceptable for an application to extend the indications of an already registered medicine. Literature publications support the claimed anti-microbial and anti-inflammatory activity of dapsone.
- Overall, the pharmacokinetic profile in animals appeared to be qualitatively similar to that of humans. Dapsone was poorly absorbed following dermal application (≤25%), with less than dose proportional systemic exposure. Plasma half-life was long in animals, with repeated dosing leading to increased systemic exposure. Plasma protein binding of dapsone was approximately 70% in rodents and humans, based on published data. Volume of distribution indicated extensive tissue distribution, but penetration into the brain, spinal cord and reproductive tissues was not investigated. The main human metabolite (N-acetyl dapsone) was a significant metabolite in animals. The toxic human metabolite, dapsone hydroxylamine, was present in rats (in particular males) and rabbits. Available data indicate little or no formation of DHA in mice or mini-pigs. Drug related material was excreted predominantly via urine in humans, but urinary excretion appeared to be low in rats.
- Dapsone gel had a low order of acute oral toxicity in rats.
- Repeat dose toxicity studies by the dermal route were conducted in mice (up to 4 weeks), rats (up to 6 months), rabbits (up to 9 months), and by the oral route in rats (3 months). Two studies were also conducted in mini-pigs, but these were not considered as pivotal studies. Maximum exposures (AUC) were low in mice following dermal application, but moderate to very high in rats and rabbits. High relative exposures for

[34] US Food and Drug Administration, "M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk Guidance for Industry", May 2015.
[35] International Conference on Harmonisation, "ICH Harmonised Tripartite Guideline: Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorisation for Pharmaceuticals [M3(R2)]", 11 June 2009.

the toxic metabolite, dapsone hydroxylamine, were also demonstrated in rats. Target organs for toxicity included known effects of dapsone on the haematopoietic system (anaemia and methaemoglobinaemia), spleen (changes secondary to anaemia), liver (elevated liver enzymes) and kidney (pigmentation, iron accumulation, vacuolation and increased blood urea nitrogen and albumin). In addition, dapsone was associated with CNS effects (mice only; hyperactivity, ataxia, lethargy), thyroid hypertrophy and/or hyperplasia in rodents, uterine dilatation in rats, inflammation of mesenteric fat in rats, and left ventricular hypertrophy with or without myocyte degeneration in the heart of mice.

- Dapsone was not mutagenic in the bacterial mutation assay or genotoxic *in vivo* (in the mouse and rat micronucleus test and rat skin comet assay). Dapsone was clastogenic *in vitro* (in CHO cells) but not *in vivo*. Overall, the weight of evidence indicates little genotoxic concern for the proposed indication.
- No treatment related increase in tumour incidence was observed in a two year rat carcinogenicity study that used oral dosing which yielded systemic exposures >110 that expected at the MRHD. However, published data report that dapsone is carcinogenic in rats at higher doses (mesenchymal tumours and thyroid tumours). These are unlikely to be of clinical relevance given the low systemic exposure to dapsone with the proposed dosing regimen. A transgenic mouse study using dermal application of dapsone to Tg.AC mice was submitted, but the high mortality rate in this study limits its predictive value.
- Dapsone decreased sperm motility at doses which yielded a relative exposure of ≥16. Male fertility was functionally impaired in male rats treated with dapsone at exposure levels ≥95x the clinical AUC. Dapsone also impaired female fertility (decreased corpora lutea and implantations), but only at very high relative exposures (~900x or more than the expected clinical AUC).
- Dapsone was not teratogenic in rats or rabbits at very high relative exposures (>400x), but there was an increase in early resorptions at these doses. This known embryocidal effect of dapsone is unlikely to be of clinical concern with the proposed dosing regimen. Dapsone increased the rate of stillbirths and decreased pup weight and growth during lactation in a pre/postnatal study in rats, also at very high relative exposures. However, the excipient DGME also increased stillbirths at an estimated relative exposure of 2x. There were no other effects of dapsone or DGME on growth, development or reproductive function in the offspring of dams treated with dapsone from implantation through to the end of lactation.
- Concentrations of up to 10% dapsone did not induce dermal irritation, and up to 5% dapsone did not cause ocular irritation *in vivo*. *In vitro*, the clinical formulation of 7.5% dapsone was not identified as an ocular irritant when applied to bovine cornea.
- There was no clear evidence of phototoxicity or photoallergy in rats or guinea pigs which received single or repeated dermal application of dapsone in combination with UV exposure. A photocarcinogenicity study in hairless mice indicated that dapsone did not augment the papilloma development in response to UV irradiation.
- Studies and literature publications demonstrated that the excipient, DGME:
  - had moderate dermal bioavailability (~50%).
  - a low order of acute toxicity
  - appeared well tolerated following repeated to oral administration in rats and dermal application to rabbits at doses exceeding the maximum expected human dose based on body surface area by at least 5x.

- was not genotoxic (*in vitro* or *in vivo*) and was not carcinogenic in rats at the single dose tested.
- did not affect male or female fertility, and was not teratogenic. High oral doses of DGME given throughout the period of organogenesis led to an increase in skeletal variations (incomplete ossification, extra ribs). As reported above, DGME increased the rate of still births at low estimated relative exposure (2x based on body surface area)
- was not a dermal irritant (even when undiluted), but was a mild ocular irritant in *in vivo* studies (using concentrations ≥30%).

· The proposed limits for two impurities in the drug substance meet the qualification limits, but require investigation of their genotoxic potential as they exceed the less-than-lifetime limit. One degradant in the drug product has been adequately qualified.

Conclusions and recommendation

· There were no major deficiencies in the nonclinical data.

· Only limited pharmacokinetic data were provided for metabolism and excretion. This is not a major concern given the relatively low systemic exposure to dapsone.

· The main toxicities observed were known effects (anaemia and methaemoglobinaemia, liver enzyme elevation and renal injury). These effects were observed at high relative exposures and are of limited clinical concern.

· The available data indicate that topical dapsone does not pose a genotoxic or carcinogenic risk.

· Impaired male fertility was observed at relatively high dapsone exposures. High doses of dapsone increased early resorptions and decreased live litter size when administered during the period of organogenesis. Increased stillbirths were observed at high relative exposures to dapsone, but at low relative exposures to the excipient DGME. The proposed Pregnancy Category B3 is acceptable based on the animal findings. However, the Clinical Delegate should consider whether case reports of adverse effects in human pregnancy warrant a different Pregnancy Category.

· Mild ocular irritation may occur clinically due to the presence of 30% DGME in the proposed formulation.

· There are no nonclinical objections to the registration of 7.5% dapsone gel for the proposed indication provided adequate warning regarding the potential for stillbirths associated with the excipient are including in the PI.

· The sponsor was requested to revise the proposed PI document as directed at Round 1. For Round 2, the PI should be further revised as directed.

· The RMP evaluator should consider comments on the accuracy of the nonclinical statements in the RMP as shown.

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

Clinical rationale

Acne vulgaris is the most common dermatological disorder in the US where it is estimated to affect approximately 40 to 50 million people. It is most common in adolescents, affecting approximately 80%, but may also occur in 54% of adult women and 40% of adult men. Globally, acne vulgaris is the eighth most prevalent disease (645.5 million patients).[36] In a study published in 1998, the prevalence was 93% in 16- to 18-year-old students in Victoria, Australia.[37]

Acne vulgaris is a complex skin disorder involving multiple abnormalities of the pilosebaceous unit, including: (1) hyperkeratinisation, (2) increased sebum production, (3) bacterial proliferation, and (4) inflammation. The face, anterior trunk, and upper back are the most commonly affected areas due to a greater concentration of sebaceous glands in these areas. Clinically, acne is graded according to the number and types of lesions present: open and closed comedones, inflammatory papules, pustules, cysts, nodules, and even scarring may be seen.

A number of topical and systemic products are approved in Australia for treatment of acne vulgaris. The pharmacologic categories of therapies for acne vulgaris include topical retinoids (for example, adapalene, tazarotene, and tretinoin), topical antibiotics (for example, erythromycin and clindamycin), topical benzoyl peroxide, oral retinoids (for example, isotretinoin), and systemic hormonal therapies (for example, ethinyl oestradiol/levonorgestrel). Combination therapy utilising agents with complementary mechanisms (such as an antimicrobial and a topical retinoid) is often prescribed in the management of acne vulgaris, since most anti-acne medications do not act against all of the major pathophysiologic processes or types of lesions of acne vulgaris.

Despite the well-known role of inflammation in acne, no primarily anti-inflammatory topical therapy is currently available in Australia for treatment of acne. Aczone 7.5% provides both the anti-inflammatory and antimicrobial properties of dapsone while greatly limiting the risk of complications associated with systemic exposure from oral administration of dapsone for acne vulgaris.

Guidance

There is no adopted EU guideline relating to the treatment of acne.

Contents of the clinical dossier

The submission contained the following clinical information:

- 1 x clinical pharmacology studies, including 1 that provided pharmacokinetic data and none that provided pharmacodynamic data
- 2 x pivotal efficacy/safety studies
- 3 other efficacy/safety studies related to the 7.5% gel
- Studies related to 5% gel
  - 3 x clinical pharmacology studies, including 3 that provided pharmacokinetic data and none that provided pharmacodynamic data

[36] Hay RJ, et al. The global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. *J Invest Dermatol.* 134:1527-1534 (2014).
[37] Kilkenny M, et al. The prevalence of common skin conditions in Australian school students: 3. acne vulgaris. *Br J Dermatol.* 139: 840-5 (1998).

- 1 x pivotal efficacy/safety studies
- 3 x other efficacy/safety studies

· 2 x other (Integrated Summary of Efficacy, Integrated Summary of Safety tabulations)

Paediatric data

The submission included paediatric pharmacokinetic and efficacy and safety data.

Good clinical practice

The study reports state that all studies were conducted in compliance with Good Clinical Practice (GCP). For subjects under age of 18, written minor assent and/or parental/guardian consent was obtained in accordance with local laws and appropriate ethics committee requirements.

There were a number of GCP compliance issues identified at one centre in the USA in Study 225678-006 and due to resulting concerns over data integrity, it was decided to exclude all 51 patients at that centre from all analysis populations in that study. Sensitivity analyses were performed to evaluate the impact of excluding those patients and the results of sensitivity analyses including patients from the centre were consistent with analyses excluding those patients.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 6 shows the studies relating to each pharmacokinetic topic.

Table 6: Submitted pharmacokinetic studies.

7.5% dapsone gel:

PK topic	Subtopic	Study ID	Primary aim
PK in special populations§	Bioequivalence† - Multi-dose	225678-004	Bioequivalence

5% dapsone gel:

PK topic	Subtopic	Study ID	Primary aim
PK in special populations§	Bioavailability – oral vs topical	DAP110	Bioavailability
	Dose Ranging	DAP9903	Dose range
PK interactions	Trimethoprim/sulfamethoxazole	03-0-182	Interaction

† Bioequivalence of different formulations.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

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

Evaluator's conclusions on pharmacokinetics

It is difficult to assess the PK of dapsone 7.5% gel when so little information is provided on this strength and formulation. The majority of the data presented is for the dapsone 5% gel. There is very minimal systemic absorption of dapsone from 5% gel applied twice daily and as the 7.5% gel provides less dapsone exposure than 5% gel applied twice daily it would appear even less likely to be of any significant systemic absorption of dapsone from the 7.5% gel.

Pharmacodynamics

Studies providing pharmacodynamic data

No studies were submitted related to the pharmacodynamic action of dapsone. The information provided comes from selected literature references. A formal literature based submission was not done.

Evaluator's conclusions on pharmacodynamics

No new information on pharmacodynamics was provided.

Dosage selection for the pivotal studies

The pivotal studies evaluated dapsone 7.5% formulation 11080X with once-daily dosing. This dapsone 7.5% formulation was evaluated in a 5-week Phase 1 PK study (Study 225678-004), the results of which indicated that dapsone 7.5% formulation dosed once daily demonstrated systemic exposures 28.6% and 28.7% lower than Aczone 5% dosed twice daily (as defined by the geometric mean ratio for C_{max} and AUC_{0-24}, respectively), and was therefore not expected to raise additional safety concerns. It was anticipated that simplification of the dosing regimen from twice daily to once daily would be more convenient to patients and yield better compliance compared with twice daily dosing with 5% gel.

Efficacy

Studies providing efficacy data

Pivotal efficacy studies:

- Study 225678-006: A Safety and Efficacy Study to Compare Dapsone Dermal Gel with Vehicle Control in Patients with Acne Vulgaris
- Study 225678-007: A Safety and Efficacy Study to Compare Dapsone Dermal Gel with Vehicle Control in Patients with Acne Vulgaris

Other efficacy studies:

- The sponsor provided 5 additional studies conducted using dapsone 5% gel which had a different formulation and was applied twice daily.

Evaluator's conclusions on efficacy

The sponsor has claimed this submission is a proposed extension of indication but the sponsor does not have an existing approved product to which this is an extension. Further, in addition to a proposed extension of indication, this submission is also for a proposed

new dosage from and a new route of administration. The submission is clearly based on the US application where the product is a new strength and dose regimen as a 5% gel formulation is approved for the treatment of acne and has been marketed for many years.

Also, the whole application is premised on the efficacy of the 5% gel which is not approved in Australia. The reformulation of the product resulted in a 7.5% gel which can be applied once per day, rather than the twice per day of the 5% gel. The once a day application of 7.5% gel results in lower systemic absorption.

Only 1 study is provided which compares the 5% gel applied twice day and the 7.5% gel applied once per day and efficacy was not 1 of the primary objectives of the study. Study 225678-004 was a PK and safety study of 28 days treatment duration. Efficacy measures were only an exploratory objective and while all efficacy measures were comparable between treatment groups, the 28 days treatment period was really too short to evaluate efficacy effectively.

The efficacy then rests on 2 placebo (vehicle) controlled trials of similar design in which treatment was assessed after 12 weeks of treatment. The trials are of significant size with a total of 4,340 patients treated (2,162 on active and 2,178 on vehicle) and the results of the trial are consistent, demonstrating that the 7.5% gel was statistically significantly better than vehicle in GAAS and both inflammatory and non-inflammatory lesion counts.

To support the efficacy studies the sponsor provided 3 studies using the 5% gel applied twice daily. While the 5% gel is a different formulation the results indicate that the 5% gel was statistically significantly better than vehicle in GAAS and both inflammatory and non-inflammatory lesion counts.

The studies show that twice a day therapy with 5% gel is effective and once a day therapy with 7.5% gel is acceptable. The real clinical question is: is 7.5% once a day therapy better or at least equal to 5% twice a day therapy? Is the 7.5% gel better because of the lower systemic exposure? No data is presented that the 5% gel poses any safety issues. Should the sponsor have submitted the twice daily 5% gel rather than the 7.5% gel?

This cannot be answered from the data in this submission as there is no comparative study. Why this was not done is unclear. Can the 7.5% gel be approved rather than the 5%? The sole reason for the 7.5% appears to be compliance and yet no data is presented to state that there is a problem with compliance in the proposed patient population.

While it is difficult to compare results from different studies the following table compares the results for the primary and secondary results collated from the studies of the 2 formulations.

Table 7: Comparison of results from dapsone 7.5% and dapsone 5% clinical studies.

Measure	Variable	Aczone 7.5%	Vehicle	P-value Difference
Dapsone 7.5% gel (pooled studies)				
	N	2162	2178	
GAAS	Success [a] (%)	29.8	21.1	< 0.001
Total lesion count	Mean reduction from baseline	36.5	32.0	< 0.001
	% Change from baseline	48.8	42.8	< 0.001
Inflammatory lesion count	Mean reduction from baseline	15.8	13.9	<0.001
	% Change from baseline	54.6	48.1	< 0.001
Non-inflammatory lesion count	Mean reduction from baseline	20.7	18.0	<0.001
	% Change from baseline	45.1	39.4	< 0.001
Dapsone 5% gel				
Study DAP004	N	330	166	
GAAS	Success [a]	26.7	18.7	0.042
Total lesion count	Mean reduction from baseline	28.5	18.3	<0.001
	% Change from baseline	32.0	21.9	0.001
Inflammatory lesion count	Mean reduction from baseline	12.8	9.3	0.003
	% Change from baseline	37.2	26.6	0.001
Non-inflammatory lesion count	Mean reduction from baseline	15.7	9.2	0.004
	% Change from baseline	27.5	16.8	0.001
Study DAP0203	N	745	7400	
GAAS	Success [a]	44.2	35.9	0.0003
Total lesion count	Mean reduction from baseline	30.4	24.6	0.0001
	% Change from baseline	38.3	32.0	0.0004
Inflammatory lesion count	Mean reduction from baseline	113.7	12.3	0.0265
	% Change from baseline	45.9	41.7	0.0302
Non-inflammatory lesion count	Mean reduction from baseline	16.4	12.1	0.0001
	% Change from baseline	31.1	23.9	0.0022
DAP0204	N	761	764	
GAAS	Success [a]	36.9	29.8	0.0017
Total lesion count	Mean reduction from baseline	28.4	21.7	0.0001
	% Change from baseline	37.4	29.3	<0.0001
Inflammatory lesion count	Mean reduction from baseline	14.3	12.0	0.0001
	% Change from baseline	47.6	40.3	<0.0001
Non-inflammatory lesion count	Mean reduction from baseline	13.9	9.7	0.0001
	% Change from baseline	29.6	21.1	<0.0001

a. Percentage of patients with 0 or 1 score

While comparisons across studies are not ideal, the results for the studies appear to be comparable.

In the long term (12 months) study with the 5% gel (DAP0114) efficacy was observed as early as Month 1 and showed further improvement throughout the 12-month treatment period. The mean percent reduction from Baseline to Month 12 was -58.2% for inflammatory lesions, -19.5% for non-inflammatory lesions, and -49.0% for total lesions.

Safety

The Aczone 7.5% safety profile is based on analyses from 6 clinical studies conducted in 4,741 subjects/patients (328 healthy subjects and 4,413 patients with acne vulgaris), of

whom 2,547 subjects/patients received at least one dose of Aczone 7.5%. In the 2 pivotal phase 3 studies, Aczone 7.5% and vehicle were applied once daily for up to 12 weeks in 4,336 patients with acne vulgaris. Across the 4 Phase I studies, Aczone 7.5% was applied topically for up to 6 weeks.

Studies providing safety data

The following studies provided evaluable safety data.

Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- General AEs were assessed by examining and interviewing the patient at each study visit
- Laboratory tests were not done in the pivotal studies.
- Local tolerability (face only) was assessed based on patient-rated stinging/burning, and investigator or trained evaluator assessments of dryness, scaling, and erythema. Dryness, scaling, and erythema were to be assessed by the same person throughout the study whenever possible.
  - Stinging and burning on the face was defined as a prickling pain sensation within 5 minutes after dosing for post-baseline visits and was rated by the patient as follows:
    - None (0) = No stinging/burning
    - Mild (1) = Slight warm, tingling/stinging sensation; not really bothersome
    - Moderate (2) = Definite warm, tingling/stinging sensation that was somewhat bothersome
    - Severe (3) = Hot, tingling/stinging sensation that had caused definite discomfort
  - Dryness was defined as brittle or tight sensation and rated by the investigator/trained designee as follows:
    - None (0) = No dryness
    - Mild (1) = Slight but definite roughness
    - Moderate (2) = Moderate roughness
    - Severe (3) = Marked roughness
  - Scaling was defined as abnormal shedding of the stratum corneum and rated by the investigator/trained designee as follows:
    - None (0) = No scaling
    - Mild (1) = Barely perceptible shedding, noticeable only on light scratching or rubbing
    - Moderate (2) = Obvious but not profuse shedding
    - Severe (3) = Heavy scale production
  - Erythema was defined as abnormal redness of the skin and rated by the investigator/trained designee as follows:
    - None (0) = No erythema
    - Mild (1) = Slight pinkness present

- § Moderate (2) = Definite redness, easily recognised
- § Severe (3) = Intense redness

· Vital signs including heart rate, systolic/diastolic blood pressure, and body temperature were recorded at each study visit

· Physical examination was done at each study visit

Pivotal studies that assessed safety as a primary outcome

Not applicable.

Dose-response and non-pivotal efficacy studies

· Laboratory testing was done in the Phase I studies for the 7.5% gel and in the 5% gel studies. The test included haematology (white blood cell count [WBC] with differential, red blood cell count [RBC], red blood cell morphology/blood film, haemoglobin concentration [Hg], haematocrit value [HCT], mean corpuscular volume, mean corpuscular haemoglobin. and platelet count); serum chemistry (glucose, urea nitrogen creatinine, total protein, albumin. calcium, phosphorus, electrolytes [Na, K, Cl], bicarbonate [HCO3], total cholesterol. triglycerides, total bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, creatinine kinase, and lactate dehydrogenase)

Clinical pharmacology studies

Individual study summaries including safety are provided. No new safety issues were identified.

Patient exposure

See Tables 8-11.

Table 8: Exposure in the clinical development programme for Aczone 7.5%

Study Number	Duration	Regimen	Test Product	Number of Evaluable Subjects/Patients [a]	
				Safety Population	Receiving Aczone 7.5%
Phase III studies					
225678-006	12 weeks	Applied topically to the face and acne-affected areas once daily	Aczone 7.5% gel	2101	104 4
225678-007	12 weeks	Applied topically to the face and acne-affected areas once daily	Aczone 7.5% gel	2235	111 7
Total in pooled safety analysis (Studies 225678-006 and 225678-007):				4336	216
Phase I studies					
225678-004	28 days	2 grams of 3 dapsone 7.5% gel formulations (dosed once daily) or dapsone 5% gel (dosed twice daily) applied topically	Aczone 7.5% gel	77	5 8
225678-009	~6 weeks	200 µL per occlusive patch applied to the left upper back (up to 22 patches per subject)	Aczone 7.5% gel	237	23 7
225678-010 [b]	1 day	0.2 g per occlusive patch applied to the upper back (2 patches per subject)	Aczone 7.5% gel	33	3 3
225678-011	~6 weeks	200 µL per occlusive patch applied to the upper back (14 patches per subject)	Aczone 7.5% gel	58	5 8
Total in all studies:				**4741**	**254**

a. Subjects/patients who were enrolled in the studies (excluding study centre 16078 in Study 225678-006) and who received a dose of study product (safety population); b. Due to an equivocal phototoxicity finding on day 4, one subject had a retest, receiving an additional application of Aczone 7.5% at 2 sites. This subject received a total dose of 0.8 g of Aczone 7.5%.

Table 9: Exposure to study treatment (Safety population) – Pooled studies 225678-006 and 225678-007.

Duration	Statistic	Treatment Group	
		Aczone 7.5% (N = 2161)	Vehicle (N = 2175)
Study duration (days) [a]	N	2161	2175
	Mean (SD)	82.6 (13.64)	82.6 (12.77)
	Median	85.0	85.0
	Min to max	6 to 168	6 to 160
Treatment duration (days) [b]	N	2161	2175
	Mean (SD)	79.4 (17.05)	79.7 (16.54)
	Median	84.0	84.0
	Min to max	1 to 147	1 to 124
Cumulative exposure (N [%])	At least 1 day	2161 (100.0)	2175 (100.0)
	At least 4 weeks	2083 (96.4)	2093 (96.2)
	At least 8 weeks	2013 (93.2)	2036 (93.6)
	At least 12 weeks	1296 (60.0)	1302 (59.9)

Max = maximum; Min = minimum; SD = standard deviation

a. Study duration is defined as date of study exit minus date of first dose plus 1. If the date of exit is missing, the date of the last visit was used; b. Treatment duration is defined as date of last dose minus date of first dose plus 1.

Table 10: Clinical study exposure to Aczone 7.5% w/w by age group and gender: All studies.

Total population				
Age group	**Persons**		**Person-Years**	
Gender	**Male**	**Female**	**Male**	**Female**
12-17 years	634	454	138	100
≥ 18 years	416	1043	76	169
Total	1050	1497	214	268

Table 11: Clinical study exposure to Aczone 7.5% w/w by ethnic or racial origin: All studies.

Ethnic/racial origin	Persons	Person-Years
Caucasian	1468	282
Black	468	87
Asian	87	18
Hispanic	430	76
Other	94	19
Total	2547	482

Safety issues with the potential for major regulatory impact

Not applicable.

Post marketing data

There is no post marketing data with Aczone 7.5% in the submission.

A post-marketing review of safety information was reported through 31 December 2014 for dapsone 5% gel. The AEs showed no pattern as to the nature or severity of the events to indicate a change to the benefit-risk profile of dapsone 5%. However, methaemoglobinaemia is included in both the US approved Package Inserts for the 5% gel and the 7.5% gel based on 2 post-marketing cases of methaemoglobinaemia (1 spontaneous and 1 literature report).[38]

Evaluator's conclusions on safety

It is stated that based on the lower systemic exposure with Aczone 7.5% compared with dapsone 5%, the results of the dapsone 5% studies, including the long term, open label Study DAP0114 that demonstrated safety and continued efficacy of dapsone 5% over 12 months an agreement was made with the US FDA that the sponsor (Allergan) was not required to conduct a long term safety study or a thorough QT/QTc study with Aczone 7.5%, and did not have to include an assessment of systemic safety (for example, laboratory analyses or ECG monitoring) in the Phase III studies of Aczone 7.5%.

The safety is therefore based on only 2 studies of 12 weeks duration plus 4 phase 1 studies of duration of 1 dose to ~6 weeks.

In Phase I dermal tolerability studies (Studies 225678-009, 225678-010, and 225678-011), Aczone 7.5% did not show any potential for cumulative irritation, sensitisation, phototoxicity, or photoallergy under the conditions employed in the studies.

No new safety issues have been identified in the clinical studies with the 7.5% gel.

[38] Swartzentruber GS, et al. Methemoglobinemia as a complication of topical dapsone. Poster session presented at: American College of Medical Toxicology Annual Scientific Meeting; 28-30 Mar 2014; Phoenix, AZ.

Application site reactions were common but appear to be similar to that seen with the 5% gel although this is hard to assess. A good summary of the local adverse reactions for 5% gel is provided in the approved US Package Insert as it is not addressed in the Clinical Summaries.

First round benefit-risk assessment

First round assessment of benefits

The benefits of Aczone 7.5% gel in the proposed usage are:

- Consistent results in 2 identical randomised, vehicle controlled studies
- Combined results in the 2 pivotal studies demonstrated a benefit in both the primary outcomes – global acne score and lesion counts
- The combined results in the 2 pivotal studies showed on average, a 55% reduction in inflammatory lesions and a 45% reduction in non-inflammatory lesions over a 12 week treatment period which was statistically significantly better ($p<0.0001$) than results for vehicle
- Results were sustained through 12 weeks (results with 5% gel twice daily demonstrated continued efficacy through 52 weeks)
- Incidence of skin reactions was low and no indication of sensitisation or phototoxicity
- No new safety issues were identified in the clinical studies

First round assessment of risks

The risks of Aczone 7.5% gel in the proposed usage are:

- Skin reactions particularly skin dryness and application site pruritus are most common
- Methaemoglobinaemia has been reported for oral dapsone and in post-marketing experience with topical dapsone 5%
- Concomitant treatment with dapsone and TMP/SMX may increase the likelihood of haemolysis in patients with G6PD deficiency

First round assessment of benefit-risk balance

The benefit-risk balance of Aczone 7.5% gel, given the proposed usage, is favourable.

The efficacy results are consistent in the clinical studies and appear comparable to the 5% gel applied twice daily.

The results of Phase IV Study ACZ ACN 01 showed no evidence of haemolytic anaemia in G6PD-deficient patients with acne who were treated with dapsone 5%, and any minor changes in haemoglobin were not associated with any other evidence of haemolysis. In the pivotal studies with Aczone 7.5% applied once daily there was no clinical evidence of haemolysis or haemolytic anaemia. Concomitant treatment with dapsone and TMP/SMX may increase the likelihood of haemolysis in patients with G6PD deficiency. Methaemoglobinaemia has been reported for oral dapsone and in post marketing experience with topical dapsone 5% and so remains a risk for the 7.5% gel.

First round recommendation regarding authorisation

Based on the data presented, it is recommended that the application be approved for the indication requested.

Clinical questions

None

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted an Australian Risk Management Plan (AUS-RMP) version 1.0 dated 29 October 2015 (data lock point 31 May 2015), which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 12.

Table 12: Ongoing safety concerns.

Important identified risks	Methaemoglobinaemia
Important potential risks	Haemolytic anaemia
Missing information	Use in children under the age of 12 years Use during pregnancy and lactation

RMP evaluator comment

It is recommended that the 'Local cutaneous irritation' and 'Hypersensitivity are added to the AUS-RMP as 'important identified risks' to reflect advice in the draft PI.

The sponsor states in the AUS-RMP that patients with severe cystic acne, acne conglobate, acne fulminans, and secondary acne have been excluded from clinical trials because the two clinical trials were designed to test the product in the treatment of moderate acne. It is recommended that 'use in patients with more severe forms of acne: severe cystic acne, acne conglobate, acne fulminans' be listed as missing information in the RMP.

The evaluator has noted that patients who had undergone certain topical acne treatment have been excluded from clinical trials:

- 1 week: phototherapy devices (for example, ClearLight), energy based devices, adhesive cleansing strips (for example, Pond's, Biore), or cosmetic procedures (for example, facials, peeling, comedo extraction)
- 2 weeks: anti-inflammatory drugs, salicylic acid (for example, Clearasil, Clean & Clear); corticosteroids, antibiotics, antibacterials (including benzoyl peroxide containing products [for example, benzamycin]), retinoids; other topical acne treatments (for example, photodynamic therapy, medicated soaps such as those containing benzoyl peroxide, salicylic acid, sulfur, or sodium sulfacetamide)

These are commonly seen treatments in the community including over-the-counter and cosmetic products. The evaluator has noted that these patients were excluded to minimise

confounding factors. However, the safety of sequential use of topical products/procedures, especially the increased risk of skin irritation, inflammation and hypersensitivity remains unclear. Therefore, it is recommended that 'use in patients who have undergone phototherapy, anti-inflammatory treatment, and other topical acne treatment' is listed as 'missing information'.

Therefore, it is recommended that the following safety concerns are added to the AUS-RMP:

- Local cutaneous irritation [important identified risk]
- Hypersensitivity [important identified risk]
- Use in patients with more severe forms of acne: severe cystic acne, acne conglobate, acne fulminans [missing information]
- Use in patients who have undergone phototherapy, anti-inflammatory treatment, and other topical acne treatment [missing information]
- Ocular irritation associated with systemic exposure to the excipient DGME [important potential risk]
- Stillbirths associated with systemic exposure to the excipient DGME [important potential risk]

Pharmacovigilance plan

Routine pharmacovigilance activities[39] have been proposed to monitor all the safety concerns. The sponsor has not proposed any additional pharmacovigilance activities.

RMP evaluator comment

The evaluator has noted the requirement of a post-authorisation paediatric study by the US FDA. The sponsor should add this to the pharmacovigilance plan. Significant safety findings should be reported to the TGA for assessment at the same time as they are reported to the overseas regulators.

Risk minimisation activities

The sponsor has not proposed additional risk minimisation activities.

RMP evaluator comment

The sponsor should provide justification to why it considers routine risk minimisation[40] is sufficient for all the safety concerns and no additional risk minimisation is required.

- Potential for overdose

The sponsor states in the AUS-RMP:

> *Aczone 7.5% w/w gel is not for oral use. Overdosage information with Aczone 7.5% w/w is unavailable. If oral ingestion occurs, the patient should be monitored and appropriate supportive measures should be administered as necessary.*

- Potential for transmission of infectious disease

[39] Routine pharmacovigilance practices involve the following: (a) All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner; (b) Reporting to regulatory authorities; (c) Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling; (d) Submission of Periodic Safety Update Reports (PSURs); and (e) Meeting other local regulatory agency requirements.

[40] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the PI or by careful use of labelling and packaging.

The sponsor states in the AUS-RMP:

> *There are no products of animal or human origin used in the manufacturing of Aczone 7.5% w/w. Aczone 7.5% w/w is manufactured and filled under controlled conditions. The potential for the transmission of infectious agents is therefore remote.*

· Potential for misuse for illegal purposes

The sponsor states in the AUS-RMP:

> *There is no evidence to suggest that Aczone 7.5% w/w is a drug product with abuse potential and there are no concerns regarding diversion.*

· Potential for off-label use

The sponsor states in the AUS-RMP:

> *It is not anticipated that Aczone 7.5% w/w will be used off-label for the treatment of diseases outside of the indication.*

· Potential for paediatric off-label use

The sponsor states in the AUS-RMP:

> *Aczone 7.5% w/w is indicated for children aged 12 years and older. Significant acne in patients 7 to 11 years of age is unusual and typically a marker of early puberty. Preadolescent acne demonstrates a considerable predominance of comedonal lesions rather than inflammatory lesions.[41] The face is most commonly affected, particularly the forehead, nose, and chin, and the trunk is usually substantially less affected. Preadolescent acne is typically mild[42] and therefore is often untreated[43] but may be a marker for more severe acne later in adolescence.*
>
> *There is no postmarketing data with Aczone 7.5% w/w. Allergan has investigated postmarketing use of dapsone 5% in children under the age of 12 years and found this to be negligible. On the basis of Aczone (dapsone) Gel 5% prescription data available from IMS from January 2012 through to December 2012, Allergan calculated that the absolute number of total prescriptions for Aczone was 1734 for children in the age range from birth to 11 years compared with 125,814 prescriptions for children aged 12 to 17 years. On further in-depth analysis of total prescriptions used for paediatric patients from birth to 11 years for treatment of acne, Aczone (dapsone) Gel 5% has limited market share of < 1%. Although these data indicate there has been off-label prescribing of Aczone® 5% by physicians, the data confirm that Aczone (dapsone) Gel 5% is not used for the treatment of a substantial number of patients below 12 years of age. Therefore, it is not predicted that physicians would choose to treat patients in the age range from birth to 11 years with Aczone 7.5% w/w topical gel.*
>
> *Allergan is unaware of any therapeutic uses for Aczone 7.5% w/w topical gel in paediatric patients beyond the treatment of acne vulgaris.*
>
> *It should be noted that the safety and effectiveness of Aczone 7.5% w/w in children under 12 years of age has not been established. This information is adequately described in the proposed Product Information.*

[41] Lucky AW, et al. Acne vulgaris in early adolescent boys. Correlations with pubertal maturation and age. *Arch Dermatol.* 127: 210-6 (1991); Lucky AW, et al. Predictors of severity of acne vulgaris in young adolescent girls: results of a five-year longitudinal study. Lucky AW, et al. *J Pediatr.* 130: 30-9 (1997).
[42] Friedlander SF, et al. The acne continuum: an age-based approach to therapy. *Semin Cutan Med Surg.* 30(3 Suppl): S6-11 (2011).
[43] Eichenfield LF, et al. Tretinoin microsphere gel 0.04% pump for treating acne vulgaris in preadolescents: a randomized, controlled study. *Pediatr Dermatol.* 29: 598-604 (2012).

RMP evaluator comment

The sponsor's assessment on the issue of overdose, potential for transmission of infectious disease, misuse for illegal purposes, and potential for off-label use are acceptable.

The evaluator has noted that the sponsor's post-market data indicates that there has been off-label use of Aczone 5% w/w gel in paediatric population under < 12 years. This lower strength formulation of Aczone 5% is not available in Australia. Given that the proposed indication for the 7.5% w/w gel does not exclude comedonal lesions, it is likely that the 7.5% w/w gel could be used off-label in children < 12 years of age with comedonal lesions. However, the evaluator has also noted that 'use in children < 12 years of age' is listed as missing information in the RMP, and this advice is provided in the draft PI. The evaluator considers that the sponsor has provided satisfactory routine risk minimisation for 'use in children < 12 years' at this stage.

Reconciliation of issues outlined in the RMP report

The following section summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA RMP reviewer, and the RMP reviewer's evaluation of the sponsor's responses.

Recommendation #1 in RMP evaluation report

Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated Section 31 request and/or the nonclinical and clinical evaluation reports 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, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

Sponsor response

Allergan would like to advise TGA that the draft PI has been amended as required to incorporate all the changes recommended in the nonclinical evaluation report and most of the changes recommended in the clinical evaluation report. All of these changes are provided as annotations with comments in the draft PI provided.

Evaluator's comment

The sponsor's response is satisfactory.

Recommendation #2 in RMP evaluation report

5% dapsone has been approved for twice daily topical application in the US since 2005 for acne vulgaris. The evaluator has noted that the application in the US has been approved by the US FDA in February 2016. The sponsor should provide an update on the overseas regulatory action since 31 May 2015.

Sponsor response

Allergan would like to advise the TGA that the Overseas Regulatory Action Section has been updated as required.

Evaluator's comment

The sponsor's is satisfactory. The evaluator has noted the updated table of foreign regulatory status. No new regulatory actions due to safety issues are identified through the updates.

Recommendation #3 in RMP evaluation report

It is recommended that the following safety concerns are added to the AUS-RMP:

- Local cutaneous irritation [important identified risk]
- Hypersensitivity [important identified risk]
- Use in patients with more severe forms of acne: severe cystic acne, acne conglobate, acne fulminans [missing information]
- Use in patients who have undergone phototherapy, anti-inflammatory treatment, and other topical acne treatment [missing information]
- Ocular irritation associated with systemic exposure to the excipient DGME [important potential risk]
- Stillbirths associated with systemic exposure to the excipient DGME [important potential risk]

Sponsor response

As per the recommendations of the RMP Evaluator, Allergan agrees to add the following safety concerns to the RMP:

- Local cutaneous irritation as an important identified risk
- Use in patients with more severe forms of acne: severe cystic acne, acne conglobata, acne fulminans as missing information.
- Use in patients who have undergone phototherapy, anti-inflammatory treatment, and other topical acne treatment as missing information.

Allergan proposes to include Hypersensitivity as an important potential risk, rather than an important identified risk, until such time that we receive data that credibly links hypersensitivity with our product. As an important potential risk, any reports of hypersensitivity events will be presented in detail in all Periodic Safety Update Reports (PSURs). At such time, if such events link with the use of Aczone 7.5% w/w, Allergan would change the risk definition in the RMP.

Allergan proposes not to include Ocular irritation associated with systemic exposure to the excipient DGME as an important potential risk in the RMP. There is no evidence from nonclinical studies that systemic exposure to DGME causes ocular irritation. A single adverse event related to ocular irritation was reported in Study 225678-007; a patient randomised to Vehicle (contained DGME 30%) reported an adverse event of Eye irritation, which was non-serious, mild and considered by the investigator not to be related to treatment. There were no reports of ocular irritation from Studies 225678-004, 225678-006, 225678-009, 225678-010 and 225678-011. A postmarketing search up until 30 June 2016 revealed 2 reports of ocular irritation for 5% dapsone, both non-serious; no cases were revealed for 7.5% dapsone.

Allergan proposes not to include Stillbirths associated with systemic exposure to the excipient DGME as an important potential risk. 7.5% dapsone has a topical route of administration and has been used only by 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 foetus having been observed. Pregnancy and Lactation are already included as missing information in the RMP and will remain categorised that way. As such, all reports of pregnancy complications and outcomes, including any pregnancies resulting in stillbirth, would be described in PSURs. Allergan therefore, is of the opinion that inclusion of stillbirth due to systemic exposure to DGME should not be a requirement for the proposed topical Aczone formulation.

Evaluator's comment

The sponsor's response is acceptable. Pending the TGA Delegate's decision on the submission, the sponsor should provide the updated RMP to the TGA within three months following the approval.

Recommendation #4 in RMP evaluation report

The evaluator has noted the requirement of a post-authorisation paediatric study by the US FDA. The sponsor should add this to the pharmacovigilance plan. Significant safety findings should be reported to the TGA for assessment at the same time as they are reported to the overseas regulators.

Sponsor response

Allergan would like to advise the TGA that the Company will incorporate this requirement to the pharmacovigilance plan. Any significant safety findings will be reported to the TGA for assessment at the same time as they are reported to the overseas regulators.

Evaluator's comment

The sponsor's response is acceptable.

Recommendation #5 in RMP evaluation report

The following recommendations are made in the nonclinical evaluation report. The sponsor should address the following comments.

- There are some discrepancies in the doses at which adverse effects were observed in the male fertility studies. These are described in the comments on the Product Information in the Nonclinical Evaluation Report (under Effects on fertility)
- There were two important potential risks for the excipient, DGME. These are (i) an increase in stillbirths at low relative exposure, and (ii) ocular irritation. These findings should be captured in the RMP.
- Some signs of hepatotoxicity (elevated liver enzymes) and nephrotoxicity (BUN and albumin elevation and histopathology changes) were observed at high exposures in nonclinical studies, and these should be reported for completeness.
- The conclusion regarding dermal carcinogenicity should be qualified by the limitations of the study; all mice receiving 10% dapsone died prematurely, as did all female mice receiving 5% dapsone. This compromised the predictive value of this study. In addition, the published carcinogenic potential for dapsone in rats should be acknowledged.
- The RMP evaluator should be aware that the Pregnancy Category stated in the Risk Minimisation Measures may change and therefore may require updating.

Sponsor response

Allergan would like to advise the TGA that the draft PI has been amended as required, to incorporate all the changes recommended in the nonclinical evaluation report. Please refer to the responses above.

All of these changes are provided as annotations with comments in the draft PI provided.

Allergan would like to further advise the TGA that the Company will incorporate the risks to the AUS-RMP once the Delegate's Overview has been received and the RMP is to be finalised. Please see response above.

Evaluator's comment

The sponsor's response is acceptable. The adequacy of the PI is to be determined by the TGA Delegate.

Recommendation #6 in RMP evaluation report

The evaluator has noted that there is a lack of consistent clinical classification for acne and different countries and professional bodies tend to use different classification systems. The sponsor uses 'Global acne assessment score (GAAS)'. The sponsor states in the PI that the clinical trials were conducted on patients with 'moderate acne vulgaris' ('Clinical studies', PI), which is grade 3 on the GAAS, while it is unclear whether the indication of 'acne vulgaris' is limited to grade 3 acne only or not. The evaluator recommends that the Delegate considers the ambiguity in the proposed indication.

Sponsor response

Allergan agrees with the evaluator that there are different classification systems used to evaluate the overall acne severity. The Global Acne Assessment Score (GAAS) is a static ordinal scale with five severity grades (reported only in integers, for example, 0 to 4) that was previously used during the development of Aczone (dapsone) 5% w/w gel. Therefore for consistency and ability to allow comparisons in calculations of the sample size between both strengths, this scale was also used in the Aczone (dapsone) 7.5% w/w gel pivotal studies.

In order to determine treatment or efficacy success the pivotal Phase III studies were conducted in patients meeting severity criteria of 'moderate acne vulgaris (grade 3)' and with the following lesion counts criteria of a minimum of 20 but not more than 50 inflammatory lesions (papules and pustules) on the face and a minimum of 30 but not more than 100 noninflammatory lesions (open comedones and closed comedones) on the face. However, Allergan believes the indication of acne vulgaris is appropriate. This would align with the wording of the PI recently approved by the United States (US) FDA for Aczone (dapsone) 7.5% w/w gel on February 24, 2016 which includes that Aczone (dapsone) 7.5% w/w gel is currently indicated for the treatment of acne vulgaris with no specific limitation on the acne severity.

Evaluator's comment

The sponsor's response is noted. The recommendation to the TGA Delegate remains for the Delegate's consideration.

Recommendation #7 in RMP evaluation report

In regard to the proposed routine risk minimisation activities, the evaluator has noted that patients who had undergone certain topical acne treatment have been excluded from clinical trials:

- 1 week: phototherapy devices (for example, ClearLight), energy based devices, adhesive cleansing strips (for example, Pond's, Biore), or cosmetic procedures (for example, facials, peeling, comedo extraction)
- 2 weeks: anti-inflammatory drugs, salicylic acid (for example, Clearasil, Clean & Clear); corticosteroids, antibiotics, antibacterials (including benzoyl peroxide containing products [for example, benzamycin]), retinoids; other topical acne treatments (for example, photodynamic therapy, medicated soaps such as those containing benzoyl peroxide, salicylic acid, sulfur, or sodium sulfacetamide)

These are commonly seen treatments in the community including over-the-counter and cosmetic products. It is recommended to the Delegate that the sponsor should provide advice on whether concomitant treatment is allowed or should be avoided in the PI and CMI to improve safety and to provide clear guidance.

Sponsor response

As noted by the evaluator, the products excluded from use in the Aczone (dapsone) 7.5% w/w gel pivotal trials are commonly used over-the-counter and/or cosmetic products.

These products are typically excluded from pivotal trials to avoid confounding of efficacy assessments. These products were not excluded due to safety concerns. Therefore Allergan does not believe that there is any specific safety reason that would require further advice with regard to use of these products within the Aczone PI or CMI.

Evaluator's comment

The sponsor's response is noted.

The evaluator has noted the comments regarding concomitant use with topical benzoyl peroxide and drugs that induce methamoglobinaemia in the draft PI:

> *Topical Benzoyl Peroxide*
>
> § *Topical application of Aczone 7.5% w/w gel followed by benzoyl peroxide in patients with acne vulgaris may result in a temporary local yellow or orange discolouration of the skin and facial hair.*
>
> *Concomitant Use with Drugs that Induce Methaemoglobinaemia*
>
> § *Concomitant use of Aczone 7.5% w/w gel with drugs that induce methaemoglobinaemia such as sulfonamides, acetaminophen, acetanilide, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, paraaminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine and quinine may increase the risk for developing methaemoglobinaemia (See Precautions).*

The sponsor has agreed to add 'use in patients who have undergone phototherapy, anti-inflammatory treatment, and other topical acne treatment' as missing information and monitor the safety. These are acceptable at this stage.

Summary of recommendations

Outstanding issues

Issues in relation to the RMP

Details on the following outstanding issues:

- TGA recommendation: The sponsor's response is acceptable – they have agreed to add the recommended safety concerns or provided adequate justification not to. Pending the TGA Delegate's decision on the submission, the sponsor should provide the updated RMP to the TGA within three months following the approval.
- TGA recommendation: the sponsor's response regarding the use of different acne classification systems is noted. The recommendation to the TGA Delegate on the indication remains for the Delegate's consideration.

Comments on the safety specification of the RMP

Clinical evaluation report

TGA's Prescription Medicines Authorisation Branch (PMAB) has provided the following comments in the clinical evaluation report:

> *The Safety Specifications in the draft RMP are satisfactory.*

Nonclinical evaluation report

Recommendations provided in the first round nonclinical evaluation report has been included in the first round RMP evaluation report. No new recommendations on the RMP documents were made in the second round nonclinical evaluation report.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether or not they are included in the currently available version of the RMP document. The suggested wording is:

> *Implement AUS-RMP version 1.0 dated 29 October 2015 (data lock point 31 May 2015) and any future updates as agreed with TGA.*

VI. Overall conclusion and risk/benefit assessment

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

Quality

The development and manufacture of the Aczone dapsone 7.5% w/w topical gel was based on an existing dapsone 5% w/w topical gel currently marketed in the US. Quantities of the solubiliser, DGME, were increased proportionally, and a new thickener was used. No further changes were made, and the proposed commercial formulation is identical to that used in the toxicology and clinical studies.

There are some minor issues that are expected to be resolved (related to drug product specification for particle size distribution and GMP clearance). Otherwise, the submission was acceptable in terms of chemistry and quality control.

Nonclinical

Dapsone was not teratogenic in rats or rabbits at very high relative exposures (>400x), but there was an increase in early resorptions at these doses. This known embryocidal effect of dapsone is unlikely to be of clinical concern with the proposed dosing regimen. Dapsone increased the rate of stillbirths and decreased pup weight and growth during lactation in a pre/postnatal study in rats, also at very high relative exposures. However, the excipient DGME also increased stillbirths at an estimated relative exposure of 2x. There were no other effects of dapsone or DGME on growth, development or reproductive function in the offspring of dams treated with dapsone from implantation through to the end of lactation. High oral doses of DGME given throughout the period of organogenesis led to an increase in skeletal variations (incomplete ossification, extra ribs). The bioavailability of DGME is around 50% after topical application. This information is included in the PI. There is limited data for the use of topical dapsone during pregnancy.

There were no nonclinical objections to approval.

Clinical

The sponsor has proposed a 7.5% gel for once daily use to improve patient compliance. However there was no evidence of compliance being a problem with the twice daily formulation.

Pharmacology

Pharmacokinetics

48 Subjects with mild-moderate acne were treated with 1% or 5% dapsone given once or twice daily to deliver a total daily dose of 10-100 mg of dapsone. There was little difference between 1% gel given once or twice daily. The 5% gel resulted in greater systemic absorption. The twice daily administration resulted in 50% C_{max} and 20% increase in AUC.

Table 13: Study DAP9903: Summary of Day 28 PK parameters of plasma dapsone by treatment group.

PK Parameter	1% Once Daily		5% Once Daily		1% Twice Daily		5% Twice Daily	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
C_{max} (ng/mL)	5.537	(4.380)	10.828	(6.985)	6.291	(3.406)	15.117	(7.496)
T_{max} (hr)	11.4	(9.15)	10.9	(7.52)	8.52	(6.74)	7.49	(8.65)
$AUC_{(0-24)}$ (ng*hr/mL)	280.1	(240.0)	524.0	(286.1)	290.4	(146.0)	678.9	(360.2)
$T_{½\ el}$ (hr)	31.9	(8.88)	30.5	(8.37)	30.1	(9.99)	27.8	(8.31)

Bioavailability of 5% gel compared to oral tablet

18 patients were treated with the 5% gel twice daily to the face, back, chest and shoulders at a mean dose of 2 g/day (equivalent to 110mg/day dapsone) for 14 days. This was compared to a dose of 100 mg oral dapsone after a 14-day washout. The exposure after oral dapsone was 100 times greater than the topical gel.

Bioavailability of the 7.5% compared to the 5% gel

Once daily 7.5% gel was compared to twice daily 5% gel applied for 28 days. The AUC and C_{max} were around 28% lower with the once daily 7.5% gel compared to the twice daily 5% gel.

Efficacy

There were two identical efficacy studies, 225678-006 and 225678-007.

Both were 12 week RCT of dapsone 7.5% gel compared to vehicle gel. Inclusion criteria: patients aged over 12 years with acne grade 3 using the global acne assessments core, 20-50 inflammatory lesions and 30-100 non-inflammatory lesions. Patients with severe acne or who were using other topical treatments were excluded. The co-primary efficacy endpoints were GAAS and lesion count at week 12. This is consistent with that described in the FDA guidelines for acne. However, it is important to note that the GAAS is a subjective scale and the use of photographs to standardise responses between centres is not described in the protocol. It is also noted that there were a number of protocol deviations related to untrained people using the GAAS. Secondary endpoints are described.

Around 90% of patients completed the study. The study population was reasonably representative of the patients in the community who would have acne.

Table 14: Primary efficacy analysis at Week 12 – Pooled studies 225678-006 and 225678-007 (ITT population).

Measure	Variable	Treatment Group		P-value Difference 95% CI
		ACZONE 7.5% (N = 2162)	Vehicle (N = 2178)	
GAAS	Success [a]	29.8% (27.9%, 31.8%)	21.1% (19.3%, 22.8%)	< 0.001 [b] 8.8% [c] (6.1%, 11.4%)
Inflammatory lesion count	Change from baseline	-15.8 (baseline about 30)	-13.9	< 0.001 [e]
				-1.9 (-2.55, -1.20)
Non-inflammatory lesion count	Change from baseline	-20.7 (baseline about 48)	-18.0	< 0.001 [e]
				-2.7 (-3.74, -1.59)

The difference in GAAS was seen by Week 8. The difference between inflammatory lesions was seen by week 2, but a difference in non-inflammatory lesions was not seen until week 8. Although the 7.5% gel had approximately a 50% decrease in inflammatory lesion count and 40% reduction in non-inflammatory lesion count, the relative improvement to the vehicle was small, 2 inflammatory lesions and < 3 non-inflammatory lesions.

Compared to the 5% gel, the 7.5% gel had similar reduction from baseline but less relative improvement than the vehicle. This may be a reflection of the patient population or severity of acne at baseline.

Secondary endpoints: Analyses for the Acne Symptom Impact Score (ASIS)

A greater proportion of the dapsone 7.5% group compared with the vehicle group reported "Very good" or "Excellent" in ASIS Item 10 (facial appearance) at each assessment and showed further improvement throughout treatment; at Week 12, the difference between groups was statistically significant in favour of dapsone 7.5% group (23.8%) versus the vehicle group (19.2%) (p = 0.015), but the absolute difference was small.

Table 15: Study 225678-006: ASIS Item 10: Proportion of patients who reported 'Very good' or 'Excellent' at each follow-up visit (ITT population).

Visit (Week)	Number (%)		p-value [a]	Difference	95% CI [b]
	Dapsone 7.5% (N = 910)	Vehicle (N = 913)			
4	83 (9.1)	67 (7.3)	0.153	1.8%	(-0.7%, 4.4%)
8	143 (15.7)	118 (12.9)	0.083	2.8%	(-0.4%, 6.1%)
12	217 (23.8)	175 (19.2)	0.015	4.7%	(0.9%, 8.5%)

Table 16: Study 225678-007: ASIS Item 10: Proportion of patients who reported 'Very good' or 'Excellent' at each follow-up visit (ITT population).

Visit (Week)	Number (%)		p-value [a]	Difference	95% CI [b]
	Dapsone 7.5% (N = 926)	Vehicle (N = 961)			
4	93 (10.0)	84 (8.7)	0.336	1.3%	(-1.3%, 3.9%)
8	151 (16.3)	128 (13.3)	0.069	3.0%	(-0.2%, 6.2%)
12	224 (24.2)	211 (22.0)	0.252	2.2%	(-1.6%, 6.0%)

Analyses of ASIS at visits other than Week 12

At each assessment the number of subjects reporting "Very good" or "Excellent" in the ASIS Item 10 (facial appearance) in the dapsone 7.5% group compared with the vehicle group was not statistically significant.

Safety

Safety data included 2 Phase III studies in 4336 patients treated with topical 7.5% dapsone for 12 weeks, and 2 Phase I studies where 7.5% dapsone was used for up to 6 weeks.

In the clinical trials, AE were found in 18.3% patients treated with Aczone 7.5% and 18.8% with vehicle.

Table 17: TEAEs that occurred in ≥ 1% of patients in any treatment group by System Organ Class (Safety Population): Pooled Studies 225678-006 and 225678-007.

System Organ Class	Adverse Event (Preferred Term)	Number (%) of Patients	
		Aczone 7.5%	Vehicle
Overall		396 (18.3)	409 (18.8)
General disorders and administration site conditions	Overall	95 (4.4)	92 (4.2)
	Application site dryness	26 (1.2)	22 (1.0)
	Application site pruritus	23 (1.1)	14 (0.6)
	Application site pain	11 (0.5)	33 (1.5)

In clinical studies using 5% gel, no safety signals were identified.

Routine laboratory tests were not performed in any of the studies involving dapsone7.5%. safety haematology and laboratory tests were done at baseline and week 12 in the 3 pivotal trials for 5% gel. No significant changes were reported.

The dermal tolerance was similar for the vehicle and 7.5% dapsone gel.

There was no evidence of cumulative sensitisation, phototoxicity or photosensitisation.

A Phase IV safety study was performed in patients with G6PD deficiency (defined as G6PD value below the lower limit of normal at the reference laboratory (7 U/gHb) as a post approval commitment to the FDA. There were 56 subjects who were at least 50%

compliant with the 5% dapsone gel twice daily regime. After 2 weeks, the mean change from baseline in Hb was -0.32g/dL in the dapsone group and 0.01g/dL in the vehicle control.

After 12 weeks of treatment, there were no significant differences between the two groups. There were no AE for haemolytic anaemia.

Risk management plan

Table 18 compares Summary of Safety Concerns.

Table 18: Summary of Safety Concerns: comparison.

	EU	Additional terms in ASA
Important identified risks	Methaemoglobinaemia	Local cutaneous reaction
Important potential risks	Haemolytic Anaemia	Hypersensitivity
Missing information	Use in children under the age of 12 years Use during pregnancy and lactation	Use in patients with more severe acne Use in patients who have undergone phototherapy, anti-inflammatory treatment, or other topical treatment

Ocular sensitivity and stillbirths associated with the use of excipient DMGE were not considered potential risks by the sponsor as clinical studies and use of the 5% topical gel had not been associated with such AEs. Routine pharmacovigilance and risk minimisation are proposed. There is an ongoing paediatric study.

Risk-benefit analysis

Delegate's considerations

Efficacy:

- The Delegate's main concern is whether the small improvement in acne score is clinically sufficient to describe the efficacy.
- There is no comparison of 7.5% dapsone to placebo or other currently approved treatments for acne
- The patient population is not well defined in the indications – is it mild, moderate or severe acne?

Safety:

- There is a lack of long term safety data
- There is minimal data for the use of 7.5% dapsone with other topical treatments
- The toxicology delegate mentioned some concerns of the excipient DMGE
  - Potential increase risk of stillbirths at 2 X systemic exposure

- USA PI: "There are no adequate and well controlled studies in pregnant women. Aczone Gel, 7.5%, should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus"
- The delegate would recommend the wording in the Australian PI be strengthened to state ' Aczone should not be used during pregnancy' in view of the potential risk of still birth with a small increase in systemic exposure, high concentration of DMGE in the gel, lack of data in humans

Questions for sponsor

1. Is there any information about the use of the gel vehicle alone versus no treatment of a different cream/lotion for acne?
2. What is the status of any paediatric studies?
3. Does dapsone exert anti-microbial activity on skin flora?
4. In the nonclinical studies, the systemic exposure increased with increasing duration of use. What is the maximal duration of use where systemic exposure has been measured in humans? Is there evidence of increased systemic exposure with increased duration of use? Please include data for DMGE and dapsone.

Question for clinical experts/ACPM

5. Is it appropriate to use the gel vehicle as a comparator?
6. Are the results clinically significant?
7. What proportion of patients with acne of this severity would have resolution of their lesions with no treatment over 12 weeks?
8. Is the indication appropriate or should it specify the severity of acne?
9. Where would this product be placed in the treatment algorithm for acne?

Summary of issues

· Are the primary endpoints robust and clinically meaningful?

· Is their sufficient safety data?

Advice sought

· Is efficacy satisfactorily established?

Pre ACPM preliminary assessment

The Delegate is not in a position to say, at this time, that the application for Aczone should be approved for registration.

Response from sponsor

Allergan Australia Pty Ltd refers to the Delegate's Overview and Request for ACPM's advice, and does not concur with the Delegate's preliminary assessment that they

> *are not in a position to say, at this time, that the application for Aczone 7.5% should be approved for registration*

Allergan would point out the unusual lateness of these questions in the evaluation time line. These types of questions would normally be raised in the Section 31 Consolidated

Questions and the fact that these have been included at the pre-ACPM stage has resulted in less time for us to reply. We would also point out that the original Delegate for this evaluation did not see a need to request ACPM advice, given the fact that the Clinical Evaluator recommended for approval based on a positive risk benefit.

However, we understand the Delegate's request for further clarity on the clinical benefits of Aczone 7.5% and have therefore requested clinical opinion from four Key Opinion Leaders (KOLs) based in the US and in Australia. These KOLs have addressed the questions from the Delegate under the heading "Question for clinical experts/ACPM". In addition, Allergan has responded to the Questions for sponsor below. We believe our responses and the KOL commentary provided alleviate any concerns regarding the safety and efficacy of Aczone 7.5% and the benefit it will provide patients.

- *1. Is there any information about the use of the gel vehicle alone versus no treatment or a different cream/lotion for acne?*

Sponsor response

Allergan has not conducted any clinical study comparing the Aczone gel vehicle alone versus no treatment or a different cream/lotion for acne. However, as pointed out by the KOLs, it would be unnecessary to conduct such a study given that it is appropriate and indeed current practice to use the vehicle as a comparator when first trying to determine if the active formulation is statistically superior in efficacy based on primary and secondary endpoints.

- *2. What is the status of any paediatric studies?*

Sponsor response

Allergan has recently initiated a FDA required Post Marketing Requirement (PMR 3017-1) Study 1679-401-006 for NDA 207154 with First Patient Enrolled (FPE) achieved on October 31, 2016. This is an open label, Phase IV trial of Aczone 7.5%. The objective of the study is to evaluate the safety, tolerability and PK of Aczone 7.5% administered topically once daily for 12 weeks in 100 paediatric patients aged 9 to 11 years with acne vulgaris. Specifically for the PK patients, the peak and trough plasma drug concentration will be evaluated in at least 16 evaluable patients under maximal use conditions for the first 8 days (+2 days). In addition, the study will explore the efficacy of Aczone 7.5% administered topically once daily to 9 to 11 year olds with acne vulgaris.

- *3. Does dapsone exert anti-microbial activity on skin flora?*

Sponsor response

It is thought that dapsone inhibits growth of certain species of bacteria through inhibition of folic acid synthesis. Dapsone competitively inhibits dihydropteroate synthase, which is the enzyme responsible for the incorporation of paraaminobenzoic acid into dihydropteroic acid (the immediate precursor of folic acid).[44] Microorganisms that need to synthesise their own folic acid are sensitive to this class of compounds (sulfones), while bacteria that utilise folate from their environment are not affected. The mechanism through which dapsone ameliorates acne is unclear, although reducing the bacterial count may reduce the size and quantity of lesions by reducing inflammation. This provides an explanation of how dapsone may exert anti-microbial activity on the skin flora. Recently, an *in vitro* study assessed the antibiotic activity of dapsone versus various clinical gram-positive and gram-negative bacterial pathogens obtained from patients with infections.[45] Dapsone demonstrated relatively poor activity versus gram-negative bacilli but dapsone

[44] Coleman MD. Dapsone: modes of action, toxicity and possible strategies for increasing patient tolerance. *Br J Dermatol.* 129: 507-513 (1993).
[45] Zhanel GG, Del Rosso JQD: Activity of dapsone versus commumity and hospital pathogens from the CANWARD Study. *J Clin Aesthet Dermatol.* 9: 42-47 (2016).

demonstrated activity versus grampositive cocci, such as Staphylococcus, Streptococcus, and Enterococcus as well as strains of Enterococcus faecalis and several strains of Streptococcus agalactiae and Streptococcus pyogenes. However, clinical relevance of these *in vitro* finding is unknown.

- *4. In the nonclinical studies, the systemic exposure increased with increasing duration of use. What is the maximal duration of use where systemic exposure has been measured in humans? Is there evidence of increased systemic exposure with increased duration of use? Please include data for DGME and dapsone.*

Sponsor response

Systemic exposure of dapsone and its metabolites (N-acetyl dapsone and dapsone hydroxylamine) were measured in a clinical pharmacokinetics study, where male and female subjects 16 years of age or older with acne vulgaris (N = 19) received 2 grams of Aczone 7.5% topically to the face, upper chest, upper back and shoulders once daily for 28 days (Study 225678-004). Steady state for dapsone and its metabolites appeared to be reached within 7 days of dosing. Additional once daily dosing beyond Day 7 did not appear to increase the mean plasma trough concentrations for all 3 analytes.

Table 19: Study 225678-004: Mean Plasma Trough Concentrations Following Once Daily Topical Dermal Administration of Aczone 7.5% (ng/mL).

Day	Time (Hours)	Dapsone		N-Acetyl Dapsone		Dapsone Hydroxylamine	
		Mean	SD	Mean	SD	Mean	SD
1	0	BLQ	NC	BLQ	NC	BLQ	NC
7	0	10.7	5.7	5.67	5.82	0.883	0.495
14	0	11.7	5.6	5.86	4.95	1.01	0.63
18	0	10.5	5.4	5.45	5.02	0.844	0.482
21	0	11.1	5.5	5.56	5.27	0.936	0.545
26	0	10.4	5.8	5.43	5.10	0.835	0.555
27	0	10.5	5.9	5.60	5.58	0.862	0.593
28	0	11.1	6.5	5.52	4.89	0.860	0.475

BLQ = Below lower limit of quantitation; NC = Not calculable.

Allergan does not have any systemic exposure data of DGME following once daily administration of Aczone 7.5% in humans. However, systemic exposure of DGME was measured following twice daily administration of Aczone 5%. In Study DAP0110, male and female subjects 18 years of age or older with acne vulgaris (N = 18) received Aczone 5% topically to the face, upper back, shoulders, and upper chest twice daily for 14 days (average amount applied per day was 2.2 grams). The mean ± SD plasma DGME C_{max} (0.880 ± 0.884 µg/mL) and AUC_{0-24} (4.72 ± 6.03 µg·hr/mL) on Day 14 did not appear to be significantly increased when compared to the plasma DGME C_{max} (0.550 ± 0.564 µg/mL) and AUC_{0-24} (3.12 ± 5.17 µg·hr/mL) on Day 1.

As there were no apparent increase in systemic exposure of DGME following twice daily administration of Aczone 5% for 14 days in Study DAP0110, and the total daily dose of DGME from Aczone 7.5% once daily is approximately 40% less than that from Aczone 5% twice daily, Allergan believes that the systemic exposure of DGME would not be significantly different or increased following repeated once daily administration of Aczone 7.5%.

- *5. Is it appropriate to use the gel vehicle as a comparator?*

Sponsor response

It is appropriate to use the gel vehicle as a comparator in the pivotal Phase III trials during clinical development of Aczone 7.5%. Consistent with ICH E8,[46] the primary objectives of the Phase III trials are to confirm efficacy and establish the safety profile for Aczone 7.5%. As such, adequate, well controlled, double-blinded, randomised studies are required in order to minimise bias in the study. Randomisation and blinding in the studies were the two major factors in minimising the chance of bias. Randomisation avoids systematic differences between groups with respect to known or unknown baseline variables that could affect outcome. Blinding minimises the potential biases resulting from differences in management, treatment, or assessment of patients, or interpretation of results that could arise as a result of investigator knowledge of the assigned treatment.

As specified in ICH E10,[47] the choice of control group can greatly affect the degree in which bias in conducting and analysing the study can be minimised. The ICH guidance also outlines that there is one major purpose for the control groups and that is to allow discrimination of patient outcomes caused by the test treatment from outcomes caused by other factors, such as the natural progression of the disease, observer or patient expectations, or other treatment. The control group basically answers what would happen to the patient if they had not received the test treatment or if they had received a different treatment known to be effective.

As noted in ICH E10,[48] not all placebos are completely inactive. A specific example given is that of vehicle controls used in studies of topical skin preparations which may have beneficial activity. This does not impair the ability of the design to measure the specific effect of the test agent. Consistent with this guideline, the Aczone gel vehicle was used as a comparator to ensure that the study meets the requirement of a well-controlled, double blinded, randomised study so that the effectiveness of dapsone can be demonstrated. As specified in the guideline, if the chosen vehicle control may have harmful effects a "no treatment" arm would allow the measurement of the total effect of the test agent plus its vehicle. Consistent with the ICH guideline, the "no treatment" arm was not included in the Aczone 7.5% studies because the gel vehicle was not known to be associated with harmful effects. Therefore, the Aczone gel vehicle is the appropriate comparator.

Responses from the 4 KOLs also confirm that use of the gel vehicle as a comparator is appropriate as this is standard/common practice and routinely done in trials for topical products.

- *6. Are the results clinically significant?*

Sponsor response

Allergan conducted 2 pivotal Phase III multicentre, randomised, double blind, vehicle controlled trials of identical design to evaluate efficacy, safety and tolerability in patients 12 years of age and older with acne vulgaris (4,391 patients; 2153 and 2238, respectively). Both the individual study data (Study 225678-006 and 225678- 007)[49] and the pooled

[46] International Conference on Harmonisation, "General Considerations for Clinical Trials (E8)", 17 July 1997.
[47] International Conference on Harmonisation, "Choice of Control Group and Related Issues in Clinical Trials (E10)", 20 July 2000.
[48] International Conference on Harmonisation, "Choice of Control Group and Related Issues in Clinical Trials (E10)", 20 July 2000.
[49] Stein Gold LF, et al. Efficacy and Safety of Once-Daily Dapsone Gel, 7.5% for Treatment of Adolescents and Adults With Acne Vulgaris: First of Two Identically Designed, Large, Multicenter, Randomized, Vehicle-controlled Trials. *J Drugs Dermatol.* 15: 553-561 (2016); Eichenfield LF, et al. Efficacy and Safety of Once-Daily Dapsone Gel, 7.5% for Treatment of Adolescents and Adults With Acne Vulgaris: Second of Two Identically Designed, Large, Multicenter, Randomized, Vehicle-Controlled Trials. *J Drugs Dermatol.* 15: 962-969 (2016).

analysis of data[50] demonstrated the efficacy, safety, and tolerability of once-daily administration of Aczone 7.5% over 12 weeks of treatment.

The pooled analysis confirm that a large cohort of adolescents and adults, with substantial representation of both males and females and Caucasian and non-Caucasian patients were included in assessment of Aczone 7.5%. The primary endpoints (GAAS success rates and mean reduction in inflammatory and non-inflammatory lesion counts at Week 12) were statistically superior ($p<0.001$) for Aczone 7.5% treatment compared with vehicle. The clinical improvement in acne severity was supported by substantial decreases in inflammatory, non-inflammatory, and total lesion counts at Week 12. Significant differences ($p<0.05$) in favour of Aczone 7.5% compared with vehicle appeared early in treatment: by Week 2 for decreases in mean inflammatory lesion count and by Week 4 for total lesion counts (percentage change from baseline) (pooled analysis of data). These numerical values are consistent with the photographs in the abovementioned publications of the pivotal data and are considered clinically significant as individual studies or as the pooled analysis of the data.

Actual patient photos from the Phase III trials have been provided to demonstrate the impact of the benefit seen with Aczone 7.5% treatment. Thus, the results demonstrate that Aczone 7.5% applied topically once daily for 12 weeks is an effective treatment for acne vulgaris. This is supported by the statements from the KOLs who agree that the benefits to the patient of Aczone 7.5% treatment are clinically significant with even a change of one grade on the GAAS scale being seen as impactful on a patient's quality of life and similarly relevant from a physician's perspective.

For example, one KOL states:

> *Aczone can be used effectively in adolescents and adults with AV, regardless of gender, with the expectation that clinically relevant improvement will occur in most cases, especially as lack of cutaneous irritation will promote better adherence to treatment in the 'real world'.*

Another KOL states:

> *The clinical benefits seen are clinically significant. A change in the Global Acne Assessment Score of one grade is clinically significant from both the physician's perspective and also that of the patient including on patient quality of life.*

- *7. What proportion of patients with acne of this severity would have resolution of their lesions with no treatment over 12 weeks?*

Sponsor response

Since the objective of the pivotal Phase III studies was to assess safety and effectiveness of dapsone, the studies did not assess 'no treatment' effect over the 12 weeks of the study. Spontaneous resolution rate over the 12-week period in absence of any intervention is unknown. It should be noted, however, that improvement is typically seen with all types of locally applied non-comedogenic products such as drug vehicles or cosmetics as well as with placebo of orally administered products and reference arms of photodynamic therapy. The KOLs concur that it would be difficult to provide an absolute figure as acne is a chronic but fluctuating condition and 2 have provided an opinion that approximately 25% of patients may have resolution, perhaps temporarily, from their acne condition with no treatment.

- *8. Is the indication appropriate or should it specify the severity of acne?*

[50] Thiboutot DM, et al. Efficacy, Safety, and Dermal Tolerability of Dapsone Gel, 7.5% in Patients with Moderate Acne Vulgaris: A Pooled Analysis of Two Phase 3 Trials. *J Clin Aesthet Dermatol.* 9: 18-27 (2016).

Sponsor response

Allergan believes the indication of acne vulgaris is appropriate. This would align with the wording of the PI recently approved by the US FDA for Aczone 7.5% on 24 February 2016 which includes that Aczone 7.5% is currently indicated for the treatment of acne vulgaris with no specific limitation on the acne severity. The consensus from the KOLs supports this. Allergan would therefore request that the indication remain as is.

- *9. Where would this product be placed in the treatment algorithm for acne?*

Sponsor response

Allergan has raised this as a discussion point in a recent Advisory Board panel which included 7 KOLs in dermatology across Australia. Provided below is a summary of their comments which formed part of the minutes:

- *Defining the patient group*
  - *The clinical trials indicate that adult females have the most to gain from Aczone 7.5%. Persistent or late-onset acne in this group is a significant clinical challenge. Such patients often feel they are 'over' their acne problem, and have tried many products with varying degrees of success over the years.*
  - *However, younger women and males (especially adolescents) will also benefit. They are a substantial proportion of the potential market, and should not be neglected.*
  - *It is very positive to have a new option for patients who have 'tried everything', and also for those who are unwilling or unable to be treated with a retinoid.*
- *Combination treatment*
  - *Aczone 7.5% is likely to be an appropriate first-line monotherapy for less severe acne, especially in primary care. In more severe disease, use with a retinoid would be logical. In comedonal acne, it may a useful alternative to other strategies such as salicylic acid skin peels.*

The Australian KOLs whose statements are attached formed part of the above mentioned Advisory Board. Additionally, as stated in one of the KOL's statements, they are well aware of the acne algorithm guidelines as they sat on the Global Alliance panel upon which the Australian treatment algorithm is based. The two US KOLs additionally provide their expertise as to where Aczone 7.5% would be best placed in the treatment algorithm for acne based on their extensive experience.

Product Information

Allergan has made the amendments to the PI as suggested with the following exceptions:

- Allergan proposes not to include the following statement "The use of Aczone in pregnancy is not recommended" in the "Use in Pregnancy" section of the Product Information. Aczone 7.5% has a topical route of administration and has been used only by a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or observation of other direct or indirect harmful effects on the human foetus. Use of Aczone 7.5% during Pregnancy and Lactation is included in the RMP as missing information and, as such, all reports of pregnancy complications and outcomes will be described in Periodic Safety Update Reports. Currently, the PI states "There are no adequate and well controlled studies in pregnant women" and "Aczone 7.5% w/w gel should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus." In Allergan's assessment, this wording is an accurate reflection of the known benefit/risk profile of Aczone 7.5% w/w with regards to pregnancy and therefore, is of the opinion that there is no current need to state that Aczone 7.5% is not recommended during pregnancy. If new

information is obtained and/or a new safety signal occurs, Allergan will reassess and amend this section of the PI as appropriate.

- Based on the points listed below, as well as the relatively higher tolerability and lower AE profile seen with Aczone, Allergan respectfully disagrees with TGA on the "inclusion of the maximal total dose that can be applied per day":
  - Allergan has not conducted studies specifically to determine maximum total dose allowed per day as there was no safety concerns to do so nor was it an FDA requirement.
  - A review of other topical acne treatments in the Australian market, for both OTC and prescription, show that such information does not form part of the Dosing and Administration information.
  - As part of our Phase I pharmacokinetic study, 2 g daily dose of Aczone 7.5% was used and this figure has been captured under the "Pharmacokinetic" section in the PI and hence is available for review by the prescribing physician and
  - This would not be consistent with our current US label
- For the recommendation to include "dimension to the description 'pea-sized'", Allergan proposes the following two options for review by TGA:
  - To retain the wording "pea-sized" as is with no amendment as Allergan believes this wording provides an imagery which the patient can easily understand rather than dimensions or weight which would be hard for the patient to quantify in the real-world setting; or
  - After consideration of other local labels for dermatological products used in the treatment of acne, as most other formulations do not specify dimensions or weight, Allergan proposes to remove the term "pea-sized" and just retain instructions to apply as a thin layer as per existing wording.

Advisory Committee considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered Aczone gel containing 7.5% of dapsone to have an overall positive benefit-risk profile for the amended indication:

> *Aczone is indicated in the treatment of acne vulgaris in patients aged 12 years and older.*

In making this recommendation, the ACPM:

- Noted characteristics of the patients enrolled in the pivotal trials included only those with moderate disease, over 12 years and that patients with severe acne were thus excluded

Proposed conditions of registration

The ACPM agreed with the delegate on the proposed conditions of registration and advised on the inclusion of the following;

- Subject to satisfactory implementation of the RMP most recently negotiated by the TGA,
- Negotiation of PI and CMI to the satisfaction of TGA.

Proposed PI/CMI amendments

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

- a statement in the relevant sections of the PI and the CMI to include the information that patients enrolled in the pivotal trials included only those moderate disease (GAAS score of 3) disease, over 12 years and that patients with severe acne were thus excluded.
- a statement in the relevant sections of the PI and the CMI to include the information that there is limited experience with topical 7.5% dapsone in pregnant women. It should be clear that use in pregnancy is not recommended.

Specific advice

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

The Delegate has some concerns as to whether submission established meaningful efficacy.

- *1. Is it appropriate to use the gel vehicle as a comparator?*

The ACPM noted that in the PI, DGME, Simulgel 600 PHA, and methyl hydroxybenzoate (methylparaben) are listed as solubiliser, thickening agent, and preservative, respectively. Purified water (not gel) is listed as vehicle. However, animal studies describe the vehicle as containing these non-water ingredients. This should be clarified with the sponsor.

DGME may cause mild skin irritation while methylparaben is a known skin allergen. Greater efficacy of the vehicle control would be expected in the absence of irritants or allergens, thus reducing significance of a comparison between drug and control.

- *2. Are the results clinically significant?*

The pivotal studies show statistically significant benefit of the 7.5% dapsone gel over control in the co-primary endpoints.

The twice daily 5% gel has been approved for a decade in North America and no safety signals have emerged; the proposed use of a 7.5% had a favourable safety profile in the pivotal studies and involves less systemic exposure than the 5% gel; however, pregnancy data are lacking for a product which the sponsor suggests has an advantage over oral antibiotics and retinoids for women of reproductive age.

The ACPM advised that statistically significant efficacy had been demonstrated and that even a GAAS score reduction of one grade is clinically significant, as greater disfigurement and a higher risk of scarring are related to acne severity.

- *3. What proportion of patients with acne of this severity would have resolution of their lesions with no treatment over 12 weeks?*

The sponsor does not provide an answer to this question but the pivotal studies suggest it might be 20-25%. However, efficacy data submitted are for moderate acne (GAAS score of 3) which is commonly not self-limiting.

- *4. Is the indication appropriate or should it specify the severity of acne?*

The ACPM advised that as the pivotal studies excluded subjects with severe acne the indication should be qualified.

- *5. Where would this product be placed in the treatment algorithm for acne?*

The clinical trials recruited subjects aged ≥ 12 y with moderate acne (GAAS score of 3). While conservative, non-pharmaceutical measures may improve such acne significantly, resolution is uncommon without maintenance topical and/or oral therapy.

Resolution of acne within 12 weeks of topical dapsone as monotherapy is realistic for mild acne, but sustained resolution with no ongoing treatment is unlikely.

Topical dapsone likely will be a used as an addition to existing treatment options for acne, in monotherapy, combination therapy and/or maintenance treatment.

The ACPM expressed some concern over the lack of data on bacterial resistance. The ACPM advised to facilitate responsible management of antibiotic medicines as a general standard that all antibiotic use should be carefully monitored for the appearance of resistance.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of 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 Aczone dapsone 7.5% w/w topical gel bottle indicated for:

The topical treatment of acne vulgaris in patients 12 years of age and older

Specific conditions of registration applying to these goods

- The Aczone (dapsone) Australian RMP, version 1.0, dated 29 October 2015 (data lock point 31 May 2015), and any subsequent revisions, as agreed with TGA will be implemented in Australia

Attachment 1. Product Information

The PI approved for Aczone at the time this AusPAR was published is at Attachment 1. For the most recent PI, 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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