Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Ivermectin

Proprietary Product Name: Soolantra and Vastreka

Sponsor: Galderma Australia Pty Ltd

December 2015

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.

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Common abbreviations

Abbreviation	Meaning
ABC B1	ATP binding cassette B1 (p-glycoprotein)
ACPM	Advisory Committee for Prescription Medicines
AE	Adverse event
ATP	Adenosine triphosphate
AUC_{0-24}	Area under the curve time 0 to 24 hours
$AUC_{0-24\ Last}$	Area under the curve during 24 hours after the last dose
$AUC_{0-\tau}$	Area under the curve time 0 to tau (last measurable concentration point)
BD	Twice daily
BCRP	breast cancer resistance protein
BP	British Pharmacopeia
BW	Body weight
CII	Cumulative irritancy index
CMH	Cochran-Mantel-Haenszel
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CNS	Central nervous system
CRC	Child resistant cap
Crl:CD1 (ICR)	A mouse strain
CYP	cytochrome
CYP 450	Cytochrome P450
ECG	Electrocardiogram
EP	European Pharmacopeia
EU SmPC	European Summary of Product Characteristics
$F_{Relative}$	Relative bioavailability

Abbreviation	Meaning
$F_{Absolute}$	Absolute bioavailability
GABA-A	Gamma-aminobutyric acid receptor class A
GCP	Good clinical practice
HDPE	High-density polyethylene
HPLC	High performance liquid chromatography
ICH	International conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use
IDMC	Independent data monitoring committee
IGA	Investigator global assessment
ITT	Intention to treat
IV	intravenous
LD_{50}	Lethal dose 50%
LLQ	Lower limit of quantification
LOAEL	Lowest observed adverse effect level
LOCF	Last observation carried forward
MI	Multiple imputation
NCC	Neutrophil cell count
NOAEL	No observable adverse effect level
PP	Per protocol
PPR	Papulo-pustular rosacea
QD	Once daily
QTcF	Corrected Q-T interval Fridericia
SAE	Serious AE
SARI	Subject's assessment of rosacea improvement
SD	Standard deviation
SOC	System organ class

Abbreviation	Meaning
T_{SS}	Time taken to get a steady state of plasma concentration
$T_{½}$	Time for plasma concentration half-life
USP	United States Pharmacopeia
UVR	Ultra violet radiation
$V_{D\ SS}$	volume of distribution at steady state
w/w	weight/ weight

I. Introduction to product submission

Submission details

Type of submission:	Major variation (new indication and new dose form)
Decision:	Approved
Date of decision:	9 September 2015
Date of entry onto ARTG:	14 September 2015
Active ingredient:	Ivermectin
Product names:	Soolantra and Vastreka
Sponsor's name and address:	Galderma Australia Pty Ltd PO Box 502 Frenches Forest NSW 2086
Dose form:	Cream
Strength:	10 mg/g
Container:	Tube
Pack sizes:	2g, 15 g, 30 g, 45 g and 60 g
Approved therapeutic use:	*Soolantra / Vastreka is indicated for the topical treatment of inflammatory lesions of rosacea (papulo-pustular) in adult patients 18 years and over.*
Route of administration:	Topical
Dosage:	One application a day for up to 4 months. Soolantra should be applied daily over the treatment course. The treatment course may be repeated. In case of no improvement after 3 months, the treatment should be discontinued. For optimal facial treatment, it is recommended that five small pea-size amounts, the total estimated to be no more than 1 g, are applied to the main areas of the face (that is forehead, chin, nose, each cheek) daily. The cream should be spread as a thin layer across the entire face, avoiding the eyes and lips. Soolantra should be applied only to the face. Hands should be washed after applying Soolantra. Soolantra is not for oral, ophthalmic, or intravaginal use.
ARTG numbers:	227125, 227242

Product background

This AusPAR describes the application by Galderma Australia Pty Ltd (the sponsor) to register Soolantra, for an extension of indications, a new dosage form and dosage strength of ivermectin (w/w; 10 mg/g or 1% in an oil-in-water cream emulsion). The proposed indications are:

> *Soolantra / Vastreka is indicated for the topical treatment of inflammatory lesions of rosacea (papulo-pustular) in adult patients 18 years and over.*

Ivermectin is a semi-synthetic drug derived from the Streptomyces avermitilis metabolite and is active at low doses against a wide range of helminths and ectoparasites. Ivermectin is currently registered for human use in Australia by Merck, Sharpe and Dohme Australia Ltd (Stromectol 3mg tablets, AUST R 181338, for the treatment of onchocerciasis, intestinal strongyloidiasis (anguillulosis), crusted scabies and human sarcoptic scabies).

The efficacy of ivermectin in human and animal demodicidosis (sensitivity to and overpopulation of Demodex canis) and its anti-inflammatory properties suggested that ivermectin could also be effective in the treatment of inflammatory lesions of rosacea. This prompted the development of Soolantra.

Rosacea is a skin disorder that causes flushing, papules, pustules, and telangiectasias (small, dilated surface capillaries) on the convex surfaces of the face. It is a common, chronic dermatological disease, with a prevalence reported of up to 10%. Onset typically occurs between 30 to 50 years of age, with women more commonly affected than men.

Regulatory status

Ivermectin is currently registered for human use in Australia (Stromectol 3mg tablets), for the treatment of onchocerciasis, intestinal strongyloidiasis (anguillulosis), crusted scabies and human sarcoptic scabies).

Soolantra/ Vastreka received registration on the Australian Register of Therapeutic Goods (ARTG) on 14 September 2015.

At the time the TGA considered this application, a similar application had been approved or was under consideration in other jurisdictions as shown in Table 1

Table 1. Overseas regulatory status.

Country/Region	Date submitted or intend to submit	Approval date	Proposed indication
United States of America	20 December 2013	19 December 2014	Soolantra cream is indicated for the topical treatment of inflammatory lesions of rosacea.
Europe (De-centralised procedure)		22 March 2015	Soolantra is indicated for the topical treatment of inflammatory lesions of rosacea (papulo-pustular) in adult patients.
Austria, Estonia, Germany, Malta and Spain	8 April 2014	AT: 02 June 2015 ET: 08 June 2015 DE: 29 April 15 Malta: 02 April 2015	

Country/Region	Date submitted or intend to submit	Approval date	Proposed indication
		ES : 02 June 2015	
Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Hungary, Ireland, Latvia, Luxembourg, Lithuania, Poland, Portugal, Romania, Slovakia and United Kingdom	9 April 2014	BE: 03 April 2015 BG : 10 June 2015 CZ : 13 May 2015 DK : 22 April 2015 FI: 26 June 2015 FR: 21 July 2015 HU: 14 April 2015 IE: 24 April 2015 LV: 13 July 2015 LU: 01 July 2015 LT: 13 may 2015 PL: 23 July 2015 PT: 08 April 2015 RO: 26 May 2015 SK: 11 june 2015 UK: 17 April 2015	
Cyprus, Greece, Iceland, Italy, The Netherlands, Norway and Sweden	10 April 2014	Cyprus: pending Greece: pending IS: 29 April 2015 IT: 13 July 2015 NL: 04 may 2015 NO: 23 April 2015 SE: 22 April 2015	
Canada	15th April 2014	23rd April 2015	Rosiver (ivermectin) cream, 1% is indicated for the topical treatment of inflammatory lesions (papules and pustules) of rosacea in adults 18 years of age or older.
Russia	1 August 2014 Resubmission on 14 September 2015	MAA Withdrawal Pending	

Country/Region	Date submitted or intend to submit	Approval date	Proposed indication
Colombia	5 September 2014	Pending	Soolantra is indicated for the cutaneous treatment of inflammatory lesions of rosacea in adult patients.
South Africa	3 October 2014	Pending	
Chile	10 November 2014	6 May 2015	
Mexico	27 February 2015	Pending	
Argentina	7 April 2015	Pending	
Brazil	14 April 2015	Pending	
Switzerland	17 September 2015	Pending	Soolantra is indicated for the topical treatment of inflammatory lesions of moderate to severe (papulopustular) rosacea (Investigator Global Assessment Grade 3 and 4) in adult patients

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>.

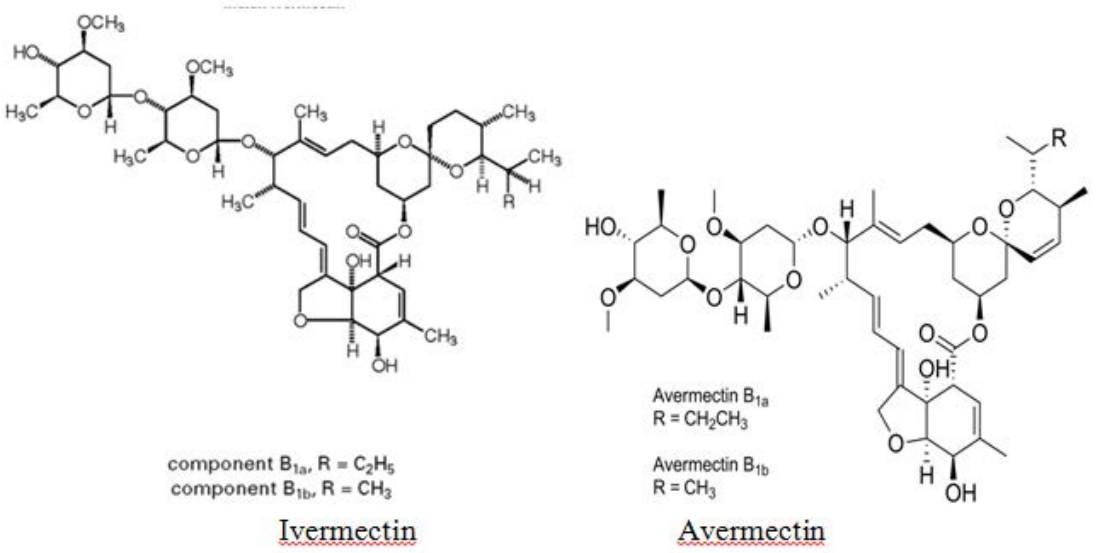
II. Quality findings

Drug substance (active ingredient)

The drug substance, ivermectin is a semi synthetic broad spectrum antiparasitic drug derived from the Streptomyces avermitilis metabolite, 'avermectin', traditionally used against parasitic worms. In veterinary medicine ivermectin is used against many intestinal worms, most mites, ticks and some lice.

Ivermectin is a 16-membered macrocyclic lactone, consisting of a > 9:1 mixture of two homologous components, ivermectin B1a and ivermectin B1b, differing only with respect to the incorporation of an ethyl or methyl substituent, respectively.

Figure 1. Structure of ivermectin and avermectin.



Ivermectin is a white or yellowish white, slightly hygroscopic crystalline powder, which is practically insoluble in saturated hydrocarbons such as cyclohexane, insoluble in water, soluble in ethanol and highly soluble in methylene chloride and propylene glycol. The drug substance is the subject of harmonised European Pharmacopeia (EP)/ British Pharmacopeia (BP) and United States Pharmacopeia (USP) monographs.

Drug product

The proposed product is a white to pale yellow homogeneous cream containing 1% weight/ weight (w/w) (10 mg/g) of ivermectin as the drug substance.

The cream consists of a two phase system made of two immiscible liquids, one of which is dispersed as droplets (lipophilic phase: active drug substance) within the other liquid (hydrophilic phase). This two phase system is stabilised by two main emulsifying agents thus giving an oil-in-water emulsion. The excipients used are registered as part of topical products registered in Australia and there are no novel excipients.

The efficacy of the preservatives and other microbiological aspects of the proposed product have been evaluated and found acceptable by the TGA Laboratories Branch.

Ivermectin cream was characterised during development by macroscopic aspect (lack of phase separation on centrifugation), pH (6.0 to 6.6; to avoid drug substance hydrolysis and to neutralise the acidic carbomer copolymer), emulsion type and rheological properties (oil in water emulsion, droplet size and viscosity).

The proposed finished product specifications included controls on identity and levels of the drug substance and preservative excipients, pH, viscosity, assay, levels of 4 specified degradants and unspecified degradants and microbial limits. These have been adequately justified and comply with TGA requirements. They are considered adequate to ensure the quality of the finished product at release and throughout the shelf life.

The cream shows good physical and chemical stability and a shelf life of 24 months when stored below 30°C, in the original packaging, has been established.

Ivermectin cream is to be packaged within 15 g, 30 g, 45 g and 60 g laminated High-density polyethylene (HDPE) tubes with a polypropylene child-resistant closure (CRC). In addition the company will also register a 2g physician's sample pack size but will have a non-CRC polypropylene cap.

Quality summary and conclusions

Registration of the proposed 'Soolantra' and 'Vastreka' ivermectin 1% (w/w; 10 mg/g) cream in pack sizes of 2g, 15 g, 30 g, 45 g and 60 g in laminated HDPE tubes with polypropylene caps, is recommended with respect to quality and biopharmaceutic aspects. All issues raised during the initial evaluation of this application have been satisfactorily resolved.

As no significant pharmaceutical chemistry issues were identified, the submission was not referred to the Pharmaceutical Subcommittee of the Advisory Committee for Prescription Medicines (ACPM).

III. Nonclinical findings

Introduction

While there are extensive existing dossiers and toxicological evaluations available for the agrochemical/veterinary use of ivermectin and other members of the avermectin 16-membered macrocyclic lactone actinomycete exotoxin family, the sponsor has provided a completely new package of nonclinical studies. This package of studies has, for the most part, corroborated the findings of the currently existing nonclinical dossiers and toxicological evaluations of ivermectin.

The principle that competitive substrates for adenosine triphosphate (ATP) binding cassette B1 (p-glycoprotein) (ABC B1) or inhibitors of this transporter affect the actions and toxicity of ivermectin is well established and there are very strong mechanistic reasons to expect interactions between ivermectin and the large number of drugs that affect ABC B1 function or whose pharmacokinetics is affected by this transporter. Thus the overall limitation of the sponsor's dossier is the failure to systematically evaluate the potential for adverse ivermectin associated pharmacokinetic interactions associated with pharmacogenetic, phenotypic and xenobiotic induced effects/ionteractions at ABC B1 (p-glycoprotein) efflux transporters, particularly in the blood brain barrier, the blood testis barrier, the placental xenobiotic efflux system and the intestinal enterothelium.

This overall weakness is somewhat tempered by the fact that systemic ivermectin exposure associated with topically applied Soolantra is relatively low relative bioavailability ($F_{Relative}$) (Dermal: Oral) approximately 16%, with a very crudely approximated absolute bioavailability ($F_{Absolute}$) (Dermal: intravenous (IV)) of approximately 8%; systemic exposure due to the repeated topical application of Soolantra cream under steady state conditions would be expected to be approximately 7.5 times lower than that associated with a single 200 µg/kg body weight (BW) oral dose of Stromectol (not accounting for cumulative effects). Specific studies to determine $F_{Absolute}$ were not performed and the animal topical exposure studies that could potentially have been used for this purpose were probably (and demonstrated to be in some cases) systematically confounded by concurrent ingestion associated with grooming at the site of application and/or coprophagy.

Pharmacology

Primary pharmacology

There are no acceptable animal models of human rosacea. The modes of action of ivermectin treatment on this disease are unknown. Ivermectin has at least two main effects relevant to the treatment of facial papulo-pustular rosacea: (a) mitocidal effects on

Demodex species; and (b) modulation of inflammation. There is modest clinical (case study) evidence of the efficacy of ivermectin as a treatment for confirmed cases of Demodex species infection in humans and domestic animals. Members of the related milbemycin parasiticide family (for example moxidectin) have also been used for this purpose in domestic animals. All members of the avermectin family primarily exert their effects on invertebrates by acting as positive allosteric modulators of glutamate gated chloride channels on neurons and pharyngeal muscle cells. Glutamate gated chloride channel receptors have not been demonstrated in vertebrates and most of the adverse effects of the avermectin class in mammals pertain to their positive allosteric modulator effects on gamma-aminobutyric acid receptor class A (GABA-A) gated chloride channels, particularly in the central nervous system (CNS) under overdose conditions or in animals displaying a blood brain barrier ABC B1 transporter (the major blood brain barrier ivermectin efflux transporter) deficiency phenotype. Both the GABA-A and glutamate receptor types belong to the ligand gated ion channel superfamily and exert their effects by potentiating ligand gated ion currents (notably glutamate gated chloride channels in the CNS of invertebrates and GABA type A gated chloride currents in the mammalian CNS).

Avermectins are also reported to inhibit lipopolysaccharide (LPS) induced inflammation and the sponsor has presented data that demonstrates ivermectin induced anti-inflammatory effects in animal models of skin inflammation and atopy. These studies are evaluated in the secondary pharmacodynamics section since they are not the primary pharmacological action of ivermectin and may have a somewhat different mode of action than its effects on ligand gated ion channels.

Based on the models of acute inflammation evaluated, 1% topical ivermectin appeared to display greater efficacy over the lower tested concentrations. However since relevant animal models of human rosacea are not available, efficacy, efficacy thresholds and dose selection could not be assessed in the nonclinical evaluation.

The proposed repeated sub-acute to sub-chronic pattern of use of Soolantra cream is markedly different from the currently approved pattern of human use of ivermectin in Australia (Stromectol for the treatment of parasitism). Stromectol is administered at 150 to 200 µg/kg BW, with repeat dose intervals of intervals of ≥ 7 days for scabies (maximum of 2 doses), and ≥ 3 months for internal parasitism.[1] The oral bioavailability of ivermectin in the form of Stromectol administered in the fasting state is approximately 40 to 50% (dosing following a high fat meal resulted in an approximate 2.5 fold increase in bioavailability). The scheduled dosing intervals are such that there is no systemic ivermectin bioaccumulation.

The sponsor has not provided studies that specifically examined the absolute or relative ivermectin bioavailability of Soolantra cream, although they have clearly demonstrated slow accumulation of this drug. The sponsor has provided a rough estimate of topical ivermectin relative bioavailability from Soolantra cream under steady state conditions in humans of 16% (based on Study RD.06.SRE.18120; 4 weeks of once per day (QD) topical application of 1 g of 1% ivermectin cream applied to 3% of body surface area of patients with severe papulo-pustular rosacea using the proposed market formulation, that is 10 mg/day or approximately 167 µg/kg BW (topical exposure) based on a body weight of 60 kg) relative to a single oral 6 mg dose of Stromectol in humans (approximately 82 µg/kg BW based on mean study subject body weight of 73.5 kg) administered under fasting conditions.

Based on the known bioavailability of oral Stromectol under fasting conditions of 50%, an 82 µg/kg BW dose would have resulted in a systemic exposure of approximately 41 µg/kg BW. Using crude comparisons, the use of Soolantra cream under the steady state conditions described above would have resulted in a systemic exposure of 16% of that of

[1] https://www.tga.gov.au/auspar/auspar-ivermectin

oral Stromectol that is 16% of 50% = 8% or 0.08 x 167 µg/kg BW approximately 13.4 µg/kg BW. Thus using very approximate and crude comparisons, the systemic exposure due to the use of Soolantra cream under steady state conditions was approximately 3 times lower than that associated with a single, acute 6 mg oral dose of Stromectol. Applying this calculation to the maximum approved dose level of Stromectol in Australia, the systemic exposure due to the use of Soolantra cream under steady state conditions would be expected to be approximately 7.5 times lower than that associated with a 200 µg/kg BW oral dose of Stromectol. However it should be noted that these crude systemic exposure comparisons are based on comparing a 4 week repeated dermal exposure study with a single acute oral exposure and do not necessarily take into account all potential effects, particularly any cumulative effects.

Since one of the major pathways of systemic ivermectin elimination is via enterothelial ABC B1(P-gp) efflux transporter mediated excretion into the gut lumen, the chronic low level systemic exposures associated with Soolantra raise possible concerns regarding the induction of human relevant anthelmintic resistance to ivermectin. Helminth and other parasite resistance to ivermectin and selection of resistance traits that reduce the effectiveness of the entire avermectin class have become a very substantial problem in veterinary medicine and this problem already critically limits control of parasites in humans. Selection pressure associated with under dosing and parasite under exposure has been classically associated with the emergence of this phenomenon.

Secondary pharmacodynamics and safety pharmacology

The sponsor has provided clear evidence of ivermectin induced suppression of acute (single exposure) skin irritant induced inflammation in relevant mouse models and some atopy like effects in a Dermatophagoides farinae (American house dust mite) antigen mouse model of human atopic dermatitis. Notably these effects were only evaluated in female Balb/c mice. The inherent assumption associated with this evidence base is that suppression of acute skin inflammation will also provide suppression of cumulative skin irritancy associated with papulo-pustular rosacea. Notably the nonclinical studies suggest 1% ivermectin is superior to 0.3% or 0.1% in terms of anti-inflammatory effects. However given the lack of animal models of rosacea the data are insufficient to determine if ivermectin concentrations < 1% can be used.

Supra therapeutic doses of ivermectin reduce gastric emptying and intestinal transit time (probably via actions on gut metabotropic GABA B receptors). This has potential implications for oral drug absorption. Additionally, supra therapeutic doses of ivermectin result in reductions in motor activity (probably via effects on CNS GABA A systems following overwhelming of blood brain barrier ABC B1 efflux transporters). The CNS effects will be at least additive/subtractive with the effects of other CNS GABA A agents, notably ethanol. Ivermectin is an efficient inhibitor of human breast cancer resistance protein (BCRP, ABC G2) which may increase fetal and neonatal trans mammary exposure to BCRP relevant pharmaceutical substrates due to inhibition of this placental and mammary gland efflux transporter.

Pharmacokinetics

Absorption

Dermal application of Soolantra results in relatively low absorption of ivermectin (very crude approximated $F_{Absolute}$ (Dermal: IV) approximately 8%; approximately 7.5 times lower than that associated with a single 200 µg/kg BW oral dose of Stromectol in humans under steady state conditions, not accounting for any cumulative effects). Systemic exposure displays flip flop, absorption limited pharmacokinetics. Accordingly the time

taken to get a steady state of plasma concentration (T_{SS}) and time for plasma concentration half-life ($T_{½}$) are relatively long (T_{SS} approximately 9 to 20 days in humans; $T_{½}$ approximately 45 to 97 hours).

Distribution

The majority of topically applied ivermectin distributes to the lipophilic compartments of the skin. Systemically absorbed ivermectin is almost completely protein bound. The volume of distribution at steady state (V_{DSS}) in all examined species, including humans, is > 1 L/kg implying the presence of substantial sequestration with the major site for this being the adipose tissues (particularly brown fat). Repeated topical exposure was associated with a low level of diffusion into non-treated skin as well as progressive accumulation and redistribution to adipose tissues, particularly brown adipose tissue. The rate of decline of ivermectin levels in skin and adipose tissues is very slow and these sites act as 'deep storage' compartments.

Penetration of ivermectin across the blood brain barrier, across the blood testis barrier and across the placenta is limited in normal animals due to the actions of ABC B1 efflux transporters.

Rat data demonstrates that the level of ivermectin in milk is 3 to 4 fold higher than those in the maternal plasma and this causes significantly higher levels of ivermectin in the brain and plasma of nursing offspring. Ivermectin is detectable in human milk following oral dosing. Significant exposure of neonates to ivermectin via the trans-mammary route is highly likely.

Metabolism

Systemically absorbed ivermectin undergoes limited metabolism in mammals with much of the systemically absorbed material being excreted unchanged. Ivermectin is extensively hydroxylated and/or demethylated to at least 10 metabolites with cytochrome (CYP) 3A4 is the main CYP450 isoform responsible for human hepatic microsomal metabolism. There are notable species differences in metabolism. The major in vivo metabolites in cattle, sheep and rats are 24-OH-H2B1a and 24-OH-H2B1b and 3'-O-desmethyl-H2B1a and 3'-O-desmethyl-H2B1b in pigs. Metabolism tends to be more extensive in pigs and mice compared with other species. The H2B1b enantiomer is typically more extensively metabolised than the H2B1a enantiomer in all studied species. The major known human microsomal metabolites are: (a) 3'-O-desmethyl-H2B1a; and (b) 4a-hydroxy ivermectin.

Excretion

Ivermectin is predominantly excreted in faeces with minimal amounts excreted in urine. A repeatable gender difference in urinary excretion was noted in Sprague Dawley rats following IV and oral dosing: urinary excretion of radioactivity was approximately 2 times higher in males than females. However given that the level of urinary excretion is low (approximately0.8% to 2%) this gender difference is biologically unimportant. Additionally, this gender difference was not noted in dogs and pigs demonstrating that it is most likely a rat specific effect.

Faecal excretion was similar following oral and IV dosing implying that biliary and/or intestinal excretion is the major route of elimination. Studies in rats using the intestinal closed-loop model have demonstrated that ABC B1 transporter mediated trans-epithelial intestinal elimination is a major pathway of ivermectin elimination accounting for 27% of total drug clearance (compared with biliary excretion which only accounts for 5.5% of total drug clearance).

Pharmacokinetic drug interactions

The safety properties of ivermectin are critically dependent on the presence of ABC B1 efflux transporter function in the blood brain barrier, the blood ocular barriers, the blood testis barrier and in the placenta. The effectiveness of these biological barriers to ivermectin can be overwhelmed either by ivermectin overdose, drugs that inhibit ABC B1 function or disease states that affect the integrity of these biological barriers. Concurrent administration of drugs that block or suppress ABC B1 efflux transporter function with ivermectin can result in toxicity (potentially severe if high doses of ivermectin are administered). Lethality and other forms of severe toxicity have occurred with the veterinary medical use of ivermectin because of these types of interactions (classically concurrent use of spinosad with ivermectin). In these situations the most commonly noted events are sustained GABA A mediated CNS depression which may extend to unconsciousness and death from central respiratory failure. In animals, ivermectin induced coma is difficult to reverse. Flumazinel (a GABA A receptor antagonist) is typically only transiently effective in animals with ivermectin poisoning (although it has been used diagnostically in this situation).

It should be noted that the central GABA-A allosteric agonist effects of ivermectin will be at least additive, and possibly supra additive, to the effects of other GABA-A agonist pharmaceuticals and products (including ethanol).

Compromise of the blood retinal barrier also increases the risk of ivermectin induced retinopathies. Compromise of the blood testis barrier combined with repeated ivermectin exposure has been associated with male infertility in animals. Ivermectin induced severe pre-natal developmental effects can also occur in animals if placental ABC B1 efflux transporters have been pharmaceutically compromised. Pharmacological inhibition of enterothelial ABC B1 efflux transporters will decrease the rate of active intestinal elimination of ivermectin (an important elimination pathway for systemically absorbed ivermectin).

Ivermectin is an efficient inhibitor of human breast cancer resistance protein (BCRP, ABC G2). Ivermectin induced inhibition of BCRP during pregnancy will increase fetal exposure to BCRP relevant pharmaceuticals due to inhibition of this placental efflux transporter. This results in a number of potential pharmacokinetic interactions with substrates of BCRP.

Because of the relatively small amount of ivermectin systemically absorbed following topical application of Soolantra, metabolic interactional effects at CYP3A4 are expected to be quantitatively small.

Notably, the unique pharmacokinetics associated with Soolantra (that is slow flip-flop absorption kinetics resulting in long time to plasma steady state, long ivermectin half-life, slow whole body elimination, accumulation and sequestration in lipophilic tissues) increases the risk of these types of adverse pharmacokinetic interactions compared with the single acute episodic use of ivermectin as a parasiticide in humans.

Pharmacogenetic interactions

Heritable loss of blood brain barrier ABC B1 efflux transporters in dogs (classically collies and related breeds) results in a substantial (> 200 times) increase in the risk of ivermectin induced CNS toxicity. This pharmacogenetic effect has been associated with ivermectin induced lethality in dogs and impacts upon the safety properties of many members of the avermectin drug class in this species. This particular pharmacogenetic effect does not appear to occur to the same extent in humans (although only relatively small human populations have been evaluated). Severe ivermectin poisonings in humans that do not involve product misuse are rare.

Pharmacological and/or disease induced compromises to the blood brain barrier appear to be a more likely cause of adverse effects of ivermectin in humans.

Toxicology

Acute toxicity

Predictably, ivermectin is only modestly toxic following single (acute) oral gavage dosing in ABC B1 phenotypically normal rats and mice. The rodent maximum non-lethal dose following single (acute) oral gavage dosing is 20 to 40 mg/kg BW with a 50% lethal dose (LD_{50}) > 40 mg/kg BW. It should be noted that these results will overestimate the maximum non-lethal dose and LD_{50} in animals displaying the 100% defective ABC B1 phenotype.

Repeat dose toxicity

The sponsor's study package was generally consistent with current International conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) guidance requirements and of acceptable quality. All of the sponsor's topical repeat exposure studies in animals were probably (and confirmed to have been in some cases) confounded by ingestion exposure. Additionally, many of the topical repeated exposure studies did not use the same final formulation as Soolantra. Although relevant exposure bridging studies for the different formulations were not provided by the sponsor, systemic ivermectin exposure following topical application was demonstrated in many of the keystone studies and the supplied studies are generally fit for purpose given the ultimate pattern of use of Soolantra in humans. Predictably, the sponsor's studies do not provide any new information regarding the repeated exposure toxicology of ivermectin and its vehicle (with the exception of photocarcinogenesis and potential cumulative skin irritancy).

Excluding local application site effects, the chronic near lifetime exposure topical exposure no observable adverse effect level (NOAEL) in mice was ≥ 1% (w/w) ivermectin cream, from 1 mL/kg/day covering approximately 10% body surface area, non-occlusive (equivalent to area under the curve from time 0 to 24 hours (AUC_{0-24}) 48,519 ng·h/mL in males and 26,461 ng·h/mL in females). The highest mean AUC_{0-24} for Soolantra use in humans was 75.16 ng·h/mL (clinical Study 40064); thus the animal NOAEL mean AUC_{0-24}: human mean AUC_{0-24} exposure ratio under these conditions is ≥ 1,342.5 (not taking allometric scaling or relative surface area of application into account). The highest individual human AUC_{0-24} at steady state under maximal use conditions was 75.16 ng·h/mL (clinical Study 40064). Thus the animal NOAEL mean AUC_{0-24}: human mean AUC_{0-24} exposure ratio under these health protective conditions is ≥ 645.5.

Apart from site of application effects (predominantly cumulative irritancy) adverse non-neoplastic adverse events were generally not observed in the keystone repeated topical application studies except at extreme doses and under conditions where combined dermal and oral exposure were likely. Non occlusive topical exposure to 1% ivermectin (w/w) cream applied to a minimum of 10% of the body surface area at a dosage volume of 5 mL/kg/day (corresponding to 50 mg/kg/day) resulted in mortality consistent with systemic ivermectin neurotoxicity (GABA A positive allosteric modulation resulting in generalised CNS depression, coma and death) was observed in one CD-1 mouse study. Methods to prevent grooming ingestion were not used in this study, thus it is likely that the observed mortalities were associated with a combination of ingestion as well as topical exposure. Similarly, clinical signs consistent with ivermectin neurotoxicity (tremor, decreased motor activity, bradypnoea, ptosis, hunched posture etcetera) were present in hairless mice topically treated with 1% ivermectin (w/w) applied at 50 µg/day/mouse.

Again it should be noted that precautions against grooming-associated ingestion were not used in this study and that hairless mice have a relatively thin epidermis compared with normal mouse strains. This is likely to have resulted in increased dermal absorption in this strain. It should also be noted that the ABC B1 phenotype of SKH:Hr-1 hairless mice is not known.

Signs of systemic ivermectin CNS toxicity were also observed at high exposure in the non pivotal oral repeated exposure studies. Repeated oral gavage exposures of beagle dogs (likely normal ABC B1 phenotype) at > 1.5 mg/kg BW resulted in ivermectin induced CNS toxicity requiring euthanasia. Exposure at 1.5 mg/kg BW resulted in reversible mydriasis in dogs (a classical clinical sign associated with ivermectin positive allosteric modulation of CNS GABA A systems). CNS toxicity resulting in lethality and spongiform leukoencephalopathy was present in Wistar rats repeatedly exposed by oral gavage to 12 mg/kg BW/day of ivermectin. Slight effects on food consumption and body weight were also present at doses ≥ 3.0 mg/kg BW/day.

Retinal atrophy was noted in the non pivotal oral gavage near lifetime exposure carcinogenesis study in rats. The rat lowest observed adverse effect level (LOAEL) for ivermectin induced retinal atrophy was 1 mg/kg BW/day (equivalent to area under the curve during 24 hours after the last dose ($AUC_{0\text{-}24\ Last}$) of 5,241.02 ng·h/mL and 4,335.89 ng·h/mL in males and females respectively) due to the presence of an increased incidence of retinal atrophy at this dose rate. The highest mean $AUC_{0\text{-}24}$ for Soolantra use in humans was 36.14 ng·h/mL (clinical Study 40064), thus the systemic exposure at the LOAEL in rats is ≥ 1,342.5 higher than the expected human systemic ivermectin exposure. Ivermectin induced retinal atrophy is undoubtedly relevant to humans and has been noted in cases of overt ivermectin poisoning in dogs.[2, 3]

Relative exposure

The highest mean $AUC_{0\text{-}24}$ for Soolantra use in humans was 36.14 ng·h/mL (clinical Study 40064) and the highest individual human $AUC_{0\text{-}24}$ at steady state under maximal use conditions was 75.16 ng·h/mL (clinical Study 40064). In general the animal: human exposure ratios were high with the exception of the topical repeat exposure studies in mini-pigs. The health protective method of using the highest individual human $AUC_{0\text{-}24}$ at steady state under maximal use conditions was used to calculate the relative exposures following dermal application in the following table (Table 2) (Note: relative body surface area of exposure and allometric scaling have not been taken into account).

Table 2. Relative exposures following dermal application.

Species	Study duration	NOAEL/NOEL (mg/kg/day)	AUC_{0-24h}§ (ng·h/mL)	Exposure ratio#
Mouse (CD-1)	13 weeks RDS.03.SRE.12500	10	32493.5(m)/27408.9(f)	432.3(m)/364.7
	104 Weeks RDS.03.SRE.12508	10	48519 (m)/26461 (f)	645.54(m) /352 (f)

[2] Epstein SE, Hollingsworth SR. (2013) Ivermectin-induced blindness treated with intravenous lipid therapy in a dog. *J Vet Emerg Crit Care (San Antonio)*. 2013; 23:58-62

[3] Kenny PJ, et al. Retinopathy associated with ivermectin toxicosis in two dogs. *J Am Vet Med Assoc.* 2008; 23:279-84.

Species	Study duration	NOAEL/NOEL (mg/kg/day)	AUC_{0-24h}§ (ng·h/mL)	Exposure ratio#
Rat (SD)	4 Weeks RDS.03.SRE.8547	20	33566	446.59
	2 year RDS.03.SRE.12507	Oral human-relevant non-neoplastic LOAEL• = 1 mg/kg BW/day	Oral $AUC_{0-12\ Last}$ = 5241.02 (m) 4335.89 (f)	69.7(m)/57.7(f)
		Oral human-relevant NOAEL accounting for neoplasia = 9 mg/kg BW/day	Oral $AUC_{0-12\ Last}$ = 62567.60 (m) 69406.70 (f)	832.5(m)/ 923.5(f)
Mini-pig	4 weeks RDS.03.SRE.12447	5	38.05(m)/46.14(f)	0.5(m)/0.61(f)
	13 Weeks RDS.03.SRE.12491	20	95.4(m)/161.9(f)	1.3(m)/2.15(f)
	9 Months RDS.03.SRE.12510	20	66.48(m)/139.46(f)	0.88(m)/1.86(f)
Rabbit (NZW)	Embryofetal Development RDS.03.SRE.12460 RDS.03.SRE.1263	3.5	5,159	68.6
Rat (SD)	Embryofetal Development RDS.03.SRE.12461	4	25,099	333.9
Human (Severe papulo-pustular rosacea under maximal use conditions)	steady state (day 28)	10 mg/day	75.16†	–

§ = highest recorded mean (male or female) during the experiment # = animal: human plasma AUC_{0-24h} • = due to retinopathy † = highest mean human AUC_{0-24} observed (clinical Study RD.03.SRE.40064) m = male f = female.

Major toxicities

Predictably, the major site of action of ivermectin toxicity is in the CNS GABA A systems. Evidence of cumulative dermal irritancy was present in a number of the animal topical

exposure studies. Dermal cumulative irritancy was most likely to be associated with the vehicle rather than ivermectin per se.

Retinal atrophy was noted in the non pivotal oral gavage near lifetime exposure carcinogenesis study in rats. The rat LOAEL for ivermectin induced retinal atrophy was 1 mg/kg BW/day (equivalent to and $AUC_{0\text{-}24\ Last}$ of 5,241.02 ng·h/mL and 4,335.89 ng·h/mL in males and females respectively) due to the presence of an increased incidence of retinal atrophy at this dose rate. The highest mean $AUC_{0\text{-}24}$ for Soolantra use in humans was 75.15 ng·h/mL (clinical Study 40064), thus the systemic exposure at the LOAEL in rats is ≥ 57.7 times higher than the highest expected human systemic ivermectin exposure (based on $AUC_{0\text{-}24}$ ratio). Ivermectin induced retinal atrophy is undoubtedly relevant to humans and has been noted in cases of overt ivermectin poisoning in dogs.[4, 5]

Genotoxicity

Predictably ivermectin is not genotoxic in Tier 1 in vitro assays and in an in vivo rodent micronucleus test.

Carcinogenicity

As expected, ivermectin is not a human relevant carcinogen. The carcinogenesis package supplied by the sponsor consists of two pivotal dermal exposure studies in mice (including a photocarcinogenesis study in hairless mice) and a non pivotal oral gavage study in rats. The doses used, dose ranging and other study parameters were acceptable and compliant with current guidelines.

Following topical exposure of mice, and with the exception of local site of first contact effects at the site of application, the NOAEL was ≥ 1% ivermectin cream, 1 mL/kg/day covering approximately 10% body surface area, non-occlusive, chronic exposure (equivalent to $AUC_{0\text{-}24}$ 48519 ng·h/mL in males and 26461 ng·h/mL in females). The highest mean $AUC_{0\text{-}24}$hr for Soolantra use in humans was 75.16 ng·h/mL (clinical Study 40064); thus the male animal NOAEL mean $AUC_{0\text{-}24}$: human highest $AUC_{0\text{-}24}$ exposure ratio under these conditions is ≥ 57.7 (not taking allometric scaling or relative surface area of application into account). The highest individual human $AUC_{0\text{-}24}$ at steady state under maximal use conditions was 75.16 ng·h/mL (clinical Study 40064). Thus the male animal NOAEL mean $AUC_{0\text{-}24}$: human mean $AUC_{0\text{-}24}$ exposure ratio under these health-protective conditions is ≥ 645.5. When local site of first contact cumulative irritancy effects are taken into account, the NOAEL was 0.3% ivermectin cream, 1 mL/kg/day, covering approximately 10% body surface area, non occlusive, chronic exposure. Since the likely major mode of action of is the 'cell membrane effects' of the oil-in-water emulsion vehicle, the equivalent NOAEL for site of first contact effects in humans will be equivalent to that in mice (the typical interspecies toxicodynamic and toxicokinetic adjustment factor for these types of effects by oil-based products is 1 that is human sensitivity = animal sensitivity).[6]

Lymphoid hyperplasia was seen in the Peyer's patches, the thymus, the spleen (recorded as 'increased white pulp development'), the mandibular and mesenteric lymph nodes as well as other lymph nodes sampled either because they showed necropsy abnormalities or because they were draining lymph nodes for masses. Concern was raised in the study report because of apparent test article associated associations between reactive and focal lymphoid hyperplasia (most notably in the mandibular lymph node). The incidence of

[4] Epstein SE, Hollingsworth SR. Ivermectin-induced blindness treated with intravenous lipid therapy in a dog. *J Vet Emerg Crit Care (San Antonio)* 2013; 23:58-62.
[5] Kenny PJ et al. Retinopathy associated with ivermectin toxicosis in two dogs. J Am Vet Med Assoc. 2008; 233:279-284.
[6] Boogaard PJ et al. A consistent and transparent approach for calculation of Derived No-Effect Levels (DNELs) for petroleum substances. *Regul Toxicol Pharmacol*. 2012; 62: 85-98.

lymph node hyperplasia (a change associated with aging that is more common in Crl:CD1 (ICR) mice older than 60 weeks) reported in the study is higher than the normal back ground incidence of these common lesions in the Crl:CD1 (ICR) mouse at the end of a 104 week carcinogenesis study (2.65%).[7] The background incidence of benign thymic lymphoid hyperplasia is known to be higher in the Crl:CD1 (ICR) mouse compared with other laboratory mice strains. The study authors regarded focal lymph node hyperplasia as a potentially pre-neoplastic condition. However the current consensus is that this type of lesion in the lymph node is not a pre-neoplastic state and it is not a carcinoma in situ.[8] Lymph node hyperplasia is a relatively common background finding in near life-time oral exposure studies in mice.[9] A more likely explanation, particularly in the case of the mandibular lymph nodes (a component of mandibular lymphocenter that drains the lips, eyelids, auricular areas and tongue), is that these changes are reactive due to chronic ingestion of the test article following grooming. Notably Elizabethan collars (to prevent grooming of test article application sites) were not used in the study.

In mice, repeated daily application of the vehicle cream was generally well tolerated. However as could be expected, there is some evidence ($p < 0.05$) of cumulative irritancy associated with repeated topical exposure to the cream vehicle (epidermal hyperplasia: 80% in vehicle treated versus 14.1% in water treated controls; amyloidosis: 15% in vehicle-treated versus 0.8% in water treated controls; inflammation 14.2 % in vehicle-treated versus 5 % in water treated controls).

Of greater concern is that the cream vehicle was associated with an increased incidence of skin ulceration (10.8% in vehicle treated versus 3.3% in water treated controls). Notably the incidence of vehicle associated inflammation (12 out of 60 in females versus 5 out of 60 in males) and skin ulceration (11 out of 60 in females versus 2 out of 60 in males) was higher in females compared with males. The incidence of pustule formation was higher in vehicle treated animals versus the water control groups (14.2% in vehicle treated versus 3.3% in water treated). The incidence of pustule formation in vehicle treated females animals was almost twice that in vehicle treated males. Pustule formation with the oil in water emulsion cream vehicle is an expected consequence of repeated application since such preparations are typically comidomogenic. However, the rabbit ear is the classical animal model used to evaluate such effects.[10]

The cream vehicle used in the mouse photo carcinogenesis study undoubtedly enhanced non-melanoma skin cancer development (tumour potency factor 1.68 to 2.1). The NOAEL in the photo carcinogenesis study could not be determined because of these effects. Notably 0.1% ivermectin co-exposure is no worse than exposure to the cream vehicle that is the NOAEL relative to the control cream vehicle 0.1% ivermectin, 25 µL/kg BW/day, topical non-occlusive applied to approximately 10% body surface area. Repeated topical administration of the cream vehicle elicited primary irritation in the skin of male and female hairless mice that were also exposed to ultra violet radiation (UVR) when compared with mice only exposed to an equivalent UVR dose. In addition, repeated topical administration of ivermectin at concentrations of 0.3% and 1% exacerbated the primary

[7] Bradley A., et al. Incidences and range of spontaneous findings in the lymphoid and haemopoietic system of control Charles River CD-1 mice (Crl: CD-1(ICR) BR) used in chronic toxicity studies. *Toxicol Pathol.* 2012; 40: 375-381.
[8] Elmore SA. Histopathology of the lymph nodes. *Toxicol Pathol.* 2006; 34: 425-454.
[9] Littlefield NA., et al. (1991) National Toxicology Program. NTP Toxicology and Carcinogenesis Studies of 3,3'-Dimethylbenzidine Dihydrochloride (CAS No. 612-82-8) in F344/N Rats (Drinking Water Studies). Natl Toxicol Program Tech Rep Ser. 390:1-238; National Toxicology Program. NTP Technical Report on the Toxicology and Carcinogenesis Studies of 2,4-Diaminophenol Dihydrochloride (CAS NO. 137-09-7) in F344/N Rats and B6C3F1 Mice (Gavage Studies). Natl Toxicol Program Tech Rep Ser. 1992; 401:1-232; National Toxicology Program (1993) NTP Toxicology and Carcinogenesis Studies of Acetaminophen (CAS No. 103-90-2) in F344 Rats and B6C3F1 Mice (Feed Studies). Natl Toxicol Program Tech Rep Ser. 394:1-274; National Toxicology Program. (1993) NTP Toxicology and Carcinogenesis Studies of Triamterene (CAS No. 396-01-0) in F344/N Rats and B6C3F1 Mice (Feed Studies). Natl Toxicol Program Tech Rep Ser. 420:1-367.
[10] Nguyen SH, et al. Comedogenicity in rabbit: some cosmetic ingredients/vehicles. *Cutan Ocul Toxicol.* 2007;26:287-292.

irritation. Therefore, there was good concordance between this induction of cutaneous primary irritancy and the enhancement of photo carcinogenesis with topical placebo administration and the amplification of the placebo effect with test article formulation administration. This implies that the mode of action of enhanced photo carcinogenesis observed with the cream vehicle and the ivermectin cream test articles was due to irritancy associated stimulation of tumour promotion/progression. Chronic skin inflammation is known to promote and/or stimulate the progression of UVR-induced non-melanoma skin cancer.[11, 12]

Neoplastic and pre-neoplastic lesions (hepatic ademonas, pancreatic islet cell adenomas in male rats, female mammary fibroadenomas, pituitary pars distalis adenomas, thyroid adenomas of doubtful human relevance were identified in the non-pivotal near-lifetime repeat gavage oral carcinogenesis study in rats.

Retinal atrophy was noted in the rat carcinogenesis study and this effect is likely to be human relevant. Individuals with compromised blood retinal barrier function will have an increased susceptibility for ivermectin induced adverse effects on the retina. The rat LOAEL for retinal effects was 1 mg/kg BW/day (equivalent to and $AUC_{0\text{-}24\ Last}$ of 5,241.02 ng·h/mL and 4,335.89 ng·h/mL in males and females respectively). The highest mean $AUC_{0\text{-}24}$ for Soolantra use in humans was 75.16 ng·h/mL (clinical Study 40064), thus the systemic exposure at the LOAEL in rats is ≥ 1,342.5 higher than the expected human systemic ivermectin exposure.

The study dose and dose ranging for the oral rat carcinogenesis study was selected based on the maximum tolerated dose derived from the rat sub chronic oral study. Given that there were > 25 animals/gender/dose at the end of the study the highest dose was appropriate. The human relevant LOAEL was 1 mg/kg BW/day (equivalent to and $AUC_{0\text{-}24}$ Last of 5,241.02 ng·h/mL and 4,335.89 ng·h/mL in males and females respectively) due to the presence of an increased incidence of retinal atrophy at this dose rate. The highest mean $AUC_{0\text{-}24}$ for Soolantra use in humans was 75.16 ng·h/mL (clinical Study 40064), thus the systemic exposure at the LOAEL in rats is ≥ 57.7 higher than the highest expected human systemic ivermectin exposure (based on $AUC_{0\text{-}24}$ ratio).

Reproductive toxicity

Unsurprisingly ivermectin is not a reproductive or developmental toxicant in animals with normal ABC B1 phenotype. It should be noted that ivermectin is prevented from crossing the blood brain barrier by the actions of the ABC B1 (p-glycoprotein) efflux transporter. In humans, ABC B1 expression in the blood brain barrier develops between 18 and 22 weeks of gestation with effective efflux transporter activity likely by mid-gestation.[13] It is thus theoretically possible that fetal CNS exposure prior to 18 and 22 weeks of gestation may occur. However, the fetus is substantially protected from ivermectin exposure by the substantial presence of ABC B1 efflux transporters in the placenta.[14] Animal studies have demonstrated that drug interactional conditions that reduce placental ABC B1 ivermectin efflux transporter activity increase fetal ivermectin exposure and are associated with ivermectin induced adverse effects on fetal development.[15]

[11] Maru GB, et al. The role of inflammation in skin cancer. *Adv Exp Med Biol.* 2014; 816:437-469.
[12] Sharma SD, et al. IL-12 deficiency suppresses 12-O-tetradecanoylphorbol-13-acetate-induced skin tumor development in 7,12-dimethylbenz(a)anthracene-initiated mouse skin through inhibition of inflammation. *Carcinogenesis.* 2009;30:1970-1977.
[13] Virgintino D, et al. Fetal blood-brain barrier P-glycoprotein contributes to brain protection during human development. *J Neuropathol Exp Neurol*. 2008; 67:50-61.
[14] Staud F, *et al.* Pharmacotherapy in pregnancy; effect of ABC and SLC transporters on drug transport across the placenta and fetal drug exposure. *J Drug Target.* 2012; 20:736-763.
[15] el-Ashmawy IM, el-Nahas AF, Bayad AE. (2011) Teratogenic and cytogenetic effects of ivermectin and its interaction with P-glycoprotein inhibitor. *Res Vet Sci.* 2011; 90:116-123.

Table 3. Relative exposure

Species	Study	NOAEL (mg/kg/day)	$AUC_{0-24\,h}$ (ng·h/mL)	Exposure ratio#
Rat (SD)	Fertility	0.1	130.95 (m)	1.74
		1	2413.80 (m)	32.12
		9	36379.10 (m)	484.02
	Embryofetal development	1.5	7829*	105.49
		4	25099*	333.94
		12	67625*	899.75
Rabbit (NZW)	Embryofetal development	0.5	403‡	5.36
		1.5	2766‡	36.80
		4.5	12556‡	167.06
Rabbit (NZW)	Embryofetal development	2.5	2545‡	33.86
		3.5¤	5159‡	68.64
Rabbit (NZW)	Embryofetal development Dose-Ranging Study	1.5	No Data	No Data
		3.0		
		6.0		
Rat (SD)	2 generation multigenerational study with cross fostering study	0, 0.4, 1.2, 3.6 mg/kg/day PO gavage (experiment 1); 0, 0.05, 0.1, 0.4 (experiment 2).	No Data	No Data
Human (Severe papulo-pustular rosacea under maximal use conditions)	steady state	10 mg	75.16†	–

= animal: human plasma $AUC_{0-24\,h}$ * = at gestation day 17 ‡ = at gestation day 20 ¤ = NOAEL for embryofetal development † = highest mean AUC_{0-24} observed

The reproductive and developmental NOAEL is derived from the rat fertility study: 1.0 mg/kg/day (equivalent to AUC_{0-24} in males of 2,413.8 ng·h/mL and 2,887.32 ng·h/mL in females); oral; gavage due to parental mortality and elongated precoital period in the 9 mg/kg BW/day group. This provides an exposure ratio in humans of approximately 32 to 38.

The sponsor's data demonstrate that under normal conditions (that is no inhibition of ABC B1 or ABC B1 low functional phenotype) fetal exposure to ivermectin in rats following oral dosing is low. These data are consistent with other species. Studies in sheep indicate that

materno fetal placental transfer of ivermectin following IV maternal injection is relatively limited (fetal $AUC_{0-\tau}$ 89.1 ± 11.4 ng.h/mL versus maternal area under the curve time 0 to tau (last measurable concentration point) ($AUC_{0-\tau}$) 2,925.2 ± 1,076.0).[16] Similar results have been reported in cattle where the materno-fetal placental transfer of ivermectin was below the level of detection.[17]

The mechanistic explanation for these effects is the presence of the ABC B1 efflux transporter in the placenta which actively pumps ivermectin back to the maternal circulation thus limiting trans placental exposure of the fetus.[18] Animal studies have demonstrated that drug interactional conditions that reduce placental ABC B1 ivermectin efflux transporter activity increase fetal ivermectin exposure and are associated with ivermectin induced adverse effects on fetal development.[19]

Critically, protection of neonates from the adverse developmental effects of trans mammary ivermectin is dependent on the presence of an intact blood brain barrier. In rats, maternal oral ivermectin exposure of ≥ 0.4 mg/kg BW/day substantially increases neonatal mortality and induced developmental delay prior to maturation of the neonatal blood brain barrier due to trans mammary transfer. The effect is exacerbated with chronic maternal exposure (higher mobilisation of body fat sequestered ivermectin into milk). In rats the period of highest trans mammary exposure correlates with low neonatal blood brain barrier ABC B1 function, resulting in high neonatal brain exposures. Critically, human blood brain barrier ABC B1 function develops at ≥ 12 weeks gestation, not after birth. Human neonates are therefore resistant to these effects.

Ivermectin is detectable in human milk following oral dosing; however milk steady state levels are low following single acute exposures. However rodent data indicates that chronic maternal ivermectin exposure will result in milk ivermectin levels at least 3 to 4 times higher than those observed with single acute exposures due to greater mobilisation of body fat sequestered ivermectin. This effect is greatest during early lactation when mobilisation of maternal body fat is highest.

Pregnancy classification

The sponsor has proposed Category B3.[20] This is acceptable. The Australian pregnancy category (Stromectol) is currently B3. The USA category for Soolantra is C[21]. There are no adequate and well controlled studies in pregnant women. However pregnant women have undoubtedly been exposed to ivermectin over the course of global parasitism control programs. Soolantra should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Co-exposure to drugs that compete with ivermectin at placental ABC B1 efflux transporters or inhibit these transporters will likely increase fetal exposure. Such effects

[16] Pérez R et al.Pharmacokinetics of ivermectin after maternal or foetal intravenous administration in sheep*. J Vet Pharmacol Ther*. 2008 ;31:406-414.
[17] Chamberlain PL, et al. Preliminary studies of offspring exposure to phenylbutazone and ivermectin during the perinatal period in a Holstein cow-calf model. *Toxicol Appl Pharmacol.* 2004; 187:198-208.
[18] Ceckova-Novotna M. et al. P-glycoprotein in the placenta: expression, localisation, regulation and function. *Reprod Toxicol.* 2006; 22:400-410.
[19] el-Ashmawy IM. et al. Teratogenic and cytogenetic effects of ivermectin and its interaction with P-glycoprotein inhibitor. *Res Vet Sci.* 2011; 90:116-123.
[20] Australian Category B3 for the use of medicines in pregnancy is defined as: *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.*
[21] USA Category C for the use of medicines in pregnancy is defined as*: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.*

have been demonstrated to cause ivermectin induced adverse effects on development in animal models.

Oral terate-genotoxicity studies in the rabbit demonstrated maternal toxicity and carpal flexures of doubtful human relevance in the fetus at a dose of 4.5 mg/kg/day. The NOAEL was established at 3.5 mg/kg/day, a dose corresponding to plasma levels 68 times higher than those obtained at the maximum recommended human dose by topical route (1 g application of Soolantra once daily). In the rat, cleft palates were observed at the maternotoxic oral dose of 12 mg/kg/day. The dose of 4 mg/kg/day was the NOAEL for maternal toxicity and embryofetal development, a dose corresponding to plasma levels 334 times higher than those obtained at the maximum recommended human dose by topical route (1 g application of Soolantra once daily).

Local tolerance

Soolantra is a mild primary skin irritant in rabbits and it displays cumulative contact irritancy properties in guinea pigs. Exposure to the cream vehicle was undoubtedly cumulatively irritant in many of the animal topical exposure studies. Critically the presence of ivermectin did not exacerbate the more severe forms of the cumulative irritancy reaction (inflammation and ulceration) or pustule formation.

Soolantra is not an acute eye irritant in rabbits. However it does display contact hypersensitivity properties under strong sensitising conditions in guinea pigs and it may be a contact sensitiser in some people.

Long term, repeated exposure to the cream vehicle may be comedomogenic. This potential effect was not examined in the most appropriate animal model (rabbit ear model).

Exposure to the cream vehicle undoubtedly enhances photo carcinogenesis in the hairless model of human Fitzpatrick Type II skin. The mode of action of this effect is most probably cumulative irritancy stimulation of tumour promotion/tumour outgrowth.

Soolantra is not an acute ocular irritant, a skin sensitiser or a photo allergen.

Impurities

The proposed specifications for impurities/degradants in ivermectin are consistent with those already evaluated and approved for Stromectol and have been adequately qualified.

Paediatric use

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

Nonclinical summary and conclusions

Summary

- Overall there are no nonclinical objections to registration.
- Topical Soolantra undoubtedly enhances non-melanoma skin photo carcinogenesis in a human relevant mouse model. Long term, repeated topical application of Soolantra in sun exposed areas should be avoided or sun protection strategies should be used.
- Active elimination of systemically absorbed ivermectin into the gut raises concerns regarding induction of anthelmintic resistance to ivermectin. No data was provided on this issue.

- The local tolerance of topical Soolantra is generally acceptable; however sub chronic to chronic cumulative skin irritancy (due to the vehicle) occurs in laboratory animals. Soolantra is also a mild primary skin irritant in rabbits and displays contact hyper sensitising properties under strongly sensitising conditions. Long term, repeated exposure to the cream vehicle may be comedomogenic however no relevant nonclinical data was supplied. The proposed PI adequately addresses these issues.
- Competitive substrates and/or inhibitors of ABC B1 can substantially affect the safety properties of ivermectin. No nonclinical data was provided on these issues. These interactions have resulted in unexpected animal deaths and other severe effects in veterinary medicine (notably spinosad with ivermectin). The pharmacokinetic properties of Soolantra will tend to exacerbate these effects. However, Soolantra generally has relatively high animal: human AUC ratios at the NOAEL and given the topical route of exposure and relatively low systemic exposure, the risks of these types of effects with ivermectin use are greatly reduced.
- The presence of an intact blood brain barrier critically affects the safety properties of ivermectin. No nonclinical data was provided on these issues. Pharmacogenetic effects on ABC B1 in the blood brain barrier, the blood testis barrier, placenta and the intestinal enterothelium, substantially increase the risk of ivermectin toxicity (including fertility, reproductive and developmental toxicity) in animals. These pharmacogenetic differences are poorly documented in humans. The lethal pharmacogenetic phenotype in dogs (complete loss of blood brain barrier ABC B1 function) has not been documented in humans (only small populations evaluated). Blood brain barrier abnormalities due to disease or other processes will also affect the safety properties of ivermectin. The pharmacokinetic properties of Soolantra will tend to exacerbate these effects. However Soolantra generally has relatively high animal: human AUC ratios at the NOAEL and given the topical route of exposure and relatively low systemic exposure, the risks of these types of effects with ivermectin use are greatly reduced.
- There are no acceptable animal models of human rosacea. The primary pharmacology mode of action is unknown. Ivermectin mediated down regulation of acute inflammation in vitro and in various in vivo animal models was demonstrated. No data on the mitocidal mode of action was provided.
- Other than the concerns described above, there are no other nonclinical secondary or safety pharmacological properties that preclude registration.
- Retinal atrophy was noted in rats (probably due to overwhelming of blood retinal barrier ABC B1). This effect is undoubtedly human relevant but is not a practical concern for Soolantra.
- Questionably test article related reductions of blood neutrophils were noted in 3 human subjects in clinical Study RD.03.SRE.40051. While effects on CFU-GM formation, reductions of neutrophil oxidative burst activity, increased pulmonary alveolar histiocytosis in rats and increased incidence of spontaneous interstitial pneumonia in rats was observed these issues do not appear to be a practical concern for Soolantra under normal conditions of use.
- Predictably, topically applied ivermectin largely partitions into the lipophilic skin compartments. Steady state (SS) systemic ivermectin exposure following repeated topical application of Soolantra is low (crudely approximated $F_{Absolute}$ (Dermal: IV) approximately 8%): approximately 7.5 times lower than that associated with a single 200 µg/kg BW oral dose of Stromectol[22] in humans). However there are very

[22] Stromectol; 3 mg ivermectin tablet intended for the treatment of onchocerciasis and intestinal strongyloidiasis

substantial pharmacokinetic differences between chronic repeated topical Soolantra application and episodic single exposures to Stromectol (absorption kinetics of Soolantra result in a greatly extended ivermectin $T_{½}$, much slower whole body clearance and duration of systemic exposure).

- Predictably, ivermectin displays tissue sequestration (adipose tissues, particularly brown fat). Topical ivermectin application consistently displays flip-flop, absorption-limited pharmacokinetics resulting in high T_{SS}, high $T_{½}$ and slow whole body clearance (multiple days to weeks).
- Ivermectin is modestly toxic following single (acute) oral gavage dosing in ABC B1 phenotypically normal rats and mice; however acute toxicity thresholds will be greatly affected by ABC B1 efflux transporter dysfunction. All of the animal topical repeat exposure studies were confounded by ingestion exposure. Excluding local application site effects, the chronic near lifetime exposure topical exposure NOAEL in mice was ≥ 1% (W/W) ivermectin cream, 1 mL/kg/day covering approximately 10% body surface area, non occlusive (animal NOAEL mean AUC_{0-24}:human mean AUC_{0-24} exposure ratio is ≥ 645.5).
- Ivermectin is not mutagenic and is not a human relevant carcinogen (see carcinogenicity section above for a discussion on the lack of human relevancy of the observed rodent neoplasms); nor is it a reproductive and prenatal developmental toxicant at sub materno toxic doses. Critically, prevention of prenatal developmental toxicity is dependent on intact placental ABC B1 function. Ivermectin is potentially a male reproductive toxicant if the blood testis barrier ABC B1 is compromised. Again, given the topical route of exposure and relatively low systemic exposure, the risks of these types of effects with ivermectin use are greatly reduced.
- Critically, protection of neonates from the adverse developmental effects of trans mammary ivermectin is dependent on the presence of an intact blood brain barrier. In rats the period of highest trans-mammary exposure correlates with low neonatal rat blood brain barrier ABC B1 function, resulting in high neonatal rat brain exposures. Critically, human blood brain barrier ABC B1 function develops at ≥ 12 weeks gestation, not after birth.[23] Human neonates are therefore resistant to these effects and are protected in utero by placental ABC B1 efflux transporters. Again, given the topical route of exposure and relatively low systemic exposure, the risks of these types of effects with ivermectin use are greatly reduced.
- Ivermectin is detectable in human milk following oral dosing; however milk steady state levels are low following single acute exposures. However rodent data indicates that chronic maternal ivermectin exposure will result in milk ivermectin levels at least 3 to 4 times higher than those observed with single acute exposures due to greater mobilisation of body fat sequestered ivermectin. This effect is greatest during early lactation when mobilisation of maternal body fat is highest.
- Soolantra is not an acute eye irritant in rabbits and ivermectin is not a photo allergen.

Conclusions and recommendation

- There are no nonclinical objections to registration.
- Soolantra should be used in conjunction with sunscreens and other solar UV protection methods.

[23] Virgintino D. et al. Fetal blood-brain barrier P-glycoprotein contributes to brain protection during human development. *J Neuropathol Exp Neurol*. 2008; 67: 50-61.

- Because of the lack of nonclinical drug interaction data, some care should be exercised when drugs that are known to completely block or very substantially inhibit ABC B1 (P-glycoprotein) efflux transporters are used concurrently with Soolantra. Theoretically drug interactions at ABC B1 (p-glycoprotein) efflux transporters will affect the safety properties of Soolantra and adverse drug interactions may occur via these mechanisms that could affect human CNS function (particularly level of consciousness), human retinal function, human fetal development, human neonatal development and male fertility. However, Soolantra appears to have adequate animal: human AUC ratios at the relevant nonclinical NOAELs. Given the topical route of exposure and relatively low systemic exposure, the risks of these types of effects with ivermectin use are greatly reduced.
- There is potential for Soolantra use to contribute to the induction of anthelmintic resistance to ivermectin and other members of the avermectin parasiticidal drug class because an important pathway of excretion is active transport in to the gut via enterothelial ABC B1 efflux transporters.
- The mode of action of ivermectin treatment of rosacea is not fully established. Possible modes of action include suppression of inflammation a mitocidal effects on Demodex species. Notably ivermectin has often been combined with a pyrethroid or neonicotinoid arthrocide when used to treat demodicosis, presumably in the hope of increased efficacy.
- Long term, repeated topical application of Soolantra may result in cumulative skin irritancy and (rarely) skin contact sensitisation. However, these issues are adequately dealt with in the PI.
- Overall, Soolantra does not present any particularly overt safety pharmacology concerns with the proposed pattern of use.
- Because of the pharmacokinetic and dosing pattern differences between Stromectol (that is occasional single dose oral parasiticide use) and Soolantra, some degree of caution should be applied if Soolantra is used during pregnancy (particularly during brain development) and substantial compromise (for example complete blocking) of placental ABC B1 function is likely. Again because of the topical route of exposure and relatively low systemic absorption, the risks of these types of effects with ivermectin are substantially reduced.
- Ivermectin is detectable in human milk following oral dosing; however milk steady state levels are low following single acute exposures. Unlike the single episodic use of ivermectin for treatment of parasitic diseases, the chronic use of Soolantra will result in sustained neonatal trans mammary exposure. Based on rodent studies, chronic maternal exposure will result in milk ivermectin levels at least 3 to 4 times higher than those observed with single acute ivermectin exposures. Provided that the human neonatal blood brain barrier ABC B1 function remains intact, these phenomena should not adversely effect on human neonatal development. Trans mammary ivermectin exposures should probably be avoided in situations where human neonatal blood brain barrier ABC B1 function may be substantially compromised. Again because of the topical route of exposure and relatively low systemic absorption, the risks of these types of effects with ivermectin are substantially reduced.
- Recommendations with regard to the PI have been made but these are beyond the scope of this AusPAR.

IV. Clinical findings

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

Introduction

Clinical Rationale

The sponsor explains that the efficacy of ivermectin in human and animal demodicidosis and its anti-inflammatory properties suggested that ivermectin could also be effective in the treatment of inflammatory lesions of rosacea. This prompted the development of Soolantra. Note that no particular evidence is offered in the present clinical dossier that the mode of action of Soolantra in the indication for which approval is now sought depends upon its antiparasitic properties.

Contents of the clinical dossier

The clinical dossier included;

- 2 clinical pharmacology studies, including 2 that provided pharmacokinetic data.
- 2 pivotal efficacy/safety studies.
- 1 dose finding study.
- 10 other efficacy/safety studies.

The submission also contained;

- Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

Table 4 summarises the studies that were submitted.

Table 4. Studies presented in the dossier, not previously evaluated.

Study no.	Title
RD.03.SRE.19055	Evaluation of the cumulative irritancy potential of Ivermectin 1% cream compared to vehicle in healthy volunteers
RD.03.SRE.19081	Evaluation of the cumulative irritancy potential of different vehicle prototypes of Ivermectin after repeated applications in healthy subjects
RD.03.SRE.40023	Evaluation of the irritation and sensitisation potential of 4 concentrations of CD5024 cream 0.03%, 0.1%, 0.3%, 1% and of its vehicles following repeated applications to the skin of healthy subjects
RD.03.SRE.40007	Plasma pharmacokinetics of CD5024 (1%) cream following single and repeated topical applications in healthy subjects
RD.03.SRE.40064	Plasma pharmacokinetics study of CD5024 1% cream in subjects with papulo-pustular rosacea
RD.03.SRE.40006	Exploratory clinical study comparing the efficacy of a twice-daily application of Ivermectin 1% cream versus its vehicle and

Study no.	Title
	metronidazole 0.75% cream (Rozex) in subjects with papulo-pustular rosacea
RD.03.SRE.40027	Assessment of the efficacy and safety of three concentrations: 1%, 0.3%, 0.1% of CD5024 cream once daily and CD5024 1% cream twice daily, versus its vehicle and versus Metronidazole (0.75% cream Rozex), in patients with papulo-pustular rosacea over 12 weeks
RD.03.SRE.40106	A double-blind, vehicle-controlled, parallel group study assessing the activity of CD5024 1% cream in subjects with papulopustular rosacea over 12 weeks treatment
RD.03.SRE.40173	Efficacy and safety of CD5024 1% cream versus metronidazole 0.75% cream in subjects with papulo-pustular rosacea over 16 weeks treatment, followed by a 36-week extension period
RD.06.SRE.18170	A Phase III randomised, double-blind, 12-week vehicle-controlled, parallel-group study assessing the efficacy and safety of CD5024 1 % cream versus vehicle cream in subjects with papulo-pustular rosacea, followed by a 40-week investigator-blinded extension comparing the long-term safety of CD5024 1% cream versus azelaic acid 15% gel
RD.06.SRE.18171	A Phase III randomised, double-blind, 12-week vehicle-controlled, parallel-group study assessing the efficacy and safety of CD5024 1 % cream versus vehicle cream in subjects with papulopustular rosacea, followed by a 40-week investigator-blinded extension comparing the long-term safety of CD5024 1% cream versus azelaic acid 15% gel
RD.03.SRE.40051	A multicentre, open-label study to evaluate the long-term safety and efficacy of CD5024 1% cream treatment for up to 52 weeks in subjects with papulo pustular rosacea
RD.06.SRE.18120	A positive and placebo controlled, double-blind, parallel, single dose, thorough QTc study of oral Ivermectin at a supra-therapeutic dose in healthy subjects
RD.03.SRE.40037	An exploratory study to evaluate relapses following an initial 12 weeks dose-range study with CD5024 cream versus its vehicle and versus metronidaxzole 0.75% cream in papulo-pustular rosacea – a 6 month follow-up treatment-free study
RD.03.SRE.2894	Clinical study comparing the efficacy of a twice daily application of Ivermectin 1% cream versus its vehicle and metronidazole 0,75% emulsion (Rozex) in subjects with papulo-pustular rosacea

Paediatric data

The submission did not include paediatric data.

Good clinical practice

Good clinical practice (GCP) compliance was asserted for all studies included in the dossier.

Pharmacokinetics

Summaries of the pharmacokinetic studies were provided. Table 5 shows the studies relating to each pharmacokinetic topic.

Table 5. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	General PK	
	Single dose	RD.03.SRE.40007
	Multi-dose	RD.03.SRE.40007
	Bioequivalence	
	Single dose	None
	Multi-dose	None
	Food effect	Not relevant
PK in special populations	Target population	
	Single dose	RD.03.SRE.40064
	Multi-dose	RD.03.SRE.40064 RD.03.SRE.40027
	Renal impairment	None
	Neonates/infants/children/adolescents	None
	Elderly	None
Genetic/gender-related PK	Males versus. females	None
PK interactions		None
Population PK analyses	Healthy subjects	None
	Target population	None

Studies providing pharmacokinetic data

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

Pharmacokinetics in healthy subjects

No reports were presented of the PK in healthy subjects using the formulation to be marketed.

Pharmacokinetics in the target population

Absorption

PK following single and repeated dosage in patients with severe papulo-pustular rosacea (PPR) were examined in Study RD.03.SRE.40064 (see Table 6). AUCs were similar at Weeks 2 and 4, suggesting that steady state conditions were achieved by Week 2. Ivermectin measurements were also made during chronic dosing in Studies RD.03.SRE.40027, RD.03.SRE.40106, RD.03.SRE.40051, RD.06.SRE.18170 and RD.06.SRE.18171, and results are shown in the Table 7 below.

Table 6. Study RD.03.SRE.40064 PK results.

Parameter	Day 0[2]	Day 7[3]	Day 14[4]	Day 21	Day 28
C_{min} [1]: Mean (sd) (ng/mL)	0.37 (0.21)	1.17 (0.88)	1.26 (0.53)	1.36 (0.66)	1.36 (0.63)
C_{max} : Mean (sd) (ng/mL)	0.69 (0.49)		2.10 (1.04)		1.74 (0.77)
C_{max} : Range (ng/mL)	0.19 to 1.76		0.69 to 4.02		0.58 to 3.36
T_{max} : Mean (sd) (h)	9 (6)		10 (8)		11 (4)
$AUC_{0\text{-}24h}$: Mean (sd) (h.ng/mL)	9.29 (5.40)		36.14 (15.56)		35.43 (14.42)
$AUC_{0\text{-}24h}$: Range (h.ng/mL)	3.16 to 21.28		13.69 to 75.16		12.89 to 70.08

[1] Pre-dose, [2] N=17, [3] N=13, [4] N=14

Table 7. Ivermectin measurements during chronic dosing in Studies RD.03.SRE.40027, RD.03.SRE.40106, RD.03.SRE.40051, RD.06.SRE.18170 and RD.06.SRE.18171.

Treatment duration	Ivermectin concentration (ng/mL): mean ± SD (range)					
	40064[1]	40027 N=50	40051 N=79	40106[2]	18170 N=109	18171 N=105
Week 2	1.26±0.5 (0.58 to 2.34)			0.77±0.71 (to 3.66)		
Week 4	1.36±0.6 (0.53 to 3.00)	0.72±0.7 (to 4.05)		0.95±0.88 (to 4.55)		
Week 6				1.07±0.97 (to 5.78)		

Treatment duration	Ivermectin concentration (ng/mL): mean ± SD (range)					
Week 8				1.11±1.06 (to 5.66)		
Week 10			0.90±0.90 (to 5.48)	1.13±1.25 (to 6.66)		
Week 12		0.77±1.05 (to 6.13)		1.06±1.12 (to 6.75)	0.46±0.70 (to 5.95)	0.43±0.49 (to 2.81)
Week 32					0.35±0.44 (to 3.13)	0.40±0.49 (to 2.89)
Week 52					0.31±0.40 (to 2.15)	0.41±0.61 (to 3.80)

Evaluator's conclusions on pharmacokinetics

The data submitted are sufficient to characterise the PK following topical application of the product in patients with PPR, and to provide reassurance that accumulation is not likely to be significant.

Pharmacodynamics

Studies providing pharmacodynamic data

None submitted.

Dosage selection for the pivotal studies

Dose-finding studies

Study RD.03.SRE.40027

The objective of this study was selection of dose and regimen for further study. Design was multicentre, randomised, investigator blinded, parallel group with 6 arms:

Group 1: ivermectin 1% cream (formulation proposed for registration) twice daily (BD)

Group 2: ivermectin 1% cream (formulation proposed for registration) daily

Group 3: ivermectin 0.3% cream daily

Group 4: ivermectin 0.1% cream daily

Group 5: vehicle cream daily

Group 6: metronidazole 0.75% cream (Rozex) BD.

For further details please see Attachment 2.

Summary

Statistical tests were based on the distributions of the percent change in inflammatory lesion counts from Baseline and were interpreted stepwise from the highest dose to the lowest dose to minimise multiplicity issues. At Week 12; LOCF (intention to treat (ITT)),

efficacy of ivermectin 1% daily and BD was statistically superior to that of the vehicle (p = 0.006 and p = 0.014); ivermectin 0.1% daily and 0.3% BD were not statistically different from the vehicle (p values > 0.06), the per protocol analysis confirmed these findings. None of the ivermectin doses was statistically different from metronidazole 0.75% BD.

Efficacy

The efficacy was assessed for the topical treatment of inflammatory lesions of rosacea.

Studies providing efficacy data

Study RD.06.SRE.18170

The first, 12 week part of the study (Part A) assessed the efficacy and safety of ivermectin 1% cream versus vehicle cream in subjects with PPR. This was followed by a second, 40 week extension (Part B) comparing the long term safety of ivermectin 1% cream versus azelaic acid 15% gel. The final part of the study (Part C) was a 4 week follow up period assessing safety after treatment cessation. Thus, the total study duration was 56 weeks.

Study RD.06.SRE.18171

The design and objectives were as for Study RD.06.SRE.18170.

Other efficacy studies

Study RD.03.SRE.40006

This was a preliminary efficacy and safety study of ivermectin 1% cream (formulation proposed for registration). Design was multicentre, randomised, investigator blinded, parallel group with 3 arms: active cream, vehicle, and Rozex (metronidazole), applied BD for 9 weeks in patients with PPR.

Study RD.03.SRE.40027

This was a dose finding study.

Study RD.03.SRE.40037

This was a treatment free extension of Study RD.03.SRE.40027. Its objective was to evaluate relapses in patients successfully treated in Study RD.03.SPR.40027.

Study RD.03.SRE.40173

The objective of this study was to evaluate the efficacy and safety of once daily application of ivermectin 1% cream versus twice daily application of metronidazole 0.75% cream (Rozex) in subjects with papulo pustular rosacea, for 16 weeks with a 36 week extension period. The report submitted is complete for the first 16 weeks of the study ('Period A'), and provides preliminary data on the extension ('Period B') up to the cut-off date of 8 April 2013.

For further details of the efficacy studies and their outcomes see Attachment 2.

Evaluator's conclusions on efficacy

In the pivotal Studies RD.06.SRE.18170 and RD.06.SRE.18171 Soolantra was shown to be superior to vehicle, consistent with the Phase II Studies RD.03.SRE.40027and RD.03.SRE.40106. The Phase III Study RD.03.SRE.40173 provided statistically significant evidence of the superiority of daily Soolantra over BD Rozex. Data on relapse rates from the 36 week extension of Study RD.03.SRE.40173 are awaited.

No convincing evidence was presented of superiority of different dosages of ivermectin cream versus other dosages (see Study RD.03.SRE.40027).

Safety

Studies providing safety data

Pivotal efficacy studies

Pivotal studies that assessed safety as a primary outcome

Studies RD.06.SRE.18170 and RD.06.SRE.18171 were pivotal studies that assessed safety as well as efficacy as a primary outcome.

Dose-response and non-pivotal efficacy studies

The dose response and non pivotal efficacy studies provided safety data, as follows:

Studies RD.03.SRE.40027, RD.03.SRE.40106 and RD.03.SRE.40173 provided data on AE monitoring including AEs of special interest.

Regular laboratory monitoring was carried out in Studies RD.03.SRE.40106 and RD.03.SRE.40173, and at screening and Week 12 in Study RD.03.SRE.40027.
Study RD.03.SRE.40173 provided full data on routine AE monitoring for Period A only.

Study RD.03.SRE.40006 provided data on AE monitoring.

Other studies evaluable for safety only

Study RD.03.SRE.19055

The aim of this study was to assess cumulative irritancy potential of ivermectin 1% cream versus vehicle and white petrolatum, applied for 21 days under occlusive conditions to the upper back of healthy volunteers.

Study RD.03.SRE.19081

The aim of this study was to assess cumulative irritancy potential of 2 new proposed vehicles versus the initial vehicle and white petrolatum, applied for 21 days under occlusive conditions to the upper back of healthy volunteers.

Study RD.03.SRE.40023

The aim of this study was to assess the potential of repeated applications of 4 concentrations of ivermectin cream (none of which was the product for which registration is sought) or vehicle to induce irritation or sensitisation in the skin of healthy subjects.

Study RD.03.SRE.40051

The primary objective as originally planned was to document the long term safety of ivermectin 1% cream once daily, for up to 52 weeks of topical treatment in subjects with PPR. This objective was changed to an evaluation up to subject's termination as a result of the sponsor's decision to discontinue the study prematurely, following adverse laboratory findings in some patients: at Week 10 of treatment, the neutrophil cell count had decreased in 3 subjects below the threshold value of $1.5x10^9$/L defining a neutropenia.

Study RD.06.SRE.18120

The primary objective was to evaluate the effect of a single orally administered dose of ivermectin on ventricular repolarisation in healthy adult subjects.

Patient exposure

The sponsor states:

'A total of 2,431 of the 3,999 subjects in the clinical development program were exposed to ivermectin 1% cream: 268 healthy subjects and 2,163 subjects with PPR. The figure of 2,163 subjects with PPR includes 116 subjects exposed to ivermectin 1% cream BD, which was

explored in Phase II before the QD regimen was confirmed for the Phase III program. Consequently, a total of 2,047 subjects with PPR were exposed to the to-be-marketed formulation and regimen: ivermectin 1% QD.'

Only studies in which at least 1 subject was treated with the formulation proposed for registration contribute data to the two tables below Tables 8 and 9.

Table 8. Exposure to Soolantra and comparators in clinical studies.

Study type/ Indication	Controlled studies				Un-controlled studies	Total Sool
	Sool	Vehicle	Other iver cream	Other active cream	Sool	
Clinical pharmacology					17	17
Indication 1						
Pivotal	909	461	0	418	0	909
Other	731	206	146	532	484	1215
Subtotal Indication 1	1640	667	146	950	484	2124
TOTAL	1640	667	146	950	501	2141

Table 9. Exposure to Soolantra in clinical studies according to dose and duration.

Study type/ Indication	Proposed dose				Other dose			
	≥ 3 mo.	≥ 6 mo.	≥ 12 mo.	Any dur'n	≥ 3 mo.	≥ 6 mo.	≥ 12 mo.	Any dur'n
Clinical pharmacology				17				0
Indication 1								
Vehicle-controlled[1]				104[2]				
Active-controlled	839	784	717	1439[4]				97
Uncontrolled				484[3]				
Subtotal Indication 1	839	784	717	2027				97
TOTAL	839	784	717	2044				97

Safety issues with the potential for major regulatory impact

Laboratory tests

Haematology

Neutropenia

Study RD.03.SRE.40051

Three cases of neutrophil cell counts < $1.5x10^9$/L were observed under treatment, without any associated clinical signs or symptoms (for example, fever), corresponding to an incidence of 0.98%. This was reversible in all 3 subjects. One subject's neutropenia reversed while under active treatment.

Study RD.03.SRE.40106

The primary rationale for this study was to investigate whether the product proposed for registration may be causally associated with neutropenia. Thus, it is of particular interest in that blood samples were drawn frequently for laboratory assessment.

Percent changes from Baseline in NCCs were compared at each post Baseline visit between ivermectin cream and its vehicle, and also for the lowest value observed after Baseline (retests and unscheduled visits included). At each time point, no meaningful between group differences were observed.

Overall, there were 5 subjects reported with neutrophil counts below 1.5 $x10^9$/L, 4 (3.9%) in the ivermectin group and 1 (0.9%) in the vehicle group. One of these subjects in the active treatment group also had a neutrophil count below 1.5 $x10^9$/L at Baseline before treatment; a retest performed two days later (after one application of study drug) also produced a low neutrophil count and this subject discontinued study participation. Subsequent neutrophil counts obtained at two re-tests were all within the normal range. Therefore, four subjects had single treatment-emergent neutrophil counts below 1.5 $x10^9$/L. Among the 4 'treatment emergent' cases of neutrophil counts below 1.5 $x10^9$/L, the neutrophil count had normalised under treatment for 3 cases and after a temporary discontinuation of the treatment in the fourth case. In this subject from the ivermectin group, study drug was temporarily stopped (as specified in the protocol) due to the presence of infectious signs and re-administered after normalisation of the neutrophil count at retest, without any recurrence of the neutropenia. No subject reported severe (< 0.5 x 10^9/L) neutropenia. At no point during the study did the independent data monitoring committee (IDMC) consider it necessary to unblind the data or to definitely stop the treatment. All cases of neutrophil count ≤ 1.5 x 10^9/L were assessed as 'not related' to the study drug by the IDMC and by the investigators.

Thus, there appears to be no evidence of a causal relationship between treatment with ivermectin 1% cream and neutropenia.

Cutaneous toxicity

Local tolerance was generally assessed via AE reports. Cumulative irritancy potential was assessed specifically in Studies RD.03.SRE.19055 (which, however, did not use the formulation proposed for registration) and RD.03.SRE.19081 (which used vehicles only). Study RD.03.SRE.40023 assessed irritation and sensitisation potential (but did not use the formulation proposed for registration). Thus, the specific studies, RD.03.SRE.19055, RD.03.SRE.19081 and RD.03.SRE.40023, contributed little useful information.

Specific phototoxicity studies have not been presented.

Post marketing data

Not applicable.

Evaluator's conclusions on safety

In assessing safety information which comprises the results of clinical trials done with different product formulations; particularly topical products, in which the vehicle may have a major effect; a cautious approach is to maintain vigilance for an adverse signal from any formulation but to accept reassurance regarding lack of toxicity only from studies done with the formulation proposed for marketing. The clinical evaluator has adopted this approach in the clinical evaluation report.

Specific studies of photo safety have not been presented. However, it is likely that any problem of this nature would have emerged in the pivotal studies.

Studies of topical ivermectin in patients with renal or hepatic disease have not been presented.

At the present stage of product development, no specific safety concerns remain.

First Round Benefit-Risk Assessment

First round assessment of benefits

The benefits of Soolantra in the proposed usage are:

- Proven efficacy.
- Convenience of once daily application.

Note that no convincing evidence has been presented that the 1% cream is significantly more efficacious than 0.3% cream (Study RD.03.SRE.40027).

First round assessment of risks

The risks of Soolantra in the proposed usage are:

- Hypothetical effects of systemic exposure. The difference in systemic exposure between 0.3% and 1% creams (Study RD.03.SRE.40027) is noted.
- Possible skin toxicity; in particular, photosensitivity or photoallergy and contact allergy.

First round assessment of benefit-risk balance

The benefit-risk balance of Soolantra, given the proposed usage, is favourable.

However, some doubt remains as to whether the benefit-risk balance would have been more favourable with the 0.3% cream.

First Round Recommendation Regarding Authorisation

The clinical evaluator recommends approval of the application.

Clinical Questions

No questions were raised.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan EU-RMP Version 1 (dated 25 March 2014, DLP 10 October 2013) and Australian Specific Annex (ASA) (version 1.0, dated July 2014) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 10.

Table 10. Summary of safety concerns.

Summary of safety concerns	
Important identified risks	None
Important potential risks	Skin sensitisation (hypersensitivity) Accidental oral ingestion
Missing information	Exposure during pregnancy Exposure during lactation Use longer than one year Off label use Use with other concomitant topical rosacea treatments Use with laser or UV radiation

Pharmacovigilance plan

No studies are ongoing or planned for the product.

The sponsor proposes to use only routine risk minimisation activities to address all ongoing safety concerns.

Risk minimisation activities

The sponsor concludes that routine risk minimisation activities are sufficient to address the ongoing safety concerns associated with use of the product.

RMP evaluator comment:

There are no objections to use only routine risk minimisation activities at this time.

Potential for medication errors

The sponsor states: A total of four medication errors occurred during the two pivotal Phase III studies all of which concerned the administration of the incorrect randomised treatment.

Preventive measures for the final product(s) being marketed: Related to the possible risk associated with accidental oral ingestion by children, a child resistant cap is added to the final 15, 30, 45 and 60 g marketed product. The product is also presented as a 2 g tube without a child resistant cap intended as a patient sample. The 2 g tube represents at most

2 days of treatment at the recommended dose (approximately 1 g per day) and is expected to be used very quickly (over 1 to 2 days) limiting the amount of time during which accidental exposure could occur. Additionally, the 2 g tube will be clearly labelled and supplied in individual packaging with a PIL which communicates the risk of accidental ingestion to the patient and clearly instructs not to swallow and to keep it out of the sight and reach of children.

Reconciliation of issues outlined in the RMP report

Table 11 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the RMP evaluator and the evaluation of the sponsor's responses.

Table 11. Reconciliation of issues outlined in the round 1 RMP Evaluation Report.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
1. Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated request for information 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.	The sponsor acknowledges the comment made by the evaluator and has ensured that any issues raised in other part of the consolidated request for information reports have been assessed to check their impact on the ASA to the Global RMP. An update to the ASA has been provided along with the current Global RMP.	The sponsor's response has been noted.
2. Amendments to the table of ongoing safety concerns as detailed. A.) The following exclusion criteria applied for the clinical development program: Subjects exposed to excessive UV radiation within two weeks prior to the Baseline visit, or subjects planning exposure during the study (for example phototherapy, occupational exposure to the sun, planned holidays in the sun during the study, tanning salon). Furthermore, a photocarcinogenicity study in hairless mice indicated '*Repeated topical administration of ivermectin cream at concentrations of 0.3% and 1.0% enhanced photocarcinogenesis as compared with Vehicle cream'*. Given the increased UV exposure of patients through sun light in Australia, compared to most other parts of the	A.) and B.) The sponsor acknowledges the comment made by the evaluator; however, as explained in previous responses to comments made in the first round RMP evaluation report, no update of the global RMP is planned. Further clarifications have been added to the PI and CMI so as to take into account these safety considerations. In addition, the ASA of the global RMP will be updated.	This recommendation remains. These patient groups were excluded from the clinical development program and therefore, no information is available regarding the safe use of the product for these patients groups. Of note, these patient groups will be relevant for the real world use of the product.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
world, this is considered important missing information in the Australian context. Consequently, '*Effects of significant UV exposure*', which should also include occupational and leisurely exposure to sun, should be added as missing information. B.) The following exclusion criteria applied for the clinical development program: Subjects suffering particular forms of rosacea (rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin) or other facial dermatoses that may be confounded with PPR such as peri-oral dermatitis, facial keratosis pilaris, seborrheic dermatitis and acne. Hence, no safety data was collected for these particular patient groups during the clinical development program. It is recommended that these patient groups be added as missing information. Pharmacovigilance and risk-minimisation activities are to be assigned to this missing information as appropriate.		
3. The sponsor should confirm whether the 2 g cream tube will be sealed with an aluminium lid which needs to be punctured in order to retrieve the cream form in the tube. If this is the case, the handling of the issue of medication errors by the sponsor would be considered acceptable. If this is not the case, then it is recommended that the 2 g cream tube also be fitted with a child resistant cap (CRC).	The 2 g non-child resistant cap tube of ivermectin 1% cream is a physician's sample only. Published data[24] have shown that oral administration of ivermectin tablets to adult subjects at doses up to 2 mg/kg was not associated with any adverse reactions and was generally well tolerated. An accidental oral ingestion of a full tube containing 2 g ivermectin 1% cream (20 mg of ivermectin) by a child weighing ≥ 10 kg would correspond to a dose (≤ 2 mg/kg) which did not induce signs of toxicity in the above mentioned safety and tolerability study. The 2 g tube represents at most 2 days of treatment at the recommended dose (approximately 1 g per day) and is expected to be used very quickly (over 1 to 2 days), thus limiting the amount of time during which accidental exposure could occur. It is	The sponsor's response has been noted.

[24] Guzzo C A. et al. Safety, tolerability, and Pharmacokinetics of Escalating High Doses of Ivermectin in Health Adult Subjects. *J Clin Pahrmacol* 2002; 42; 1122-1133.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	anticipated that the first dose (1 g) will be applied in the doctor's clinic, demonstrating how the cream is to be applied. Thus, it is expected that most patients will only take home a tube with 1 g inside. Additionally, the 2 g tube will be clearly labelled and supplied in individual packaging with a Consumer Medicines Information (CMI) leaflet which communicates the risk of accidental ingestion to the patient, and clearly instructs not to swallow and to keep it out of the reach of children. The risk of accidental oral ingestion medication errors with a 2 g tube is considered negligible. The sponsor confirms that 2 g sample tubes are not sealed with an aluminium lid nor fitted with a CRC, however given the negligible safety risk for accidental oral ingestion, the sponsor believes that the implementation of the seal or CRC is not necessary.	
4. The sponsor should provide a table which includes a comparison of the actual content and wording of the European Summary of Product Characteristics (EU SmPC) and the proposed Australian PI and CMI for all the specified ongoing safety concerns and missing information.	The sponsor has made a comparison of the EU SmPC with the proposed amended Australian PI and CMI. The resulting table is provided in the ASA.	This is considered acceptable.
5. The following patient populations were excluded from the clinical development program: Subjects exposed to excessive UV radiation within two weeks prior to the Baseline visit, or subjects planning exposure during the study (for example, phototherapy, occupational exposure to the sun, planned holidays in the sun during the study, tanning salon). The sponsor should describe in the PI that no data about the safety of the product in these patient populations is available	The sponsor agrees with the RMP evaluator with regards to the lack of safety data available in patients exposed to excessive UV radiation. Steps were taken in the clinical development program of ivermectin 1% cream to exclude participants with previous exposure to ultraviolet (UV) light, and to avoid excessive sun exposure during the studies. Therefore no safety data have been obtained in subjects exposed to excessive UV light. In addition, it has been published that all patients with rosacea should be recommended a gentle skin care routine and a photo protection regimen due to the sensitivity of the skin.[25] Therefore, the sponsor agrees that appropriate protection from UV light must be applied by patients. The PI and CMI have been updated accordingly: '*High sunscreen protection factor (SPF) sunscreens or other sun-exposure reduction methods should be used when Soolantra / Vastreka is applied to the face or other sun-*	Pending the Delegate's approval, the amendments are considered acceptable.

[25] Del Rosso JQ et al. Consensus recommendations for the American Acne and Rosacea Society on the management of rosacea, Part 5: a guide on the management of rosacea. *Cutis.* 2014; 93: 134-138

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	exposed area.' (Precautions section of the PI). '*After Soolantra / Vastreka has dried, a high sunscreen protection factor (SPF) sunscreen should be applied on treated areas that are likely to be exposed to the sun, or other sun-exposure reduction methods should be used (e.g. hats, clothing*.' (Dosage and administration section of the PI). '*After applying Soolantra/ Vastreka use a non-comedogenic, broad spectrum, SPF 50+sunscreen and wear protective clothing to protect your skin from UV rays*.' (Section; How to use it of the CMI).	
6. The sponsor describes in the RMP: A photocarcinogenicity study in hairless mice indicated '*Repeated topical administration of ivermectin cream at concentrations of 0.3% and 1.0% enhanced photo carcinogenesis as compared with Vehicle cream*'. It is suggested that the sponsor includes statements in the PI stating that appropriate protection from UV light should be applied by patients.	The sponsor has determined the potential of ivermectin 1% cream and vehicle cream to influence the development or growth of skin tumours in hairless mice exposed to simulated solar UV radiation (Study 12597) is very likely to be due to the increased incidence of early skin irritation in these groups. In addition, ICH guidance[26] states that '*testing for photocarcinogenicity in rodents using currently available models (for example, hairless rodent) is not considered useful in support of pharmaceutical development and generally is not recommended*.' Despite these reservations on the relevance of these nonclinical findings, the sponsor agrees with the evaluator's recommendation for appropriate protection of patients with rosacea from UV light, in consideration of the known sensitivity of their skin. Consequently, the sponsor agrees that additional statements should be included in the PI stating that appropriate protection from UV exposure should be adopted by patients.	See point 5 above.
7. The sponsor should describe in the PI that the following patient population was excluded from the clinical development program and therefore, no data about the safety of the product in these patient populations is available: Patients suffering a particular forms of rosacea (rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin) or other facial dermatoses that may be	The sponsor agrees that the patients suffering from other forms of rosacea such as rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin, and ocular rosacea, or other facial dermatoses that may be confounded with PPR, such as perioral dermatitis, facial keratosis pilaris, seborrheic dermatitis, and acne, did not participate in the studies. In addition, the sponsor agrees that there is no specific safety data available in the sponsor's studies on those patient populations.	This outstanding issue is referred to the Delegate for consideration. It is also brought to the Delegate's attention that the proposed indication in Europe differs from the proposed indication for

[26] M3(R2) Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorisation for Pharmaceuticals

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
confounded with papulo-pustular rosacea, such as peri-oral dermatitis, facial keratosis pilaris, seborrheic dermatitis and acne.	However, the sponsor believes that at this time, the proposed indication in the PI clearly stipulates the patient population without the need to additionally state that there is no safety data in other rosacea subtypes.	Australia and is as follows: Soolantra is indicated for the topical treatment of inflammatory lesions of rosacea (papulo-pustular) in adult patients.
8. No risk-minimisation is proposed to be conducted in the Australian PI for the important missing information of '*Use longer than one year*', '*Use with other concomitant topical rosacea treatments*' and '*Use with laser or UV radiation*'. Provision of information for all these missing information is recommended to be included in the Australian-PI. This will ensure that physicians are comprehensively informed about the safety profile of the product, and will allow balancing the benefit of treatment versus the missing information for each individual patient.	Use longer than one year: Efficacy and safety information has been collected in the development program of ivermectin 1% cream in subjects with PPR, including during long term extensions of the clinical studies. The global analysis of treatment duration presented indicates that, in terms of categories of durations, a total of 519 subjects (33.6%) were treated with ivermectin 1% cream for more than 359 days. See also, PI, Adverse effects: '*During clinical trials, 2,047 subjects with inflammatory lesions of rosacea received Soolantra cream once daily. A total of 1,555 subjects were treated once daily for more than 12 weeks, and 519 for approximately one year.*' Overall, the data obtained in the clinical development program showed the absence of any trend toward emerging safety signals with the use of ivermectin 1% cream over time and the persistence of a favourable benefit/risk ratio for periods of up to 1 year of daily treatment. The sponsor acknowledges that, at this point, no safety information is available for treatment durations beyond the 1 year duration of the pivotal studies and their long term extension. However, rather to include a specific statement about the lack of safety information beyond 1 year for this product into the PI, the sponsor has proposed the following wording in the dosage and administration section in the PI: '*One application a day for up to 4 months. Soolantra should be applied daily over the treatment course. The treatment course may be repeated. In case of no improvement after 3 months, the treatment should be discontinued.*' In addition, the CMI has also been updated accordingly (Section; How long to use it):'*You should use Soolantra / Vastreka daily over the treatment course. The doctor may decide that the treatment course should be repeated. The duration of treatment can vary from person to person and depends on the severity of your skin condition.*' Use with other concomitant topical rosacea	Use longer than one year: Pending the Delegate's approval, the addition of the proposed statements in the CMI/PI are considered acceptable. Use with other concomitant topical rosacea treatments: This is considered acceptable. Use with laser or UV radiation: The sponsor's response is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	treatments: During the clinical studies performed by the sponsor in subjects with PPR, only moisturisers and sunscreens were permitted as topical therapies on the face. The sponsor agrees that there is no safety information available in case of concomitant use of ivermectin 1% cream (with the exception of antibiotics for prophylaxis and anti-infective use which were permitted during the long term extension of the pivotal studies). As such, the sponsor has included the following information in the PI: Section dosage and administration of the PI: '*Cosmetics and sunscreens may also be applied after Soolantra has dried.*' Section interactions with other medicines of the PI: '*Concomitant use of Soolantra / Vastreka with other topical or systemic medicinal products for the treatment of rosacea has not been investigated.*' Use with laser or UV radiation: Please refer to information presented in point 5 and point 6 above. The sponsor would like to additionally highlight that the dose-ranging, Phase II Study 40027 comparing the efficacy and safety of three concentrations of ivermectin cream once daily (0.1%, 0.3%, and 1%) with ivermectin 1% cream twice daily, metronidazole 0.75% cream twice daily, and Vehicle cream, was conducted in 296 subjects with PPR enrolled in a total of 26 investigator sites including 6 sites in Australia (67 subjects). As presented, suspected photosensitivity reactions were reported for 2 subjects under treatment with the lower concentrations of ivermectin cream (< 1%). These reactions were observed during the Australian summer in 1 of the Australian centres and were considered related to treatment by the investigators. The first case occurred in 1 subject (2.0%) treated with ivermectin 0.1% cream once daily. The second case occurred in 1 subject (2.1%) treated with ivermectin 0.3% cream once daily. Further to a photopatch testing study conducted according the methodology described in Study RD.03.SRE.40027, no phototoxic reactions were recorded in both subjects. Thus, the suspected photosensitivity reactions were not confirmed. Overall, none of the photodermatosis /photosensitivity reactions reported throughout the development program for subjects receiving ivermectin 1% cream were considered related to treatment in any investigator site in any country, that is, the United States, European Union, Australia,	

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	Russia and Ukraine. In all studies, the majority of subjects were White/Caucasian. Available data show the occurrence of only 1 case (0.04%) of moderate sunburn reaction considered related to ivermectin 1% cream by the investigator, in 2,431 subjects exposed at least once to ivermectin 1% cream. These observations indicate a low incidence of potential sunburn reactions after application of ivermectin 1% cream. The 4 sunburn reactions reported by 4 subjects of the ivermectin group of the pivotal studies (0.3%), all of mild intensity and not considered treatment related by the investigators, were reported with the same incidence as those reported for subjects in the vehicle group in these studies (0.3%). Information provided to the healthcare professional and the patient regarding protection from UV light is given in the response provided to TGA request for information.	

Summary of recommendations

Outstanding issues

Issues in relation to the RMP

1. 'Effects of significant UV exposure' and 'Use in patients with particular forms of rosacea ((rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin) or other facial dermatoses that may be confounded with papulo-pustular rosacea, such as peri-oral dermatitis, facial keratosis pilaris, seborrheic dermatitis and acne))', should be added as missing information to the table of ongoing safety concerns.
2. The sponsor should describe in the PI that the following patient population were excluded from the clinical development program and therefore, no data about the safety of the product in these patient populations is available: Patients suffering a particular forms of rosacea (rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin) or other facial dermatoses that may be confounded with papulo-pustular rosacea, such as peri-oral dermatitis, facial keratosis pilaris, seborrheic dermatitis and acne.

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

ACSOM advice was not sought for this submission.

Key changes to the updated RMP

Australian Specific Annex Version 1.0, dated July 2014 has been superseded by:

Australian Specific Annex Version 1.1, dated March 2015.

An updated version of the EU-RMP was not provided.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

The European Risk Management Plan (version 1.0, dated 25-Mar-2014, DLP 10-Oct-2013), with Australian Specific Annex (version 1.1, dated March 2015), to be revised to the satisfaction of the TGA, must be implemented.

VI. Overall conclusion and risk/benefit assessment

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

Quality

Registration of the proposed Soolantra and Vastreka ivermectin 1% (w/w; 10 mg/g) cream in pack sizes of 2 g, 15 g, 30 g, 45 g and 60 g in laminated HDPE tubes with PP caps, is recommended with respect to quality and biopharmaceutic aspects. All issues raised during the initial evaluation of this application have been satisfactorily resolved.

As no significant pharmaceutical chemistry issues were identified, the submission was not referred to the Pharmaceutical Subcommittee of the ACPM.

Nonclinical

There are no nonclinical objections to registration.

Topical Soolantra undoubtedly enhances non melanoma skin photocarcinogenesis in a human relevant mouse model. Long term, repeated topical application of Soolantra in sun exposed areas should be avoided or sun protection strategies should be used.

Long term, repeated topical application of Soolantra may result in cumulative skin irritancy and (rarely) skin contact sensitisation. However, these issues are adequately dealt with in the PI.

Because of the lack of nonclinical drug interactional data, some care should be exercised when drugs that are known to completely block or very substantially inhibit ABC B1 (p-glycoprotein) efflux transporters are used concurrently with Soolantra. Theoretically drug interactions at ABC B1 (p-glycoprotein) efflux transporters will affect the safety properties of Soolantra and adverse drug interactions may occur via these mechanisms.

The presence of an intact blood brain barrier critically affects the safety properties of ivermectin. No nonclinical data was provided on these issues. Pharmacogenetic effects on ABC B1 in the blood brain barrier, the blood testis barrier, placenta and the intestinal enterothelium, substantially increase the risk of ivermectin toxicity (including fertility, reproductive and developmental toxicity) in animals. These pharmacogenetic differences are poorly documented in humans. However, Soolantra appears to have adequate animal: human AUC ratios at the relevant nonclinical NOAELs. Given the topical route of exposure and relatively low systemic exposure, the risks of these types of effects with ivermectin use are greatly reduced.

There is potential for Soolantra use to contribute to the induction of anthelmintic resistance to ivermectin and other members of the avermectin parasiticidal drug class because an important pathway of excretion is active transport in to the gut via enterothelial ABC B1 efflux transporters.

The mechanism of action of ivermectin treatment of rosacea is not fully established. Possible mechanisms of action include suppression of inflammation, a mitocidal effect on Demodex species. Notably ivermectin has often been combined with a pyrethroid or neonicotinoid arthrocide when used to treat demodicosis, presumably in the hope of increased efficacy.

Overall, Soolantra does not present any particularly overt safety pharmacology concerns with the proposed pattern of use.

Because of the pharmacokinetic and dosing pattern differences between Stromectol (that is occasional single dose oral parasiticide use) and Soolantra, some degree of caution should be applied if Soolantra is used during pregnancy (particularly during brain development) and substantial compromise (for example complete blocking) of placental ABC B1 function is likely. Again because of the topical route of exposure and relatively low systemic absorption, the risks of these types of effects with ivermectin are substantially reduced.

Ivermectin is detectable in human milk following oral dosing; however milk steady state levels are low following single acute exposures. Unlike the single episodic use of ivermectin for treatment of parasitic diseases, the chronic use of Soolantra will result in sustained neonatal trans mammary exposure. Based on rodent studies, chronic maternal exposure will result in milk ivermectin levels at least 3 to 4 times higher than those observed with single acute ivermectin exposures. Provided that the human neonatal blood brain barrier ABC B1 function remains intact, these phenomena should not adversely effect on human neonatal development.

Clinical

Pharmacology

Pharmacokinetics following single and repeated dosage of ivermectin 1% cream 1g daily in patients with severe PPR were examined in Study RD.03.SRE.40064. Minimum concentration (C_{min}) mean concentrations were 1.26 ng/mL at Day 14 and 1.36 ng/mL at Day 28. Maximum concentration (C_{max}) upper range was 4.02 ng/mL. Ivermectin measurements were also made during chronic dosing in Studies RD.03.SRE.40027, RD.03.SRE.40106, RD.03.SRE.40051, RD.06.SRE.18170 and RD.06.SRE.18171. Results are presented in Table 7 above. The data submitted are sufficient to characterise the PK following topical application of the product in patients with PPR, and provide reassurance that accumulation is not likely to be significant.

Dose selection

Study RD.03.SRE.40027 is a dose finding study in patients with PPR. Treatment was applied for 12 weeks and treatment arms were:

- Group 1: ivermectin 1% cream (formulation proposed for registration) BD
- Group 2: ivermectin 1% cream (formulation proposed for registration) daily
- Group 3: ivermectin 0.3% cream daily
- Group 4: ivermectin 0.1% cream daily

- Group 5: vehicle cream daily
- Group 6: metronidazole 0.75% cream (Rozex) BD.

Primary efficacy endpoint was percentage change in inflammatory lesion counts (papules, pustules) at Week 12. The intention to treat (ITT) population numbered 296, and the per protocol population numbered 271.

Results are shown in Table 7 of Attachment 2. At Week 12, last observation carried forward (LOCF) (ITT) analysis mean % reduction in inflammatory lesions was 46.5% in vehicle QD group, 65.5% in 0.1% ivermectin QD group, 67.5% in 0.3% ivermectin QD group, 70% in 1% ivermectin QD group and 69.2% in 1% ivermectin BD group. At Week 12-LOCF (ITT), efficacy of ivermectin 1% daily and BD was statistically superior to that of the vehicle ($p = 0.006$ and $p = 0.014$); ivermectin 0.1% daily and 0.3% BD were not statistically different from the vehicle (p-values > 0.06). None of the ivermectin doses was statistically different from metronidazole 0.75% BD.

Efficacy

Two pivotal efficacy/safety studies were submitted.

Study RD.06.SRE.18170

Study RD.06.SRE.18170 is described in Section 7.1.1 of Attachment 2. This was a multicentre, randomised, parallel group study conducted at 50 sites in USA and Canada between December 2011 and July 2013. Up to and including Week 12, the design was double blind and vehicle controlled. In a 40 week extension the design was investigator blind and azelaic acid 15% gel was comparator.

Inclusion criteria were adults with PPR, investigator global assessment (IGA) score of 3 (moderate) or 4 (severe) and at least 15 but not more than 70 inflammatory lesions on the face. Exclusion criteria included particular forms of rosacea or other facial dermatoses that may be confounded with PPR. Excessive UV radiation within 2 weeks prior to baseline or planned during the study was an exclusion criteria. Exclusion treatments and washout periods are listed (Attachment 2 Section 7.1.1.2.)

The main efficacy variables are described in Attachment 2 Section 7.1.1.4 and were:

- Investigator Global Assessment (IGA) score (preferably but not necessarily determined by the same investigator for each given subject at each time-point)
- Inflammatory lesion count (preferably but not necessarily determined by the same investigator for each given subject at each time-point)
- Subject's Assessment of Rosacea Improvement (SARI) score.

The co-primary efficacy endpoints were Success Rate (defined as the percentage of subjects with '0 = Clear' or '1 = Almost Clear' on the IGA) and absolute change in inflammatory lesion counts from Baseline to Week 12 (ITT-LOCF).

Some 683 subjects were randomised in a 2:1 ratio to ivermectin 1% cream and vehicle/azelaic acid. Subject disposition is shown in Attachment 2 Figure 2. In the ivermectin group 91.8% completed Part A and 85% continued in Part C. In the vehicle/azelaic acid group 90.5% completed Part A and 83.3% continued in Part C. A total of 77 subjects (11.3%) had protocol deviations that were classified as major at the Blind Review Meeting: 49 subjects (10.9%) in the ivermectin 1% cream group and 28 subjects (12.1%) in the Vehicle cream daily group.

Demographic and Baseline disease characteristics were similar between treatment groups. The majority of subjects were female (68.2%) and White (96.2%). The mean overall age was 50.4 years. Hispanic/Latino subjects comprised 11.4% of all enrolled subjects, and

most subjects (77.3%) had a skin phototype of II or III. All subjects presented with a Baseline IGA score of 3 (moderate) or 4 (severe) and most subjects (560 subjects, 82.0%) had a Baseline IGA score of 3. The overall mean inflammatory lesion count was 30.9±14.33 lesions at Baseline.

Success Rate based on IGA was 38.4% for ivermectin 1% cream daily and 11.6% for Vehicle cream daily at Week 12 (ITT-LOCF), a statistically significant difference ($p < 0.001$). At Week 12 (ITT-LOCF), the mean (±SD) Absolute Change in Inflammatory Lesion Counts from Baseline was -20.5 ± 15.95 in subjects treated with ivermectin 1% cream daily versus -12.0 ± 13.55 in subjects treated with Vehicle cream daily. The difference was statistically significantly in favour of ivermectin 1% cream daily ($p < 0.001$).

'*Time to onset of efficacy analysis*' was changed from being a secondary endpoint to a '*supplemental analysis of co-primary endpoints at earlier time points*'. The time to onset of efficacy, defined as the earliest time-point at which a statistically significant difference between treatment groups was seen for both primary endpoints, was observed beginning at Week 4 and was sustained through to Week 12 (ITT-LOCF).

The SARI was performed at Week 12. For the ITT population, in the Soolantra group, 149 subjects (34.3%) reported excellent improvement and 151 subjects (34.7%) reported good improvement in their rosacea with use of the study drug. In the Vehicle group, 21 subjects (9.5%) reported excellent improvement and 64 subjects (29.1%) reported good improvement in their rosacea with use of the study drug. There was a statistically significant difference ($p < 0.001$) favouring ivermectin 1% over its vehicle.

Study RD.06.SRE.18171

Study RD.06.SRE.18171 is described in Attachment 2, Section 7.1.2. This was a multicentre, randomised, parallel group study conducted at 50 sites in USA and Canada between December 2011 and August 2013. Study design and objectives were as for RD.06.SRE.18170.

Some 688 subjects were randomised and in a 2:1 ratio to ivermectin 1% cream and vehicle/azelaic acid. Patient disposition is shown in Figure 3 Attachment 2. In the ivermectin group 93.5% completed Part A and 82.5% continued in Part C. In the vehicle/azelaic acid group 90.8% completed Part A and 76.4% continued in Part C. A total of 92 subjects (13.4%) had protocol deviations that were classified as major at the Blind Review Meeting, with similar percentages in each treatment group.

Demographic and Baseline disease characteristics were similar between treatment groups. In the ITT Population, the majority of subjects were female (66.7%) and White (95.3%), and the mean age was 50.2 years (range: 18 to 89 years). Most subjects were of skin phototypes II or III. All subjects presented with a Baseline IGA score of 3 (moderate) or 4 (severe), and most (522 subjects, 75.9%) had an IGA score of 3 at Baseline. Overall, at Baseline, the mean inflammatory lesion count was 32.9, with a range of 14 to 70 lesions. Baseline papule and pustule counts were similar across the treatment groups.

Success rates, based on IGA where success was defined as achieving a 'clear' (IGA = 0) or 'almost clear' (IGA = 1) outcome at Week 12 (ITT-LOCF), were 40.1% for the ivermectin 1% cream daily group and 18.8% for the Vehicle cream daily group. The difference between the two treatment groups was statistically significant at Week 12 (ITT-LOCF; $p < 0.001$). Both active and vehicle treatment groups had reduced inflammatory lesion counts compared to Baseline at each post Baseline time point up to the end of Part A. At Week 12 (ITT-LOCF), the mean (± SD) Absolute Change in Inflammatory Lesion Counts from Baseline was -22.2 ± 14.87 for the ivermectin 1% cream daily group and -13.4 ± 14.48 for the Vehicle cream daily group. The difference between the two treatment groups was clinically relevant and statistically significant at Week 12 (ITT-LOCF; $p < 0.001$).

The SARI was performed at Week 12. For the ITT Population, in the Soolantra group, 143 subjects (32.0%) reported excellent improvement and 153 subjects (34.2%) reported good improvement in their rosacea with use of the study drug. In the Vehicle group, 16 subjects (7.3%) reported excellent improvement and 59 subjects (27.1%) reported good improvement in their rosacea with use of the study drug. There was a statistically significant difference ($p < 0.001$) favouring ivermectin over its vehicle.

Study RD.03.SRE.40173

Study RD.03.SRE.40173 is described in Attachment 2, Section 7.2.5. This was a multicentre, randomised, parallel group Phase III study conducted at 64 sites in Europe to evaluate the efficacy and safety of once daily application of ivermectin 1% cream versus twice daily application of metronidazole 0.75% cream (Rozex) in subjects with PPR, for 16 weeks with a 36 week extension period. The submitted report with a cut-off date of April 2013 is complete for the first 16 weeks of the study and provides preliminary data on the 36 week extension.

Some 478 subjects received ivermectin and 484 received metronidazole 0.75% cream. Demographic and Baseline disease characteristics were similar between treatment groups. The majority of subjects were female (65%) and White (99%), and the mean age was 51.5 years. Most subjects were of skin phototypes II or III. All subjects presented with a Baseline IGA score of 3 (moderate) or 4 (severe), and most (801 subjects, 83%) had an IGA score of 3 at Baseline. Overall, at Baseline, the mean papule count was 25 and pustule counts were 7.4 and similar across the treatment groups.

Primary efficacy endpoints were:

- Percent change in inflammatory lesions from Baseline to Week 16 (ITT-LOCF).
- Time to first difference between treatment, determined by sequentially analysing preceding time points, once there was a statistically significant difference between groups in percent change in inflammatory lesion count. Superiority analysis was stipulated.

In the Week 16 LOCF –ITT analysis present mean change from baseline was -83% in the ivermectin 1% and -73.7% in metronidazole group ($p < 0.001$) and median change from baseline was -92% and -88.3% The Phase III Study RD.03.SRE.40173 provided statistically significant evidence of the superiority of daily ivermectin 1% over BD Rozex. Data on relapse rates from the 36 week extension of study are pending.

Other Efficacy Studies

Study RD.03.SRE.40006

Study RD.03.SRE.40006 was a preliminary efficacy and safety study of ivermectin 1% cream (formulation proposed for registration). Design was multicentre, randomised, investigator blinded, parallel group with 3 arms: active cream, vehicle, and Rozex, applied BD for 9 weeks in patients with PPR. The ITT population numbered 147. The differences between ivermectin and vehicle, and between ivermectin and metronidazole, did not reach statistical significance, for either the ITT or the per protocol set.

Study RD.03.SRE.40037

Study RD.03.SRE.40037 was a treatment free extension of Study RD.03.SRE.40027. The objective of Study RD.03.SRE.40037 was to evaluate relapses in patients successfully treated in the dose finding study. Some 149 subjects were enrolled in Study RD.03.SRE.40037, of whom 101 completed. The main efficacy endpoints stipulated on the Protocol were (1) Time to relapse and (2) Relapse rate. With Definition 1 and Convention 1, 36 (24.8%) subjects had relapsed by Day 84 whatever the treatment in Study RD.03.SRE.40027; this number increased to 53 (37.9%) subjects by Day 168. In other words, > 75% of patients remained 'clear' and 'almost clear' three months after an initial

successful treatment and > 60% remained so even six months after the initial treatment was stopped.

Clinical evaluator's Conclusions on Efficacy

In the pivotal Studies RD.06.SRE.18170 and RD.06.SRE.18171, Soolantra was shown to be superior to vehicle; consistent with the Phase II Studies RD.03.SRE.40027 and RD.03.SRE.40106. The Phase III Study RD.03.SRE.40173 provided statistically significant evidence of the superiority of daily Soolantra over BD Rozex. Data on relapse rates from the 36 week extension of Study RD.03.SRE.40173 are pending.

Safety

A total of 2,431 of the 3,999 subjects in the clinical development program were exposed to ivermectin1% cream, 268 healthy subjects and 2,163 subjects with PPR. A total of 2,047 subjects with PPR were exposed to the formulation and regimen proposed for registration.

Pivotal studies assessed safety as well as efficacy as a primary outcome

Study 18170

Table 27 Attachment 2 shows AE in pivotal Study 18170. Overall 69.5% of subjects in the ivermectin group and 70.3% in the vehicle/azelaic acid group had AEs. In Part A, 40.5% of subjects in the ivermectin group and 39.4% in the vehicle group had AEs. In Part B, 60.4% in the ivermectin group and 60.5% in the azelaic acid group had AEs. Overall 14.4% of subjects had skin and subcutaneous AE in the ivermectin group and 19.4% in the vehicle/azelaic acid group. In Part A, 7.5% of subjects had skin and subcutaneous AE in the ivermectin group and 10% in the vehicle group. In Part B, 7.8% of subjects had skin and subcutaneous AE in the ivermectin group and 12.9% in the azelaic acid group.

Table 42 Attachment 2, shows AEs classified as related to study drug in Study 18170. Overall 6% of subjects in the ivermectin group and 12% in the vehicle/azelaic acid group had related AEs. In Part A, 4.2% of subjects in the ivermectin group and 7.8% in the vehicle group had such AEs. In Part B, 1.9% of and 6.7% in the azelaic acid group had such AEs. In the ivermectin group overall 23 related AEs were skin and subcutaneous disorders of the total of 35 related AEs. In the ivermectin group, other related AE included neutropenia (n=1), lacrimation increased (n=1), hepatic enzyme increase (n=1), flushing n=1), and overdose (n=1).

Table 49 Attachment 2 shows SAE in pivotal Study 18170 which did include AE terms classified as related to study drug. No deaths were reported. Overall, 12 subjects (2.7%) in the Soolantra (Part A and Part B) group prematurely discontinued the study due to AEs and 9 subjects (3.9%) in the Vehicle/Azelaic acid group prematurely discontinued the study due to AEs. For both treatment groups, the majority of subjects who discontinued the study did so due to AEs in the system organ class (SOC) Skin and subcutaneous tissue disorders: 8 subjects (1.8%) in the Soolantra (Part A and Part B) group and 6 subjects (2.6%) in the Vehicle/Azelaic acid group. All remaining subjects who discontinued the study reported isolated incidences of AEs that occurred in various other SOC categories. 6 subjects (1.3%) in the Soolantra (Part A and Part B) group reported 8 AEs leading to discontinuation that were considered by the investigator to be related to the study drug: Dermatitis allergic, Pain of skin, Skin burning sensation (2 events), Skin irritation (3 events), and Flushing. 5 subjects (2.2%) in the Vehicle/Azelaic acid group reported 7 AEs leading to discontinuation that were considered by the investigator to be related to the study drug: Rosacea, Skin irritation (3 events), Eye irritation, Irritant dermatitis, Pain of skin, and Skin burning sensation.

Study 18171

Table 28 Attachment 2 shows AE in pivotal Study 18171. Overall 68% of subjects in the ivermectin group and 66.7% in the vehicle/azelaic acid group had AEs. In Part A, 36.5% of subjects in the ivermectin group and 36.5% in the vehicle group has AEs. In Part B, 59.3 % in the ivermectin group and 58.7% in the azelaic acid group had AEs. Overall 14.1% of subjects had skin and subcutaneous AE in the ivermectin group and 24.2% in the vehicle/azelaic acid group. In Part A, 6.1% of subjects had skin and subcutaneous AE in the ivermectin group and 11.3% in the vehicle group. In Part B, 9.8% of subjects had skin and subcutaneous AE in the ivermectin group and 16.3% in the azelaic acid group.

Table 43 Attachment 2 shows AEs classified as related to study drug in pivotal Study 18171. Overall 4.6% of subjects in the ivermectin group and 11% in the vehicle/azelaic acid group had related AEs. In Part A, 2.6% of subjects in the ivermectin group and 6.5% in the vehicle group had such AEs. In Part B, 2.1% of the ivermectin group and 5.8% in the azelaic acid group had such AEs. In the ivermectin group overall 11 related AEs were skin and subcutaneous disorders of the total of 27 related AEs. In the ivermectin group, other related AE included eye disorders (n=5), sunburn (n=1), alcohol intolerance (n=1), paraesthesia (n=1)and overdose (n=1).

Table 50 Attachment 2 shows SAE in pivotal Study 18171 which did include AE terms classified as related to study drug. No deaths were reported. Overall, 9 subjects (2.0%) in the Soolantra (Part A and Part B) group prematurely discontinued the study due to AEs and 9 subjects (3.9%) in the Vehicle/Azelaic Acid group prematurely discontinued the study due to AEs. For the Soolantra (Part A and Part B) group, the majority of subjects who discontinued the study did so due to AEs in the SOC Neoplasms: 3 subjects (0.7%). For the Vehicle/Azelaic Acid group, the majority of AEs leading to discontinuation were in the SOC Skin and subcutaneous tissue disorders: 6 subjects (2.6%). All remaining subjects who discontinued the study reported isolated incidences of AEs that occurred in various other SOC categories. One subject (0.2%) in the Soolantra (Part A and Part B) group reported an AE leading to discontinuation, facial dry skin, which was considered by the investigator to be related to the study drug. Six (2.6%) subjects in the Vehicle/Azelaic Acid group reported 7 AEs leading to discontinuation that were considered by the investigator to be related to the study drug: Skin irritation (2 episodes), Tachycardia, Skin burning sensation (2 episodes), Skin discomfort, and Pruritus.

Study 40173

Table 39 Attachment 2, shows AE reported in Period A in Phase III Study 40173. Some 32.4% of subjects in the ivermectin group and 33.1% in the metronidazole had AEs. Skin and subcutaneous disorders were reported in 4.6% of the ivermectin group and 4.1% of the metronidazole group.

Table 47 Attachment 2shows AE classified related to study drug. 2.3% of subjects in the ivermectin group and 3.7% in the metronidazole had related AEs. In the ivermectin group neutropenia (n=1) and hypersensitivity (n=1) were reported in addition to skin and subcutaneous tissue disorders.

Studies evaluable for safety only

Five studies were evaluable for safety only (see Attachment 2, Section 8.1.4).

Study RD.03.SRE.19055

The aim of this study was to assess cumulative irritancy potential of ivermectin 1% cream versus vehicle and white petrolatum, applied for 21 days under occlusive conditions to the upper back of healthy volunteers. The study was conducted in 2001 and the formulation of ivermectin cream is not that proposed for registration. Some 18 healthy adults (5 male, 13 female) with white skin, aged 24 to 59 were enrolled and treated. Results are shown at Attachment 2 Section 8.4.1.2.1. The cumulative irritancy index (CII) was calculated for

each treatment for each subject as: (Sum of all erythema scores read from Day 1 to Day 21)/ (Number of readings). The mean CII was 0.13 for ivermectin cream, 0.07 for vehicle and 0.12 for white petrolatum. The worst erythema score was barely visible for 50% of subjects for each treatment. Moderate erythema score was reported for 2 subjects with ivermectin cream, 1 subject with vehicle and 1 subject with white petrolatum.

Study RD.03.SRE.19081

The aim of this study was to assess cumulative irritancy potential of 2 new proposed vehicles versus the initial vehicle and white petrolatum, applied for 21 days under occlusive conditions to the upper back of healthy volunteers. 19 healthy adults (5 male, 14 female) with white skin, aged 22 to 71 were enrolled and treated. Erythema was assessed using the same scale as in Study 19055 above. The mean CII across all subjects ranged from 0.049 to 0.151 for the 3 vehicles and 0.10 for white petrolatum. Worst erythema score was moderate for 1 subject with each of the test products.

Study RD.03.SRE.40023

The aim of this study was to assess the potential of repeated applications of 4 concentrations of ivermectin cream (none of which was the product for which registration is sought) or vehicle to induce irritation or sensitisation in the skin of healthy subjects. The study was conducted at a single location in France, October to December 2005. Some 218 subjects were enrolled and treated.

The mean CII across all subjects is tabulated below in Table 12 (all patients treated, less 4 who lacked post baseline observations).

Table 12. Study RD.03.SRE.40023. Mean CII across all subjects.

	1% cream 0575.0755	0.3% cream 0575.0765	0.1% cream 0575.0764	0.03% cream 0575.0766	White petrolatum	Vehicle 0575.0755P
N	214	214	214	214	214	214
Mean CII (SD)	0.12 (0.19)	0.11 (0.19)	0.13 (0.21)	0.12 (0.21)	0.14 (0.21)	0.12 (0.19)

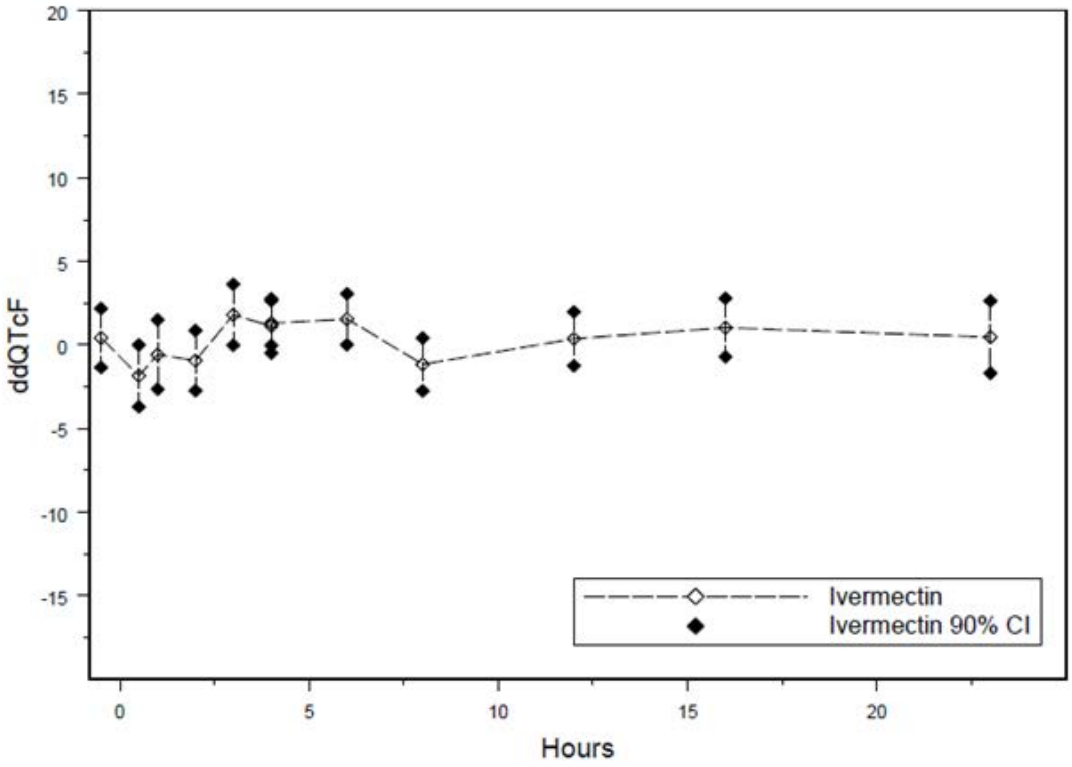
During challenge phase there was no evidence of sensitisation.

Study RD.06.SRE.18120

The primary objective was to evaluate the effect of a single orally administered dose of ivermectin on ventricular repolarisation in healthy adult subjects. The study was conducted at a single location in USA, 12 September to 3 November 2008.

Subjects were randomised to 1 of 3 arms, and treated with one of the following using a double dummy technique: ivermectin 6 mg, moxifloxacin 400 mg or placebo. Treatment was administered in the fasting state on Day 1. Electrocardiograms (ECGs) were extracted from Holter recordings at pre morning dose through to 23 hours post dose. Some 166 were randomised and treated. Results for ivermectin are shown in Figure 2. No change in corrected Q T interval Fridericia (QTcF) from baseline was seen for ivermectin in contrast to the positive control moxifloxacin.

Figure 2. Study RD.06.SRE.18120: Ivermectin: Mean difference from placebo in time matched change in QTcF.



Study RD.03.SRE.40051

The primary objective as originally planned was to document the long term safety of ivermectin 1% cream once daily, for up to 52 weeks of topical treatment in subjects with PPR. The study commenced on 27 August 2008, and was halted on 16 January 2009 when all study subjects were required to stop treatment immediately, and were asked to participate in a 1 month safety follow-up. This followed adverse laboratory findings: at Week 10 of treatment, the neutrophil cell count had decreased in 3 subjects below the threshold value of 1.5 x 10^9/L defining a neutropenia. Some 484 subjects were enrolled and treated (151 male, 333 female); mean age 50.8 (standard deviation (SD) 12); 399 with IGA score 3, 85 with IGA score 4; mean inflammatory lesion count 31.9 (SD 12). The duration of study treatment ranged from 4 to 196 days.

Study RD.03.SRE.40106

The primary rationale for this study was to investigate whether the product proposed for registration may be causally associated with neutropenia. Thus, blood samples were drawn frequently for laboratory assessment. Percent changes from Baseline in Neutrophil cell counts (NCCs) were compared at each post Baseline visit between ivermectin cream and its vehicle, and also for the lowest value observed after Baseline (retests and unscheduled visits included). At each time point, no meaningful between group differences were observed.

Overall, there were 5 subjects reported with neutrophil counts below 1.5 x10^9/L, 4 (3.9%) in the ivermectin group and 1 (0.9%) in the vehicle group. One of these subjects in the active treatment group also had a neutrophil count below 1.5 x10^9/L at Baseline before treatment; a retest performed two days later (after one application of study drug) also produced a low neutrophil count and this subject discontinued study participation. Subsequent neutrophil counts obtained at two re tests were all within the normal range. Therefore, four subjects had single treatment emergent neutrophil counts below 1.5 x 10^9/L. Among the 4 'treatment emergent' cases of neutrophil counts below

1.5 x 10^9/L, the neutrophil count had normalised under treatment for 3 cases and after a temporary discontinuation of the treatment in the other case.

The sponsor's clinical overview states: '*Throughout the whole clinical program, values of NCC < 1.5 G/L, whether considered clinically significant or not, were reported for 27 of 2,047 subjects (1.3%) randomised to ivermectin 1% cream QD, 1 of 98 subjects (1.0%) randomised to lower concentrations of ivermectin cream, 5 of 617 subjects (0.8%) in the vehicle group, 9 of 418 subjects (2.2%) in the azelaic acid group, and 4 of 532 subjects (0.8%) in the metronidazole group. Therefore, the incidence of low NCCs was comparable across the treatment groups, without any indication of a trend towards a higher incidence in subjects treated with ivermectin cream. During the long term part of the pivotal studies, the incidence of NCCs < 1.5 G/L was similar or lower in the ivermectin group compared to the azelaic group across the 3 quarters of Part B of the studies. After 1 year of exposure, the cumulative incidence of NCCs < 1.5 G/L adjusted for drop outs was 2.18% in the ivermectin group and 2.36% in the vehicle/azelaic group*.'

The clinical evaluator accepts that there appears to be no evidence of a causal relationship between treatment with ivermectin 1% cream and neutropenia.

Specific clinical studies of photo safety have not been presented.

The clinical evaluator concludes that at the present stage of product development, no specific safety concerns remain.

Clinical evaluator's Benefit-Risk Balance

The clinical evaluator concluded benefits of Soolantra in the proposed usage are proven efficacy and convenience of once daily application. Note that no convincing evidence has been presented that the 1% cream is significantly more efficacious than 0.3% cream (Study 40027).

The clinical evaluator concluded the risks of Soolantra in the proposed usage are:

- Hypothetical effects of systemic exposure. The difference in systemic exposure between 0.3% and 1% creams (Study RD.03.SRE.40027) is noted.
- Possible skin toxicity; in particular, photosensitivity or photoallergy, contact allergy.

Clinical evaluator's recommendation

The clinical evaluator concluded benefit-risk balance of Soolantra, given the proposed usage, is favourable.

Risk management plan

The RMP evaluator in the second round advice considered that the sponsor's response to the TGAs request for further information had not adequately addressed all of the issues identified in the RMP evaluation report.

Outstanding issues

'Effects of significant UV exposure' and 'Use in patients with particular forms of rosacea ((rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin) or other facial dermatoses that may be confounded with papulo-pustular rosacea, such as peri-oral dermatitis, facial keratosis pilaris, seborrheic dermatitis and acne)', should be added as missing information to the table of ongoing safety concerns.

ACSOM advice was not sought for this submission.

Risk-benefit analysis

Delegate's considerations

Discussion

In the pivotal clinical Studies RD.06.SRE.18170 and RD.06.SRE.18171, Soolantra was shown to be superior to vehicle, which is consistent with the Phase II studies RD.03.SRE.40027and RD.03.SRE.40106. The Phase III Study RD.03.SRE.40173 provided statistically significant evidence of the superiority of daily Soolantra over BD metronidazole 0.75% cream. Data on relapse rates from the 36 week extension of Study RD.03.SRE.40173 are awaited.

The clinical evaluator comments that no convincing evidence has been presented that the 1% cream is significantly more efficacious than 0.3% cream. (Study RD.03.SRE.40027).

A treatment course duration of 4 months has been introduced to draft PI submitted in the response to TGAs request for it to align with EU SmPC. In clinical Study 40037, in patients successfully treated in the dose finding study for 12 weeks, > 75% of patients remained 'clear' and 'almost clear' three months after an initial successful treatment and > 60% remained so even six months after the initial treatment was stopped.

In pivotal clinical studies adverse effects classified related to study drug were more common in the vehicle/azelaic acid group than the 1% ivermectin cream group. The majority of drug related adverse effects were skin and subcutaneous disorders. In Study RD.03.SRE.40173 Period A, adverse effects classified as related to study drug were more frequent in the metronidazole group than the ivermectin group.

Study RD.03.SRE.40051 was discontinued because 3 subjects treated with ivermectin 1% cream developed neutropenia. Study RD.03.SRE.40106 investigated whether the product proposed for registration may be causally associated with neutropenia. The clinical evaluator accepts that there appears to be no evidence of a causal relationship between treatment with ivermectin 1% cream and neutropenia.

Specific clinical studies of photo safety have not been presented. In nonclinical Study RDS.03.SRE.12438, in guinea pigs exposed to 1% ivermectin cream +/- UVA and UVB, no phototoxic potential of 1% ivermectin cream was shown and the test cream was concluded unlikely to be a photo allergen. Concurrent vehicle and UVR nonclinical studies have not been conducted.

The nonclinical evaluation recommends '*Long term, repeated topical application of Soolantra in sun exposed areas should be avoided or sun protection strategies should be used as topical Soolantra undoubtedly enhances non-melanoma skin photocarcinogenesis in a human-relevant mouse model*'. The draft PI submitted with response to TGAs request for information includes recommendations under Precautions and Dosage and Administration, 'High sunscreen protection factor (SPF) sunscreens or other sun-exposure reduction methods should be used when Soolantra is applied to the face or other sun-exposed areas'.

The mechanism of action of 1% ivermectin cream in PPR has not been definitively investigated in nonclinical or clinical studies.

Proposed action

The Delegate had no reason to say, at this time, that the application for Soolantra should not be approved for registration.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Does the ACPM agree with the clinical evaluator's conclusion that at the present stage of product development, no specific safety concerns remain?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from Sponsor

Indication, Dosage and Administration and Registration

The company agrees with the Delegate to recommend approval of Soolantra/Vastreka for the following indication:

> *Soolantra/Vastreka is indicated for the topical treatment of inflammatory lesions of rosacea in adult patients.*

The company agrees that the risk-benefit profile is acceptable for registration.

The dosage and administration in the initial submission was updated during evaluation to align with the EU SmPC as well as under recommendation from the second round RMP evaluation report.

Regarding the TGA comment: Advice Sought: Safety

1. *Does the ACPM agree with the clinical evaluator's conclusion that at the present stage of product development, no specific safety concerns remain?*

Sponsor's response:

The sponsor acknowledges the Delegate's statement that there are no outstanding specific safety concerns remaining for Soolantra/Vastreka at the present stage of product development. All the Clinical, Nonclinical, Chemistry, Quality and Biopharmaceutical and RMP issues identified in the second round evaluation reports have been resolved and the recommended updates have been made to the Product Information and the Consumer Medicine Information.

Regarding the TGA comment: Dose Effect Relationship

The clinical evaluator comments that no convincing evidence has been presented that the 1% cream is significantly more efficacious than 0.3% cream dose finding was not definitive. (see Study RD.03.SRE.40027).

Sponsor's response:

Numerical trends in favour of a dose response relationship was observed in Study 40027 with increasing dose (that is, ivermectin at concentrations of 0.0%, 0.1%, 0.3%, and 1%) when ivermectin cream was applied QD. The 1% concentration was selected as the only dosage which provided statistically significant demonstration of efficacy.

The primary efficacy endpoint in Study 40027 was the Percent Change in Inflammatory Lesion Counts from Baseline at Week 12 (ITT-LOCF). A pairwise comparison versus vehicle of each concentration of ivermectin cream (that is, 0.1%, 0.3%, and 1% all administered QD and 1% administered BD) revealed a statistically significant difference between ivermectin 1% cream administered QD ($p \leq 0.006$) or BD ($p \leq 0.014$) versus vehicle cream QD at Week 12. Neither ivermectin 0.1% cream nor ivermectin 0.3% cream was statistically superior to the vehicle. In order to minimise multiplicity issues, a sequential stepwise analysis was conducted to confirm a dose response relationship at Week 12. This stepwise analysis started from ivermectin 1% cream BD down to ivermectin 0.1% cream QD by removing the highest dose until non significance was

reached. Results demonstrated a statistically significant dose response from vehicle up to ivermectin 1% QD (p = 0.004, ITT-LOCF) and confirmed results obtained through the pairwise comparison.

A tabulated overview of AEs reported in Study 40027 is provided (see Table 13). These data show that the incidence of AEs was similar in the ivermectin 0.3% QD and 1% QD groups. Overall 138 out of the 296 subjects randomised reported at least one AE: 21 (41.2%) subjects for ivermectin 0.1% cream QD, 23 (48.9%) subjects for ivermectin 0.3% cream QD, 21 (40.4%) subjects for ivermectin 1% cream QD, 28 subjects (58.3%) for ivermectin 1% cream BD and 26 (52%) subjects for vehicle.

Table 13. Overview of Adverse Events in Study 40027 (Safety population).

	CD5024 0.1% QD (N=51)		CD5024 0.3% QD (N=47)		CD5024 1% QD (N=52)		CD5024 1% BID (N=48)		metronidazole 0.75% BID (N=48)		vehicle QD (N=50)	
	n events	n(%) subjects	n events	n(%) subjects	n events	n(%) subjects	n events	n(%) subjects	n events	n(%) subjects	n events	n(%) subjects
All AEs	37	21 (41.2)	38	23 (48.9)	34	21 (40.4)	46	28 (58.3)	31	19 (39.6)	54	26 (52.0)
Related AEs	9	5 (9.8)	8	6 (12.8)	5	3 (5.8)	7	7 (14.6)	6	4 (8.3)	6	5 (10.0)
All dermatologic AEs	13	8 (15.7)	9	8 (17.0)	8	5 (9.6)	7	7 (14.6)	7	5 (10.4)	12	10 (20.0)
Related dermatologic AEs	8	4 (7.8)	5	5 (10.6)	5	3 (5.8)	4	4 (8.3)	5	3 (6.3)	5	5 (10.0)
All serious AEs	1	1 (2.0)	0	0	0	0	2	2 (4.2)	1	1 (2.1)	0	0
Related serious AEs	0	0	0	0	0	0	0	0	0	0	0	0
AEs of special interest	0	0	1	1 (2.1)	2	1 (1.9)	2	2 (4.2)	1	1 (2.1)	0	0
Related AEs of special interest	0	0	1	1 (2.1)	2	1 (1.9)	2	2 (4.2)	1	1 (2.1)	0	0
AEs leading to discontinuation	1	1 (2.0)	4	2 (4.3)	2	1 (1.9)	2	2 (4.2)	3	2 (4.2)	0	0
Related AEs leading to discontinuation	0	0	4	2 (4.3)	2	1 (1.9)	1	1 (2.1)	3	2 (4.2)	0	0
Deaths	0	0	0	0	0	0	0	0	0	0	0	0

The number of subjects with related AEs were 5 (9.8%) for ivermectin 0.1% QD, 6 (12.8%) for ivermectin 0.3% cream QD, 3 (5.8%) for ivermectin 1% cream QD, 7 (14.6%) for ivermectin 1% cream BD and 5 (10.0%) for vehicle.

Dermatologic adverse events were reported in 8 subjects (15.7%) treated with ivermectin 0.1% cream QD, 8 subjects (17.0%) with ivermectin 0.3% cream QD, 5 subjects (9.6%) with ivermectin 1% cream QD, 7 subjects (14.6%) with ivermectin 1% cream BD and 10 subjects (20.0%) with vehicle.

No subjects in either treatment group were discontinued due to abnormal laboratory results. Globally, no dose effect relationship was observed on any of the cutaneous signs and symptoms: no clear difference on the severity grades was observed between ivermectin treatment groups, metronidazole group and vehicle group.

Thus, efficacy and safety results from Study 40027 support the good benefit/risk ratio for ivermectin 1% cream QD. These data informed the sponsor's choice of 1% dosage and regimen for further clinical development.

TGA comment: Superiority to Vehicle

Soolantra was shown to be superior to vehicle.

Sponsor's response:

In a response to the clinical evaluator's comment the draft PI was amended to include the following sentence: '*Soolantra/Vastreka demonstrated a significantly superior efficacy versus vehicle on both co-primary endpoints (reduction of inflammatory lesions and IGA success rate) which occurred as early as Week 4 and continued up to and including the 12-week time point.*'

TGA comment: Mechanism of Action

The mechanism of action of 1% ivermectin cream in papulo-pustular rosacea has not been definitively investigated in nonclinical or clinical studies.

Sponsor's response:

With topical application of ivermectin, anti-inflammatory properties have been observed in animal models of skin inflammation. The anti-inflammatory potential of topical application of ivermectin has been evaluated in pharmacology studies in mice that were conducted by the sponsor, using ear oedema models and an allergen induced atopic dermatitis model. Ivermectin also causes death of parasites, primarily through binding selectively and with high affinity to glutamate gated chloride channels, which are present in invertebrate nerve and muscle cells. The mechanism of action of ivermectin 1% cream in treating the inflammatory lesions of rosacea may be linked to anti-inflammatory effects of ivermectin as well as the death of Demodex mites that have been reported to be a factor in inflammation of the skin. However, this mechanism has not been investigated in detail since the exact physiopathology of rosacea is unknown. The sponsor considers that this is not a key issue, since the efficacy and safety of topical ivermectin have been clearly demonstrated. In line with the Delegate's statement, the following sentence is now included in the Pharmacology/Mechanism of action section of the PI: '*The mechanism of action of Soolantra cream in treating rosacea lesions is unknown.*'

TGA comment: Data on Relapse Rates

Data on relapse rates from the 36 week extension of Study RD.03.SRE.40173 are awaited.

Sponsor's response:

The objective of the second study period (Period B) of Study RD.03.SRE.40173 was to generate efficacy data of ivermectin 1% cream versus metronidazole 0.75% cream, for subjects successfully treated over the initial 16 weeks of treatment, by assessing the time of first relapse, the relapse rate, the number of days free of treatment, and subject's global improvement of rosacea at Week 52/ET visit during a 36 week extension period. The safety objective was to assess the overall safety of ivermectin 1% cream applied once daily up to 28 weeks during this Period B compared to metronidazole 0.75% cream.

Subjects eligible for Period B had a success, defined as an IGA of 0 or 1 (that is, subjects assessed as 'Clear' or 'Almost Clear' rosacea) at the outcome (Week 16 visit) of Period A, and their study treatment was to be stopped. The decision to restart the treatment was made by the investigator at each study visit (every 4 weeks) strictly if the IGA score became at least 2. In this case, the subjects were re treated with the same treatment as received in Period A for a maximum duration of 16 weeks. The re treatment was to last until IGA was back to 0 or 1 then the investigator stopped the treatment and the subject continued to attend the scheduled study visits. If IGA did not come back to 0 or 1 after 16 weeks of retreatment, the treatment was discontinued and the subject was withdrawn from the study.

At the end of Period A, 762 subjects were eligible for entering in Period B and 757 out of these subjects decided to continue in Period B: 399 subjects in the ivermectin 1% cream group (abbreviated to 'ivermectin group') and 358 subjects in the metronidazole 0.75% cream group (abbreviated to 'metronidazole group'). Disease characteristics were comparable in the 2 treatment groups in terms of inflammatory lesion, nodule, papule and pustule counts. From the start of Period B, the median time to first relapse was significantly longer in the ivermectin group (115.0 days) than in the metronidazole group (85.0 days) ($p = 0.0365$). The relapse rates were 62.7% in the ivermectin group and 68.4% in the metronidazole group. Hence, at the end of the study, 37.3% of subjects in the ivermectin group and 31.6% in the metronidazole group did not relapse in Period B. The mean number of days free of treatment was significantly higher in the ivermectin group (183.4 days) than in the metronidazole group (170.4 days) ($p=0.026$).

In conclusion, with a similar systemic safety profile and a better local tolerance, treatment with ivermectin 1% cream once daily resulted in an extended remission of rosacea when

compared to metronidazole 0.75% cream twice daily in subjects who were successfully treated after a 16 week treatment period. Study RD.03.SRE.40173 Period B synopsis was provided.

TGA comment: Treatment Duration

A treatment course duration of 4 months has been introduced to draft PI submitted in response TGAs request for information to align with EU SmPC.

Sponsor's response:

In a response to the RMP evaluator's request, the sponsor provided a comparison of the EU SmPC (approved in the Decentralised Procedure D210 stage) with the proposed amended Australian PI and CMI.

The confirmatory Phase III program conducted by the sponsor included two identically designed, independent, adequate and well controlled 12 week pivotal studies versus vehicle cream (Studies 18170 and 18171), and one investigator blind, active controlled, supportive study versus metronidazole 0.75% cream (Study 40173). The duration of Study 40173 was 16 weeks in order to ensure that a maximum treatment effect (that is, difference between ivermectin and metronidazole arms) would be attained. Studies 18170 and 18171 where the products were applied for 12 weeks showed the continuous improvement of the symptoms of PPR upon treatment with ivermectin 1% cream QD over time and the statistical superiority of ivermectin 1% cream QD compared to Vehicle cream QD; Study 40173 showed that beyond 12 weeks of treatment, that is, up to 4 months, daily applications of ivermectin 1% cream resulted in further improvement of rosacea symptoms, while the safety profile remained comparable to that observed over the preceding 12 weeks of treatment. A treatment course duration of 4 months has been proposed in the EU SmPC accordingly.

TGA comment: Neutropenia

Study RD.03.SRE.40051 was discontinued because 3 subjects treated with ivermectin 1% cream developed neutropenia. Study RD.03.SRE.40106 investigated whether the product proposed for registration may be causally associated with neutropenia. The CER accepts that there appears to be no evidence of a causal relationship between treatment with ivermectin 1% cream and neutropenia.

Sponsor's response:

As presented, further to the sponsor's decision to discontinue the long term open label safety Study 40051 during the development of the product, the sponsor submitted an information package dated December 2010 in response to an FDA Request for Information, including a retrospective analysis of all available neutrophil data obtained in nonclinical and clinical studies performed, as well as a thorough in vitro investigation of ivermectin effects on human neutrophils and neutrophil precursors. Based on this information and endorsement by the FDA, the sponsor conducted the subsequent Study 40106 in subjects with PPR, to investigate a potential effect of ivermectin 1% cream QD on the induction of neutropenia in comparison to its vehicle. This study generated evidence to support the conclusion that a drug related adverse effect of ivermectin on neutrophils of rosacea subjects was unlikely to occur. This provided adequate evidence of safety to resume the confirmatory Phase III program. This program confirmed the absence of any risk of neutropenia arising from the use of ivermectin 1% cream in subjects with PPR.

TGA comment: Photocarcinogenicity

The nonclinical evaluation recommends any long term, repeated topical application of Soolantra in sun exposed areas should be avoided or sun protection strategies should be used as topical Soolantra undoubtedly enhances non melanoma skin photocarcinogenesis in a human relevant mouse model.

Sponsor's response:

The potential of ivermectin cream and vehicle cream to influence the development or growth of skin tumours in hairless mice exposed to simulated solar UV radiation was determined in Study 12597, in compliance with FDA Guidance for Industry: Photo safety Testing, May 2003. However, the sponsor considers that the mouse model of photocarcinogenicity has little, if any relevance to humans, and therefore that the rationale for the recommended protection of sun exposed areas during topical treatment with ivermectin 1% cream cannot be based on enhanced non melanoma skin photocarcinogenesis.

In a response to the nonclinical reviewers request for information, the sponsor suggested removing the paragraph dedicated to photocarcinogenicity from the Carcinogenicity Section of the PI, considering that the mouse data are of doubtful relevance directly to humans. In agreement with the nonclinical evaluator's proposal in the second round evaluation report, the sponsor has included the following statements in the PI:

- Section Precautions/Carcinogenicity: '*Chronic (1 year) repeated topical application of Soolantra enhanced simulated solar ultraviolet radiation-induced non-melanoma skin carcinogenesis in albino Skh HR-1 hairless mouse (tumour potency factor in both sexes combined was 1.69; and 1.74 in male mice and 1.51 in female mice; compared with an expected no adverse effect tumour potency factor of 1.00). The albino Skh HR-1 hairless mouse is more sensitive to ultraviolet radiation induced carcinogenesis than humans. Accordingly the clinical relevance of these findings is uncertain. However repeated unprotected exposure of Soolantra treated skin to ultraviolet radiation sources (including sunlight) should be avoided (see Precautions)'*.
- Section Precautions: '*High sunscreen protection factor (SPF) sunscreens or other sun exposure reduction methods should be used when Soolantra is applied to the face or other sun exposed areas.*'

TGA comment: Anthelmintic Resistance

There is potential for Soolantra use to contribute to the induction of anthelmintic resistance to ivermectin and other members of the avermectin parasiticidal drug class because an important pathway of excretion is active transport in to the gut via enterothelial ABC B1 efflux transporters.

Sponsor's response:

Animal studies performed by the sponsor have shown that after a 6 hour topical application of (^{3}H)-ivermectin 1% cream in minipigs, the majority of absorbed radioactivity was excreted in the faeces. There are no corresponding human excretion data. The full PK assessment conducted by the sponsor has demonstrated that, under the proposed conditions of topical application of ivermectin 1% cream in subjects with rosacea, plasma exposure to ivermectin was low and there was no plasma accumulation on long term use. Intestinal concentrations of ivermectin under clinical use conditions are expected to be even lower. Therefore, the induction of anti helminthic resistance is very unlikely. This situation is clearly different from the potential risk of resistance induction on veterinary use of ivermectin.

TGA comment: Safety

The Table which shows SAE in pivotal Study 18170 which did include AE terms classified as related to study drug.

The Table which shows SAE in pivotal Study 18171 which did include AE terms classified as related to study drug. No deaths were reported.

Sponsor's response:

None of the Serious Adverse Events (SAEs) reported in the pivotal studies was considered related to ivermectin 1% cream. In addition, none of the Preferred Terms (PTs) listed for SAEs in the tables (for Study 18170 and for Study 18171) has its counterpart in the list of PTs for related adverse events (Study 18170) and (Study 18171).

TGA comment: CER Benefit-Risk Balance

Hypothetical effects of systemic exposure. The difference in systemic exposure between 0.3% and 1% creams (Study RD.03.SRE.40027) is noted.

Sponsor's response:

Exposure data obtained from dose ranging Study 40027 conducted in subjects with PPR demonstrated that ivermectin plasma concentrations increased with the applied doses. Arithmetic mean values for ivermectin plasma concentrations at steady state (4 weeks) were 0.31 ± 0.33 ng/mL and 0.72 ng/mL in the ivermectin 0.3% cream QD and ivermectin 1% cream QD groups, respectively. In terms of safety margin for use, however, it should be noted that high safety ratios were obtained with the 1% cream under maximised use conditions, ranging from 68 based on a teratogenicity study in the rabbit, to 329 based on an oral carcinogenicity study in rats for which an absence of tumorigenic effects were demonstrated. Additionally, Study 40027 demonstrated a statistically significant dose response in terms of efficacy from vehicle up to ivermectin 1% QD. Of the QD groups in this study, only ivermectin 1% cream QD was statistically superior to vehicle, whereas the safety of ivermectin 1% cream QD was similar to that observed with ivermectin 0.3% cream QD. In conclusion, ivermectin 1% cream QD combines optimal efficacy while retaining a high safety margin of use in subjects with PPR.

TGA comment: RMP Evaluation

Outstanding issues

'Effects of significant UV exposure' and 'Use in patients with particular forms of rosacea ((rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin) or other facial dermatoses that may be confounded with papulo-pustular rosacea, such as peri-oral dermatitis, facial keratosis pilaris, seborrheic dermatitis and acne) should be added as missing information to the table of ongoing safety concerns.

Sponsor's response:

The sponsor acknowledges the request for addition of missing information on (1) effects of significant ultraviolet exposure and (2) use in patients with the above list of particular forms of rosacea and other facial dermatoses that may be confounded with papulo-pustular rosacea. This information has been added to the Precautions section of the PI. Additionally, the ASA of the Risk Management Plan has been updated accordingly.

TGA comment: Review of the Product Information

Patients suffering particular forms of rosacea (rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin) or other facial dermatoses that may be confounded with papulo-pustular rosacea, such as peri-oral dermatitis, facial keratosis pilaris, seborrheic dermatitis and acne'.

Sponsor's response:

The Precautions section of the PI has been amended to include the following statement: '*Safety and efficacy have not been established in patients suffering from particular forms of rosacea (rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin) or other facial dermatoses that may be confounded with papulo-pustular rosacea, such as peri-oral dermatitis, facial keratosis pilaris, seborrheic dermatitis and acne*.'

Advisory Committee Considerations

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

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Soolantra/ Vastreka cream containing 10 mg/g (1% w/w) of ivermectin to have an overall positive benefit–risk profile for the indication:

> *Soolantra/Vastreka is indicated for the topical treatment of inflammatory lesions of rosacea (papulo-pustular) in adult patients 18 years and over.*

In making this recommendation the ACPM;

- Noted the mechanism of action has not been definitively investigated.
- Noted the decision to choose 1% cream was not robust. There was no evidence of clinical superiority of 1% strength over 0.3% strength.
- Noted there is still relapse data to be reported.
- Noted treatment course duration and frequency are not clearly defined by the data.

Proposed conditions of registration

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

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

Specific Advice

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

1. *Does the ACPM agree with the clinical evaluator's conclusion that at the present stage of product development, no specific safety concern remains?*

The ACPM agreed there were no specific safety concerns but acknowledged that the biopharmaceutic and pharmacology data are limited and that assumptions on systemic effects from topical dosing have been made.

The ACPM was of the view that the lack of long term safety data combined with treatment (albeit interrupted) over years, required long term pharmacovigilance for systemic adverse events and resistance and agreed with measures, particularly on skin carcinoma, in the RMP and the PI.

The ACPM was of the view that the choice of ivermectin 1% over the 0.3% strength appears inappropriate on Quality Use of Medicines principles and should have been investigated further.

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

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Soolantra ivermectin 10 mg/g for cream tube for topical administration, indicated for:

Soolantra/Vastreka is indicated for the topical treatment of inflammatory lesions of rosacea (papulo-pustular) in adult patients 18 years and over.

Specific conditions of registration applying to these goods

The Soolantra/Vastreka containing ivermectin 10 mg/g cream Risk Management Plan (RMP): EU RMP (version 1.0, dated 25 March 2014, DLP 10 October 2013) with Australian Specific Annex (version 1.2, dated July 2015), included with submission PM- 2014-01877-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI approved for Soolantra 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>. The PI Vastreka is identical except for the product name.

Attachment 2. Extract from the Clinical Evaluation Report

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