



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Diltiazem hydrochloride

Proprietary Product Name: Ano-Cream

Sponsor: AFT Pharmaceuticals Pty Ltd

May 2017

TGA Health Safety
Regulation

About the Therapeutic Goods Administration (TGA)

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- 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.
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Common abbreviations

Abbreviation	Meaning
AAF	acute anal fissure
ACPM	Advisory Committee on Prescription Medicines
ADR	adverse drug reaction
AE	adverse event
AF	anal fissure
AUC	area under the plasma drug concentration-time curve
BP	blood pressure
CI	confidence interval
Cmax	maximum serum concentration of drug
CMI	Consumer Medicine Information
DTZ	diltiazem hydrochloride
DTZ 2%	diltiazem hydrochloride 2% w/w cream
DTZ 4%	diltiazem hydrochloride 4% w/w cream
ECG	electrocardiogram
GI	gastrointestinal
GTN	glyceryl trinitrate
HCl	hydrochloride
IC50	inhibitory concentration 50%
IV	intravenous
LD50	lethal dose 50%
NRS	numerical rating scale
PD	pharmacodynamic(s)
PI	Product Information
PK	pharmacokinetic(s)
PR	pulse rate

Abbreviation	Meaning
RMP	Risk Management Plan
TID	ter in die (three times a day)
Tmax	time taken to reach the maximum concentration (Cmax)

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Major variation (new dosage form)
<i>Decision:</i>	Rejected
<i>Date of decision:</i>	14 November 2016
<i>Active ingredient:</i>	Diltiazem hydrochloride
<i>Product name:</i>	Ano-Cream
<i>Sponsor's name and address:</i>	AFT Pharmaceuticals Pty Ltd 113 Wicks Road Lane Cove NSW 2066
<i>Dose form:</i>	Cream
<i>Strength:</i>	2% w/w
<i>Container:</i>	Aluminium tube
<i>Pack size:</i>	1 x 30 g tube
<i>Route of administration:</i>	Transdermal
<i>Dosage:</i>	Proposed maximum dosing is 8.5 mg, to be applied, perianally, three times daily, at approximately 8 h intervals.

Product background

This AusPAR describes the application by AFT Pharmaceuticals Pty Ltd to register Ano-Cream¹ (diltiazem hydrochloride). Diltiazem hydrochloride is an inhibitor of L-type calcium channels. It inhibits calcium influx into myocardial cells, vascular smooth muscle and smooth muscle in the gastrointestinal (GI) tract. Diltiazem is marketed under several brand names for the treatment of hypertension, angina and various cardiac rhythm disorders.

The proposed new indication is:

2% w/w cream in adults for the relief of pain associated with chronic anal fissure.

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

Cream in a 30g aluminium tube containing diltiazem cream 2% w/w. A nominal dose of 450 mg cream contains diltiazem hydrochloride 20 mg/g delivering 8.5 mg diltiazem hydrochloride per application.

Diltiazem hydrochloride 8.5 mg TID (ter in die; three times a day) given topically to the anal canal via a nominal application of 450 mg diltiazem 2% cream.

¹ Initial trade name proposed at submission to TGA was Anoheal; this trade name is also used in this report.

Regulatory status

Ano-Cream is not registered in any country. According to the sponsor:

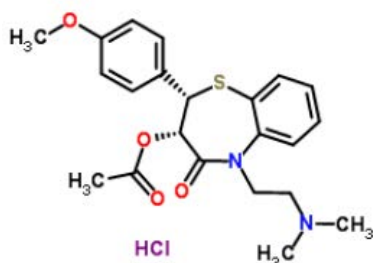
This product is currently available on an unlicensed basis (equivalent to named patient basis in Australia) in the UK.

II. Quality findings

Introduction

Film coated and uncoated tablets and modified release capsules containing the calcium ion influx inhibitor diltiazem (as the hydrochloride; see Figure 1) are currently registered in Australia by a number of sponsors.

Figure 1: Chemical structure of diltiazem hydrochloride.



In the present submission, AFT Pharmaceuticals Pty Ltd seeks to register a New Dosage Form (a cream) containing diltiazem hydrochloride 2% w/w for administration via the transdermal route originally under the trade name “Anoheal”. However, the originally proposed trade name was deemed clinically unacceptable, and the trade name subsequently accepted by TGA was “Ano-Cream”. The cream is indicated for the relief of pain associated with chronic anal fissure in adults. The maximum recommended daily dose is 3 perianal applications of the cream, corresponding to a total of 25.5 mg of diltiazem hydrochloride. Treatment may be continued for up to 8 weeks until the pain has abated.

Drug substance (active ingredient)

Diltiazem hydrochloride, the 1:1 hydrochloric acid salt of diltiazem, is the subject of monographs in the European Pharmacopoeia (Ph Eur) (Ph Eur 04/2013:1004), British Pharmacopoeia (Ph Eur monograph 1004) and US Pharmacopoeia.

The drug substance has two chiral centres, with a 2S,3S absolute configuration. The isomeric structure with a 2R,3S absolute configuration is limited in the drug substance specification to $\leq 0.10\%$. Other structures with alternative absolute configuration at C-2 or alternative disposition of the 1,5-benzothiazepin-4(5H)-one ring substituents are precluded by the route of synthesis.

The drug substance is manufactured from 4-methoxybenzaldehyde, methylchloroacetate and 2-aminothiophenol by a relatively simple achiral synthesis combined with a chiral resolution step.

No evidence of true or pseudo-polymorphism of diltiazem hydrochloride has been reported in the literature.²

The BCS Class of the drug substance is irrelevant to the dosage form.

The literature³ reports the drug substance has a pKa value of 7.7, and a value logP_{App} of 3.53 at pH 7.4; elsewhere logP_{octanol/water} is reported to be 2.8⁴ and 3.63.⁵ LogD is reported to be 0.76 at pH 5.5.⁶

No limits are applied to the particle size distribution of the drug substance; this has been accepted given that the API is in aqueous solution in the finished product.

The impurities controlled in the drug substance are those specified in the Ph Eur monograph <04/2013:1004>.

A number of issues relating to the quality control of the diltiazem hydrochloride drug substance were raised with AFT; all have been resolved.

Drug product

The finished product is described as a “smooth white cream packed in an aluminium tube sealed with a polypropylene screw cap closure”, packaged in an outer cardboard carton (pack of 1 x 30 g).

No overage is employed.

The company has justified the respective release and expiry limits of $\leq 0.5\%$ and $\leq 5.0\%$ applied to the desacetyl diltiazem HCl degradant on the basis of this physiologically active substance being one of the two principal human metabolites.⁷ The toxicology evaluator has agreed that there are no safety issues with an expiry limit of $\leq 5.0\%$. Further, levels were found to increase to $\leq 4.6\%$ during 36 months storage of the 2% w/w cream at 5°C for 36 months, which supports the proposed expiry limit.

Based on a maximum recommended daily dose of 25.5 mg, the common release and expiry limit of $\leq 0.2\%$ for Individual Unknown Impurities corresponds to the identification threshold in ICH 3QB.⁸ The release and expiry limits of $\leq 0.7\%$ and 5.2% applied to Total Impurities correspond to the sum of the limits applied to the desacetyl diltiazem HCl degradant and to Individual Unknown Impurities, and were accepted on that basis.

The stability data in the original dossier support a shelf life of 36 months stored at 2-8°C with the additional storage conditions “Refrigerate” and “Do not freeze” for the unopened 2% w/w cream packaged in either of the aluminium tubes proposed for Australia. An interim in-use shelf life of 4 weeks stored below 25°C with the additional warning “Discard 4 weeks after opening” is also accepted for cream, subject to satisfactory

² Mazzo DJ, et al. Diltiazem hydrochloride, *Analytical Profiles of Drug Substances and Excipients* 23: 53-98, (1994); Adibkia K, et al. Effect of solvent type on retardation properties of diltiazem HCl form liquisolid tablets. *Colloids Surf B Biointerfaces* 113: 10-14 (2014).

³ Sousa RG, et al. Dependence of copolymer composition, swelling history, and drug concentration on the loading of diltiazem hydrochloride (DIL.HCl) into poly[(N-isopropylacrylamide)-co-(methacrylic acid)] hydrogels and its release behaviour from hydrogel slabs. *J Control Release* 102: 595-606 (2005).

⁴ Drugbank.ca online resource.

⁵ Silva SM, et al. A combination of nonionic surfactants and iontophoresis to enhance the transdermal drug delivery of ondansetron HCl and diltiazem HCl. *Eur J Pharm Biopharm.* 80: 663-673 (2012).

⁶ Silva SM, et al. A combination of nonionic surfactants and iontophoresis to enhance the transdermal drug delivery of ondansetron HCl and diltiazem HCl. *Eur J Pharm Biopharm.* 80: 663-673 (2012).

⁷ Molden E, et al. Desacetyl-diltiazem displays severalfold higher affinity to CYP2D6 compared with CYP3A4. *Drug Metab Dispos.* 30: 1-3 (2002).

⁸ European Medicines Agency, “ICH Topic Q 3 B (R2) Impurities in New Drug Product: Note for Guidance on Impurities in New Drug Products (CPMP/ICH/2738/99)”, June 2006.

outcomes being obtained from the additional in-use stability trials which the manufacturer has committed to perform.

The company has yet to provide satisfactory release and expiry specifications for the finished product, and this issue remains unresolved.

Biopharmaceutics

Because there is no product currently on the market that uses diltiazem hydrochloride in the same strength for the same indications, in any dose form, biopharmaceutic studies are not required. However, the results from one bioequivalence study (#VEN307-PK-001) were submitted in support of the application. This study, which was an open label, single and multi-dose pharmacokinetic study of oral diltiazem and topical diltiazem hydrochloride cream in subjects with anal fissure, was not evaluated.

Quality summary and conclusions

There are no objections in respect of biopharmaceutics to registration of the product. However, suitable release and expiry specifications for the finished product and a suitably amended Product Information (PI) document need to be submitted, and current GMP evidence for the site of manufacture of the diltiazem hydrochloride drug substance needs to be obtained before approval can be recommended from a Quality perspective.

III. Nonclinical findings

Introduction

AFT Pharmaceuticals Pty Ltd has applied to register Ano-Cream, a 2% w/w cream formulation of diltiazem hydrochloride for the relief of pain associated with chronic anal fissure at thrice daily perianal doses of 450 mg cream (containing 8.5 mg diltiazem hydrochloride per application). Diltiazem hydrochloride is currently approved for the treatment of hypertension, angina and various cardiac rhythm disorders for oral administration at doses up to 360 mg/day.

Nonclinical data submitted in support of this application include repeat dose toxicity/local tolerance in dogs, local tolerance studies in rabbits, and guinea pig skin sensitisation studies for the topically (anally) proposed or simplified diltiazem hydrochloride formulations. Literature data have also been provided regarding the pharmacology, pharmacokinetics and toxicology of diltiazem. However, given the extensive history of oral or parenteral diltiazem, only literature papers providing pertinent information relating to the pharmacology and pharmacokinetics of the new cream formulation or indication or providing pertinent information relating to the safety profile or Product Information document for diltiazem have been evaluated and summarised below.

Pharmacology

Primary pharmacology studies submitted that are relevant to the current application are limited to a single literature paper demonstrating the smooth muscle relaxant properties of diltiazem on internal anal sphincter in vitro. Diltiazem is an inhibitor of L-type calcium channels, which relaxes smooth muscle, notably vascular smooth muscle, and these smooth muscle relaxant properties form the basis of a potential mechanism of action of diltiazem in reducing the pain associated with anal fissure. Diltiazem was shown to cause a concentration-dependent inhibition (0.01-10 µmol/L) of sodium orthovanadate-induced

myogenic tone in isolated strips of sheep internal anal sphincter muscle in vitro, with a maximum response of approximately 84% at 10 $\mu\text{mol/L}$ ($\sim 4.5 \mu\text{g/mL}$). This in vitro study therefore suggests that diltiazem has the potential to relax the internal anal sphincter muscle. In terms of plasma concentration, diltiazem induced muscle relaxant activity was observed at concentrations well above anticipated clinical plasma diltiazem levels of 1.5 ng/mL (refer to “Comparative Exposure” section).⁹ However, given the potential mode of diltiazem action for the proposed indication are local smooth muscle effects, few conclusions can be drawn regarding its relative potency in vivo by comparing systemic exposure levels.

No primary pharmacology studies were performed with diltiazem in animal models of anal fissure. Therefore, evidence of efficacy will rely on clinical data.

No novel secondary or safety pharmacology papers were provided. However, the physiological effects of diltiazem on the cardiovascular, respiratory and central nervous systems have been well described. Of particular note are diltiazem’s negative inotropic, chronotropic, and dromotropic and smooth muscle relaxant effects, which form the basis for its cardiodepressive, antiarrhythmic and antihypertensive therapeutic indications. Given the markedly lower levels of diltiazem and its major metabolites following topical administration relative to the currently approved oral administration route (refer to “Comparative Exposure” section), no additional safety concerns are anticipated with the proposed indication and dosing regimen.

Pharmacokinetics

No traditional pharmacokinetic studies have been undertaken with diltiazem hydrochloride cream. However, the pharmacokinetic properties of diltiazem following oral or parenteral administration have been well characterised. Diltiazem is well absorbed from the GI tract and undergoes extensive first pass metabolism. It is also extensively distributed after both oral and intravenous (IV) dosing and has moderate-high protein binding in all species examined (52-82% in rats, dogs, monkeys and humans). Diltiazem undergoes extensive metabolism in the liver via the deacetylation, N-demethylation, and O-demethylation pathways. The former process is mediated by esterases, whereas the two latter reactions are catalysed by cytochrome P450 (P450) isoenzymes. Desacetyl diltiazem and N-desmethyl diltiazem are the principal metabolites formed. The metabolites are excreted in the urine and faeces, which indicates that biliary excretion occurs.¹⁰

Importantly, new literature references have been provided clarifying the role of CYP450 isozymes in diltiazem metabolism in vitro and the potential for pharmacokinetic drug interactions. Diltiazem is a substrate for the CYP3A4 and CYP2D6 liver isozymes which mediate the N-demethylation and O-demethylation pathways, respectively. Since the estimated K_m value of diltiazem to CYP2D6 ($\sim 200 \mu\text{M}$) is considerably higher than that of CYP3A4 (20-50 μM), CYP3A4 is likely to play a more prominent role than CYP2D6 in the metabolism of diltiazem. In contrast, CYP2D6 ($K_m \sim 5 \mu\text{M}$) is likely to play a more prominent role than CYP3A4 ($K_m \sim 540 \mu\text{M}$) in the metabolism of desacetyl diltiazem (the major pharmacologically active diltiazem human metabolite).

Diltiazem and its N-desmethyl and N,N-didesmethyl metabolites were inhibitors of CYP3A4 activity in human liver microsomes in vitro. O-desmethyl diltiazem was without remarkable effect. The N-desmethyl ($\text{IC}_{50} = 11 \text{ mM}$) and N,N-didesmethyl ($\text{IC}_{50} = 0.6 \text{ mM}$) metabolites were 11 and 200 times, respectively, more potent than diltiazem ($\text{IC}_{50} = 120 \text{ mM}$), suggesting they may contribute to CYP3A4 inhibition in vivo. However, it is noted

⁹ The total concentration range tested (0.01-10 $\mu\text{mol/L}$) is 3-3000x clinical plasma C_{max} .

¹⁰ Piepho RW, et al. Pharmacokinetics of diltiazem in selected animal species and human beings. *Am J Cardiol* 49: 525-528 (1982).

that the concentrations of diltiazem and its major metabolites shown to inhibit CYP3A4 activity in vitro are well above those anticipated clinically with perianal diltiazem administration. None of the other major CYPs 1A2, 2E1 or 2C9 were affected by diltiazem and its major metabolites in vitro, therefore pharmacokinetic interactions between diltiazem and drugs metabolized by these CYPs are unlikely. CYP2D6 was not examined in this study.

Toxicokinetic data were obtained in repeat dose toxicity/local tolerance studies in dogs following intrarectal, intraanal and perianal administration and systemic exposure also determined in patients with an anal fissure given perianal diltiazem with the new topical administration route. Systemic exposure to diltiazem (and desacetyl diltiazem in the perianal study) was demonstrated in dogs following application via all administration routes and patients, with exposure the highest, as anticipated, in dogs following intrarectal and intraanal administration, a route chosen to assess toxicity following inadvertent internal administration. Evidence of accumulation with repeated dosing was evident in both dogs and humans.

It should also be noted that, subsequent literature studies in animals have also been provided demonstrating placental and milk transfer of diltiazem in rabbits. Bregante et al.¹¹ demonstrated that in pregnant NZW rabbits given a single 5 mg/kg IV dose of diltiazem on gestation day (GD) 28, foetal blood concentrations of diltiazem and its metabolites desacetyl diltiazem and N-desmethyl diltiazem were similar to those observed in maternal blood, suggesting that diltiazem and its metabolites readily diffuse through the placenta. The concentrations of diltiazem and its metabolites in selected foetal tissues were either higher or lower than that observed in maternal tissues, suggesting a different tissue affinity and/or a different metabolic activity in the foetuses compared to the mothers. Rueda et al.¹² demonstrated that diltiazem and desacetyl diltiazem are present in the milk of lactating rabbits following IV administration of a 5 mg/kg diltiazem dose. A mean diltiazem maximum concentration of 3.1 ng/mL was detected in the milk, which was almost three times higher than that detected in the blood. Diltiazem and its metabolites, desacetyl diltiazem and N-desmethyl diltiazem were detected in the blood, but only the desacetyl diltiazem metabolite was detected in the milk. These results demonstrate that diltiazem and desacetyl diltiazem diffuse freely into milk.

Comparative exposure

The pharmacokinetic properties of diltiazem following oral and IV administration have been studied extensively. Targeting the internal anal sphincter with topically applied diltiazem relies on the effective transcutaneous flux of drug substance. Since local (anal sphincter tissue) diltiazem levels were not determined and plasma levels are unlikely to determine the magnitude of effect, the sponsor's development program focused on determining systemic exposure following topical application as an index of safety risk, rather than attempting to relate plasma levels to therapeutic benefit. This is acceptable.

Clinical exposure: topical versus oral administration route

Comparison of diltiazem and its major metabolite systemic exposure levels following administration of a 120 mg oral dose or thrice daily topical doses (8.5 mg; 2% w/w cream) of the commercial cream diltiazem formulation, demonstrated substantially lower levels of diltiazem and its major metabolites with the proposed new dose regimen and administration route. Systemic diltiazem exposure was lower by more than 30-fold and 80-fold based on AUC and C_{max} respectively (refer to "Plasma kinetics in human

¹¹ Bregante MA, et al. Diltiazem blood pharmacokinetics in the pregnant and non-pregnant rabbit: maternal and foetal tissue levels. *Xenobiotica* 30: 831-841 (2000).

¹² Rueda S, et al. Penetration of diltiazem into breast milk and its pharmacokinetics in the lactating rabbit. *Xenobiotica* 32: 119-130 (2002).

subjects”), for the topical compared to oral route at the lowest dose generally employed clinically for cardiovascular indications (120-360 mg/day). Similar observations were made for diltiazem metabolites. Thus, with markedly reduced systemic exposure to diltiazem and its metabolites, no novel safety concerns are anticipated.

Animal to clinical exposure: topical administration route

At the highest intrarectal, intraanal and perianal doses (4-8%; ~40-80 mg; ~6-12 mg/kg) administered in dog repeat dose toxicity/local tolerance studies, systemic plasma exposure levels were ~20-40 fold and 70-185-fold the anticipated clinical systemic exposure (30 ng.h/mL and 1.5 ng/mL), based on AUC and C_{max}, respectively following repeated perianal administration at 8.5 mg thrice daily. While the toxicological profile of diltiazem has previously been well-characterised, it is noted that no novel safety concerns were identified in these studies at sufficient clinical exposure multiples.

Toxicology

The toxicological profile of diltiazem has been well-characterised in several animal species (rodent, rabbit, dog and/or monkeys) for the oral and/or parenteral administration routes, therefore newly submitted studies focused on assessing the potential for inadvertent systemic exposure and/or local effects with the topical (intrarectal, intraanal and perianal) application routes. This is acceptable.

The LD₅₀ for diltiazem hydrochloride by the oral route is 415-740 mg/kg in the mouse and 560-810 mg/kg in the rat. For the IV route, the corresponding values are 60 mg/kg (mouse) and 38 mg/kg (rat). The oral LD₅₀ of diltiazem hydrochloride is greater than 50 mg/kg in dogs. Doses of 360 mg/kg were lethal in monkeys. Toxic effects occurred rapidly and included reduction of spontaneous activity, ptosis, piloerection, ataxia, loss of muscle tone and loss of righting reflex.¹³

In oral subacute and chronic repeat dose toxicity studies in rats and dogs, the liver and kidneys were identified as the primary target organs of toxicity. Organ weight increases, fatty and degenerative changes were generally observed at doses from ≥100 and ≥20 mg/kg/day, in rats and dogs respectively, in 1-12 month studies.

In the newly submitted GLP compliant repeat dose toxicity/local tolerance dog studies, thrice daily (with the general exception of the first and last days) intrarectal, intraanal or perianal diltiazem administration of the proposed formulation at identical or greater strengths (2-8% w/w), for 1, 8 or 2 weeks, respectively, did not raise any new safety concerns. In all studies, diltiazem was well tolerated with no remarkable systemic effects. This is not unexpected given the relatively low systemic exposure from the topical administration routes.

Genotoxicity

Two in vitro diltiazem genotoxicity studies have been reported in the literature. A Rec-assay measured the relative inhibition of growth of *Bacillus subtilis* H 17 Rec⁺ and *B. subtilis* M45 Rec⁻ in a paper disk soaked with the test compound diltiazem. The drug was considered negative for DNA-damaging potential.¹⁴

¹³ AHFS Diltiazem Hydrochloride Monograph. American Society of Health-System Pharmacists, Inc., 7272 Wisconsin Avenue, Bethesda, Maryland 20814 Selected Revisions 2011.

¹⁴ FDA (Food and Drug Administration). Review and Evaluation of Pharmacology and Toxicology Data. Cardizem (diltiazem HCL). NDA No. 18502 (March 1983).

Diltiazem was not mutagenic in the bacterial reverse mutation assay (Ames test) using 5 strains of *Salmonella typhimurium* and *Escherichia coli* WP2 in the presence or absence of metabolic activation (activated rat liver S-9).¹⁵

The sponsor also noted that diltiazem was negative for clastogenic effects in an in vitro chromosomal aberration assay in mammalian cells and in vivo micronucleus assay in mice. However, no further information has been provided for evaluation.

No novel genotoxicity safety concerns are anticipated with the perianal use of diltiazem hydrochloride cream.

Carcinogenicity

Carcinogenicity studies conducted in mice and rats at oral diltiazem doses up to 30 mg/kg/day (50 mg/kg/day for first 6 weeks only due to high mortality rate) for 21 months and 100 mg/kg/day for 24 months, respectively, showed no evidence of diltiazem related neoplastic findings.¹⁶ Given the high oral doses employed in these studies, no altered carcinogenic risk is anticipated with the perianal use of diltiazem hydrochloride cream.

Reproductive toxicity

The reproductive toxicity of diltiazem has been well characterised in mice, rats and rabbits. These studies have demonstrated embryotoxic and foetotoxic effects, foetal abnormalities of the skeleton, heart, retina and tongue, reductions in early individual pup weights and pup survival rates as well as prolonged delivery times and an increased incidence of stillbirths.¹⁷ Although reproductive toxicity studies were not submitted with this application, given the number of animal studies with consistent adverse findings, the results are summarised below and appropriate PI statements are recommended.

In male and female rats given oral diltiazem hydrochloride doses up to 100 mg/kg/day, no treatment related effects on fertility were observed.

In mice, rats and rabbits given oral diltiazem hydrochloride doses during embryogenesis, embryotoxicity, foetotoxicity and teratogenicity were observed. In mice, diltiazem hydrochloride doses ≥ 10 mg/kg/day given during gestation days (GD) 7-12 were embryotoxic (increased early resorptions and decreased live litters). Doses ≥ 50 mg/kg/day given during GD 7-12 or one of GD 7-14 were associated with a high incidence of skeletal (vertebral column, brachydactyly, bent tails), cleft palate/lips, and extremity or trunk malformations. Foetotoxicity (increased post-implantation loss and decreased live foetal weights) was also observed at diltiazem hydrochloride doses ≥ 25 mg/kg/day when administered as a single dose, particularly during GD 9, 10 or 11. In rats, embryo- and foetotoxicity (increased resorptions, decreased live fetuses, decreased body weight values and/or increased post-implantation loss) and an increased duration of pregnancy were observed in rats at doses ≥ 200 mg/kg/day when given during GD 9-14. A short or missing tail and general oedema was observed in rats given a single diltiazem dose of 600 mg/kg on GD 12 and skeletal malformations were observed in rats given a single diltiazem dose ≥ 300 mg/kg on or after GD 11. In rabbits, oral diltiazem hydrochloride doses ≥ 35 mg/kg/day given during GD 6-18 were associated with embryotoxicity (embryonic

¹⁵ FDA (Food and Drug Administration). Review and Evaluation of Pharmacology and Toxicology Data. Cardizem (diltiazem HCL). NDA No. 18502 (March 1983).

¹⁶ AHFS Diltiazem Hydrochloride Monograph. American Society of Health-System Pharmacists, Inc., 7272 Wisconsin Avenue, Bethesda, Maryland 20814 Selected Revisions 2011; Cardizem CD Product Monograph. Biovail Pharmaceuticals Canada, 2008; FDA (Food and Drug Administration). Review and Evaluation of Pharmacology and Toxicology Data. Cardizem (diltiazem HCL). NDA No. 18502 (March 1983).

¹⁷ AHFS Diltiazem Hydrochloride Monograph. American Society of Health-System Pharmacists, Inc., 7272 Wisconsin Avenue, Bethesda, Maryland 20814 Selected Revisions 2011.

deaths) and skeletal malformations. Major malformations including microphthalmia, cardiac defect, hydronephrosis and/or hydroureter in 3 fetuses from 17.5 mg/kg/day treated does and subretinal haemorrhage, internal hydrocephaly and disorganisation of the cranial bone in 4 fetuses from 35 mg/kg/day treated does were observed. Agenesis of the intermediate lobe of the lung was increased in fetuses of 17.5 mg/kg/day treated does. All does aborted between GD 21-25 at 70 mg/kg/day.

In a peri and postnatal study in rats given oral diltiazem hydrochloride at ≥ 30 mg/kg/day from GD 14 through day 21 post partum, there was a reduction in individual pup weights and pup survival, and a dose related increased incidence of retinal and tongue malformations. Dystocia and very slightly delayed gestation was also evident at ≥ 100 mg/kg/day.¹⁸

Overall, reproduction studies in several animal species have demonstrated significant embryotoxic, foetotoxic and potential teratogenic effects of diltiazem hydrochloride at oral doses ranging from 10 to 600 mg/kg/day, which, excluding differences in absorption and systemic exposure, is well in excess of the proposed topical clinical dose on a mg/kg basis alone (0.5 mg/kg/day: 25.5 mg over 3 doses in a 50 kg person). Thus, while no novel reproductive safety concerns are therefore anticipated with the perianal use of diltiazem hydrochloride cream, as with other diltiazem therapeutic products, relevant warnings contraindicating its use in pregnancy and breast feeding remain valid.

Pregnancy classification

The sponsor has proposed Pregnancy Category C,¹⁹ which is consistent with other diltiazem products and is acceptable.

Local tolerance

Diltiazem hydrochloride was well tolerated when administered thrice daily (with exception of the first and last treatment days) intrarectally, perianally or intraanally to dogs for 1, 2 or 8 weeks respectively using 2%, 4% and/or 8% cream strengths of the intended commercial formulation. The presence of the primary metabolite desacetyl diltiazem at a 5% concentration in a 4% commercial cream formulation did not alter perianal tolerance of diltiazem hydrochloride in dogs. However, the presence of polyvinylpyrrolidone (PVP) may have slightly decreased gastrointestinal tolerance (increased faecal excretion changes) in the 8 week intraanal study in dogs, with similar findings in the 8% diltiazem hydrochloride cream plus PVP and the PVP vehicle group alone. However, since this excipient is not present in the commercial formulation intended for clinical use, no novel gastrointestinal tolerance issues are anticipated.

Diltiazem hydrochloride cream was also well-tolerated when administered perianally/intraanally twice daily to rabbits for up to 90 days using the intended commercial 2% or a simplified 2% cream formulation. No dermal or rectal irritancy above that of the vehicle control was observed.

Guinea pig sensitisation studies demonstrated that both the intended commercial 2% and a simplified 2% cream diltiazem hydrochloride formulation did not cause any dermal or contact sensitisation and therefore it is classified as a non-sensitiser.

¹⁸ Cardizem CD Product Monograph. Biovail Pharmaceuticals Canada, 2008; FDA (Food and Drug Administration). Review and Evaluation of Pharmacology and Toxicology Data. Cardizem (diltiazem HCL). NDA No. 18502 (March 1983).

¹⁹ Category C: "Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details."

Impurities

The proposed specifications for impurities in the drug substance and degradants in the drug product are acceptable.

Nonclinical summary and conclusions

- AFT Pharmaceuticals Pty Ltd has applied to register Ano-Cream, a 2% w/w (20 mg/g) cream formulation of diltiazem hydrochloride for the relief of pain associated with chronic anal fissure at thrice daily perianal doses of 8.5 mg diltiazem hydrochloride per application for up to 8 weeks.
- Diltiazem hydrochloride (Cardizem and others) is currently approved for the treatment of hypertension, angina and various cardiac rhythm disorders at oral doses of up to 360 mg/day.
- The pharmacology, pharmacokinetics and toxicology profile of diltiazem have been well characterised following oral or parenteral administration. Thus, nonclinical data submitted in support of this application were bridging studies examining repeat dose toxicity/local tolerance in dogs, local tolerance in rabbits and skin sensitisation in guinea pigs. A range of pharmacology, pharmacokinetic and toxicology literature papers provided were evaluated, as deemed relevant.
- Diltiazem was shown to relax sheep internal anal sphincter muscle *in vitro* at concentrations in excess of clinical plasma concentrations (although local clinical concentrations may be greater). No primary pharmacology studies were performed with diltiazem in animal models of anal fissure. Thus, evidence of efficacy will rely on clinical data.
- The physiological effects of diltiazem on the cardiovascular, respiratory and central nervous systems have been previously characterised. No additional safety concerns are anticipated with the proposed dose and administration route, given the substantially lower systemic diltiazem exposure (30x and 80x based on plasma AUC and C_{max}, respectively) anticipated clinically, compared to oral dosing.
- Diltiazem was a substrate for CYP3A4 and CYP2D6 and an inhibitor of CYP3A4 *in vitro* at supratherapeutic concentrations. While there is potential for diltiazem to interact with other drugs that are substrates, inhibitors or inducers of these enzymes, given the low anticipated systemic diltiazem exposure, it is of lesser clinical concern compared to oral dosing.
- The toxicological profile of diltiazem has been previously well characterised in several animal species for the oral and/or parenteral administration routes, with the liver and kidneys identified as target organs for toxicity. In newly submitted repeat dose toxicity/local tolerance dog studies, thrice daily intrarectal, intraanal or perianal diltiazem administration of the proposed formulation at ≥2% strengths for 1-8 weeks did not raise any new safety concerns. Systemic diltiazem exposure following repeated topical dosing in these studies was ~20-40 fold and 70-185 fold the anticipated clinical systemic exposure, based on plasma AUC and C_{max}, respectively.
- The genotoxicity, carcinogenicity and reproductive toxicity of diltiazem hydrochloride has been previously characterised and is consolidated in this report, as necessary, to validate PI statements. No novel genotoxicity, carcinogenicity or reproductive toxicity concerns are anticipated with perianal use of diltiazem as proposed, given the substantially lower clinical systemic concentrations compared to those following therapeutic oral daily doses.

- Diltiazem was well tolerated following thrice daily intrarectal, intraanal and/or perianal administration in dogs for 1-8 weeks and twice daily perianal/anal administration in rabbits for up to 13 weeks using the proposed commercial formulation (2%) or simplified formulations at similar or greater strengths than those intended clinically. Diltiazem hydrochloride was also not a contact sensitiser in guinea pigs.
- There are no nonclinical objections to the registration of diltiazem hydrochloride (Ano-Cream) for the treatment of pain associated with chronic anal fissure as proposed.
- The Risk Management Plan (RMP) and draft PI documents should be amended as indicated.

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 1.

Introduction

This is a submission to extend the indication for diltiazem hydrochloride.

Clinical rationale

Anal fissures occur in otherwise healthy subjects irrespective of race, age and gender with a life time incidence of approximately 11%.²⁰ Acute anal fissures may occur after the passage of an abnormally large or hard stool and a low fibre intake in Western diets is often implicated. Anal fissures are linear ulcers in the epithelium of the anal canal, occurring most commonly in the posterior midline. The diagnosis is made by direct visualisation and endoscopy is not usually required. Anal fissures typically cause bleeding and pain during defaecation which may last for two hours or more. Most acute anal fissures heal spontaneously but some become chronic. In patients with chronic anal fissure, pain after defaecation is persistent and associated with resting anal hypertonia and poor spontaneous relaxation as measured by ambulatory manometry. Higher anal sphincter pressures are associated with lower anorectal blood flow, and ischaemic ulceration in the posterior segment is widely assumed to be the cause of persistent fissures. In patients who fail to respond to conservative or medical therapy, surgeries such as sphincterotomy can restore normal blood flow. Surgery provides healing and symptomatic relief in 90-95% of subjects; however, surgery is commonly associated with mild to moderate faecal incontinence.

Medical therapies designed to reduce anal sphincter tone and reduce ischaemia have been widely used in the last 20 years.²¹ However, randomised, controlled trials of numerous therapies have largely failed to demonstrate improved AF healing rates compared with placebo. In a systematic review of nine medical therapies, treatments including glyceryl trinitrate (GTN), nifedipine, botulinum toxin, hydrocortisone, and diltiazem were considered only marginally superior to placebo.²² An updated review conducted on behalf of the Cochrane Collaboration in 2012 reached the same conclusion with no evidence for

²⁰ Lock MR, Thompson JPS. Fissure-in-ano: the initial management and prognosis. *Br J Surgery* 64: 355-358 (1977).

²¹ Carpeti EA, et al. Topical and oral diltiazem lower anal sphincter pressure. *Br J Surgery* 85: 80-81 (1998).

²² Nelson R. A systematic review of medical therapy for anal fissure. *Dis Colon Rectum* 47: 422-431 (2004).

the value of diltiazem compared with placebo.²³ GTN was found to be marginally but significantly better than placebo in healing anal fissure (48.9% versus 35.5%, $p < 0.0009$). Botox and calcium channel blockers had similar efficacy to GTN with fewer adverse events but the studies were mostly small and poorly controlled and the benefits were not statistically significant. A systematic review of seven randomised controlled trials showed comparable efficacy for GTN and topical diltiazem with a lower incidence of headache in diltiazem subjects (Sajid, 2013).²⁴ However, randomised, controlled trials conducted to date have not shown an efficacy benefit for topical diltiazem compared with placebo for AF healing. Despite this failure to demonstrate AF healing, the sponsors have conducted a clinical trial program to assess the value of topical DTZ 2% cream for relief of pain with or following defaecation in subjects with chronic AF.

Guidance

The clinical development program was planned with scientific advice from the UK and Swedish regulatory authorities.

Contents of the clinical dossier

The submission contained the following clinical information:

- Two clinical pharmacology studies, both studies provided pharmacokinetic and pharmacodynamic data.
- No population pharmacokinetic analyses.
- One pivotal efficacy/safety study DAF09.
- Four other efficacy/safety studies, DAF-0001, 99-CFAIII, VEN307-DERM-001, VEN307-DERM-002.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

All studies were conducted according to the principles of ICH GCP.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

²³ Nelson R. Non surgical therapy for anal fissure. *Cochrane Database of Systemic Reviews* Issue 2. Art. No.: CD003431 (2012).

²⁴ Sajid MS, et al. Systematic review of the use of topical diltiazem compared with glyceryltrinitrate for the nonoperative management of chronic anal fissure. *Colorectal Dis.* 15: 19-26 (2013).

Table 1: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PKs in target population – Patients with AF§	General PK	VEN307-PK-001	Single and multiple dose PK parameters for topical DTZ and single dose PK parameters for oral DTZ in subjects with AF. Evaluate pain using NRS
		SC00802	Systemic absorption following topically applied DTZ at a range of doses in patients with AF. Effects of topical DTZ on the pulse rate, blood pressure and ECG readings.

* Indicates the primary aim of the study.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

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

Evaluator's conclusions on pharmacokinetics

- Anoheal 2% w/w cream is topically administered to the perianal area. Following administration of the formulation proposed for marketing, at a dose of approximately 8.5 mg DTZ, the median Tmax (range) occurred at 4.04 h (1.00-24.0 h).
- The relative bioavailability of a single, topical, perianal administration of Anoheal cream compared to a single oral dose of DTZ was 30%.
- *In vitro* studies indicated that the proposed commercial formulation of DTZ cream demonstrated higher skin permeability than the other aqueous formulations and a non-aqueous formulation tested.
- A study, which utilised a slightly different formulation of DTZ cream to the one proposed for marketing, indicated that DTZ exposure increased dose dependently; however, the increase in exposure was not dose proportional. The systemic bioavailability of DTZ following topical administration was approximately 15% of that for a single oral dose of DTZ.
- Steady state DTZ exposure was approached following 4 days of topical dosing TID with Anoheal cream.
- Diltiazem is metabolised extensively in the liver. The principal metabolites are N-desmethyldiltiazem and O-desacetyldiltiazem.
- The systemic bioavailability of N-desmethyldiltiazem following topical administration was approximately 5% of that resulting from oral DTZ, whereas the systemic bioavailability of O-desacetyldiltiazem following topical administration was approximately 23% of that resulting from oral DTZ.
- Following TID application with Anoheal cream, the mean elimination constants for DTZ and its two principal metabolites (N-desmethyldiltiazem and O-desacetyldiltiazem), was 0.0315/h, 0.0252/h and 0.0239/h, respectively.
- As expected the SD values associated with the DTZ PKs parameters following topical administration were relatively higher than those associated with DTZ PKs following a single oral dose.

Limitations of PK studies

- No dedicated PK trials examined the PKs of DTZ cream in healthy subjects.
- No clinical studies contained in this submission examined the absolute bioavailability of Anoheal cream.
- No clinical studies directly compared the PKs of the cream formulation proposed for commercialisation and the other formulations described in the Formulation Development section of this report.
- No dedicated PK/PD studies examined dose proportionality following application of the formulation proposed for marketing.
- No clinical studies examined the distribution of DTZ following perianal application.
- No clinical studies examined the sites of DTZ metabolism and mechanisms involved following perianal application.
- No Population-PK studies examined the intra or inter subject variability associated with the PKs of DTZ following perianal application.
- No studies examined the PKs of DTZ in special populations following perianal administration of Anoheal cream.
- No studies examined drug-drug interactions (DDIs) following perianal administration of Anoheal cream.
- The proposed PI section regarding Pharmacokinetics does not specifically state that no clinical trials have examined the absolute bioavailability, distribution, metabolism and the PKs of Anoheal cream in special populations (such as patients with hepatic or renal impairment) following perianal application of DTZ cream.

Pharmacodynamics

Studies providing pharmacodynamic data

All of the PK/PD studies that contain a PD component have been previously summarised as a part of Table 1.

Evaluator's conclusions on pharmacodynamics

- Diltiazem is an inhibitor of L-type calcium channels, which induces smooth muscle relaxation, including that of the internal anal sphincter.
- Relative to baseline, the mean NRS score for worst defaecation-related pain decreased by 0.7 ± 1.86 on Day 3 following the single topical dose of DTZ 2% w/w cream, by 2.2 ± 3.70 following the administration of multiple topical doses of DTZ cream and by 4.0 ± 3.22 after a single oral dose of DTZ.
- Relative to baseline, the mean NRS score for overall daily anal fissure-related pain was decreased by 0.0 ± 2.41 following the single topical dose of DTZ, by 1.4 ± 3.32 following the administration of multiple topical doses of DTZ, and by 1.7 ± 2.71 after a single oral dose of DTZ.
- Worst defaecation related pain and overall daily anal fissure-related pain was lowest following a single oral dose of DTZ.
- Topical application of both single and multiple doses of DTZ cream appeared to have no effect on PR.

- The average BP values at 2 h, 4 h and 8 h post dosing were reduced following either a single dose or multiple TID doses of 8% w/w DTZ cream.
- The reduction in worst defaecation related pain and overall daily AF related pain following topical application of DTZ 2% w/w cream increased following multiple doses compared to a single dose.

Limitations of the PD studies

- Due to the nature of the data provided no relationship between drug concentration and PD effects could be determined.
- No studies examined genetic, gender or age related differences in PD response following perianal application of DTZ cream.
- No studies examined PD interactions following perianal application of DTZ cream.

Dosage selection for the pivotal studies

No formal dose ranging studies were submitted. However, two doses of DTZ cream (DTZ 2% and 4%) were included in the treatment arms of the pivotal study DAF09.

Efficacy

Evaluator's conclusions on efficacy

Clinical efficacy was assessed in the single pivotal DAF09. The supportive Phase II study DAF001 has no value for reasons discussed. The supportive Phase II study 99CFIII was not placebo controlled, and better healing rates and pain relief were reported in the GTN active comparator arm. Due to the lack of a placebo arm, these data can also be discounted for evaluation purposes.

The primary objective was achieved in the only pivotal Phase III, randomised, double blind, placebo controlled study (DAF09) involving 440 subjects, with a statistically significant benefit for DTZ 2% in terms of AF pain relief assessed by NRS. However, the benefit for DTZ 2% in NRS scores was marginal (less than 0.43 NRS units on an eleven point scale) and not clinically meaningful. The sponsor argues that the treatment difference in favour of DTZ 2% cream was clinically meaningful, citing the internal consistency of secondary outcomes, supporting studies, and literature studies. These arguments are tenuous but, even if they are accepted, they would support statistical robustness and not clinical significance. A responder analysis based on an accepted clinically significant treatment difference would have been useful but this was not done.

There was a trend towards increased AF healing with topical DTZ 2% compared with placebo. However, as in previous studies, the treatment difference was modest and not statistically significant. Improved pain scores with DTZ 2% might have resulted from a chance occurrence of increased AF healing rather than pharmacological reductions in anal sphincter tone. Overall, the marginal outcomes of the single pivotal study could have occurred by chance despite comparable outcomes in the DTZ 4% group. Even if the observations reflect a true therapeutic effect, they should be confirmed with a second, adequately powered study, preferably with AF healing as the primary endpoint.

Safety

Studies providing safety data

The following studies provided evaluable safety data:

Pivotal efficacy studies

In the pivotal efficacy study DAF09, the following safety data were collected:

- General AEs were elicited by asking a standard non leading question. AEs were recorded via the daily interactive voice response system (IVRS) and paper diaries. AEs were coded and reported using the MedDRA classification.
- With the exception of local AEs related to AF, no AEs of particular interest were identified.
- Standard laboratory tests were performed at local laboratories. Haematology and biochemistry testing was performed centrally.

Pivotal studies that assessed safety as a primary outcome

None submitted.

Dose-response and non-pivotal efficacy studies

The non-pivotal efficacy Study 99CFAIII provided additional safety data in subjects with AF. Data from DAF001 are reported for completeness but they are not evaluable for reasons discussed.

Other studies evaluable for safety only

Studies VEN307-DERM-001 and VEN307-DERM-002 provided assessments of local tolerability in healthy subjects.

Patient exposure

In the pivotal study DAF09, mean exposure to DTZ 4% was 54.7 days in 156 subjects. Mean exposure to DTZ 2% was 55.3 days in 154 subjects.

Safety issues with the potential for major regulatory impact

Liver toxicity

No issues identified.

Haematological toxicity

No issues identified.

Serious skin reactions

No issues identified. Rare cases of allergic skin reactions such as exanthematous pustulosis have been identified in the literature.

Cardiovascular safety

No issues identified.

Unwanted immunological events

No issues identified. Rare cases of hypersensitivity to diltiazem hydrochloride have been identified in the literature.

Evaluator's conclusions on safety

The recommended total daily dose of diltiazem hydrochloride delivered in DTZ 2% cream is approximately 25 mg, compared with the recommended oral dose range of 180-480 mg with 120 mg in elderly. Oral administration typically provides a therapeutic range of 50-200 ng/mL. This contrasts with a median plasma concentration of 1 ng/mL, and a maximum concentration of 12.6 ng/mL reported in the DTZ 2% arm of the pivotal study DAF09. The potential for systemic effects is very low but it can't be completely discounted in vulnerable groups such as the elderly, subjects with hepatic or renal impairment, and subjects with unsuspected cardiac conduction abnormalities. DTZ 2% is contraindicated for bradycardia, 2nd or 3rd degree heart block, sick sinus and LVF. No significant vital sign or ECG changes were detected in Study DAF09; however, abnormalities such as 2nd degree heart block may be silent and unsuspected. There is also a potential risk of drug interactions with a range of medications listed, notably with dantrolene. The frequency of headache was similar in the active and placebo treatment groups in keeping with low systemic exposure to diltiazem with DTZ 2% cream.

Preclinical studies of diltiazem hydrochloride have demonstrated a potential for embryo lethality and teratogenicity. This is a significant concern as AF is more common in females, many of childbearing potential. All single contraceptive methods have a failure rate of at least 1% so this is a serious potential risk in subjects with an otherwise non-life threatening condition.

The most common adverse reactions to DTZ 2% cream are related to local tolerability at the application site. In Study DAF09, proctalgia with an overall incidence of 43% was reported equally commonly in the active and placebo groups, suggesting a relationship to the underlying condition. The other events occurring more commonly in the active treatment groups compared with placebo were anal pruritus and anorectal discomfort. Anal pruritus was reported in 14.9% and 7.7% of the DTZ 2% and placebo groups, respectively, while anorectal discomfort was reported in 13.6% and 5.8% of each group, respectively. While symptomatic discomfort was more common in the active groups in DAF09 compared with placebo, no significant skin irritation was reported in studies VEN307-DERM-001 and VEN307-DERM-002 in healthy subjects. No AEs related to local tolerance were reported in the healthy subjects although at least some would be expected (see Clinical Questions). Severe skin sensitivity reactions described with oral diltiazem have been reported in the literature but none were reported in the DTZ 2% cream studies presented.

In the pivotal study, the majority of subjects were White females with a mean age of 43 years. However, males were well represented and subjects up to the age of 84 years were studied. No formal subgroup analyses were performed and numbers would be low in each group. However, numerous literature studies have been conducted in all geographic areas and races without evidence of differences in the disorder or in diltiazem metabolism or tolerability.

Overall, DTZ 2% is well tolerated. Compared with placebo, only anal pruritus and anorectal discomfort have been identified as common adverse reactions. With isolated exceptions, such events are mild to moderate in severity and resolve once treatment is stopped.

First round benefit-risk assessment**First round assessment of benefits**

The benefit of Anoheal in the proposed usage is:

- Statistically significant but marginal reduction in AF related pain. However, a treatment difference of <1 NRS unit on an eleven point scale cannot be considered clinically meaningful.

First round assessment of risks

The risks of Anoheal in the proposed usage are:

- Potential cardiac risks in subjects with undetected ECG abnormalities or borderline left ventricular function. Abnormalities such as second degree AV block may exist in otherwise asymptomatic subjects. The cardiac risk is low because systemic diltiazem exposure is markedly lower than that associated with oral administration. However, risk cannot be discounted in isolated elderly subjects, or those with unidentified significant hepatic or renal impairment.
- Drug interactions with medications outlined in the proposed PI. The risk is low as systemic exposure to diltiazem hydrochloride is low.
- Hypersensitivity to the active substance, its metabolites, or any of the excipients.
- Potential teratogenicity in the event of unplanned or unsuspected pregnancy. Women of childbearing potential, unless using adequate contraception, were excluded from study DAF0001. However, a pregnancy did occur during the study and some contraceptive failures must be expected in routine clinical practice.
- Anorectal discomfort, proctalgia, and anal pruritus are commonly observed. The symptoms are usually mild to moderate but significant local skin reactions may occur. Serious systemic skin sensitivity reactions including exanthematous pustulosis have also been reported in the literature.
- Administration site pain is reported in a small percentage of subjects.

First round assessment of benefit-risk balance

The benefit-risk balance of Anoheal, given the proposed usage, is unfavourable.

Compared with placebo, no clinically meaningful benefit in terms of pain relief has been demonstrated. The potential risks of Anoheal are generally mild to moderate, mostly related to local application site intolerance. However, severe or serious outcomes related to hypersensitivity reaction, allergic reactions or cardiac events may rarely occur.

First round recommendation regarding authorisation

Authorisation for Anoheal for the proposed usage is not recommended. Insufficient clinical efficacy has been demonstrated in the single pivotal study presented.

Clinical questions

There were no questions in reference to the pharmacokinetics and pharmacodynamics.

Efficacy

- Question 1: In the pivotal Study DAF09, the NRS treatment difference for DTZ 2% compared with placebo at Week 4 was -0.43, notably less than the 1 unit difference adopted in the sample size calculation. Please state if the 1 unit NRS difference was or was not identified a priori as a clinically meaningful treatment difference for NRS.

- Question 2: Please give a justification for adopting 97.5% CIs rather than conventional testing methods to control for multiplicity in Study DAF09.
- Question 3: In the DAF09 protocol introduction, it is stated that pain relief is as important as healing. Pain relief without healing provides temporary palliation but healing must be considered superior as it is by definition curative. Please outline the arguments provided by the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the Swedish authority in support of pain relief rather than healing as a primary efficacy outcome in the pivotal Study DAF09.
- Question 4: In the Clinical Overview, the sponsor proposes that the statistically significant reductions in NRS scores in favour of DTZ 2% cream in study DAF09 are also clinically significant. However, the arguments rely largely on the internal consistency of secondary outcomes other than pain relief, and on studies in the literature, themselves nearly all marginal, inconsistent and unconvincing. The sponsor has provided a reference supporting the use of NRS for measuring treatment responses to AF pain.²⁵ However, this reference is largely a general statement of value and there is no description of the validity, reliability and sensitivity of this method. Nor is an accepted definition of the clinical significance of changes in NRS scores provided. Please provide a primary reference for the NRS method and use it to justify the clinical significance of the marginal (but statistically significant) treatment benefit in favour of DTZ 2% cream. It would also be useful to provide a responder analysis based on the nominated clinically significant treatment difference in NRS score.
- Question 5: In DAF09, there were marginal benefits in terms of pain relief and healing (ignoring levels of statistical significance). Was pain relief associated with healing? What were the treatment emergent changes in pain scores in subjects who did/did not heal?
- Question 6: Have manometry studies of anal sphincter tone been conducted using the DTZ 2% cream formulation proposed for marketing? If so, what percentage reductions in pressure were achieved?

Safety

- Question 7: Please confirm that the cream formulations applied in Studies DAF09, VEN307-DERM-001 and VEN307-DERM-002 are identical to the formulation proposed for marketing. Was propylene glycol a component in each study?
- Question 8: In the DTZ 2% group of DAF09, anal pruritus and anal discomfort were in 14.9% and 13.6% of subjects, respectively, compared with 7.7% and 5.8% in the placebo group, respectively. However, in study VEN307-DERM-001, only five AEs (arthralgia, dizziness, and headache) were reported in 202 healthy subjects, and no AEs were reported in VEN307-DERM-002. While ADRs are obviously less common, typically the majority of healthy subjects in any Phase I study report at least one AE in response to a standard non leading question. Please explain how AEs were elicited, documented and assessed in the healthy subject studies.

Second round evaluation

Details of sponsor's responses to clinical questions and evaluator's subsequent comments are contained in Attachment 1.

²⁵ Dworkin RH, et al. Core outcome measures for chronic pain clinical trials: IMPACT recommendations. *Pain* 113: 9-19 (2005).

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Anoheal in the proposed usage are unchanged from those identified in the first round.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Anoheal in the proposed usage were assessed to be unchanged from those identified in the first round.

Second round assessment of benefit-risk balance

After consideration of the responses to clinical questions, the benefit-risk balance of Anoheal in the proposed usage were assessed to be unchanged from those identified in the first round.

Second round recommendation regarding authorisation

Authorisation for Anoheal for the proposed usage is not recommended.

Insufficient clinical efficacy has been demonstrated in the single pivotal study presented and the benefit/risk assessment remains negative. The sponsor proposes that any statistically significant improvement in pain control is clinically meaningful, however small it may be. This view is not supported by experts in the field who suggest that treatment differences of at least 1-2 NRS units may be considered clinically important. The mean treatment difference of <1 NRS unit in the pivotal study cannot be considered clinically meaningful and the sponsor has put forward no evidence to support the contrary view.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted an EU-RMP Version 1 (dated 6 February 2014, DLP 30 January 2014) and Australian Specific Annex (ASA, version unspecified, undated), which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 2.

Table 2: Ongoing safety concerns.

Ongoing safety concerns	
Important identified risks	<p>Hypersensitivity to the active substance or to any of the excipients.</p> <p>Pregnancy - Teratogenic risk potential.</p> <p>Lactation – Cardiodepressant and other pharmacological effects on the infant.</p> <p>Safety with concomitant administration of dantrolene infusion, due to the risk of ventricular fibrillation.</p> <p>Safety in subjects with cardiovascular disease history of acute myocardial infarction, severe bradycardia, evidence of left ventricular failure, second or third degree AV block and atrial fibrillation or flutter with Wolff-Parkinson-White syndrome . Diltiazem may cause a worsening of the underlying cardiac dysfunction.</p>
Important potential risks	<p>Increased plasma concentrations of diltiazem may be observed in the elderly and patients with renal or hepatic insufficiency, leading to potentially increased hazards in these patients.</p> <p>The depression of cardiac contractility, conductivity and automaticity as well as the vascular dilatation associated with anaesthetics may be potentiated by calcium channel blockers.</p> <p>Drug interactions</p>
Missing information	None

RMP reviewer comment

Most of the above safety concerns relate to the possibility of systemic absorption of the topical agent. The RMP states that “systemic exposure is low”, however this is subject to assessment by the clinical and/or nonclinical evaluators.

Subject to the evaluation of the nonclinical and clinical aspects of the Safety Specification, the summary of safety concerns is considered to be acceptable.

Pharmacovigilance plan**Proposed pharmacovigilance activities**

Routine pharmacovigilance activities are proposed. No additional activities are proposed.

RMP reviewer comment

The sponsor’s proposal to employ routine pharmacovigilance, given the proposed use, is acceptable from an RMP perspective. If the potential for systemic absorption and therefore

systemic effects is not considered to be low by the clinical evaluator, the pharmacovigilance plan may need to be reassessed.

The ASA should include confirmation that the local pharmacovigilance organisation is operating in accordance with current TGA guidelines for pharmacovigilance responsibilities of sponsors. A summary of the routine pharmacovigilance activities carried out in Australia should also be included.

Risk minimisation activities

Sponsor's conclusion in regard to the need for risk minimisation activities

Routine risk minimisation only is proposed. No additional risk minimisation activities are proposed.

RMP reviewer comment

The sponsor's proposal to employ routine risk minimisation activities only is acceptable. If the potential for systemic absorption and therefore systemic effects is not considered to be low by the clinical evaluator, the risk minimisation plan may need to be reassessed.

Reconciliation of issues outlined in the RMP report

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

Recommendation #1 in RMP evaluation report

Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated Section 31 request and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

Sponsor response

The sponsor can currently only provide a response regarding clinical aspects as we have not yet received the nonclinical evaluation report at the time of writing. This was communicated to the sponsor that it would be available in mid-January 2016. However, at the time this response was sent, we had still not yet received this report.

Evaluator's comment

The sponsor's response is noted. The nonclinical report has raised an issue requiring a revision to the RMP.

Recommendation #2 in RMP evaluation report

In the Section 31 response the sponsor should clarify whether this product is registered and supplied in any other jurisdiction, EU or otherwise.

Sponsor response

This product is not yet registered in any other jurisdiction. It is also available as an unapproved medicine in the UK and EU, generally ranging in volume from 4000-6000 units per month.

Evaluator's comment

The sponsor's response is noted.

Recommendation #3 in RMP evaluation report

The ASA states “It is a completely new chemical entity”. This is incorrect and should be amended to accommodate this extension of indications application.

Sponsor response

Please refer to updated ASA.

Evaluator’s comment

This is acceptable from an RMP perspective.

Recommendation #4 in RMP evaluation report

The sponsor should update the ASA to ensure it includes information consistent with the ASA template guidance published on the TGA website.

Sponsor response

Please refer to updated ASA.

Evaluator’s comment

The sponsor’s response is noted.

Recommendation #5 in RMP evaluation report

The sponsor’s proposal to employ routine pharmacovigilance, given the proposed use, is acceptable from an RMP perspective. If the potential for systemic absorption and therefore systemic effects is not considered to be low by the clinical evaluator, the pharmacovigilance plan may need to be reassessed.

Sponsor response

The potential for systemic absorption is considered to be low by the clinical evaluator therefore the PV plan does not need to be reassessed.

Evaluator’s comment

The sponsor’s response is noted.

Recommendation #6 in RMP evaluation report

The ASA should include confirmation that the local pharmacovigilance organisation is operating in accordance with current TGA guidelines for pharmacovigilance responsibilities of sponsors. A summary of the routine pharmacovigilance activities carried out in Australia should also be included.

Sponsor response

Please refer the appendix of this response.

Evaluator’s comment

The document provided is specific to New Zealand. The evaluator maintains that the ASA should include a confirmation that the local pharmacovigilance organisation is operating in accordance with current TGA guidelines for pharmacovigilance responsibilities of sponsors.

Recommendation #7 in RMP evaluation report

The sponsor’s proposal to employ routine risk minimisation activities only is acceptable. If the potential for systemic absorption and therefore systemic effects is not considered to be low by the clinical evaluator, the risk minimisation plan may need to be reassessed.

Sponsor response

Please refer to response to RMP evaluation.

Evaluator's comment

The sponsor's response is noted.

Summary of recommendations**Outstanding issues***Issues in relation to the RMP*

The ASA should include a statement that the local pharmacovigilance organisation is operating in accordance with current TGA guidelines for pharmacovigilance responsibilities of sponsors. The information provided in response to this recommendation appears to be New Zealand specific.

Appropriate version control should be applied to the ASA to cater for future revisions (new recommendation).

The nonclinical evaluator has recommended an amendment to the nonclinical safety specification.

Comments on the safety specification of the RMP*Clinical evaluation report*

The Safety Specification in the draft RMP is satisfactory.

The RMP identifies the safety risks and routine risk minimisation measures are identified in the proposed PI and CMI. Routine pharmacovigilance is recommended and no additional activities are planned.

Nonclinical evaluation report

Results and conclusions drawn from the nonclinical program for diltiazem hydrochloride 20 mg/g cream (Anoheal 20 mg/g cream) detailed in the sponsor's draft RMP are in general concordance with those of the nonclinical evaluator, with the exception that next to the heading "Mechanisms for drug interactions", it should state that "Diltiazem is metabolised by CYP3A4 and CYP2D6 and is an inhibitor of CYP3A4."

RMP evaluator comment

The sponsor should make the recommended revision to the safety specification whenever the RMP is next updated.

Key changes to the updated RMP

In their response to the TGA Section 31 requests, the sponsor provided an updated ASA (undated) as annex to the RMP. Key changes from the Round 1 version are summarised.

Table 3: Summary of key changes in the revised ASA.

Summary of key changes in the revised ASA	
ASA	revised to include information as per TGA guidance.

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 sponsor should respond to the outstanding issues listed. Once these issues are satisfactorily addressed the wording for the RMP condition of registration will be provided.

VI. Overall conclusion and risk/benefit assessment

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

Risk-benefit analysis

Delegate's considerations

Chronic anal fissures rarely heal completely without surgical intervention.

The clinical evaluator stated that the proposed usage is not recommended due to the insufficient clinical efficacy demonstrated in the single pivotal study submitted. I agree with the clinical evaluator's statement that Anocream has demonstrated statistically significant but marginal reduction (-0.43) in anal fissure related pain over placebo. However, given that Glyceryl trinitrate ointment (Rectogesic), which is also a vasodilator, was registered by virtue of an over the counter (OTC) quality of evidence (that is, low level) for similar condition proposed for Ano-Cream, the Delegate believes that the application is approvable. The Delegate will also expect the scheduling to be the same as for Rectogesic, that is, Schedule 3 pharmacist-only product. Furthermore, Diltiazem 2% cream has become a useful tool in contemporary medical practice to manage anal fissure. For instance in the UK alone, it is stated that the estimated use of Diltiazem 2% cream as an unlicensed drug (similar to SAS in Australia) is currently approximately 5,000 units per month.

In line with the primary objective of the pivotal study DAF09, it is recommended that the proposed indication be modified to read "Symptomatic pain management of chronic anal fissure".

There are pending Quality, Nonclinical and RMP evaluation issues which must be resolved before the registration of Ano-Cream.

In my opinion, there are no major safety concerns. The clinical evaluator was concerned about the observed symptoms of mild to moderate anal pruritus. The Delegate considers the potential risk of experiencing significantly severe cardiac events, hypersensitivity reactions or systemic drug interactions to be marginal. The rationale is based on the fact that systemic concentration will be very low with topical application. Also, the adverse effects and interactions of oral diltiazem, both as antihypertensive and antianginal medication, are well established and readily managed when arise. It is anticipated that Ano-Cream will have the same Australian categorisation risk as the oral diltiazem preparation, that is, (C), and there are no novel reproductive/teratogenicity concerns raised in the nonclinical evaluation report.

The draft PI requires modifications as suggested in the clinical, toxicological and RMP evaluation reports before finalisation of the application.

Summary of issues

The clinical evaluator found that the "primary objective was achieved in the only pivotal Phase III, randomised, double-blind, placebo-controlled study (DAF09) involving 440 subjects, with a statistically significant benefit for DTZ 2% in terms of AF pain relief assessed by NRS. However, the benefit for DTZ 2% in NRS scores was marginal (less than

0.43 NRS units on an eleven point scale) and not clinically meaningful". The sponsor explained that "the treatment difference in favour of DTZ 2% cream was clinically meaningful, citing the internal consistency of secondary outcomes, supporting studies, and literature studies". The clinical evaluator stated that "the sponsor's explanations are tenuous but, even if they are accepted, they would support statistical robustness and not clinical significance. A responder analysis based on an accepted clinically significant treatment difference would have been useful but this was not done".

The clinical evaluator further stated that "there was a trend towards increased AF healing with topical DTZ 2% compared with placebo. However, as in previous studies, the treatment difference was modest and not statistically significant. Improved pain scores with DTZ 2% might have resulted from a chance occurrence of increased AF healing rather than pharmacological reductions in anal sphincter tone. Overall, the marginal outcomes of the single pivotal study could have occurred by chance despite comparable outcomes in the DTZ 4% group. Even if the observations reflect a true therapeutic effect, they should be confirmed with a second, adequately powered study, preferably with AF healing as the primary endpoint".

Proposed action

Based on my analysis of the evidence from the submitted data evaluation and contemporary medical practice, the Delegate believes at this stage that the Ano-Cream application is approvable. The latter is subject to resolving all issues which may arise from the Advisory Committee on Prescription Medicines (ACPM) deliberations and finalisation of matters pertaining to the draft PI and RMP to the satisfaction of the TGA.

Request for ACPM advice

- Approvability of the Ano-Cream application based on the Delegate's discussion.
- Acceptability of the modified trade name and indication.
- Advice on any other issues relevant to a decision on whether or not to approve this application.

Response from sponsor

- We propose to change the indication from the original application in line with the delegate's pre ACPM advice to:
Symptomatic pain management of chronic anal fissure.
- The drug substance manufacturing site has a current clearance with an expiry date of 18/03/2019.
- The nonclinical evaluator's comments with respect to the RMP and PI have been incorporated (except for the new recommendation of version control of the ASA).
- The comment "The proposed PI section regarding Pharmacokinetics should specifically state that no clinical trials have examined the absolute bioavailability, distribution, metabolism and PKS of Anoheal in special populations (such as patients with hepatic or renal impairment) following perianal application of DTZ cream" has been addressed.
- Anoheal has been rebranded to "Ano-Cream".
- The comment "Pharmacodynamic effects: The statement in the last sentence of this section is based on hypothesis and it should be reworded as such" has been addressed.

- The comment “Clinical efficacy: The following statement is misleading and it should be removed. It implies a statistically significant benefit for AF healing ($p < 0.05$) but there was no benefit based on the pre-defined $p < 0.025$ significance level. Following treatment for 8 weeks, there was an increase in the number of subjects with healed fissures (defined as complete epithelialisation) in the Anohal 20 mg/g group 31.2% healed compared to the placebo group in which 23.9% healed ($p = 0.0426$)” has been addressed.
- The comment “Contraindications: Calcium channel blockers were prohibited in study DAF09. Consequently, the safety of DTZ 2% cream has not been established in subjects taking oral diltiazem or other calcium channel blockers. Despite the low levels of systemic absorption of diltiazem, it would appear prudent on safety grounds to contraindicate DTZ 2% cream in these subjects who already have therapeutic diltiazem levels. Moreover, superior efficacy for DTZ 2% cream compared with placebo has not been established in subjects receiving diltiazem or calcium channel blockers. DTZ 2% cream is contraindicated in women of child bearing potential. However, its use under precaution is advised in women of childbearing potential who are using effective contraception. The risks associated with DTZ 2% cream clearly outweigh the possible benefit of temporary AF pain. As such, the wording of the precaution should be strengthened and include an accepted definition of effective contraception” has been addressed.
- The comment “Paediatric population: The statement referring to the EMA should be deleted. It should be replaced with a statement that DTZ 2% cream has not been studied in children” has been addressed.
- Regarding the outstanding issues to the RMP, please be advised that the inclusion of a statement in the ASA that “The local pharmacovigilance organisation is operating in accordance with current TGA guidelines for pharmacovigilance responsibilities of sponsors. The information provided in response appears to be New Zealand specific” has been addressed.
- The comment appropriate version control should be applied to the ASA to cater for future revisions is noted by AFT and will be incorporated when the ASA is revised as “V2” and incorporate the date of the update.
- The nonclinical evaluator’s comment regarding the amendment to the non-clinical safety specification that “next to the heading ‘Mechanisms for drug interactions’ it should state that ‘Diltiazem is metabolised by CYP3A4 and CYP2D6 and is an inhibitor of CYP3A4’ ” has been addressed.
- Regarding the comment “The Elderly sub-section of the Dosage and Administration section should cross-reference the Use in Elderly precaution” has been addressed.
- Regarding the comment “The revised CMI does not specifically address the recommendation made by the evaluator regarding topical nitrates” has been addressed.
- Regarding the proposed clinical trial section to follow the Pharmacology section in the PI, please refer to the updated PI (both annotated and clean versions).
- With regard to the suggestion for the PI, please refer to the updated overdose section of the PI provided in this response.
- Regarding the suggestion for an update to the ‘adverse effects’ section of the PI, please refer to the update PI provided as part of this pre ACPM response.

Advisory Committee considerations

The ACPM resolved to recommend to the TGA Delegate of the Secretary that taking into account the submitted evidence of pharmaceutical efficacy, safety and quality, Ano-Cream (Anoheal initially proposed) cream containing 2% w/w of diltiazem hydrochloride was considered to have an overall negative benefit-risk profile.

In making this recommendation, the ACPM:

- advised that the evidence provided in the sponsor's submission did not satisfactorily establish the efficacy of diltiazem hydrochloride cream and that any clinical benefit was marginal;
- was of the view that the sponsor should provide further studies that demonstrate a meaningful clinical benefit with more objective evidence (such as using anal manometry or proctometry);
- advised that studies on acute anal fissure may also be useful.

Specific advice

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

- Approvability or otherwise of the Anocream application based on the Delegate's discussion.

The ACPM was of the view that, at the present time, diltiazem hydrochloride cream was unapprovable. The ACPM considered that there was no evidence available supporting diltiazem in the healing of anal fissure. The ACPM noted that the only product currently available with evidence in healing is GTN.

The ACPM noted the emphasis of pain reduction in the registration of topical diltiazem for anal fissure, however from evidence submitted, a 0.43 point reduction in pain on a 11-point scale presented a very marginal clinical benefit at best.

The ACPM also noted that no objective studies had been conducted to support the clinical efficacy of topical diltiazem for anal fissure, with the notable the absence of anorectal manometry studies which could provide more objective evidence of clinical benefit and/or give power to the results of the Phase III trial. Currently, the only direct evidence of a relaxant effect was in vitro data from sheep smooth muscle.

From the same Phase III trial that produced the 0.43 point pain reduction, the ACPM also noted that the pain reduction was noticeable by 8 weeks, but this follows the natural history of a healing anal fissure anyway (approximately 4-6 weeks), questioning the clinical efficacy of diltiazem either for pain relief or smooth muscle dilatation. The ACPM queried whether smooth muscle dilatation should in theory be an acute effect of diltiazem application. The ACPM was also concerned that in the design of the study, patients with chronic constipation as a cause or symptom of anal fissure were excluded. The ACPM noted that chronic constipation is very likely to be the primary cause behind anal fissure development and a key symptom (other than pain on defecation).

The ACPM also noted expert opinion on diltiazem being a more tolerable option to GTN in patients severely affected by AEs such as headache. The ACPM was still of the view that GTN unlike diltiazem has a more substantial amount of supportive evidence behind its use, and the presence of AEs such as headache with GTN use may be due to poor patient education regarding the dosing of GTN (volume of agent used) and method of application.

- Acceptability or otherwise of the modified trade name and indication as per the reasons specified in the delegate's discussion.

The ACPM advised that 'Ano-Cream' is preferable to 'Anoheal' as there is no evidence of healing properties of diltiazem.

- Advice on any other issues relevant to a decision on whether or not to approve this application.

The ACPM was concerned about use in pregnancy as anal fissures are common in this population group. The ACPM noted that the PI states that diltiazem is Pregnancy Category C and that diltiazem should not be used during pregnancy or in women of child-bearing potential not using effective contraception (hormonal and barrier methods).

Outcome

Based on a review of quality, safety and efficacy, TGA rejected the registration of Ano-Cream (diltiazem as hydrochloride 2% w/w cream) for the proposed indication of

The treatment of chronic anal fissure; specifically the reduction of pain associated with anal fissure.

Reasons for the decision

Efficacy

It was not established that Ano-Cream (diltiazem 2% w/w cream) provided a clinically significant benefit in terms of reduction in pain in patients with chronic anal fissure in the submitted pivotal study: "Phase III trial (DAF09), a randomised, double-blind, placebo-controlled, study of the safety and efficacy of two strengths formulations of diltiazem cream (2% w/w and 4% w/w) in subjects with chronic anal fissure (AF) and AF-related pain".

The primary efficacy parameter in that study was change from baseline in average of worst anal pain (assessed on an 11 point numerical rating scale) associated with or following defaecation at Week 4. The average reduction from baseline to Week 4 in average pain scores for subjects who applied diltiazem 2% w/w cream was -2.63, from a baseline average pain score of 6.21. The average reduction from baseline to Week 4 for patients who applied placebo cream was -2.20 from a baseline average pain score of 6.38. Thus, the absolute difference in mean change in pain scores for these two treatment groups was 0.43 (ITT analysis, BOCF). This small absolute difference in mean pain scores for the two treatments equates to an insignificant clinical benefit. Just as part of the evaluated data, it is notable that the situation for diltiazem 4% w/w cream compared with placebo was 0.44 at Week 4, indicating lack of cream strength application response proportionality. At Week 8, the further reductions in NRS scores from baseline observed in each treatment group (-3.69,-3.65 and -3.03 respectively for diltiazem 2%, diltiazem 4% and placebo) essentially reflect that there were no meaningful differences between treatment groups at the Week 8 time course of AF pain relief. Furthermore, the mean pain reduction differences between placebo/diltiazem 2% and placebo/diltiazem 4% were respectively -0.62 and -0.65, again indicating a lack of cream strength application-response proportionality at the Week 8 time course of AF pain relief.

It is noted, as part of the evaluated data, that about 24 to 32% ITT patients in each of the three treatment arms (two active and one placebo) achieved complete AF healing at Week 8; this is a trend which follows the natural history of a healing anal fissure (approximately 4-6 weeks). The design of the pivotal study in the absence of any supportive data could also be biased towards subjective interpretation. Objective data outcomes in the form of ano-rectal manometry or proctometry studies could have provided more objective evidence of clinical benefit and/or give power to the results of the Phase III trial.

Furthermore, the theory behind the proposed clinical indication is that diltiazem acts as a smooth muscle relaxant. However, the submission included only in vitro evidence of a relaxant effect of diltiazem in the sheep smooth muscle. At any case, smooth muscle relaxation due to diltiazem could theoretically occur only on acute application, suggesting that study of diltiazem in acute anal fissure may be warranted.

The pivotal study was weakened in its design by the exclusion of patients with chronic constipation as a cause or symptom of anal fissure given that, chronic constipation is very likely to be the primary cause behind anal fissure development and a key symptom (other than pain on defecation).

Taken as a whole, the available evidence is insufficient to demonstrate a clinically significant benefit of diltiazem 2% cream in the symptomatic management of pain associated with chronic anal fissure.

Final outcome

Following the initial decision described above, the sponsor sought a review under the provisions of Section 60 of the Therapeutics Goods Act 1989 ("the Act"). The Delegate of the Minister for the review noted that paragraph 25(1)(d) of the Act, which requires the goods to be evaluated with regard to whether the quality, safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established, is of particular relevance.

The initial proposed indication for Ano-Cream (diltiazem as hydrochloride 2% w/w cream) was:

The treatment of chronic anal fissure; specifically the reduction of pain associated with anal fissure.

This was later amended to:

Symptomatic pain management of chronic anal fissure.

Transcript of the reasons for the delegate of the minister's decision

Pursuant to subsection 60(3)(a) of the Act, the Delegate of the Minister's decision has decided to confirm the initial decision to refuse to register Ano-Cream (diltiazem as hydrochloride 2% w/w cream) for the symptomatic management of chronic anal fissure as proposed on the grounds that the submission did not satisfactorily establish the efficacy of diltiazem hydrochloride cream for the proposed indication.

Findings of fact

The application to register Ano-Cream has depended largely (but not solely) on the results of the pivotal Phase III study DAF09. The Delegate of the Minister's decision believes that it is common ground that in the ITT population of the primary efficacy outcome, the average NRS score for worst anal pain with or following defecation at Week 4 decreased over the treatment period in each treatment group. At Week 4, the adjusted mean changes (+/- SD) from baseline were -2.64 (0.15), -2.63 (0.15), and -2.20 (0.15) in the DTZ 4%, DTZ 2%, and placebo groups, respectively. The adjusted differences from placebo were -0.44 (97.5% CI: <-0.06, p = 0.011) in the DTZ 4% group, and -0.43 (97.5% CI: <-0.06, p=0.012) in the DTZ 2% group. A range of sensitivity analyses allowing for missing data confirmed the conclusions of the primary analysis. At Week 8, there were further reductions in NRS scores in each treatment group. The adjusted mean changes (+/- SE) from baseline were -3.69 (0.16), -3.65 (0.16), and -3.03 (0.15) in the DTZ 4%, DTZ 2%, and placebo groups, respectively. The adjusted differences from placebo were -0.65 (97.5% CI: <-0.25, p = 0.0008) in the DTZ 4% group, and -0.62 (97.5% CI: <-0.21, p=0.002) in the DTZ 2% group.

The clinical evaluator, the ACPM, and the Delegate of the Secretary have all taken the view that although these changes are statistically significant, they are not clinically significant and do not demonstrate a degree of efficacy that would be meaningful to prescribing doctors or their patients.

The delegate of the minister's consideration of the sponsor's submission

The Delegate of the Minister deals in turn with each of the matters that you have raised in your Request for Reconsideration. In order to bring related matters together, the Delegate of the Minister has varied the order of the matters.

Sponsor's request

The sponsor's request states that:

- *A key element is that this treatment is primarily utilised by colorectal surgeons. The assessment process has, to our knowledge, not involved any input from this group which does have the required specialist knowledge. Accordingly, the conclusions regarding lack of clinically meaningful efficacy are at odds with the trial data and their views.*
- *With regard to the results of Study DAF09: "clinical experts in the field state that this is a clinically meaningful effect."*

Response

The Delegate of the Minister has noted that the clinical evaluation (first round) requested the sponsor please:

provide a primary reference for the NRS method and use it to justify the clinical significance of the marginal (but statistically significant) treatment benefit in favour of DTZ 2% cream. It would also be useful to provide a responder analysis based on the nominated clinically significant treatment difference in NRS score.

The clinical evaluation notes that a lengthy response was provided and accepts that the value of the NRS as a measurement tool has been justified. The clinical evaluation (second round) draws attention to recommendations that thresholds for a minimal, moderate, and substantial improvements are 1 unit (or 10-20%), 2 units (or 30-36%), and 4 units ($\geq 50\%$) NRS, respectively. The clinical evaluation goes on to say that the sponsor had noted:

that patients in the diltiazem 2% group did achieve a mean reduction of at least 2 units (2.63 units or 42%), thus meeting the IMMPACT criteria.

The Delegate of the Minister agrees with the clinical evaluation that:

This argument is unacceptable as the mean difference compared with placebo was only -0.43 units.

The Delegate of the Minister also agrees with the clinical evaluation (second round) that:

The responder analysis in patients achieving ≥ 1 unit reduction is not convincing. The primary endpoint was mean NRS scores for worst anal pain at Week 4 in the ITT population. At Week 4 in the responder analysis, the odds ratio compared with placebo was 1.399 but this was not statistically significant ($p = 0.101$).

The Delegate of the Minister has noted that in the sponsor's response it is stated that:

Post-hoc analysis of DAF09 data shows 2% w/w diltiazem hydrochloride cream shows a significant ($p = 0.0120$, 2.5% significance level) positive difference for the average score of the worst anal pain associated with or following defaecation at week 8 when compared to placebo (see table 11 in 53512). This offers a clinically meaningful result in support for the indication of the reduction of pain associated with chronic anal fissure. Furthermore, it should be noted that the observed

difference was not related to differences in healing since it was associated with non-healers, as per table 11 in the post-hoc data.

The Delegate of the Minister draws attention to the fact that although statistically significant the adjusted difference from placebo in pain score was -0.50. The Delegate of the Minister does not consider this to be clinically meaningful. The Delegate of the Minister further notes that across Tables 1 to 12 in the post hoc analysis, the adjusted difference from placebo ranges from 0.57 (favouring placebo) to minus 0.58 (favouring diltiazem 2% cream). Not all of the differences in the twelve analyses were statistically significant. The Delegate of the Minister does not consider the differences to be clinically significant in favour of diltiazem hydrochloride 2% cream.

Sponsor's request

The sponsor's request states that:

- *There is a similar magnitude of effect from the registered product of topical GTN. Both the specific data and overall extensive literature data support this view (please see figure).*

Response

The Delegate of the Minister has noted that the figure cited is a graph titled "Reduction in Pain Scores over 8 week treatment period for *chronic* anal fissure." Coloured lines on the graph have been used to convey the result for diltiazem 2% from four named published studies and the submitted Study 99CFIII.

The Delegate of the Minister has reviewed the details of those five studies. The results of this review are provided in the annex to this letter and should be read as part of this letter. The following matters have been identified:

- Three of the five reports do not include declarations concerning potentially conflicting interests or sources of funding;
- Two of the five reports do not include evidence of approval by an ethics committee or equivalent body;
- In four of the five reports the Visual Analogue Scale is not described in detail and there is no evidence provided that it was a validated instrument. In the fifth study,²⁶ a Verbal Rating Scale was used. The Scale is not described in detail and there is no evidence provided that it was a validated instrument;
- In two of the five studies the subjects were not randomised or the randomisation was by an inadequate method. In a third study,²⁷ there are reasonable grounds for questioning whether the labelling put the blinding at risk.
- In two studies, diltiazem ointment was used. The relationship of the clinical efficacy of such a product to the cream proposed for marketing is unknown;
- In three studies a diltiazem cream was used but the relationship of the clinical efficacy of such a product to the cream proposed for marketing is unknown;
- In three of the five studies the comparator product was a glyceryl trinitrate ointment. In none of these studies was the comparator the Australian registered product Rectogesic Ointment 0.2%. Further, in none of these three studies was the comparator ointment said to be a product registered or licensed in the UK or Sweden, where registration is also being sought. In one study the comparator was a glyceryl trinitrate

²⁶ Hashmi F and Siddiqui FG. Diltiazem (2%) Versus Glyceryl Trinitrate Cream (0.2%) in the Management of Chronic Anal Fissure. *J Coll Physicians Surg Pak*. 19: 750-753 (2009).

²⁷ Ala S, et al. Comparison of captopril (0.5%) cream with diltiazem (2%) cream for chronic anal fissure: a prospective randomized double-blind two-centre clinical trial. *Colorectal Disease* 18: 510-516 (2015).

cream. The relationships of the clinical efficacies of the comparators to the registered products are unknown. In the fifth study, the comparator was an experimental captopril cream. The relationship of the clinical efficacy if any of this cream to the registered glyceryl trinitrate ointments is unknown;

- Some of the results concerning safety from the submitted Study 99/CFA/III have been published. Differences in the descriptions of the inclusion and exclusion criteria between the submitted report and the published paper have been identified.
- Concerning Study 99/CFA/III, the analysis presented in the submitted report appears to not be consistent with the description of the method for Intention to treat LOCF analysis for anal pain in the study report.
- Concerning the figure, this review has raised difficulties in reconciling what is shown in that figure with the results of four of the five studies.
- The figure also includes a line with six data points each marked with an asterisk. The purpose of that line and how it has been derived are not explained in your Request document. The Delegate of the Minister believes it is likely to be a form of averaged results from the five studies. The Delegate of the Minister has not pursued this matter further because, having regard to the deficiencies identified above, it is unlikely to be meaningful.

In summary, the figure is based on the results for various DTZ 2% products extracted from four published papers and a submitted clinical study report. The reports of the five studies have identified issues concerning inadequacy of randomisation and of blinding with the consequent likelihood of bias in favour of the diltiazem products. Such an analysis lacks the robustness of a well conducted randomised double blinded comparative clinical trial and the Delegate of the Minister therefore places little weight on the figure and the associated comments.

The Delegate of the Minister takes this opportunity to point out that TGA has for many years had a well-defined procedure for sponsors to have literature reports taken into account as evidence, including in “Mixed applications” consisting of a combination of complete study reports of limited clinical studies carried out by the applicant and supported by bibliographic references. In undertaking this review, the Delegate of the Minister has not enforced those requirements.

Sponsor's request

The sponsor's request states that:

- *The data submitted as part of the APCM response included data on the efficacy of diltiazem compared to GTN 0.2%: no statistically significant difference was observed in the mean change in pain scores between baseline and the end score in most of the literature and clinical trials provided, except one which was in favour of DTZ 2% (see below).*
- *This suggests very little or no difference in the efficaciousness between the two treatment options for the overall reduction of pain associated with chronic anal fissure. However a key point is the lack of headache in the DTZ group in comparison with GTN.*

Response

The Delegate of the Minister has noted that this table presents data from seven clinical studies. Five of the clinical studies are those discussed above in the concerning figure. The other two studies are those of Bielecki and Kolodziejczak²⁸ and Sanei et al.²⁹ The

²⁸ Bielecki K, Kolodziejczak M. A prospective randomized trial of diltiazem and glyceryltrinitrate ointment in the treatment of chronic anal fissure. *Colorectal Dis.* 5: 256-257 (2003).

tabulation indicates that neither paper includes the baseline and end scores, precluding any critical appraisal of these studies. It is noted that these studies are not included in the figure.

The data submitted on the efficacy of diltiazem 2% cream compared with GTN 0.2% do not relate to the glyceryl trinitrate ointment registered in Australia or to the glyceryl trinitrate products registered or licensed in the UK or Sweden, where registration is also being sought. Such data are insufficient to cause me to set aside the results of your pivotal study DAF09 conducted with the formulation proposed for registration which failed to demonstrate a clinically significant response compared with placebo. The Delegate of the Minister has given consideration to the proposition that a product with fewer or less severe adverse effects including headache than glyceryl trinitrate ointment would be valuable, but that can only be so when the product has demonstrated clinical efficacy.

Sponsor's request

The sponsor's request states that:

- *It appears that that the clinical evaluator has assessed the data as if the patients enrolled in the pivotal study suffered from acute anal fissures (AAF). In the protocol for the clinical trial DAF09 it is clearly stated as an inclusion criterion that patients with at least a 4-week history of painful anal fissure prior to screening, where anal fissure-related pain associated with, or following defaecation is experienced at least twice a week for the 4 weeks prior to screening, with an average of ≥ 3 on an 11-point NRS scale, will be enrolled in the study. Patients in this study had an anal fissure present for a period of at least 4 weeks prior to commencement of treatment and were therefore not suffering from acute, but rather chronic, anal fissure.*
- *Further, the suggestion by the clinical evaluator that acute anal fissure be trialled is incorrect, since acute and chronic anal fissure are different indications.*

Response

The Delegate of the Minister is satisfied that the data and information considered relates to chronic anal fissure.

Sponsor's request

The sponsor's request states that:

- *The Phase III trial is not stand alone. DAF09 was supported by a comprehensive clinical package including the Phase II study DAF0001 in which anal manometry was performed. In DAF0001, DTZ 2% resulted in a mean decrease in anal sphincter pressure of 42.4% and a median decrease of 54.7% from baseline in patients suffering from **chronic anal fissure**. Literature evidence has also been provided to show a significant decrease in the average or maximal reduction in anal sphincter pressure from baseline over an 8 week treatment period using DTZ 2% in 3 different studies in the APCM response.*

Response

The Delegate of the Minister has reviewed the submitted report of study DAF0001. The Delegate of the Minister has noted:

- The Visual Analogue Scale used to measure the severity of pain is not described in detail. No evidence is provided that it is a validated instrument.

²⁹ Sanei B, et al. Comparison of topical glyceryl trinitrate with diltiazem ointment for treatment of chronic anal fissure. A randomized clinical trial. *Ann Ital Chir.* 80: 379-83 (2009); Sanei B, et al. Comparison of topical glyceryl trinitrate with diltiazem ointment for the treatment of chronic anal fissure: a randomized clinical trial. *Acta Chir Belg.* 109: 727-730 (2009).

- The diltiazem cream used in this study is not claimed to be identical to Ano cream proposed for registration in Australia.
- No differences in efficacy between the two treatments (diltiazem cream and placebo) were demonstrated during the double blind part of the study.
- This delegate's review of the study report confirms the accuracy of the Results section of the second round clinical evaluation report,
- As noted above and in the clinical evaluation report, the study was terminated prematurely due to unspecified stability issues with the study drug formulation.
- The information in the Clinical Study Report provides comments about the future implications of the identification of problems with the stability of the formulation. No information about the exact nature of the stability problem is provided. No comment is provided about the impact of the stability problem on the results derived from the 61 treated patients. The Delegate of the Minister is inclined to agree with the clinical evaluator's view that:

As the integrity of the study formulation was uncertain, the study results have no value and should be discounted in the overall evaluation of both safety and efficacy.

- The Delegate of the Minister has not been able to confirm the results you claim concerning anal pressure changes. The Delegate of the Minister has noted that the Clinical Study Report states that:

The only manometry variable which was recorded at a follow-up visit was resting sphincter pressure. This was recorded for centre 1 only. Data were recorded on the CRF as free text, but the actual numeric data were extracted using SAS programming, assuming that the units were mmHg throughout. The data were summarised and analysed as described for the VAS scores. Due to the small numbers of patients involved no per protocol population analysis was performed for resting sphincter pressure.

The analysis was limited to 11 patients in each treatment group.

Sponsor's request

The sponsor's request states that:

- *AFT and the physicians consulted also respectfully disagree with the comment (in the Minutes of the ACPM) regarding elimination of patients with chronic constipation (defined as 2 or less defecations per week; associated with straining/passage of hard stools) as a cause or symptom of anal fissure weakening the design of the study. Note that both the reduction of pain associated with chronic anal fissure and the healing of the chronic anal fissure were being investigated in this study. Both of these results could have easily been confounded if patients had experienced a re-opening of the anal fissure due to chronic constipation.*

Response

While the Delegate of the Minister accepts the sponsor's comment, it does not change their decision.

Sponsor's request

The sponsor's request states that:

- *The treatment is by definition for a significant amount of time (8 weeks) so tolerability of the treatment is very important in the clinical setting as patients often do not complete treatment with the currently available glyceryl trinitrate 0.2% ointment (GTN 0.2%) due to the significant and common side effect of headache. The safety data that was part of*

the response to the APCM resolution clearly showed a significantly better safety profile for diltiazem 2% compared to glyceryl trinitrate, as shown by tables 1 & 2 below. The provision of a compound with similar significant efficacy as a registered compound, but with substantially less side effects, has not been adequately considered.

Response

Please see the Delegate of the Minister's response above. The Delegate of the Minister reiterates that they have given consideration to the proposition that a product with fewer or less severe adverse effects including headache than glyceryl trinitrate ointment would be valuable, but that can only be so when the product has demonstrated clinical efficacy.

Sponsor's request

The sponsor's request states that:

- *Finally, but not least, the clinical need for this product is substantial. Clinicians involved in the treatment of CAF require a treatment option in addition to GTN given that the incidence of side effects limits its utility in clinical practice. This treatment is not an expensive medicine; any successful medical treatment of CAF reduces the requirement for surgery which carries with it substantial cost and the risk of significant complications such as incontinence.*

Response

The Delegate of the Minister notes that the sponsor's Request for Reconsideration does not name any supporting references for this statement. The Delegate of the Minister has noted that the sponsor included a NICE 2013 review in the documents submitted with your Request. The Delegate of the Minister has also noted that some references were cited in the sponsor's earlier response.

- NICE 2013: This document is an Evidence Summary for an unlicensed or off-label medicine. "The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, but this summary is not NICE guidance." The NICE document states "This summary is based on evidence from a Cochrane review of 4 RCTs and 5 additional RCTs. These sources presented similar conclusions although their precise estimates of effect varied. None of the studies compared 2% topical diltiazem with 0.4% topical glyceryl trinitrate (the licensed strength), which limits the conclusions which can be drawn regarding comparative efficacy and risk of adverse effects, especially headache. Although several of the 5 additional randomised controlled trials included a power calculation, they were relatively small. Most were conducted in countries outside northern Europe (for example, Egypt, India, Iran, and Turkey), as well as the Netherlands, but the findings are still likely to be applicable to the UK population because of the simple nature of the treatment.

The studies showed some degree of heterogeneity in terms of their definition of chronic fissure: treatment duration; concurrent treatments (such as a high-fibre diet or use of laxatives), child or adult populations, methods and time points for assessing fissure healing, and length of follow-up to assess recurrence. This may partly explain the large variation in the estimates of healing and recurrence observed in the RCTs, in addition to random sampling error.

The long-term efficacy, safety and fissure recurrence while using topical diltiazem was not assessed in the randomised controlled trials because most patients underwent surgery after first recurrence or healed completely and left the studies. The authors of the Cochrane review note the relapsing-remitting nature of chronic anal fissure and suggest that short follow-up periods may give rise to misleading results.

The Delegate of the Minister notes that given the date of the NICE document it has not taken into account the results of the pivotal Phase III study D-AF-09.

- Colorectal Surgical Society of Australia and New Zealand Patients and Public document dated 4 April 2016. The document states that “Frequent warm baths and topical application of muscle relaxing ointments (0.2% GTN or 2% diltiazem) help relax the anal sphincter muscle to reduce pain and help the fissure heal.” The document provides no data or evaluable information to support the use of 2% diltiazem.
- This paper³⁰ refers to the Cochrane Review 2012. The paper does not include any evaluable data and has not taken into account the results of the pivotal Phase III study D-AF-09.
- British Medical Journal Best Practice. Anal Fissure. Last updated 1 June 2015. “Additional treatment with topical nitrates 5[B]Evidence or calcium channel blockers1[B]Evidence is appropriate in most instances. Both have been shown to be effective in treating anal fissure, and the choice should depend upon local licensing, availability, costs, and contraindications. Treatment with diltiazem has become a common first choice for most patients because of the high incidence of dose-limiting headaches following topical nitrates.”

The relevant Evidence Score states that “Fissure healing: there is medium-quality evidence that calcium channel blockers are as effective as topical glyceryl trinitrate in reducing persistence of fissure at 30 days to 6 months. Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.”

This was published in 2011 and would not have taken into account the results of the pivotal Phase III Study D-AF-09.

The Delegate of the Minister has also noted that in their Request for Review, the sponsor requested whether a meeting could be arranged between a colorectal specialist and TGA.

Section 60 (2A) of the Act provides that a request for a review under Section 60 (2) may be accompanied by information in support of the request.

Section 60 (3A) provides that in reconsidering the initial decision:

- (a) the Minister must take into account any information referred to in subsection (2A); and
- (b) the Minister must not take into account any other information provided by, or on behalf of, the person after the making of the request, other than:
 - (i) information provided in response to a request from the Minister; or
 - (ii) information that indicates that the quality, safety or efficacy of therapeutic goods is unacceptable.

Section 60 (3B) provides that Paragraph (3A)(a) does not limit the information the Minister may take into account in reconsidering the initial decision.

The Delegate of the Minister made the decision to request the details of the in-house meta-analysis of safety data, which were subsequently provided. The Delegate of the Minister decided that they had access to all the other information needed to undertake the review.

Reasons for my decision

The Act requires (Section 25) that the Secretary must evaluate the goods for registration having regard to (among other things) whether the quality, safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established.

³⁰ Schlichtemeier S, Engel A. Anal fissure. *Aust Prescr*. 39: 14–17 (2016).

As set out above, the Delegate of the Minister is of the view that the clinical information currently available does not permit to decide that the efficacy of Ano-Cream for the purpose of:

The treatment of chronic anal fissure; specifically the reduction of pain associated with anal fissure

has been satisfactorily established.

Review of decision by the Administrative Appeals Tribunal

If the sponsor is dissatisfied with the Delegate's decision then, subject to the Administrative Appeals Tribunal Act 1975, the sponsor can make an application to the Administrative Appeals Tribunal (AAT) for a review of this decision.

Attachment 1. Extract from the Clinical Evaluation Report

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