Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Pyrazinamide AFT

Active ingredient: Pyrazinamide

Sponsor: AFT Pharmaceuticals Pty Ltd

August 2025

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, Disability and Ageing and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
2HRZE/4HR	Isoniazid, rifampicin, pyrazinamide and ethambutol, for 2 months followed by isoniazid and rifampicin for 4 months
ACM	Advisory Committee on Medicines
ACV	Advisory Committee on Vaccines
ALT	Alanine aminotransferase
ARTG	Australian Register of Therapeutic Goods
ASA	Australia-specific annex
AST	Aspartate aminotransferase
AT	Aminotransferases
AUC	Area under the concentration-time curve
AUC_{0-24}	Area under the concentration time curve from time zero to 24 hours
BCG	Bacille Calmette-Guérin vaccine
CE	Clinical Evaluator
C_{max}	Maximum concentration
CMI	Consumer Medicines Information
CNS	Central nervous system
CSF	Cerebrospinal fluid
DLP	Data lock point
DNA	Deoxyribonucleic acid
ETH	Ethambutol
FDC	Fixed dose combination
HIV	Human immunodeficiency viruses
HPLC	High-performance liquid chromatography
INH	Isoniazid
LF	Loose formulation
MDR	Multi-drug resistant
MIC	Minimum inhibitory concentration
PAS	Para-aminosalicylic acid
PD	Pharmacodynamics
PI	Product Information
PK	Pharmacokinetics
POA	Pyrazinoic acid (POA)

Abbreviation	Meaning
PSUR	Periodic safety update report
PZA	Pyrazinamide
RIF	Rifampicin
RMP	Risk management plan
$T_{1/2\beta}$	Elimination half-life
TB	Tuberculosis
TBM	Tuberculous meningitis
TGA	Therapeutic Goods Administration
T_{max}	Time after administration of a drug when the maximum plasma concentration is reached
TTCC	Time to culture conversion
WHO	World Health Organisation

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Pyrazinamide AFT
Active ingredient:	Pyrazinamide
Decision:	Approved
Date of decision:	30 April 2025
Date of entry onto ARTG:	2 May 2025
ARTG number:	413090
, *Black Triangle Scheme*	Yes
for the current submission:	*The PI and CMI for Pyrazinamide-AFT must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date of first supply of the product.*
Sponsor's name and address:	AFT Pharmaceuticals Pty Ltd Suite 301, 113 Wicks Road, North Ryde, NSW 2113
Dose form:	500 mg tablet
Pack size:	HDPE bottles of 100 tablets
Approved therapeutic use for the current submission:	*Pyrazinamide-AFT is indicated in adult patients of more than 12 years of age with active drug-sensitive tuberculosis caused by Mycobacterium tuberculosis. Pyrazinamide-AFT is an anti-tuberculosis agent used in combination with other anti-tuberculosis agents and is commonly used in the first 2 months of treatment.*
Route of administration:	Oral
Dosage:	15 to 30 mg/kg once daily For further information regarding dosage, such as dosage modifications to manage adverse reactions, refer to the Product Information (PI).
Pregnancy category:	Category B2 There are no well-controlled studies in pregnant women. Pyrazinamide-AFT should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of

medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by AFT Pharmaceuticals Pty Ltd to register Pyrazinamide AFT (pyrazinamide) 500 mg tablet for the following proposed indication:[1]

> *Pyrazinamide-AFT is indicated in patients with active tuberculosis caused by Mycobacterium tuberculosis.*

Pyrazinamide is a mainstay of tuberculosis treatment and has been in use since the 1950s. There is, however, no presentation of pyrazinamide currently included in the ARTG and a lack of evidence to determine whether it has been on the ARTG in recent history.

Disease or condition

Tuberculosis (TB) is a complex communicable disease that has many presentations, although the majority of disease is pulmonary in origin. The rate of endemic transmission in Australia is low but movement of people from areas of greater TB burden, as well as reactivation of latent TB in older Australians who were exposed to disease earlier in life, means a baseline prevalence of TB is maintained.

Most TB diagnosed in Australia is sensitive to therapy with isoniazid, rifampicin, ethambutol and pyrazinamide, on which a protocol of 4-6 months treatment achieves both non-contagious levels of TB bacteria and eventual cure. Resistant strains of TB can emerge with interrupted treatment, treatment complicated by other medical conditions (e.g. immunosuppression) or when resistant strains are imported to Australia.

Current treatment options

According to recent state guidelines for healthcare providers (such as the 'Management, control and prevention of tuberculosis', Department of Health and Human Services, Victorian Government, 2015[2]), the initial phase of TB treatment in patients for whom no drug resistance is suspected is the use of 4 antibiotics:

- isoniazid (H) 300 mg orally daily (in a child 10 mg/kg up to 300 mg)
- rifampicin (R): 600 mg orally daily (in adult <50 kg, and in child 10 mg/kg up to 600 mg)
- ethambutol (E): 15 mg/kg orally daily (up to 1200 mg; in adults and children 6 years or older)
- pyrazinamide (Z) 25 mg/kg (up to 2 g) orally daily, with pyridoxine 25 mg orally daily.

The duration of the initial phase is for a minimum of 2 months or at least until sputum is culture negative for pulmonary TB and, in culture-positive cases, until drug susceptibilities are known, whichever is longer.

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.
[2] Department of Health & Human Services (2015) Management, control and prevention of tuberculosis', Victorian Government. https://www.health.vic.gov.au/sites/default/files/migrated/files/collections/policies-and-guidelines/t/tb-guidelines-2015.pdf

For drug-sensitive TB, treatment is continued after the initial phase for at least another 4 months with rifampicin and isoniazid, for a total treatment course of 6 months (2HRZE/4HR). In patients who have drug-sensitive TB who have not responded well to the intensive initial phase, the initial phase can be extended e.g., to a total of 3 months of pyrazinamide.

For drug resistant TB, with isoniazid-resistant TB, the recommended regimen is 2 months of the initial standard regimen followed by 7 months of rifampicin, pyrazinamide and ethambutol. For multi-drug resistant (MDR) TB, second line anti-TB drugs are used and include fluoroquinolones, amikacin, prothionamide and PAS (para-aminosalicylic acid). Regimens are for at least 18 to 24 months in duration.

In patients with disseminated, central nervous system (CNS) or skeletal TB (extra-pulmonary TB), it is recommended that treatment be for 9-12 months, 12 months and at least 6-9 months, respectively. However, it is noted in the Victorian guidelines that there were no good prospective data supporting these recommended durations.

Clinical rationale

Pyrazinamide (PZA) is a prodrug that is converted to the active form pyrazinoic acid (POA) by pyrazinamidase/nicotinamidase encoded by the pncA gene in Mycobacterium tuberculosis. PZA is generally active only at an acid pH. The precise mechanism of action is unknown.

Possible mechanisms of antibacterial activity include:

1. activation of the sigma factor (SigE)-dependent cell envelope stress response,
2. binding of POA to asparate decarboxylase (PanD), and
3. POA binding to ribosomal protein S1 (RpsA) of M. tuberculosis.

Inhibition of fatty acid synthesis may also contribute to the activity of POA.

Resistance develops rapidly if pyrazinamide is used as sole antitubercular agent. Loss of pyrazinamidase activity, mutations in pncA, RpsA or pan D genes may confer PZA resistance. Pyrazinamide is readily absorbed from the gastro-intestinal tract with peak serum concentration being reached about 2 hours after taking the dose. Plasma concentrations of pyrazinoic acid, which is the major metabolite, are generally greater than those of pyrazinamide and peak 4-8 hours after dosing.

Pyrazinamide is widely distributed in body tissues and fluids including the liver, lungs and CSF. It is not known if pyrazinamide crosses the placenta, but it is excreted in breast milk. Pyrazinamide is metabolised primarily in the liver by hydrolysis to pyrazinoic acid which is subsequently hydroxylated to the major excretory product 5-hydroxypyrazinoic acid. It is excreted via the kidney mainly by glomerular filtration. Approximately 70% of a dose appears in the urine within 24 hours (mainly as metabolites with 4-14% as pyrazinamide).

The plasma half-life is 9-10 hours in patients with normal renal and hepatic function. The plasma half-life may be prolonged in patients with impaired renal or hepatic function.

Regulatory status

Australian regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

International regulatory status

Pyrazinamide 500mg tablets are available in many regulatory jurisdictions including the US, Canada, UK and New Zealand. It has been in routine clinical use for several decades.

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 1: Timeline for submission PM-2023-03087-1-2

Description	Date
Designation (Orphan)	27 April 2023
Submission dossier accepted and first round evaluation commenced	8 September 2023
Evaluation completed (End of round 2)	31 January 2025
Registration decision (Outcome)	30 April 2025
Registration in the ARTG completed	2 May 2025
Number of working days from submission dossier acceptance to registration decision*	196

*Statutory timeframe for standard submissions is 255 working days

Assessment overview

A summary of the TGA's assessment for this submission is provided below.

This application was evaluated as a Literature Based Submission (LBS) supported by published literature. This is appropriate given the age of the medicine and the lack of a modern regulatory dossier.

Quality evaluation summary

The precise mechanism of action has not been fully determined but partly depends on the conversion of pyrazinamide to pyrazinoic acid. Pyrazinamide is bactericidal against Mycobacterium tuberculosis. Pyrazinamide has no activity against other Mycobacteria. Susceptible strains of *Mycobacterium tuberculosis* produce pyrazinamidase which deaminates pyrazinamide to pyrazinoic acid.

Pyrazinamide-AFT is presented as a white to off-white colour round tablet. Each tablet contains 500 mg pyrazinamide. Pyrazinamide is proposed to be administered as 15 – 30 mg/kg once daily orally. It is proposed that 3 g/day should not be exceeded.

Alternatively, a twice weekly dosing regimen (50-75 mg/kg twice weekly) has been proposed to promote compliance. Pyrazinamide is to be given with at least 1 other anti-tuberculous medicine.

Pyrazinamide-AFT presents in a HDPE bottle of 100 tablets. The expiry date can be found on the packaging, with storage recommended for 12 months, at below 30 °C.

The module 3 evaluator has raised no concerns with registration of this product.

Nonclinical evaluation summary

There are no data on secondary pharmacology or safety pharmacology. Repeat dose toxicity, reproductive and developmental toxicity were not adequately assessed. Therefore, the submitted Module 4 dossier was deemed inadequate. However, as a literature-based submission, the sponsor has provided most available relevant published studies. Reproductive toxicity and carcinogenicity studies conducted by the National Institute of Health were not provided by the sponsor, but they were sourced by the TGA evaluator.

Pyrazinamide (PZA) is a prodrug that is converted to the active form pyrazinoic acid (POA) by pyrazinamidase /nicotinamidase. PZA is generally active only at an acid pH. The minimum inhibitory concentration (MIC) against *M. tuberculosis* varied widely in various cell cultures and assay conditions and ranged from <6.25 µg/mL to 128 µg/mL. Nutrient-starved conditions enhanced the activity of PZA in cell cultures.

In vivo studies in a range of animal models of TB showed combinations of PZA with a range of drugs including the commonly used first line anti-TB drugs (isoniazid [INH], rifampicin [RIF], ethambutol [ETH]) was effective in sterilising affected tissues. Combination of RIF/PZA/INH drug treatment and BCG vaccination was more effective than drug treatment alone in reducing disease reactivation in guinea pigs infected with *M. tuberculosis*. Since PZA has been extensively used in clinical settings, its efficacy and dosing would be appropriately determined by the extensive clinical data available.

Combination of clarithromycin and PZA was found to be synergistic against *M. tuberculosis* in human macrophages with MICs 4-8-fold lower for this combination than they were for either drug alone.

Pharmacokinetic profiles available in mice and rats (species used in the repeat-dose toxicity studies) were incomplete. PZA was well absorbed in mice. No absorption data was available for rats, but excretion data indicate that PZA is orally bioavailable in rats. Metabolites and excretion profiles in rats (no data for mice) were similar to humans making it an appropriate species for the assessment of PZA toxicity.

PZA and its active metabolite, POA are converted to 5-hydroxyPZA and 5-hydroxyPOA, respectively, by xanthine oxidase. Drugs that affect xanthine oxidase activity such as caffeine and allopurinol may affect PZA metabolism. Pyrazinamide inhibited the expression of hepatic transporters, BSEP and OATP1A1 in rats. It may reduce the elimination of drugs that are cleared by BSEP-mediated biliary excretion or OATP1A1 substrates that are predominantly cleared by hepatic metabolism.

Repeat-dose toxicity via the oral route of PZA on its own was examined in mice (2 x 1 week study) and rats (9 x 1–13-week studies). These studies concentrated on hepatotoxicity. Effects of PZA on other organs were not investigated, which is considered a major deficiency. Clinical doses of PZA in rats caused liver hepatotoxicity. Metabolites POA and 5-OHPOA were more potent than PZA in the induction of hepatotoxicity, based on histopathological and serum biochemical analysis (including ALT, AST, bilirubin and bile acid), liver oxidative stress in rats and cytotoxicity in HepG2 cells *in vitro*. Hepatic toxicity of PZA was alleviated by obeticholic acid, a FXR agonist approved for the treatment of primary biliary cholangitis.

Based on the study findings, PZA is considered to be genotoxic. PZA increased bone marrow micronuclei in mice (after a single IP dose of PZA). Chromosomal aberrations of bone marrow cells and DNA damage of spleen cells were increased in rats treated with PZA in combination with INH and RIF. In another rat study, micronuclei in blood cells were not increased following

treatment with PZA or PZA in combination with other anti-TB drugs, but DNA damage was evident in liver, kidney and blood cells. PZA was not mutagenic in the Ames assay.

PZA was not carcinogenic in rats or male mice. No conclusion was possible for female mice due to insufficient numbers of surviving control mice in the 78-week carcinogenicity study.

Effects on fertility and early embryonic were not adequately assessed. In female rats, subclinical doses of PZA elicited significant disruption of endocrine balance (reduced levels of luteinizing hormones, prolactin and estrogen), and induced ovarian and uterine oxidative stress (increased oxidative stress markers) and histopathology of reproductive organs (including erosion of uterine mucosa, and congestion and underdeveloped follicles in ovaries). In male mice, subclinical doses of PZA caused histological lesions in testes (such as irregular seminiferous tubules, reduction of seminiferous epithelium, necrotic spermatogenic cells, and degeneration of Sertoli cells). Decreased testis volume and spermatogonia numbers, epithelium desquamation and exfoliation were seen in rats. Testis and epididymis DNA fragmentation were reported in male rats treated with PZA. Male rats dosed with PZA, INH, RIF and ETH at 217, 62, 74.4 and 155 mg/kg/day PO, respectively, had significantly lower fertility index and increased pre- and post-implantation losses than the control group. Considering the effects on male and female reproductive organs, and the significant decrease in fertility in the combination study, both male and female fertility and early embryonic development may be affected in patients.

In mice, embryofetal development was unaltered by PZA at PO doses up to 3000 mg/kg/day (9 times the maximum recommended clinical dose per body surface area) administered during organogenesis, but visceral and skeletal malformations were not examined in the study. Effects of embryofetal development has not been adequately assessed in nonclinical studies.

The non-clinical evaluator concluded that:

- Primary pharmacology studies support the proposed mode of action and clinical use for the treatment of TB.
- Pyrazinamide may cause liver toxicity in humans based on animal studies.
- A number of major deficiencies in the submitted nonclinical data were identified:
  - the absence of secondary and safety pharmacology data
  - repeat dose toxicity investigation limited to liver toxicity
  - absence of adequate embryofetal developmental studies (visceral and skeletal malformations were not examined)
- The major deficiencies of nonclinical toxicology data may be overcome by the long history of clinical use and available clinical data on safety and efficacy.
- The Risk Management Plan should include the mutagenic potential of PZA.

Clinical evaluation summary

Summary of clinical studies

A total of 68 publications were submitted as clinical data following a structured search of online databased which found 278 potential studies.

Table 3: Studies submitted in support of application PM-2023-03087-1-2

Level	Type of evidence	Reference submitted	Location in the dossier
I-1	Systematic review of all relevant randomised controlled trials	• Lew *et al.* (2008)	Module 5.4
I-2	Large multicentre randomized controlled trials	• Tweed *et al.* (2021) • Blanc *et al.* (2020) • Velayutham *et al.* (2020) • Tweed *et al.* (2019) • Nunn *et al.* (2019) • Boeree *et al.* (2017) • Aseffa *et al.* (2016) • Dawson *et al.* (2015) • Gillespie *et al.* (2014) • Nunn *et al.* (2014) • Nunn *et al.* (2011) • Bartacek *et al.* (2009) • El-Sadr *et al.* (1998) • Combs *et al.* (1990)	Module 5.4
II	One or more randomised controlled trials and studies	• Wu *et al.* (2022) • Qiao *et al.* (2022) • Zhang *et al.* (2021) • Misra *et al.* (2021) • Nazari *et al.* (2021) • Diao *et al.* (2020) • Hagiwara *et al.* (2019) • Sharma *et al.* (2016) • Conde *et al.* (2016) • Diacon *et al.* (2015) • Narendran *et al.* (2014) • Diacon *et al.* (2012) • Swaminathan *et al.* (2010) • Sharma *et al.* (2010) • Adhvaryu *et al.* (2008) • Jawahar *et al.* (2005) • Narayanan (2004) • Su and Perng (2002) • Teo (1999) • Yuen *et al.* (1997) • Zhang *et al.* (1996) • Kennedy *et al.* (1996) • Paramasivan *et al.* (1994) • Campbell *et al.* (1992) • (Girling and Teo 1991) • Girling and Chan (1991)	Module 5.4

Level	Type of evidence	Reference submitted	Location in the dossier
		• Cohn *et al.* (1990) • HK-Chest (1989) • Girling (1989) • HK-Chest (1987) • TB-Res-Centre (1983) • HK-Chest (1982) • TB-CT (1970) • Kent (1970) • Kent (1969)	
III-1	Controlled trials without randomisation	• Bhandari *et al.* (2014) • Tostmann *et al.* (2010) • Taki *et al.* (2008) • Mawer *et al.* (2001) • Botha *et al.* (1996) • Macnab *et al.* (1994) • East-African (1973)	Module 5.4
III-2	Cohorts; Case-control analytic studies	• Apis *et al.* (2019) • Sun *et al.* (2021) • El Hamdouni *et al.* (2020) • Mahmood *et al.* (2007)	Module 5.4
III-3	Time series; Before and after studies (premeasure/postmeasure)	None	N/A
IV	Other observational studies (e.g.: case reports)	• Sharma *et al.* (2012) • Sharifzadeh *et al.* (2005) • Park *et al.* (2004) • (Nolan and Goldberg 2002) • Schaberg *et al.* (1996) • Chan *et al.* (1994) • Paramasivan *et al.* (1993)	Module 5.4
V	Opinions of respected authorities, based on their own clinical experience, or their own (non-systematic) reviews. Reports of expert committees, consensus statements	None	N/A

Pharmacology

The Delegate noted that the pharmacology of pyrazinamide is relatively well understood given the duration of its clinical use.

Pharmacokinetics

An appropriate and thorough search of literature-based studies was provided. Table 4 summarises studies with pharmacokinetic (PK) data. Individual studies are described further below.

Table 4: Pharmacokinetic parameter of pyrazinamide observed in humans (values are in blood/plasma /serum unless specified)

Study	Number of subjects	Study characteristics	Dose	Pharmacokinetic parameters						
				C_{max}	AUC[#]	Half-life	Volume of distribution	T_{max}	K_a	Clear-ance
Panjasawatwong *et al.* (2021)	100	Children with suspected tuberculous meningitis	---	42.5 mg/l (plasma)	288 mg×h/l (plasma)	5.12 h (plasma)		1.08 h (plasma)		
				31.3 mg/l (CSF)	266 mg×h/l (CSF)	5.12 h (CSF)		3.06 h (CSF)		
Mukherjee *et al.* (2019)	--	Patients with normal renal function	--	--	--	9-10 h				
	10	Children	35 mg/kg	41.2 µg/ml	558.7 µg*h/ml					
	23		25 mg/kg	21.1 µg/ml	--					
	27		33 mg/kg	36.6 µg/ml	376 µg*h/ml					
			15 mg/kg	42.4 µg/ml	453 µg*h/ml					
	20		25 mg/kg	38.6 µg/ml	385 µg*h/ml					
	34		30 mg/kg	31.3-37.9 µg/ml	--					
	40		30 mg/kg	43.43 µg/ml	496.11 µg*h/ml					
	34		15-30 mg/kg	30.7 µg/ml	138 µg*h/ml					
	20		25 mg/kg	29.95 µg/ml	118.01 µg*h/ml					
	20		35 mg/kg	47.11 µg/ml	175.23 µg*h/ml					
	7		31.9 mg/kg	49.4 µg/ml	369.5 µg*h/ml					
	13		28.1 mg/kg	41.7 µg/ml	278.4 µg*h/ml					
	30		25.9 mg/kg	31.5 µg/ml	318.5 µg*h/ml					
	84		30.4-33.6 mg/kg	30.4 µg/ml	175.9 µg*h/ml					
	127		35.7 mg/kg	47.8 µg/ml	140.5 µg*h/ml					
Alfarisi *et al.* (2018)	243	Patients with diabetes mellitus (101 patients)	33 mg/kg	21.59 µg/ml	80.89 µg*h/ml					
		Patients without diabetes mellitus (142 patients)		32.75 µg/ml	128.43 µg*h/ml					
Vinnard *et al.* (2017)	24	HIV/tuberculosis patients					28.57 L		1.31 h^{-1}	3.52 L/h
Verbeeck *et al.* (2016)		Healthy subjects				~ 10 h	0.57 l/kg	1-2 h		
Gurumurthy *et al.* (2002)	10	Pyrazinamide alone	35 mg/kg	47.62 µg/ml	202.94 µg*h/ml	8.86 h		3.20 h		
	7	Pyrazinamide + ofloxacin		51.97 µg/ml	191.51 µg*h/ml	9.96 h		2.43 h		
	4	Pyrazinamide + ofloxacin + rifampicin + isoniazid		49.58 µg/ml	226.39 µg*h/ml	16.02 h		3.50 h		
Peloquin *et al.* (1997)	24	Isoniazid, rifampicin, pyrazinamide	1500 mg	28.80 µg/ml		10.0 h		1.0 h		
Venkatesan (1989)	4		24.6 mg/kg	30.8 mg/L	224.7 mg.h/L	7.4 h		1.5 h		
Lacroix *et al.* (1989)	9	Pyrazinamide	27 mg/kg	38.7 mg/L	520 $mg.l^{-1}.h$	9.6 h	0.71 $l.kg^{-1}$	1 h		
		PA	N/A	4.5 mg/L	100 $mg.l^{-1}.h$	11.8 h		4.9 h		
		5-OH-PZA	N/A	1.8 mg/L	35 $mg.l^{-1}.h$	9.7 h		4.0 h		
		5-OH-PA	N/A	0.58 mg/L	13 $mg.l^{-1}.h$	15.3 h		4.2 h		
Holdiness (1984)		Pyrazinamide	1000 mg	45 µg/ml				2 h		

[#]AUC values are AUC_{0-t} depending upon the study time, PA: pyrazinoic acid, 5-OH-PZA: 5-hydroxy-pyrazinamide, 5-OH-PA: 5-hydroxy-pyrazinoic acid, CSF: cerebrospinal fluid

Panjasawatwong et al. (2021)[3] assessed the population PK of isoniazid, rifampicin, pyrazinamide and ethambutol in Vietnamese children with tuberculous meningitis (TBM) to provide an optimal dosing for such patients. A total of 100 children with TBM were treated with an 8-month anti-TB regimen. Non-linear mixed-effects modelling was used to evaluate the PK properties of the drugs. The PK properties of rifampicin and pyrazinamide in plasma were described by 1-compartment disposition models whilst those of isoniazid and ethambutol were described by 2-compartment disposition models. Whilst CSF penetration of rifampicin was relatively poor, this was good with isoniazid and pyrazinamide. It was found that recommended doses of isoniazid and pyrazinamide but not ethambutol and rifampicin were adequate to achieve target exposures.

For pyrazinamide, the population PK parameter estimates at steady state in this target population are shown in Table 5. Thus, AUC_{0-24} in plasma CSF (median [range]) was 288 (108-569) and 266 (98.9-522) mg x h/L, respectively. C_{max} was similarly slightly greater in plasma vs. CSF at 42.5 (29.8-92.7) and 31.3 (19.4-72.2) mg/L, respectively. Half-life in plasma and CSF were the same, at 5.12 (3.01-14.5) hours for both groups.

Table 5: Population PK parameter estimates and post hoc secondary PK parameters from the final population PK model of pyrazinamide in children with TBM[a]

Parameter	Population estimate[b] (% RSE)	95% CI[c]	% CV for IIV[b] (% RSE[c])	95% CI for IIV[c]	% CV for IOV[b] (% RSE[c])	95% CI for IOV[c]	Plasma[d]	CSF[d]
Primary PK parameters								
F	1 (fixed)				19.0 (7.05)	16.5–21.8		
CL/*F* (liters/h)	1.07 (4.02)	0.996–1.17	20.0 (6.95)	17.0–22.6				
Vc/*F* (liters)	7.38 (2.73)	6.99–7.80	18.3 (10.6)	14.2–22.1				
MTT (h)	0.457 (10.8)	0.364–0.551	64.5 (12.0)	48.7–83.8				
MAT_{50} (mo)	12.1 (7.26)	10.2–13.7						
HILL	2.73 (29.0)	1.63–4.64						
Q_{CSF}/F (liters/h)	0.0964 (13.6)	0.0779–0.129						
f_u	0.9 (fixed)							
PC	1.02 (1.70)	0.989–1.06						
WAZ on CL/*F* (%)	4.76 (18.3)	3.36–6.68						
WAZ on Vc/*F* (%)	−4.65 (27.6)	−6.95– −1.98						
σ_{Plasma}	0.0274 (4.97)	0.0230–0.0335						
σ_{CSF}	0.0114 (12.8)	0.00652–0.0181						
Secondary PK parameters at steady state								
AUC_{0-24} (mg×h/liter)							288 (108–569)	266 (98.9–522)
C_{max} (mg/liter)							42.5 (29.8–92.7)	31.3 (19.4–72.2)
T_{max} (h)							1.08 (0.259–2.27)	3.06 (2.17–5.29)
$t_{1/2}$ (h)							5.12 (3.01–14.5)	5.12 (3.01–14.5)

[a]Abbreviations: *F*, relative bioavailability; CL/*F*, oral elimination clearance; Vc/*F*, volume of distribution of the central compartment; MTT, mean transit absorption time; MAT_{50}, postmenstrual age at which clearance is 50% of the mature clearance; HILL, Hill coefficient for maturation clearance; Q_{CSF}/F, intercompartmental clearance between central and CSF compartments; f_u, fraction unbound; PC, transfer multiplier between central and CSF compartments describing blood-brain penetration; WAZ, weight-for-age z-score; IIV, interindividual variability; IOV, interoccasion variability; σ, variance of the residual variability, incorporated as an additive error on the logarithmic scale; AUC_{0-24}, area under the concentration-time curve from 0 to 24 h; C_{max}, peak concentration; T_{max}, time to reach peak concentration; $t_{1/2}$, terminal elimination half-life.
[b]Computed population mean parameter estimates from NONMEM. Parameter estimates are scaled to typical patient at 10.9 kg and 3 years.
[c]Assessed by sampling importance resampling (SIR).
[d]Median (range).

The PK of isoniazid, rifampicin and pyrazinamide was studied in 24 healthy males as part of a randomised, cross-over, phase I study of 2 dosage forms (Peloquin et al. 1997)[4]. Single doses of isoniazid, rifampicin and pyrazinamide of 250 mg, 600 mg and 1500 mg, respectively were administered. Plasma was collected for 36 hours and measured by HPLC. Population PK modelling was conducted. The data were analysed by non-compartmental and non-parametric

[3] Panjasawatwong NWattanakul THoglund RMBang ND, Pouplin TNosoongnoen W, Ngo VN, Day JN, Tarning J 2020. Population Pharmacokinetic Properties of Antituberculosis Drugs in Vietnamese Children with Tuberculous Meningitis. Antimicrob Agents Chemother 65:10.1128/aac.00487-20. https://doi.org/10.1128/aac.00487-20

[4] Peloquin, C. A., Jaresko, G. S., Yong, C. L., Keung, A. C., Bulpitt, A. E., & Jelliffe, R. W. (1997). Population pharmacokinetic modeling of isoniazid, rifampin, and pyrazinamide. *Antimicrobial agents and chemotherapy*, *41*(12), 2670–2679. https://doi.org/10.1128/AAC.41.12.2670

modelling methods. Fast and slow acetylators of isoniazid had median concentrations in plasma (C_{max}) of 2.44 and 3.64 µg/ml, respectively occurring 1.0 hours post-dose. Pyrazinamide produced a median C_{max} of 28.80 µg/ml, a T_{max} of 1.0 hours and a $T_{½}$ of 10.0 hours.

Mukherjee et al. (2019)[5] was a review article of the PK of first-line anti-tuberculosis drugs. Relevant PK studies on pyrazinamide in children are summarised in Table 6.

Table 6: Summary of PK studies on pyrazinamide in children

Authors	Year	n	Dose (mg/kg)	Method	C_{max} (µg/ml)	AUC (µg*h/ml)
Roy et al. [34]	1999	10	35	Spectrophotometry	41.2 (11.8) [Mean (SD)]	558.7 (232.4) [AUC_{0-24}, Mean (SD)]
Zhu et al. [35]	2002	23	25	Gas chromatography	21.1 (Median)	-
Graham et al. [33]	2006	27	33[π]	HPLC	36.6 (19.7) [Mean (SD)]	376 (328) [AUC_{0-24}, Mean (SD)]
Gupta et al. [36]	2008		15	Spectrophotometry	42.4 (3.3)	453 (67)
		20	25		38.6 (3.9) [Mean (SD)]	385 (43) [AUC_{0-24}, Mean (SD)]
Thee et al. [37]	2008[€]	34	30	Mass fragmentography	31.3-37.9 (Mean in different age strata)	-
Arya et al. [38]	2008	40	30	HPLC	43.43 (6.74) [Mean (SD)]	496.11 (138.15) [AUC_{0-24}, Mean (SD)]
McIlleron et al. [16]	2009	34	15-30	LCMS	30.7 (25.5, 35) [Median (IQR)]	138 (121,157) [AUC_{0-6}, Median (IQR)]
Thee et al. [18]	2011	20	25	LCMS	29.95 (26.16–33.73)	118.01 (101.33–134.70)
		20	35		47.11 (42.64–51.58) [Mean (95%CI)]	175.23 (155.50–194.96) [AUC_{0-5}, Mean (95%CI)]
Roy et al. [39]	2012	7	31.9	Spectrophotometry	49.4 (2.8)	369.5 (35.3)
		13	28.1		41.7 (1.2) [Mean (SD)]	278.4 (16.0) [AUC_{0-24}, Mean (SD)]
Verhagen et al. [19]	2012	30	25.9	HPLC	31.5 (10.3–71.7) [Geometric mean (range)]	318.5 (108.0–1389.5) [AUC_{0-24}, Geometric mean (range)]
Ramachandran et al. [20]	2013	84	30.4-33.6[¶]	HPLC	30.4 (26.2-33.4) to 38 (30.1-45.1) [Median (IQR)][§]	175.9 (131.5- 193.9) to 226.5 (132.2-265.3) [AUC_{0-8}, Median (IQR)][§]
Mukherjee et al. [22]	2015	127	35.7	LCMS/MS	47.8 (39.4, 58.5) [Median (IQR)]	140.5 (117.4, 173.2) [Median (IQR)]

AUC Area under the curve, *CI* Confidence interval, C_{max} Maximum serum drug concentration, *HPLC* High performance liquid chromatography, *IQR* Interquartile range, *LCMS* Liquid chromatography mass spectrometry, *n* Number of children, *SD* Standard deviation, [€] Study done in 1983, [§] Range in various age strata, [π] Intermittent dosing

In a study by Graham et al. (2006)[6] a group of 27 Malawian children with TB received 3 times weekly anti-tuberculosis drugs, with a mean dose of 33 (range 25-48) mg/kg/dose of pyrazinamide. The mean (SD) C_{max} achieved was 36.6 (19.7) µg/ml and 9 (33%) of children had a concentration of <20 µg/ml. The mean (SD) AUC_{0-24} was 376 (328) µg x h/ml. In view of subtherapeutic levels of pyrazinamide being seen in some children despite increases in doses, in the PHATISA study[7] involving 31 children <10 years of age, suboptimal C_{max} and AUC of pyrazinamide was seen in 45% and 19%, respectively. The lower systemic exposure seen in the study by Graham et al. (2006)[5] in children suggests a higher metabolism compared to adults, as seen in other publications.[8]

In the paper by Zhang et al. (2021),[9] pyrazinamide PK-PD and PK-toxicity analyses were performed from extraction of the TB trials consortium (TBTC) studies 27 and 28 and pan-African consortium for the evaluation of anti-TB antibiotics (PanACEA) multi-arm, multi-stage

[5] Mukherjee, A., Lodha, R., & Kabra, S. K. (2019). Pharmacokinetics of First-Line Anti-Tubercular Drugs. *Indian journal of pediatrics*, *86*(5), 468–478. https://doi.org/10.1007/s12098-019-02911-w

[6] Graham SM, Bell DJ, Nyirongo S, Hartkoorn R, Ward SA, Molyneux EM.2006.Low Levels of Pyrazinamide and Ethambutol in Children with Tuberculosis and Impact of Age, Nutritional Status, and Human Immunodeficiency Virus Infection. Antimicrob Agents Chemother 50. https://doi.org/10.1128/aac.50.2.407-413.2006

[7] Hiruy H., Rogers Z., Mbowane C., Adamson J., Ngotho L., Karim, F., Gumbo T., Bishai W., Jeena P. Subtherapeutic concentrations of first-line anti-TB drugs in South African children treated according to current guidelines: the PHATISA study, *Journal of Antimicrobial Chemotherapy*, Volume 70, Issue 4, April 2015, Pages 1115–1123. https://doi.org/10.1093/jac/dku478

[8] Ramachandran, G., Kumar, A. K., Kannan, T., Bhavani, P. K., Kumar, S. R., Gangadevi, N. P., Banurekha, V. V., Sudha, V., Venkatesh, S., Ravichandran, N., Kalpana, S., Mathevan, G., Sanjeeva, G. N., Agarwal, D., & Swaminathan, S. (2016). Low Serum Concentrations of Rifampicin and Pyrazinamide Associated with Poor Treatment Outcomes in Children with Tuberculosis Related to HIV Status. *The Pediatric infectious disease journal*, *35*(5), 530–534. https://doi.org/10.1097/INF.0000000000001069

[9] Zhang, A., Teng, L., & Alterovitz, G. (2021). An explainable machine learning platform for pyrazinamide resistance prediction and genetic feature identification of Mycobacterium tuberculosis. *Journal of the American Medical Informatics Association : JAMIA*, *28*(3), 533–540. https://doi.org/10.1093/jamia/ocaa233

TB (MAMS-TB), multicentre phase 2 trials, in which patients received rifampicin (10-35 mg/kg), pyrazinamide (20-30 mg/kg) and 2 companion drugs.

It was found that in the TBTC studies (n=77), higher pyrazinamide C_{max} was associated with shorter time to culture conversion (TTCC) and higher probability of 2-months, culture conversion ($p<0.001$). In the PanACEA MAMS-TB (n=363), TTCC decreased as pyrazinamide C_{max} increased and varied by rifampicin AUC ($p<0.01$).

Diabetes effect on PK

In Alfarisi et al. (2018)[10] an assessment of the effect of diabetes mellitus and HbA1c values on the PK of anti-TB drugs was assessed in newly diagnosed TB patients with and without diabetes mellitus starting a fixed dose, 3 times weekly treatment regimen. PK sampling pre-dose and 0.5, 2- and 6-hours post-dose was conducted. Of 243 patients studied, 101 had diabetes. Univariate analysis showed significant reductions in C_{max} of pyrazinamide (and isoniazid) with diabetes with increasing HbA1c values. After adjusting for age, sex and weight, diabetes was associated with reduced pyrazinamide concentrations (adjusted GMR = 0.74, p=0.03). Thus, diabetes/higher HbA1c patients increased the risk of not achieving therapeutic targets for pyrazinamide but not rifampicin or isoniazid.

HIV and PK

In the article by Vinnard et al. (2017)[11] a prospective cohort study of pyrazinamide PK in HIV/TB patients in Botswana was provided. A total of 40 HIV/TB patients completed the first PK sampling visit and 24 had a second visit following anti-retroviral therapy initiation. It was found that with compartmental PK modelling, the pyrazinamide concentration vs. time data were best described by a 1-compartment model with first-order elimination and a combined additive and proportional residual error model. HIV-associated immune activation (expression of CD38 and HLA-DR on CD8 positive T-cells) was adversely related to pyrazinamide clearance with increase in immune activation being associated with decreased pyrazinamide clearance.

Ofloxacin interactions

The report by Gurumurthy et al. (2002)[12] assessed the bioavailability of ofloxacin following single oral administration together with rifampicin, isoniazid or pyrazinamide or combination of the 3 drugs. This study was undertaken in 12 healthy male volunteers on 4 different occasions at weekly intervals, in India. A partially balanced, incomplete blocked design was applied where the drugs were given to the healthy volunteers a week apart at random. These data are summarised in Figures 1 & 2. Similarly, Figure 3 reveals the mean plasma concentration-time profiles of pyrazinamide given alone or in combination. The PK parameters are summarised in Table 7 and the PK of pyrazinamide when given alone or in combination is summarised in Table 8. Plasma concentrations of each drug as well as urinary excretion of the drugs together with their primary metabolites was determined. The results confirmed that the bioavailability of ofloxacin was not affected when given with the other 3 tuberculosis drugs. Similarly, the

[10] Alfarisi O, Mave VGaikwad S, Sahasrabudhe T, Ramachandran G, Kumar H, Gupte NKulkarni V, Deshmukh S, Atre S, Raskar S, Lokhande R, Barthwal M, Kakrani A, Chon S, Gupta AGolub JE, Dooley KE.2018.Effect of Diabetes Mellitus on the Pharmacokinetics and Pharmacodynamics of Tuberculosis Treatment. Antimicrob Agents Chemother 62:10.1128/aac.01383-18. https://doi.org/10.1128/aac.01383-18

[11] Vinnard C, Ravimohan S, Tamuhla N, Pasipanodya J, Srivastava S, Modongo C, et al. (2017) Pyrazinamide clearance is impaired among HIV/tuberculosis patients with high levels of systemic immune activation. PLoS ONE 12(11): e0187624. https://doi.org/10.1371/journal.pone.0187624

[12] Gurumurthy, Prema and Hemanth Kumar, A K and Rajasekharan, A and Rehman, Fathima and Sekar, L and Narayanan, P R (2002) *The Pharmacokinetics of ofloxacin, rifampicin, isoniazid and pyrazinmide when administered alone and in combination.* Biomedicine, 22 (3&4). pp. 13-26. ISSN 0970 2067 https://eprints.nirt.res.in/569/1/200221.pdf

bioavailability of other anti-TB drugs, rifampicin, isoniazid or pyrazinamide, was not affected when given with ofloxacin.

Figure 1: Mean plasma concentration – time profiles of ofloxacin when given alone and in combinations

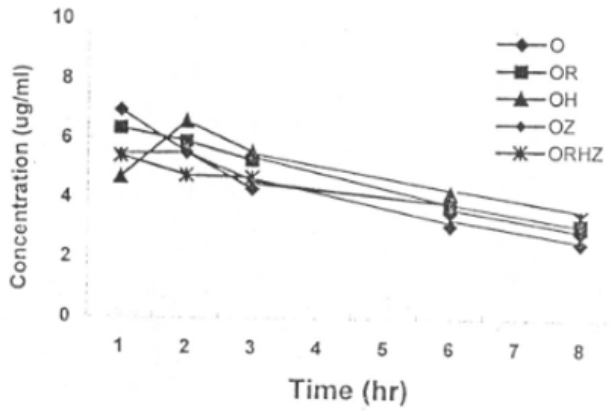

Figure 2: Urinary excretion of ofloxacin

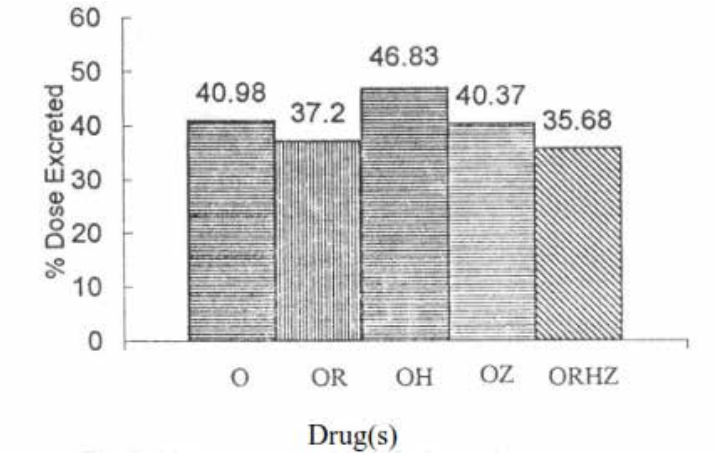

Figure 3: Mean plasma concentration-time profiles of pyrazinamide when given alone and in combinations

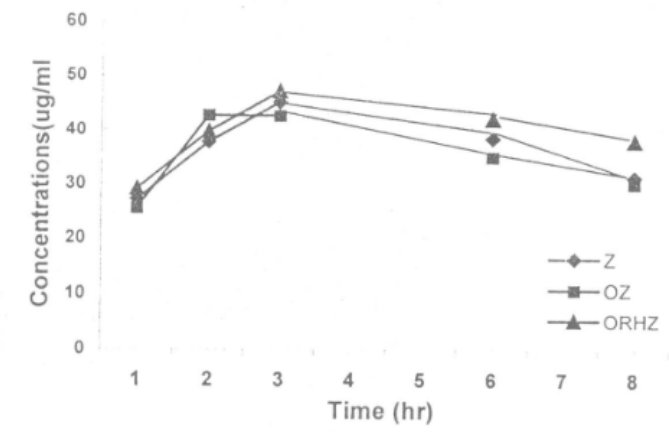

Table 7: PKs of ofloxacin in plasma when given alone and in combinations

Parameter	O n=12	OR n=6	OH n=5	OZ n=9	ORHZ n=4
C-max (µg/ml)	7.14± 1.44	6.98 ± 1.57	7.19± 2.17	6.06± 0.93	6.38± 1.45
T-max (hrs.)	1.25± 0.45	1.67 ± 0.82	1.80± 0.84	1.67± 0.71	1.50± 1.00
Halflife (hrs.)	5.21 ± 1.69	6.02 ± 1.20	6.08± 2.22	6.51± 1.81	10.00± 5.23
Coverage (hrs.)	20.27± 6.09	23.51 ± 5.79	24.45± 8.01	24.37± 7.06	34.46± 16.29
AUC (0-8 hrs.) (µg/ml.hrs)	27.49 ± 5.74	31.5 ± 12.74	32.08± 7.89	27.86± 6.05	27.98± 13.22

Table 8: PKs of pyrazinamide in plasma when given alone and in combinations

Parameter	Z n=10	OZ n=7	ORHZ n=4
Cmax (µg/ml)	47.62± 10.62	51.97± 16.82	49.58 ± 3.81
T-max (hrs.)	3.20 ± 1.62	2.43 ± 0.53	3.50 ± 1.73
Halflife (hrs.)	8.86 ± 4.30	9.96 ± 5.57	16.02 ± 8.64
Coverage (hrs.)	22.28± 9.19	24.69 ± 14.33	41.09 ± 22.76
AUC (0-8 hrs) (µg/ml.hrs)	202.94± 67.28	191.51 ± 113.84	226.39± 54.24

Single dose PK

The study by Lacroix et al. (1989)[13] described plasma and urine PK parameters of pyrazinamide and its metabolites after a single oral dose of 27 mg/kg in 9 healthy subjects. Pyrazinamide was found to be rapidly absorbed with a T_{max} ≤1 hour and an elimination $T_{1/2\beta}$ of 9.6 hours. Similar elimination rates of the metabolites (pyrazinoic acid, 5-hydroxy-pyrazinamide, 5-hydroxy-pyrazinoic acid and pyrazinuric acid) were seen.

CSF PK

In the publication by Holdiness (1985),[14] this publication reviewed CSF PK of anti-TB drugs and quoted at that time penetration of pyrazinamide in CSF in only 1 case of active meningitis.[15]

Evaluator's overall conclusion of PKs

- The literature-based submission provided a number of studies in healthy subjects and patients with TB, examining PK after 15-35 mg/kg oral pyrazinamide (n=4-23 subjects per study). C_{max} ranged from 21.1-51.97 µg/mL, AUC ~200-500 µg.h/mL, T_{max} ~1-4 hours and $T_{½}$ ~5-10 hours.
- Diabetes mellitus was associated with reduced pyrazinamide exposure.
- In HIV patients with TB, increase in immune activation was associated with reduced pyrazinamide clearance.

[13] Lacroix, C., Phan Hoang, T., Nouveau, J. *et al.* Pharmacokinetics of pyrazinamide and its metabolites in healthy subjects. *Eur J Clin Pharmacol* **36**, 395–400 (1989). https://doi.org/10.1007/BF00558302

[14] Holdiness M. R. (1984). Clinical pharmacokinetics of the antituberculosis drugs. *Clinical pharmacokinetics*, *9*(6), 511–544. https://doi.org/10.2165/00003088-198409060-00003

[15] Forgan-Smith R, Ellard G.A, Newton D, Mitchison D.A. Pyrazinamide and other drugs in Tuberculous Meningitis. Lancet 1973; 302:374 https://doi.org/10.1016/S0140-6736(73)93211-X

In summary, after a 15-35 mg/kg dose C_{max} ranged from 21.1-51.2 micrograms/mL, with a T_{max} of 1-4 hours and a plasma half-life of 5-10 hours.

The Delegate noted (as per US FDA labelling) that pyrazinamide is well absorbed and metabolized in the lever with a single major excretory product, 5-hydrozypyrazinoic acid. Approximately 70% of the dose is excreted (as transformed) in urine. The plasma half-life may be prolonged in patients with impaired hepatic or renal function.

No data is provided for Pharmacodynamics.

Efficacy

The use of pyrazinamide in combination with other anti-tuberculous agents in the treatment of active tuberculosis was solely supported by the literature-based submission provided by the sponsor, as described above. The search was carried out to identify clinical studies assessing efficacy and safety, from Medline and EMBASE databases using the TGA-approved search strategy and selection criteria.

Most studies reported after 2000 were conducted after seeking ethics approval. It was also difficult to blind investigators or patients in most studies technically because of comparison of single vs. multiple dose or combined treatments vs. separate drugs. The studies covered ranged from 13 years of age upwards to 89 years of age. They were from a large range of geographic locations, although ethnicity was not specified.

All studies used conventional oral formulations of pyrazinamide, as proposed. All studies furthermore investigated oral pyrazinamide in combination with other anti-tuberculous agents, as proposed. The main study outcome in most of the studies was absence of bacteriological response or a negative culture or disappearance of clinical symptoms at the end of treatment. This is an appropriate endpoint.

The efficacy of pyrazinamide was supported by the submission of published versions of study reports. The studies mostly examined the efficacy of pyrazinamide in the proposed dosage but in combination with other anti-TB medications, which the CE has noted is standard clinical practice.

As pyrazinamide is a standard component of initial TB treatment protocols the submitted literature does not provide evidence of its efficacy versus protocols that do not include it. However, the submitted studies have demonstrated the efficacy of pyrazinamide in a range of combination protocols and treatment durations (e.g. 6 months vs 4 months daily therapy).

Evaluator's conclusions on clinical efficacy

- Pyrazinamide is a component of an initial anti-TB regimen used in accord with guidelines promoted through Australian states as well as the WHO.
- A range of randomised, literature-based trials in the current submission involving pyrazinamide in combination with other anti-TB treatments, usually as a regimen in the first 2 months of treatment, has shown it is an efficacious component of treatment of pulmonary TB, due to *Mycobacterium tuberculosis.*
- When used as part of a multi-modal drug combination, pyrazinamide is associated with microbiological, clinical and radiological clearance in up to 80-100% of cases.
- The bulk of data for pyrazinamide use in this fashion is in patients >12 years of age. There are a lack of data in childhood use.

- The use of pyrazinamide as part of a treatment regimen for extra-pulmonary TB is less well documented but in relevant studies does show some efficacy.
- The efficacy of pyrazinamide is best demonstrated in patients with drug-sensitive TB. The use of pyrazinamide in MDR TB is not well documented.

Safety

The current submission, being literature-based, presented a range of RCT studies which were uneven in terms of safety reporting. Furthermore, the safety of pyrazinamide per se was not examined in the studies presented as the medicine was used in combination with other potentially toxic medications (e.g. ethambutol, isoniazid). Individual publications generally do not provide a statistical analysis of adverse events to the same degree of detail as do primary clinical trial reports.

The toxicity of pyrazinamide is, however, relatively well understood given its decades of use in the treatment of TB. The most frequently reported adverse effect is hepatotoxicity with increases in AT (aminotransferases), jaundice or potential hepatitis, as well as other gastrointestinal changes such as nausea and vomiting. This may be dose related, with hepatotoxicity occurring in about 15% of patients, and jaundice in 2-3%.

Pyrazinamide inhibits renal excretion of urates and frequently results in hyperuricaemia and symptomatic gout. Non-gouty polyarthralgia can occur in up to 40% of patients.

Anaemia and hypersensitivity have rarely occurred.

Generally, the medication is well tolerated in the context of supervised administration, and TB being a severe and potentially life-threatening infection.

Evaluator's conclusions on clinical safety

- Pyrazinamide when used in combination for initial induction treatment of TB (usually 2 months) is associated with varying degrees of hepatotoxicity, but other gastrointestinal side effects such as anorexia, nausea and vomiting in addition to hyperuricaemia, as highlighted in the literature-based survey, are described in up to >25-50% of patients.
- Liver function should be closely monitored during treatment which may also include other anti-TB drugs used in combination treatment and may necessitate withdrawal of treatment.

Risk management plan

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 9. The TGA may request an updated RMP at any stage of a product's life cycle, during both the pre-approval and post-approval phases.

Table 9: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Severe liver disorders	✓	_	✓	_
	Porphyria	✓	_	✓	_

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important potential risks	Interaction with other medicinal products	✓	–	✓	–
Missing information	Use in children and adolescent	✓	–	✓	–
	Use in pregnant women	✓	–	✓	–

RMP evaluator recommendations regarding conditions of registration

- Pyrazinamide-AFT (pyrazinamide) is to be included in the Black Triangle Scheme. The PI and CMI for Pyrazinamide-AFT must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date of first supply of the product.
- The Pyrazinamide-AFT AU-Risk Management Plan (RMP) version 0.3 (dated 19 February 2024, data lock point 19 February 2024), included with submission PM-2023-03087-1-2, to be revised to the satisfaction of the TGA, and any subsequent revisions, will be implemented in Australia.
- An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six-monthly reports may be submitted separately as they become available.

  If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must be submitted within ninety calendar days of the data lock point for that report.

Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach. Information on the Australia-specific annex (ASA) can be found on the TGA website.

Risk-benefit assessment

Delegate's considerations

Pyrazinamide was one of the first successful treatments for TB; developed and entering into clinical practice in 1952. In combination with rifampicin, ethambutol and isoniazid it remains the most common medication used for the initial treatment of drug-susceptible TB, and this is reflected in Australian[16] and World Health Organisation (WHO)[17] treatment guidelines.

The Delegate has considered this application in the context of this nearly 90-year history of clinical use, which provides a significant amount of 'real world' information about the safety and efficacy of pyrazinamide. However, the age of this medication also precludes basing an approval decision on a modern regulatory dossier. In particular, there is a lack of controlled trials demonstrating the absolute efficacy of pyrazinamide in comparison to treatment protocols that do not include it for first line treatment of drug susceptible TB.

The clinical evaluator has noted that there is a paucity of data supporting the use of pyrazinamide in children in this submission. That being so, TB does rarely occur in children and pyrazinamide is generally recommended for use. The Delegate feels that it is appropriate to provide an advisory regarding the lack of robust data for use in children, while acknowledging that clinical practice does include this use of necessity to treat TB.

Assessment outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register Pyrazinamide AFT (pyrazinamide) 500 mg tablet indicated for:

> *Pyrazinamide-AFT is indicated in adult patients of more than 12 years of age with active drug-sensitive tuberculosis caused by Mycobacterium tuberculosis. Pyrazinamide-AFT is an anti-tuberculosis agent used in combination with other anti- tuberculosis agents and is commonly used in the first 2 months of treatment.*

Specific conditions of registration

- Pyrazinamide-AFT (pyrazinamide) is to be included in the Black Triangle Scheme. The PI and CMI for Pyrazinamide-AFT must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date of first supply of the product.
- The Pyrazinamide-AFT AU-Risk Management Plan (RMP) version 0.3 (dated 19 February 2024, data lock point 19 February 2024), included with submission PM-2023-03087-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs). Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such

[16] CDNA National Guidelines for Public Health Units: Tuberculosis, CDNA (2022) https://www.health.gov.au/sites/default/files/documents/2022/06/tuberculosis-cdna-national-guidelines-for-public-health-units.pdf

[17] WHO consolidated guidelines on tuberculosis module 4: drug susceptible tuberculosis treatment, WHO (2022) https://iris.who.int/bitstream/handle/10665/353829/9789240048126-eng.pdf?sequence=1

reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six-monthly reports may be submitted separately as they become available.

If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII- periodic safety update report (Rev 1), Part VII.B Structures and processes.

Note that submission of a PSUR does not constitute an application to vary the registration. Each report must be submitted within ninety calendar days of the data lock point for that report.

Product Information and Consumer Medicine Information

For the most recent Product Information (PI) and Consumer Medicine Information (CMI), please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

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Reference/Publication #