



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Tolvaptan

Proprietary Product Name: Jinarc

Sponsor: Otsuka Australia Pharmaceutical Pty
Ltd

February 2018

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Contents

Common abbreviations	5
I. Introduction to product submission	8
Submission details	8
Product background	9
Regulatory status	10
Product Information	11
II. Registration timeline	11
III. Quality findings	11
Introduction	11
Drug substance (active ingredient)	12
Drug product	13
Biopharmaceutics	14
Quality summary and conclusions	14
IV. Nonclinical findings	14
Introduction	14
Pharmacology	15
Pharmacokinetics	17
Toxicology	18
Nonclinical summary and conclusions	23
V. Clinical findings	25
Introduction	25
Pharmacokinetics	27
Pharmacodynamics	28
Dosage selection for the pivotal studies	30
Efficacy	30
Safety	32
First round benefit-risk assessment	34
First round recommendation regarding authorisation	35
Clinical questions and second round evaluation of clinical data submitted in response to questions	35
Second round benefit-risk assessment	36
VI. Pharmacovigilance findings	38
Risk management plan	38
VII. Overall conclusion and risk/benefit assessment	42
Background	42

Quality	43
Nonclinical	43
Clinical	44
Risk management plan	47
Risk-benefit analysis	48
Outcome	56
Attachment 1. Product Information	56
Attachment 2. Extract from the Clinical Evaluation Report	57

Common abbreviations

Abbreviation	Meaning
ADPKD	Autosomal Dominant Polycystic Kidney Disease
AE	Adverse Event
ALT	Alanine Transaminase
API	active pharmaceutical ingredient
APTT	activated partial thromboplastin time
ARTG	Australian Register of Therapeutic Goods
AST	Aspartate Transaminase
ATP	Adenosine triphosphate
AUC	Area under the curve
AUC ₀₋₂₄	Area under the curve from 0 to 24 hours
AVP	arginine vasopressin
BD	Twice daily
BRAF	Serine/threonine protein kinase B-Raf
BT	Total Bilirubin
BUN	Blood urea nitrogen
cAMP	Cyclic adenosine monophosphate
CCDS	Company core data sheet
CI	Confidence interval
CKD	Chronic Kidney Disease
C _{max}	Maximum concentration
CMI	Consumer Medicines Information
CV	Coefficient of variation
DILI	Drug-induced liver injury
eGFR	Estimated glomerular filtration rate

Abbreviation	Meaning
eGFRCKD-EPI	Estimated glomerular filtration rate chronic kidney diseases epidemiology collaboration
ESRD	End stage renal disease
EMA	European Medicines Agency
EU-SmPC	European summary of product characteristics
FDA	Food and Drug Administration (USA)
GCP	Good Clinical Practice
GD	gestation day(s)
GFR	Glomerular Filtration Rate
GLP	Good laboratory practice
IC50	Half maximal inhibitory concentration
ICH	International Conference on Harmonisation
IV	Intravenous
L	Litre(s)
LFTs	Liver function tests
mg	Milligram(s)
mOsm	Milliosmoles
NLT	not less than
NMT	not more than
NOAEL	No observable effect level
PADER	periodic adverse drug experience report
PD	Pharmacodynamics
PI	Product Information
PK	Pharmacokinetics
PKD	Polycystic Kidney Disease
PO	Per oral

Abbreviation	Meaning
PSD	particle size distribution
PSURs	periodic safety update reports
PT	Prothrombin time
RBF	Renal blood flow
SAE	Serious Adverse Event
TGA	Therapeutic Goods Administration
TKV	Total kidney volume
T _{max}	Time of maximum concentration
ULN	Upper limit of normal

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Extension of indications, new strength and dose
<i>Decision:</i>	Approved
<i>Date of decision:</i>	10 March 2017
<i>Date of entry onto ARTG</i>	24 March 2017
<i>Active ingredient:</i>	Tolvaptan
<i>Product name:</i>	Jinarc
<i>Sponsor's name and address:</i>	Otsuka Australia Pharmaceutical Pty Ltd Suite 2.03 Level 2, 9 Help Street Chatswood NSW 2067
<i>Dose form:</i>	tablet
<i>Strengths:</i>	15 mg, 30 mg, 45 mg, 60 mg and 90 mg
<i>Container:</i>	Blister pack and composite packs
<i>Pack sizes:</i>	7 tablets and 28 tablets [15 mg and 30mg] 56 tablets [15 mg and 45 mg tablet composite pack] 56 tablets [30 mg and 60 mg tablet composite pack] 56 tablets [30 mg and 90 mg tablet composite pack]
<i>Approved therapeutic use:</i>	<i>Jinarc is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with chronic kidney disease (CKD) stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease (see PHARMACOLOGY)."</i>
<i>Route of administration:</i>	oral
<i>Dosage:</i>	Jinarc treatment must be initiated and monitored under the supervision of physicians with expertise in managing ADPKD and a full understanding of the risks of tolvaptan therapy including hepatic toxicity and monitoring requirements (see PRECAUTIONS). For the full instructions of dosage and administration please see the Product Information (PI)
<i>ARTG numbers:</i>	272785, 272786, 272787, 272788, 272789

Product background

This AusPAR describes the application by Otsuka Australia Pharmaceutical Pty Ltd (the sponsor) to register Jinarc, tolvaptan 15 mg, 30 mg, 45 mg, 60 mg and 90 mg tablets in blister packs and composite packs for the following indication:

Jinarc is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease (see PHARMACOLOGY).

This is a submission to register a new indication for tolvaptan. The submission also proposes a new trade name for the product and the registration of additional strengths.

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited disorder characterised by the formation of multiple fluid filled cysts in the kidneys. The cysts develop from mutated tubular epithelial cells scattered throughout the kidney. It is caused by a mutation in one of two genes (PKD1 or PKD2) involved in the regulation of tubular and vascular development in the kidneys and other organs. Mutations in PKD1 are more common, accounting for 85% of ADPKD cases.

Clinical manifestations of ADPKD are highly variable. Common features include hypertension, flank pain, haematuria, pyelonephritis and renal cyst infections. Renal failure requiring dialysis develops in approximately 50% of subjects, usually between the ages of 30 and 60 years.

Tolvaptan is an antagonist of the vasopressin V2 receptor. In ADPKD, cyclic adenosine monophosphate (cAMP) is known to promote abnormal cyst cell proliferation and secretion of fluid into the cysts, and vasopressin is a potent activator of renal adenyl cyclase, the enzyme responsible for conversion of adenosine triphosphate (ATP) to cAMP. ADPKD is also associated with upregulation of the vasopressin V2 receptor and increased circulating levels of vasopressin. The rationale for the development of tolvaptan as a treatment for ADPKD is based on the drug's ability to inhibit the effects of vasopressin through inhibition of the vasopressin V2 receptor.

There are currently no drugs registered in Australia for the treatment of ADPKD.

The proposed dosage regimen for Jinarc is a twice daily regimen, with the first dose taken upon waking and the second dose 8 hours later. Three dose levels are proposed:

- 45 mg + 15 mg (total 60 mg/day);
- 60 mg + 30 mg (total 90 mg/day);
- 90 mg + 30 mg (total 120 mg/day).

The morning dose is to be taken at least 30 minutes before the morning meal. The second dose can be taken with or without food.

The proposed starting dose is the 45+15 regimen. The dose is then titrated upwards (with at least weekly intervals between titrations) through the two higher regimens. Patients are maintained on the highest dose regimen tolerated. Treatment is to continue indefinitely.

Tolvaptan is currently registered in Australia under the trade name Samsca, for the treatment of clinically significant hyponatremia. Due to the need for a dose titration phase with close monitoring of serum sodium and volume status, treatment with Samsca should be initiated and re-initiated in hospital. Administration for more than 30 days is not recommended due to the risk of hepatic toxicity.

Regulatory status

Tolvaptan received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 4 April 2012 under the trade name Samsca indicated for:

“Samsca is indicated for the treatment of clinically significant hypervolemic or euvoletic hyponatremia (serum sodium less than 125 mmol/L, or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction) including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).

Important Limitations

Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms should not be treated with Samsca. It has not been established that raising serum sodium with Samsca provides a symptomatic benefit to patients.”

At the time the TGA considered this application; a similar application had been approved or was under consideration in the countries as outlined in Table 1.

Table 1: International regulatory status

Country	Submission dates and status	Indication
European Union	Submitted 22 November 2013 Approved 27 May 2015	Jinarc is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease
United States of America	Submitted 1 March 2013	
Canada	Submitted 27 March 2014 Approved 25 February 2015	Jinarc™ (tolvaptan) is indicated to slow the progression of kidney enlargement in patients with autosomal dominant polycystic kidney disease (ADPKD). In ADPKD, kidney enlargement reflects renal cyst burden.
Switzerland	Submitted 3 October 2014 Approved 21 April 2016	Same as EU
Japan	Submitted 30 May 2013 Approved 24 March 2014	Suppression of progression of autosomal dominant polycystic kidney disease (ADPKD) in patients with increased kidney volume and a rapid rate of increase

Country	Submission dates and status	Indication
Republic of Korea	Submitted 30 June 2015 Approved 1 December 2015	Same as EU

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at < <https://www.tga.gov.au/product-information-pi>>.

II. Registration timeline

Table 2: Registration timeline

Description	Date
Submission dossier accepted and 1st round evaluation commenced	29 February 2016
1st round evaluation completed	14 August 2016
Sponsor provides responses on questions raised in 1st round evaluation	4 October 2016
2nd round evaluation completed	18 November 2016
Delegate's overall risk-benefit assessment and request for Advisory Committee advice	3 January 2017
Sponsor's pre-Advisory Committee meeting response	12 January 2017
Advisory Committee meeting	3 March 2017
Registration decision	10 March 2017
Entry onto ARTG	24 March 2017
Number of TGA working days from submission dossier acceptance to registration decision *	225

* Target timeframe for standard applications: 220 working days

III. Quality findings

Introduction

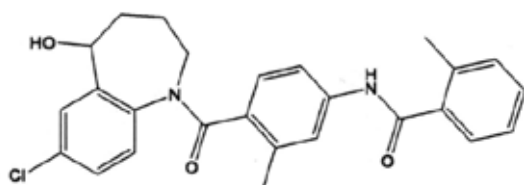
Otsuka Australia Pharmaceutical Pty Ltd seeks to register 45, 60 and 90 mg tolvaptan tablets. The tablets will be marketed in combination with sponsors registered tablets of 15 mg and 30 mg tolvaptan (under the trade name Samsca). Jinarc is to be administered twice daily in split dose regimens of 45 mg + 15 mg, 60 mg + 30 mg or 90 mg + 30 mg. The

morning dose is to be taken at least 30 minutes before the morning meal. The second daily dose can be taken with or without food.

Drug substance (active ingredient)

Tolvaptan (CAS: N-[4-(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1H-1-benzazepin-1-yl)carbonyl]-3-methylphenyl]-2-methyl-benzamide) is a white crystalline powder.

Figure 1 structure of tolvaptan



Tolvaptan is practically insoluble in water and the aqueous solubility of the drug substance is poor (approximately 0.01 mg/250 mL) across all pH ranges, as shown below. Tolvaptan is classified as a Class IV (low solubility, low permeability) compound as per the Biopharmaceutical Classification System (BCS).

Table 3: solubility profile of tolvaptan

Britton-Robinson Buffer pH	Solubility at 25°C (% w/v)
2.0	0.00004
4.0	0.00004
7.0	0.00004
10.0	0.00004
12.0	0.00003

Tolvaptan has an asymmetric centre and can exist as two enantiomers, however, the drug substance has been developed as the racemate. The octanol:water partition coefficient was reported to be greater than 5,000 at 25°C. No polymorphs or solvates have been observed.

Tolvaptan is made by chemical synthesis. The drug substance is manufactured in three major stages and involves two designated GMP starting materials. These have been justified. The manufacturing process description includes process parameters and in-process controls for all steps. Final purification is by recrystallization from an aqueous methanol (80%) solution. The retest period is 60 months when stored in the proposed container closure system and below 30°C.

The drug product manufacturer has included an intermediate step in the drug product manufacturing process to spray dry the drug substance with a water soluble polymer to enhance solubility. The spray dried material, referred as tolvaptan SD powder, is controlled by a particle size distribution mean 20 to 55 µm and D90 not more than (NMT) 75 µm.

All other tests imposed on the drug substance by the finished product manufacturer are standard for an active pharmaceutical ingredient (API) and include description, identification, melting point, heavy metals, assay, impurities, residue on ignition, loss on drying and optical rotation. The proposed drug substance specifications and specifications applied for Tolvaptan SD powder are considered adequate to ensure the quality and consistency of manufacture of the finished product.

Drug product

The proposed products are described in Table 4.

Table 4: Description of tolvaptan tablets

Dosage Form	Strength	Description
Tablet	15 mg	Blue, triangular, shallow-convex, bevelled-edge tablet, debossed with "OTSUKA" and "15" on one side
	30 mg	Blue, round, shallow-convex, bevelled-edge tablet, debossed with "OTSUKA" and "30" on one side
	45 mg	Blue, square, shallow-convex, bevelled-edge tablet, debossed with "OTSUKA" and "45" on one side
	60 mg	Blue, modified rectangular, shallow-convex, bevelled-edge tablet, debossed with "OTSUKA" and "60" on one side
	90 mg	Blue, pentagon, shallow-convex, bevelled-edge tablet, debossed with "OTSUKA" and "90" on one side

The formulation development of Samsca (tolvaptan 15 mg and 30 mg) tablets has been previously evaluated and approved by TGA. The components, manufacturing process and materials of construction of the packaging are the same for the new strengths (that is, 45, 60 and 90 mg tablets). In vivo bioequivalence has been demonstrated between 30 mg and proposed commercial 90 mg tolvaptan tablets with a dosing group of 3 x 30 mg tablets versus 1 x 90 mg tablet (Study No.156-11-295).

The particle size distribution (PSD) of the spray dried tolvaptan powder is based on that used in the manufacture of the bio-batch and is acceptable.

The finished product is appropriately controlled using the finished product specifications. The specifications include acceptable tests and limits for appearance, identification, impurities, uniformity of dosage units, dissolution, assay and microbial levels. The proposed finished specifications are considered adequate to ensure the quality of the finished product at release and throughout the shelf life.

The discriminatory power of the dissolution method has been demonstrated. Dissolution limits of not less than (NLT) 80% (Q) at 30 minutes (45 and 60 mg tablets) and NLT 80% (Q) at 45 minutes (90 mg tablets) have been set and are considered appropriate.

The container closure system is a PVC/aluminium foil blister pack stored within a carton.

A shelf life of 48 months "Store below 25°C, Store in the original package in order to protect from light and moisture" is recommended for the tolvaptan 15, 30 and 60 mg tablets.

A shelf-life of 36 months is recommended for the tolvaptan 45 and 90 mg tablets. For 45mg/15mg and 90mg/30mg combination packs, a shelf-life of 36 months will apply

Chemistry and quality control aspects are considered acceptable.

Biopharmaceutics

Study 156-11-295 was an open label, randomized, crossover trial to assess dose strength equivalence among 30 and 90 mg Strengths of oral tolervaptan tablets and to determine the effect of food (standard food and drug administration high-fat breakfast) on tolervaptan pharmacokinetics following the 90 mg tablet in healthy subjects.

The results of the log transformed pharmacokinetic data are summarised below:

Table 5: Tolervaptan (1 x 90 mg versus 3 x 30 mg)

	Reported GMR*	Reported 90% CI
C_{max}	100.2	93.1 – 107.8
AUC_t	99.0	93.5 – 104.9

* - Geometric Mean Ratio

Table 6: Tolervaptan (Fed versus Fasted)

	Reported GMR*	Reported 90% CI
C_{max}	196.0	172.6 – 222.6
AUC_t	96.8	91.2 – 102.6

* - Geometric Mean Ratio

Mean maximum concentration (C_{max}) for single oral dose of tolervaptan 90 mg tablet increased 1.96 fold in the fed state, when compared to the fasted state. These results are in line with previous studies and demonstrate increased absorption and C_{max} when taken after a high fat meal. The PI document states that the morning dose is to be taken at least 30 minutes before the morning meal and the second daily dose can be taken with or without food for the dosage regimens of 45 mg + 15 mg, 60 mg + 30 mg or 90 mg + 30 mg.

The PI states that the administration of the second daily dose may be taken with or without food. This is a clinical matter that will be considered by the clinical evaluator.

The sponsor has submitted a justification for not providing bioavailability data on the 45 mg tolervaptan tablet, which is acceptable.

Quality summary and conclusions

Approval is recommended from pharmaceutical chemistry perspective.

A GMP clearance is not in place for the site Otsuka Pharmaceutical Co. Ltd, Tokushima Factory, 463-10 Kagasuno, Kawauchi-cho, Tokushima-shi, Tokushima-7710192, Japan. The site is responsible for manufacture of the dosage form. Registration is thus not recommended with respect to chemistry and quality control perspective until a current GMP clearance is in place for the afore-mentioned site.

IV. Nonclinical findings

Introduction

Otsuka Australia Pharmaceutical Pty Ltd has applied to register a new indication, a new brand (Jinarc, specific for the new indication) and new tablet strengths (specifically for the new brand) for tolervaptan.

Tolvaptan tablets, 15mg and 30mg are currently registered under the tradename Samsca, and indicated for the treatment of clinically significant hypervolemic or euvolemic hyponatremia (serum sodium less than 125 mmol/L, or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction) including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).

The new proposed indication for Jinarc (15, 30, 45, 60 and 90 mg tablets) is to slow the progression of cyst development and renal insufficiency of ADPKD in adults with chronic kidney disease (CKD) stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease.

ADPKD is a complex syndrome characterised by progressive development of cysts that impinge on and ultimately disrupt normal kidney architecture. Defects in the ADPKD gene lead to the disruption of the normal differentiated structure of renal tubular epithelium. Symptomatic manifestations of renal dysfunction are related to cyst number, age of the patient at initial cyst appearance, cyst distribution, and rate of cyst growth.

The proposed dosage is twice daily administration in split dose regimens of 45 mg + 15 mg, 60 mg + 30 mg or 90 mg + 30 mg. The morning dose is to be taken at least 30 minutes before the morning meal and the second daily dose can be taken with or without food. According to these split dose regimens the maximum recommended human dose (MRHD) is 120 mg daily. The current maximum recommended human dose (MRHD) is 60 mg/day.

Tolvaptan is a selective arginine vasopressin (AVP) V2 receptor antagonist. It is currently approved and marketed in Australia under the Samsca brand for the treatment of adults with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH). There is no approved drug in Australia indicated to slow kidney disease progression in adults with ADPKD.

Pharmacology

Primary pharmacology

Tolvaptan inhibits AVP-V2 receptors and decreases renal growth in mouse and rat models of polycystic kidney disease (PKD). The effectiveness of tolvaptan to decrease proliferation of mural cyst epithelial cells in human ADPKD was demonstrated by a study (Study 019680) using primary cell cultures obtained from patients with ADPKD. In this study, tolvaptan inhibited AVP induced cell proliferation (half maximal inhibitory concentration (IC₅₀) approximately 0.01 to 0.1 nM), cAMP accumulation (IC₅₀ approximately 0.1 to 1 nM), and phospho-ERK¹ expression (IC₅₀ approximately 0.01 to 0.1 nM), without affecting calcium levels. There was a trend for a decrease in AVP induced increase in serine/threonine protein kinase B-Raf (BRAF). Interestingly, tolvaptan inhibited the anti-proliferative effect of AVP in normal renal cortex cells.

Three animal models of human PKD (PCK rats, 2WS25/- mice and pcy mice) were used in primary pharmacology studies. The 3 animal models displayed increased kidney weights, cyst volumes and renal cAMP when compared with normal control animals. However, in one of the studies, the cAMP levels of the pcy mice were not different from control mice, and urine volumes in the pcy mice were actually elevated compared with control mice.

In the 3 animal models of PKD, tolvaptan significantly increased urine volume when administered in the diet. When it was administered via gavage to normal rats, a dose of 300 mg/kg twice daily (not when given once daily or < 300 mg/kg) caused a sustained (for

¹ ERK = extracellular signal related kinase

24 hours) aquaretic effect. Concentrations in the diet starting at 0.01% caused significant and sustained increases in urine volume.

Tolvaptan decreased renal cAMP in the 3 animal models, but the effects were not consistently significant. In PCK rats, renal cAMP was decreased when given in the diet but not when given via gavage at 10 mg/kg twice daily (the gavage treatment was also initiated at 5 weeks of age rather than at 3 weeks as in the diet administration).

Nevertheless, kidney volume, kidney weight, cyst volume, fibrosis volume, apoptotic index and mitotic index, were consistently reduced in the 3 animal models when tolvaptan was administered in the diet (when measured, cyst density was not affected). When measured, plasma/serum sodium and creatinine were only decreased in one of the studies (Study 018373), whereas urine osmolality was consistently decreased, demonstrating a true aquaretic (and not diuretic) effect by tolvaptan. Systolic blood pressure was not affected by tolvaptan when it was measured. Blood urea nitrogen (BUN) was decreased in mice but not in rats.

It was apparent that the dose in the diet, the age at which the treatment was initiated, and the duration of treatment, were all important factors in determining the strength of tolvaptan related effects. Due to the variability of the experimental conditions, it was not possible to analyse the relationship between these variables in rats.

Levels of tolvaptan in the diet at which an aquaretic effect was observed produced serum levels of 10 to 30 ng/mL in normal male rats (Study 017316), and 35.5 to 297.9 ng/mL in pcy mice (Study 28257). The level of tolvaptan in the serum increased dose proportionally in the PKC rats and the pcy mice, and no gender differences were observed in these limited pharmacokinetic studies.

The serum concentrations of tolvaptan at pharmacologically active doses were therefore lower in rodents than those found with clinical administration of tolvaptan (mean C_{max} 716 ng/mL (patients with ADPKD receiving 90 mg in the morning and 30 mg in the afternoon for 7 days)).

In summary, the pharmacological effects of tolvaptan in rodent models of PKD support its use for the propose indication.

Secondary pharmacodynamics and safety pharmacology

Tolvaptan significantly reduced ascites and oedema in rat models of cirrhosis and edema, and these effects are consistent with the aquaretic properties of tolvaptan.

In anaesthetised dogs, tolvaptan caused a significant increase in urine volume (with no increase in urine sodium and chloride excretion), vasopressin concentration and serum osmolality (without effect on renin activity), and a decrease in pulmonary capillary wedge pressure (with no decrease in blood pressure). These results suggest that the aquaretic effect of tolvaptan has no direct action on cardiovascular or renal haemodynamic functions.

Metabolite DM-4107 showed little affinity for human oxytocin receptors.

Pharmacodynamics drug interactions

A study was submitted in which furosemide and tolvaptan were administered independently to dogs with and without heart failure. Tolvaptan and furosemide increased plasma AVP concentrations, but did not cause an increase in peripheral vascular resistance or the aggravation of cardiac afterload or renal functions in either group. Tolvaptan did not stimulate the sympathetic nerves or the renin-angiotensin-aldosterone (R-AA) system or decrease serum potassium concentrations (in contrast to furosemide).

It is expected that concomitant administration of tolvaptan and furosemide will result in an increase in plasma renin activity (due to furosemide).

Pharmacokinetics

The analytical methods used were adequately described and validated.

After the administration of tolvaptan suspensions to the stomach and different parts of the intestine (using the in situ closed loop method) at a dose of 10 mg/kg, absorption at 2 hours was (compared to total absorption from gastrointestinal tract) 2.1% in the stomach, 36.9% in the duodenum, 24.8% in the jejunum, 27.3% in the ileum, and 9.0% in the large intestine. When 10, 30 and 100 mg/kg were administered in the duodenum, the serum concentrations of tolvaptan increased with the increase of dosage.

In a tissue distribution study (to investigate the tissue distribution of radioactivity in pigmented rats), the serum concentration of radioactivity was determined following single oral administration of ^{14}C -OPC-41061 suspension at 30 mg/kg to fasted male Long-Evans rats.

Tissue time of maximum concentration (T_{max}) values were 2 hours (coinciding with serum C_{max}), and the radioactivity in all tissues decreased gradually. In the melanin-containing tissues (eyeball and pigmented skin), the radioactivity concentrations were lower than those in the serum. The radioactivity concentration in the pigmented skin was similar to that in the non-pigmented skin. No retention of tolvaptan is expected in melanin-containing tissues.

The serum levels of tolvaptan at Day 42 in juvenile rats were 4 to 7 times greater in females than males, consistent with approximately 10 times higher exposure in female than male rats in adults studies.

Pharmacokinetic drug interactions²

Studies with tolvaptan and its main metabolites to assess the potential inhibition of drug transporters (BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, BSEP, MATE1, and MATE2-K³) showed that BCRP, OATP1B3 and OCT1 are potential sites of pharmacokinetic (PK) drug interactions in vivo. Adequate cautionary statements on the tolvaptan's use with substrates for OAT3, OCT1, BCRP, OATP1B1 and 1B3A have been proposed in the PI (under 'Transporter substrates').

² The following assumptions were made:

- molecular weight, 448.94 dose, 90 mg; C_{max} , 1.5949 μM (total); free fraction, 1.5%; intestinal volume, 0.25 L; absorption rate constant, 0.1 min^{-1}
- for intestinal transporter BCRP: if the IC_{50} is ≤ 0.1 -fold the intestinal concentration, an *in vivo* interaction is considered possible
- for renal uptake and efflux transporters, and hepatic efflux transporters (OAT1, OAT3, OCT2, MRP2, BCRP, MATE1 and MATE2K): if the IC_{50} is ≤ 50 -fold the unbound clinical C_{max} , an *in vivo* interaction is considered possible
- for hepatic uptake transporters (OCT1, OATP1B1 and OATP1B3): if the IC_{50} is ≤ 25 -fold the unbound hepatic inlet concentration, an *in vivo* interaction is considered possible.

³ BCRP; breast cancer resistance protein, OATP; organic anion transporting polypeptide, OAT organic anion transporter, OCT; organic cation transporter BSEP; bile salt export pump, MATE; multi drug and toxin extrusion protein

Toxicology

Relative exposure

Exposure ratios have been calculated based on animal:human serum/plasma AUC_{0-24h} values for tolvaptan and (where data were available) its major human metabolites (see Table 7 below). Human reference values are for the maximum recommended daily dose of 120 mg in patients with ADPKD for tolvaptan (Clinical Study 156-09-285) and the metabolites (Clinical Study 156-09-284; AUC₀₋₂₄ extrapolated from AUC₀₋₅). Multiples of the human dose adjusted for body surface area (BSA) are also tabulated.

Table 7: Relative exposure

Species	Study	Sex	Dose (mg/kg/day); PO	AUC ₀₋₂₄ (µg.h/mL)			Exposure ratio based on AUC			based on BSA #
				Tolvaptan	DM-4103*	DM-4107*	Tolvaptan	DM-4103	DM-4107	
Mouse (B6C3F1)	13 weeks (013773)	M	100	830	3.80	–	1.3	0.04	–	3.8
		F		931	152	720	1.4	0.17	1.5	
	2 years (014252)	M	10	043	0.59	0.14	0.07	0.01	0.03	0.4
			30	138	1.43	0.42	0.21	0.02	0.09	1.1
			60	286	6.07	1.22	0.44	0.07	0.26	2.3
		F	10	018	1.03	0.30	0.03	0.01	0.06	0.4

Species	Study	Sex	Dose (mg/kg/day); PO	AUC ₀₋₂₄ (µg.h/mL)			Exposure ratio			
							based on AUC			based on BSA #
				Tolvaptan	DM-4103*	DM-4107*	Tolvaptan	DM-4103	DM-4107	
			30	0.90	4.41	1.51	0.14	0.05	0.32	1.1
			100	4.33	7.29	1.17	0.66	0.80	2.5	3.8
Rat (SD)	6 months (013774)	M	30	2.21	6.28	4.82	0.34	0.07	1.0	2.3
			100	7.76	7.16	2.86	1.2	0.79	6	7.6
			1000	12.7	5.81	2.98	1.9	6	6.3	7.5.8
		F	30	1.59	1.7	4.34	2.4	0.02	0.92	As above
			100	2.07	1.23	2.03	3.2	0.14	4.3	
			1000	3.34	-	-	5.1	-	-	
	2 years (01425)	M	300	7.7	2.5	6.3	1.2	2.8	1.3	2.3

Species	Study	Sex	Dose (mg/kg/day); PO	AUC ₀₋₂₄ (µg.h/mL)			Exposure ratio based on AUC			based on BSA #
				Tolvaptan	DM-4103*	DM-4107*	Tolvaptan	DM-4103	DM-4107	
	3)			8	4	4				
		F		24.7	90.9	61.9	3.8	1.0	1.3	
Dog (Beagle)	52 weeks (012707)	M	30	9.79	1.19	0.39	1.5	0.01	0.08	7.6
			100	31.5	6.36	1.48	4.8	0.07	0.31	2.5
			1000	27.1	1.62	7.40	4.1	0.18	1.6	2.52
		F	30	6.77	3.10	0.68	1.0	0.03	0.14	Ass above
			100	42.3	9.16	2.63	6	0.10	0.56	
			1000	22.8	3.46	2.20	3.5	0.38	4.7	
Human	156-09-285; 156-06-284	M / F	[90+30 mg]	6.57	90.7	4.7	–	–	–	–

#body surface-area adjusted doses have been calculated using mg/kg to mg/m² conversion factors of 3, 6, 20 and 33 in mice, rats, dogs and humans (50 kg) respectively. * = AUC_{0-5h}: 18,900 and 978 ng.h/mL for DM-4103 and DM-4107, respectively. M = male F = female

While high doses (on a body surface area basis) were used, animal:human exposure ratios for tolvaptan were low in rodents. A large multiple of the human AUC for tolvaptan was obtained at the high dose level in the pivotal dog study.

Major findings

In the previous submission, increased water consumption and urine volume, and an associated decrease in urine osmolality, were seen in all of the studies in rats and dogs, and are consistent with the drug's pharmacological action (these parameters were not assessed in the study in mice). In most studies there was evidence of at least transient body weight loss and/or a reduction in body weight gain, which was accompanied by a transient reduction in food consumption, and probably related to dehydration.

The pivotal studies established no observable effect levels (NOAELs) of 100 mg/kg/day per oral (PO) in dogs (relative exposure, approximately 5 to 6) and female rats (relative exposure, 3.2), and 1000 mg/kg/day PO in male rats (relative exposure, 1.9).

Major toxicities

The toxicity profile of tolvaptan has been established in pivotal repeat dose toxicity studies conducted by the oral route in rats (26 weeks) and dogs (52 weeks). Significant findings were consistent with exaggerated pharmacology and non-specific toxicity (stress) only. The highest doses without adverse effect were established to be 100 mg/kg/day PO in dogs and female rats, and 1000 mg/kg/day PO in male rats.

Reproductive toxicity

Reproductive toxicity studies covered all stages (fertility and early embryonic development, embryofetal development and pre-/postnatal development). Numbers of animals, the timing and duration of treatment, and the range of species (rat/rabbit) were appropriate. All studies involved oral administration. The spray dried formulation was used in all of the studies in rabbits and in the definitive studies in rats.

Relative exposure

Table 8: Relative exposure; reproductive toxicity

Species	Study; (day of sampling)	Dose (mg/kg /day); PO	AUC ₀₋₂₄ (µg.h/mL)			Exposure ratio			
						based on AUC			base d on BSA#
			Tolvaptan	DM-4103*	DM-4107*	Tolvaptan	DM-4103	DM-4107	
Rat (SD)	012903 (GD17)	100	28.7	22.7	12.0	4.4	0.3	2.6	8
		1000	113.8	203.6	192.5	17	2.2	41	76
Rabbit (NZW)	012779 (GD18)	100	3.9	259.9	35.3	0.6	2.9	7.5	15
		300	8.1	471.6	101.7	1.2	5.2	22	45
		1000	16.9	1601.6	408.5	2.6	18	87	152
	013578 (GD11)	300	17.0	325.0	87.9	2.6	3.6	19	45
		1000	48.3	831.9	327.3	7.4	9.2	70	152
Human	156-09-285; 156-06-284	[90+30 mg]	6.57	90.7	4.7	–	–	–	–

#body surface-area adjusted doses have been calculated using mg/kg to mg/m² conversion factors of 6, 12 and 33 in rats, rabbits and humans (50 kg) respectively; GD = gestation day; * = AUC_{0-5h}; 18900 and 978 ng.h/mL for DM-4103 and DM-4107, respectively.

Placental transfer of tolvaptan and/or its metabolites was demonstrated in the rat. Peak levels of ^{14}C -tolvaptan derived radioactivity in the whole fetus and the fetal liver were 27% and 54%, respectively, of the maternal serum C_{max} . Tolvaptan, DM-4103 and DM-4107 were also detected in the embryo of rabbits after oral administration of the drug. Tolvaptan and/or its metabolites were readily excreted in milk in lactating rats, with the peak concentration of ^{14}C -tolvaptan derived radioactivity almost 12 times higher in milk compared with in blood.

Male and female fertility were unaffected in rats treated with tolvaptan at $\leq 1000 \text{ mg/kg/day PO}$ (relative exposure based on AUC, 1.9 and 5.1 in the respective sexes). However, a significant increase in the incidence of altered oestrus cycles (prolonged diestrus) was observed at $\geq 300 \text{ mg/kg/day}$ (relative exposure, ≥ 3.8). Slight (approximately 10%), but statistically significant, reductions in the mean number of corpora lutea and the number of implantations were seen at 1000 mg/kg/day compared with concurrent controls. However, these were in line with historical control values and are therefore not considered to be treatment related.

Adverse effects on embryofetal development were observed in both species tested. In rats, decreased fetal weight and impaired ossification were observed at $1000 \text{ mg/kg/day PO}$ (relative exposure based on AUC, 17), a maternotoxic dose (maternal body weight gain over the treatment period was 27% lower compared with controls). More severe effects, including teratogenicity, were seen in rabbits. General toxicological effects (decreased maternal body weight gain and food consumption) were evident at $\geq 30 \text{ mg/kg/day PO}$, and abortions occurred at $\geq 300 \text{ mg/kg/day}$ (on gestation day(s) (GD) 25 to 27; relative exposure, 1.2). Treatment at $1000 \text{ mg/kg/day PO}$ was associated with increased post implantation loss (early resorptions), decreased live litter size and fetal malformations (microphthalmia, open eyelids, cleft palate, brachymelia and bent radius, tibia and fibula). A follow-up study identified GD 9 to 11 as the period of maximum sensitivity to teratogenicity by tolvaptan in the rabbit. Exposure to tolvaptan declined with ongoing treatment. Based on data for GD 11, exposure to tolvaptan at this dose in rabbits was 7.4 times that of patients at the maximum recommended dose (120 mg/day). In further studies in rabbits investigating the mechanism for teratogenicity, dehydration and plasma electrolyte changes (through water restriction) were not associated with malformations. Noting that biotin deficiency has been linked to similar teratogenic effects in other species (mouse and hamster; though not previously the rabbit), the sponsor demonstrated that treatment with tolvaptan at 1000 mg/kg/day markedly decreased maternal plasma biotin levels and significantly reduced the biotin concentration of the whole embryo (to approximately 35% of control levels) in pregnant rabbits. Exposure ratios for tolvaptan at the NOAELs for embryofetal toxicity in the rat and rabbit (100 and 300 mg/kg/day , respectively) are low (4.4 and 1.2 times the clinical AUC).

Tolvaptan had no effect on pre-/postnatal development in the rat at doses up to $\leq 100 \text{ mg/kg/day PO}$. Reduced perinatal survival and decreased postnatal body weight gain (during the lactation period and after weaning), but no effects on other developmental parameters, were observed in the offspring at 1000 mg/kg/day (a maternotoxic dose).

Pregnancy classification

The sponsor has proposed Category D, which is the category assigned to tolvaptan for a different indication. Teratogenicity and embryofetal lethality in rabbits at low or reasonably low exposure margins justify placement in Category D.⁴

⁴ Pregnancy Category D is defined as: Drugs which have caused or are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

Metabolites

In rabbits, subcutaneous administration of the metabolite DM-4103 for 3 days at 50 mg/kg provided comparable (C_{max}) or slightly lower (AUC_{24h}) exposure to DM-4103 as obtained when rabbits received 1000 mg/kg/day tolavaptan orally (Studies 022490/017547 and 021835/017040).

Paediatric use

In a rat juvenile toxicity study of 6 weeks duration, the NOAEL was 100 mg/kg/day in animals of both sexes, based on effects observed at 1000 mg/kg/day (decreased body weights and food consumption and increased prothrombin time PT and activated partial thromboplastin time APTT).

In the 26 week toxicity study with adult rats, the NOAEL was established at 1000 mg/kg/day for males and 100 mg/kg/day for females (based on adverse clinical observations and mortality in high dose females). Organ weights of thyroid, liver, kidney and adrenal glands were increased in animals receiving 1000 mg/kg/day. Effects observed at lower doses were attributed to tolavaptan's pharmacological (aquaretic) action.

The serum levels of tolavaptan at Day 42 in juvenile rats were 4 to 7 times greater in females than males, consistent with approximately 10 times higher exposure in female than male rats in adult studies. A comparison between the pharmacokinetics of the 26 week study in adult rats (Study 13774) and the 6 week study in juvenile rats (Study 025612/030396) reveals that the exposure to tolavaptan in juveniles was 0.5, 1 and 4 times the exposure of adult rats, when juvenile and adult rats were dosed at 30, 100, and 1000 mg/kg/day, respectively. No particular concerns were found for juvenile animals based on the 6 week study in juvenile rats.

Jinarc is not proposed for paediatric use, and the draft PI notes that its safety and efficacy have not been established in children and adolescents.

Comments on the Nonclinical Safety Specification of the Risk Management Plan

Results and conclusions drawn from the nonclinical program for tolavaptan detailed in the sponsor's draft Risk Management Plan (Section 1.1) are in general concordance with those of the Nonclinical Evaluator. The following comments and recommendations are made, though:

- Animal:human comparisons based on doses adjusted for body surface area are made in the Nonclinical Safety Specification (teratogenicity and fertility sections). Comparisons based on AUC, as done in this report, are considered to be more appropriate. Note that the bioavailability of tolavaptan is significantly lower, and clearance much higher, in the laboratory animal species compared with humans. Such body surface area comparisons hugely overestimate relative exposure to tolavaptan and its major circulating metabolite DM-4103.
- Under Developmental toxicity, "fused phalanx" should be replaced with "bent radius, tibia and fibula" as findings noted in the fetuses of tolavaptan treated rabbits.

Nonclinical summary and conclusions

- The sponsor has conducted adequate nonclinical studies on the pharmacodynamics, pharmacokinetics and toxicity of tolavaptan according to the relevant guidelines. All pivotal safety related studies were conducted under good laboratory practice (GLP) conditions or were otherwise of an acceptable standard.

- Tolvaptan acts as a vasopressin V2-receptor antagonist with nanomolar potency. Water reabsorption in the kidneys is promoted by activation of V2-receptors by endogenous arginine vasopressin. Oral administration of tolvaptan in mouse and rat models of polycystic kidney disease was shown to increase urine volume, and to decrease renal cAMP, urine osmolality, kidney weight and kidney volume, cyst volume (not cyst density), fibrosis volume, apoptotic index and mitotic index.
- Secondary pharmacodynamic studies in rats revealed that oral tolvaptan reduced oedema and ascites. In anaesthetised dogs, no cardiovascular or renal haemodynamic effects (for example no increase in urine sodium or chloride excretion and no change in blood pressure or renin activity) were observed in the presence of the aquaretic effects of tolvaptan (administered intravenously (IV)). Oral administration of both furosemide and tolvaptan had no effect on cardiac afterload or renal functions in dogs with normal cardiac activity and in dogs with congestive heart failure; whereas furosemide (and not tolvaptan) increased plasma renin activity and catecholamine concentrations.
- Based on in vitro studies, tolvaptan may increase the exposure of co-administered drugs that are substrates of BCRP, OATP1B3, and OCT1.
- No new targets of toxicity were identified in juvenile studies of up to 6 weeks duration submitted. The relative exposure obtained with the AUC values from clinical studies in ADPKD patients are lower than those obtained for Samsca (see Samsca AusPAR⁵).
- Genotoxicity and carcinogenicity profiles for tolvaptan have been established, with no significant risk identified, although at very low multiples of exposure (for carcinogenicity)

Conclusions and recommendation

- The nonclinical dossier contained no major deficiencies.
- Primary pharmacology studies demonstrated that tolvaptan decreases renal cAMP, urine osmolality, kidney weight, kidney volume, cyst volume, fibrosis volume, apoptotic index and mitotic index, and thus supports the proposed indication.
- Adverse findings in the repeat-dose toxicity studies were confined to effects attributable to exaggerated pharmacology or general stress. There was no evidence of histopathological changes directly caused by tolvaptan in dogs at a high margin of the human exposure (up to 41 times the clinical AUC at 120 mg/day).
- While the mouse and rat carcinogenicity studies were negative, these studies suffer from the inability to obtain high multiples of the clinical exposure to tolvaptan in rodent species. The AUC values for tolvaptan at the highest dose in the mouse and rat studies were only around 0.5 and 1.9 to 5.1 times that of patients at the maximum recommended human dose. Tolvaptan is unlikely to pose a particular risk of carcinogenicity in patients as there were universally negative findings in the assays for genotoxicity, no pre-neoplastic lesions in the rodent carcinogenicity studies, and no hyperplastic changes observed in the 52 week dog study (AUC relative exposure of ≤ 41).
- Findings of embryofetal lethality and teratogenicity in rabbits at low or relatively low exposure margins (2.6 to 7.4), albeit in conjunction with maternotoxicity, warrant placement of tolvaptan in Pregnancy Category D.

⁵ <https://www.tga.gov.au/auspar/auspar-tolvaptan>

- There are no nonclinical objections to the registration of Jinarc for the proposed indication.

The nonclinical evaluator also made recommendations relating to the Product Information but these are beyond the scope of the AusPAR.

V. Clinical findings

The clinical evaluation report can be found in Attachment 2.

Introduction

Clinical rationale

ADPKD is an inherited disorder characterised by the formation of multiple fluid filled cysts in the kidneys. The cysts develop from mutated tubular epithelial cells scattered throughout the kidney. It is caused by a mutation in one of two genes (PKD1 or PKD2) which encode transmembrane proteins (polycystin 1 and polycystin 2 respectively) involved in the regulation of tubular and vascular development in the kidneys and other organs. Mutations in PKD1 are more common, accounting for 85% of ADPKD cases.⁶

Clinical manifestations of ADPKD are highly variable. Common features include hypertension, flank pain, haematuria, pyelonephritis and renal cyst infections. Renal failure requiring dialysis develops in approximately 50% of subjects, usually between the ages of 30 and 60 years.⁶ Adverse prognostic factors for disease progression include PKD1 mutation, increased age, male sex, impaired renal function and higher total kidney volume.⁷ Extrarenal manifestations include polycystic liver disease, cysts in other organs (for example pancreas, seminal vesicles), intracranial and coronary artery aneurysms and mitral valve prolapse.⁸

In ADPKD, cAMP is known to promote abnormal cyst cell proliferation and secretion of fluid into the cysts, and vasopressin is a potent activator of renal adenylyl cyclase, the enzyme responsible for conversion of ATP to cAMP.⁶ ADPKD is also associated with upregulation of the vasopressin V2 receptor and increased circulating levels of vasopressin.⁸ The rationale for the clinical development of tolvaptan as a treatment for ADPKD is therefore based on the drug's ability to inhibit the effects of vasopressin through inhibition of the vasopressin V2 receptor.

There are currently no drugs registered in Australia for the treatment of ADPKD.

Guidance

The TGA has adopted the following EU guidelines relevant to this submission:

- Points to consider on application with: 1. Meta-analyses; 2. One pivotal study; CPMP/EWP/2330/99
- Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function; EMA/83874/2014

⁶ Grantham JJ. Autosomal Dominant Polycystic Kidney Disease. *N Engl J Med* 2008; 359:1477-85.

⁷ Ong ACM, Devuyst O, Knebelmann B et al. Autosomal dominant polycystic kidney disease: the changing face of clinical management. *Lancet* 2015; 385: 1993–2002.

⁸ Torres VE, Harris PC and Pirson Y. Autosomal dominant polycystic kidney disease. *Lancet* 2007; 369: 1287–301.

Contents of the clinical dossier

The submission included a large number of studies that had previously been evaluated by the TGA in considering the registration application for Samsca. These studies have not been reviewed in this report. The previously evaluated studies which were included in the current submission are listed in Table 1 of Attachment 2. None of these studies were conducted in subjects with ADPKD. It should be noted that several of these studies were identified by the sponsor as new studies, in the table of contents for the submission. However, review of the previous clinical evaluation report indicates that these studies have already been evaluated by the TGA.

The submission contained the following new clinical information:

- 10 clinical pharmacology studies, that in general provided both pharmacokinetic pharmacodynamic data.
- 1 population pharmacokinetic and pharmacokinetic/pharmacodynamic analysis (Study 156-11-296).
- 1 pivotal Phase III efficacy/safety study (Study 156-04-251).
- 5 open label long term extension efficacy/safety studies. Three of these were designated as Phase III studies (156-08-271, 156-09-003 and 156-10-003) and two were designated as Phase II studies (156-05-002 and 156-04-250).
- 1 pooled analysis of efficacy data from two of the extension studies (Study 156-09-283).
- 2 studies in subjects with other indications which have not previously been reviewed by the TGA (156-03-002 and 156-04-247). The safety data from these 2 studies are reviewed in this evaluation.
- Literature references.
- Clinical Overview, Summary of Biopharmaceutics, Summary of Clinical Pharmacology, Summary of Clinical Efficacy and Summary of Clinical Safety. Supplementary tables and figures for the summaries were included in the clinical dossier.

Paediatric data

The submission did not include paediatric data. The sponsor has received a waiver for paediatric data from the Food and Drug Administration (FDA) on the grounds that the drug has received orphan designation for the treatment of ADPKD. The sponsor has an agreed paediatric investigation plan (PIP) with the EMA in Europe, which includes the conduct of studies in children with polycystic kidney disease (both autosomal dominant and autosomal recessive). The plan is due to be completed by November 2020.⁹

Good clinical practice

The clinical study reports in the submission all contained an assurance that they were conducted in accordance with Good Clinical Practice (GCP) guidelines (usually the International Conference on Harmonisation (ICH) guideline) and in accordance with the principles of the Declaration of Helsinki.

⁹ European Medicines Agency decision P/0045/2016. 26 February 2016. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/pip_search.jsp&mid=WC0b01ac058001d129 (Accessed May 2016)

Pharmacokinetics

Studies providing pharmacokinetic data

The submission largely relies on previously evaluated PK data from the application to register Samsca. However, some new studies containing PK data have been submitted. Summaries of the new pharmacokinetic studies were provided. Table 9 shows the new studies relating to each pharmacokinetic topic.

Table 9: New submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK		
	Single dose (45 + 15 split dose)	156-07-262	
	Single dose (Korean subjects)	156-KOA-0801	*
	Bioequivalence† - Single dose	156-11-295	*
	Food effect	156-11-295	*
	PK in renal impairment	156-09-282	*
PK in ADPKD subjects	General PK		
	-Single dose	156-04-248	*
	-Multiple dose	156-04-001	*
	-Multiple dose	156-04-249	*
	-Multiple dose (90 + 30 split dose)	156-09-285	
	Renal impairment	156-06-260 156-09-284	
Population PK and PK/PD analyses	ADPKD subjects	156-11-296	*

* Indicates the primary aim of the study. † Bioequivalence of different formulations.

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

There were two studies listed in the table of contents for the submission as studies not previously evaluated by the TGA. However, both of these have in fact been previously reviewed by the TGA and are therefore not reviewed in this report. These studies are listed in Table 10.

Table 10: Pharmacokinetic studies not evaluated

Study ID	Subtopic(s)
156-96-205	Interactions with frusemide and hydrochlorothiazide
156-01-224	Population PK analysis in subjects with hyponatraemia or heart failure.

Evaluator's overall conclusions on pharmacokinetics

Only limited PK data were submitted with the application. In general, the PK of tolvaptan appears broadly similar in ADPKD and hyponatraemia subjects. The new PK studies indicate that:

- The proposed new 45, 60 and 90 mg tablets are bioequivalent with the currently registered 15 and 30 mg tablets.
- Co-administration of the 90 mg tablet with food results in an approximate doubling of C_{max} but no increase in AUC.
- Renal impairment increases tolvaptan systemic exposure.
- Twice daily administration of tolvaptan (as proposed for the new indication) is not associated with significant accumulation.
- The PK profiles produced by the three proposed dosage regimens have not been directly compared. This is not considered a significant deficiency, as the regimens are to be used to determine a tolerable dose for each subject. Changing regimens on efficacy grounds is not being proposed.

Pharmacodynamics**Studies providing pharmacodynamic data**

Summaries of new pharmacodynamic studies contained in the submission were provided. Table 11 shows the studies relating to each pharmacodynamic topic.

Table 11: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	Effect on urine osmolality, urine output, free water clearance, excretion, urine solute concentrations and fluid balance	156-KOA-0801	*
		156-07-262	*
		156-09-282	*
		156-04-248	*
		156-04-001	*
		156-04-249	*
		156-06-260	

PD Topic	Subtopic	Study ID	*
		156-09-284	
		156-09-285	*
	Effect on plasma vasopressin and markers of vasopressin	156-04-248	
		156-04-001	
		156-04-249	
		156-09-284	
Secondary Pharmacology	Effect on serum/plasma osmolality and concentrations of solutes	156-09-282	*
		156-04-248	*
		156-04-001	*
		156-04-249	*
		156-06-260	*
		156-09-284	*
	Effect on GFR, RBF	156-06-260	*
		156-09-284	*
	Effect on serum PTH and calcium	156-04-248	
		156-04-001	
		156-04-249	
	Effect on renin, aldosterone	156-06-260	
		156-09-284	
Population PK-PD analyses	ADPKD subjects	156-11-296	*

* Indicates the primary aim of the study. GFR = Glomerular Filtration Rate

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

Evaluator's conclusions on pharmacodynamics

The submitted pharmacodynamic (PD) studies were acceptable. The observed PD effects were consistent with tolvaptan's mechanism of action.

Dosage selection for the pivotal studies

The dosage regimens chosen for the pivotal study were based on the findings of an earlier Phase II Study (156-04-250). In the titration period of this study the maximum tolerated dose was 90 mg per day (60 + 30) and the minimum effective dose was 60 mg per day (45 + 15).

Comment: In Study 156-04-250, the highest proposed dose (90 + 30) was found to be not tolerable (because < 50% of subjects could tolerate it) and was not studied in the subsequent fixed-dose period of the study. Despite this the 90 + 30 dose was included in the pivotal study. No justification for this could be found in the pivotal study report. However, in the pivotal study 54.4% of subjects were able to tolerate 90 + 30 mg dose in the long term. The sponsor also cites the results of the PK/PD model for tolvaptan, which predicts that the 90 + 30 mg dose will be associated with improved efficacy.

Efficacy

Studies providing efficacy data

- Pivotal efficacy Study (156-04-251)
- Other efficacy studies
 - Study 156-04-250
 - Studies 156-05-002 and 156-09-003
- Analyses performed across trials (pooled analyses and meta-analyses)
 - Study 156-09-283

Evaluator's conclusions on efficacy

The efficacy data come from a single randomised controlled trial and a collection of open label, non-comparative studies.

The pivotal study was well designed and executed. The population enrolled had evidence of rapid disease progression but reasonably good renal function. Within these criteria, it is likely that the results of the study are generalizable to an Australian population of ADPKD subjects.

The primary endpoint in the pivotal study was total kidney volume (TKV). The pivotal study demonstrated that tolvaptan treatment is associated with a statistically significant reduction in the progressive increase in TKV. Rate of increase over three years in the placebo arm was 5.51% per year, whereas in the tolvaptan arm, it was 2.80% per year, a reduction of 49.2%. The absolute difference between treatment arms was 2.71% per year (95%CI 2.15% to 3.27%). TKV has been shown to be directly correlated with total cyst volume in ADPKD and a correlation has also been shown between TKV and subsequent decline in renal function. However, everolimus has been shown to decrease progression in TKV, while at the same time producing a decline in renal function.¹⁰ The validity of TKV as a surrogate endpoint for efficacy in ADPKD has therefore been questioned. Of note, the FDA did not accept TKV as a valid primary endpoint for the pivotal study, and appears to have assessed efficacy based on the study's secondary endpoints. The EMA and the Canadian regulatory authority have accepted TKV as a valid surrogate endpoint.

¹⁰ Walz G, et al. Everolimus in Patients with Autosomal Dominant Polycystic Kidney Disease. *N Engl J Med* 2010; 363: 830-40.

On the key secondary composite endpoint, tolvaptan treatment was associated with a 13.5% decrease in the risk of experiencing a clinical progression event (hazard ratio 0.865; 95% CI: 0.775 to 0.965; $p = 0.0095$). Clinical events occurred at a rate of 43.94 per 100 follow-up years in the tolvaptan arm compared with 50.04 per 100 follow-up years in the placebo arm. This benefit was largely due to a reduction in the risk of worsening renal failure events and renal pain events.

A beneficial effect of tolvaptan in terms of reducing the decline in overall renal function was also demonstrated. The effect was modest, with an overall benefit in glomerular filtration rate (GFR) of approximately 1 ml/min/1.73m² per annum (Table 12). This effect would need to be sustained for many years for the drug to produce meaningful clinical benefits such as a delay in the need for renal replacement therapy. Tolvaptan was not associated with any benefits in terms of the onset or progression of hypertension or microalbuminuria.

The findings of the pivotal study were supported by a comparison of long term data from two open label studies with historical data from observational studies. As subjects were not randomised to tolvaptan or control, the findings of this study should be interpreted with caution. Study 156-04-250 demonstrated that mean urine osmolality was maintained at < 300 mOsm/kg throughout over a period of 36 months.

The proposed dosing regimen is considered acceptable, as it is supported by pharmacodynamic data. In effect patients will be treated with a dose they can tolerate.

The proposed indication is generally acceptable, as it reflects the population enrolled in the pivotal study. However, subjects aged over 50 years were excluded from the pivotal study and this is not reflected in the indication. The sponsor has included a statement in the PI that safety and efficacy have not been established in subjects aged > 50 years, and this is considered a reasonable approach.

The submission for the new indication is based on a single pivotal study and the TGA has adopted an EMA guideline that deals with this situation.¹¹ This guideline sets out certain 'prerequisites' that must be met for approval of such a submission. These are:

1. The study must have internal validity, with no indications of potential bias;
2. The study must have external validity, with the population studied being suitable to allow extrapolation of data to the population to be treated;
3. The size of the efficacy benefit must be large enough to be considered clinically valuable;
4. The degree of statistical significance should be "considerably stronger" than $p < 0.05$, and confidence intervals should be narrow.
5. The data should be of acceptable quality;
6. There should be internal consistency, with similar effects in sub-populations and important endpoints showing similar findings;
7. Results should not differ notably between study centres;
8. The hypothesis being tested should be plausible.

Overall it is considered that these prerequisites have been met.

As discussed above there have been differing opinions among foreign agencies as to whether TKV is an acceptable surrogate endpoint for efficacy. Preservation of renal function is a more clinically relevant endpoint than kidney size and a statistically

¹¹ European Medicines Agency. Points to consider on application with 1. Meta-analyses; 2. One pivotal study; CPMP/EWP/2330/99 (2001).

significant benefit has been shown for this outcome in the pivotal study. Therefore, for this submission, the issue of whether TKV is a valid surrogate endpoint is not critical. Overall, based on the data showing a preservation of renal function, it can be concluded that tolvaptan has shown activity in the treatment of ADPKD. However, the clinical significance of this activity appears modest.

Table 12: Study 156-04-251; Rate of renal function decline Secondary endpoint; rate in change of renal function; ITT subjects with at least 4 month follow up, excluding observations deemed unreliable by investigators, within treatment period

Endpoint	Tolvaptan	Placebo
1/serum creatinine ([mg/mL] ⁻¹)		
Number of subjects	842	464
Mean rate of change per year ^a	-2.555	-3.682
Estimated slope ^b	-2.609	-3.812
Treatment effect ^c	1.203	
95% CI	0.622, 1.783	
p-value ^b	< 0.0001	
eGFR _{CKD-EPI} (mL/min/1.73 m ²)		
Number of subjects	842	464
Mean rate of change per year ^a	-2.680	-3.568
Estimated slope ^b	-2.723	-3.700
Treatment effect ^c	0.977	
95% CI	0.597, 1.357	
p-value ^b	< 0.0001	

^a Summary statistics were based on slope of change, obtained by regressing renal function data (Week 3/EOT and beyond) against time by subject. Time variable used in the regression was equal to (observation date - Week 3/EOT date)/365.25.

^b Derived from testing the time treatment interaction using linear mixed model in which both intercept and slope are fixed and random effects.

^c An estimate of the difference between the slopes of tolvaptan and placebo.

Safety

Studies providing safety data

The following studies provided evaluable safety data:

- Pivotal efficacy study
- Long term efficacy studies

Patient exposure

The safety database for the current submission consisted of a total of 1581 subjects exposed to at least one dose of tolvaptan from 16 clinical studies (including the clinical pharmacology studies). This total included 1,432 subjects with ADPKD, 37 non-ADPKD subjects with varying degrees of renal function and 112 healthy volunteers.

Duration of exposure is summarised in Table 32 of Attachment 2. A total of 1,275 subjects had been exposed to the proposed doses of tolvaptan (60 to 120 mg per day) for at least 6 months and 1,002 subjects for at least 12 months.

For the pivotal study, the modal dose over time is shown in Figure 10 of Attachment 2. While 80.9% of subjects in the tolvaptan arm were titrated up to 120 mg per day at the end of the 3 week titration period, the proportion of subjects tolerating this dose decreased over time. At Month 36, only 54.4% of subjects in the tolvaptan arm had a modal dose of 120 mg per day. Average daily dose was around 100 mg per day.

Safety issues with the potential for major regulatory impact

Liver toxicity

Tolvaptan is likely to be associated with rare cases of severe drug induced liver injury when used in subjects with ADPKD.

Haematological toxicity

As outlined, the new studies in this submission did not identify any significant haematological toxicity with tolvaptan.

Serious skin reactions

In the pivotal study there were three subjects (0.3%) with serious skin adverse events (AEs) reported with tolvaptan; hidradenitis, angioedema and urticaria; compared with none in the placebo group.

Cardiovascular safety

As outlined, the new studies in this submission did not identify any significant cardiac or vascular toxicity with tolvaptan.

Unwanted immunological events

In the pivotal study there one subject with anaphylactic shock in the tolvaptan arm, compared with none in the placebo arm. The reaction occurred after ingesting amoxycillin. Tolvaptan treatment was continued. There have been post-marketing reports of anaphylaxis with the Samsca presentation of tolvaptan and the draft PI for Jinarc contains a warning statement regarding this risk.

Post-marketing data

The submission included six periodic safety update reports (PSURs) and one periodic adverse drug experience report (PADER). Together these reports covered the period 19 May 2009 to 18 May 2012 (that is 3 years). The reports described post-marketing reports for the Samsca presentation of tolvaptan.

The estimated cumulative exposure to the drug over the three year period was 3,789.7 patient years. Reports of rapid increases in serum sodium levels led to amendments to prescribing information documents worldwide. In addition, raised intraocular pressure/glaucoma was added as an important potential risk to the risk management plan. Otherwise no significant new safety issues were raised.

A search was conducted for post-marketing reports of hepatic dysfunction. The period covered by the search was 1 June 2009 to 31 March 2012. A total of five cases were referred to the hepatic adjudication committee for review. No Hy's law cases were identified and the committee considered that the hepatic events in these cases were unlikely to be related to tolvaptan.

Comment: Tolvaptan obtained marketing approval for use in ADPKD in February 2015 in Canada and May 2015 in Europe. The sponsor should be requested to provide any available post-marketing data on tolvaptan use in ADPKD.

Evaluator's conclusions on safety

The extent of exposure to tolvaptan in ADPKD studies is considered adequate with over 1,000 subjects having been treated for at least 12 months. The monitoring of safety in the submitted clinical trials was also acceptable.

The major safety issue associated with tolvaptan in ADPKD is hepatotoxicity. Although the observed cases of hepatotoxicity in the clinical studies were reversible, the occurrence of three cases meeting Hy's law criteria indicates that the drug is likely to be associated with rare cases of severe drug induced liver injury; that is liver failure resulting in death or the need for transplantation. The sponsor is proposing a more rigorous program of liver function tests (LFTs) monitoring than was used in the pivotal study; it is recommended that LFTs be monitored at monthly intervals for the first 18 months and then at 3 monthly intervals thereafter.

The most common adverse events associated with tolvaptan were those associated with drug's mechanism of action; polyuria, nocturia, thirst, polydipsia etc. Most subjects were able to tolerate these events. However, such events led to discontinuation of treatment in approximately 5% of subjects.

Other toxicities that appeared to be associated with tolvaptan were fatigue and increased uric acid concentrations with an increased incidence of gout. It is noted that no studies have been performed examining interactions between anti-gout medications and tolvaptan.

First round benefit-risk assessment

First round assessment of benefits

The benefits of tolvaptan in the treatment of ADPKD are:

- A slowing of the decline of renal function associated with the disease. The effect is modest with a benefit in terms of GFR of approximately 1 mL/min/1.73m² per year;
- A reduction in the occurrence of events of severe renal pain. The risk of experiencing a severe renal pain event was reduced by 35.8%. The incidence of severe renal pain events was 7.30 per 100 follow-up years in the placebo group, and 4.73 per 100 follow-up years in the tolvaptan group. This difference is also modest being a reduction of only approximately 2.6 events per 100 follow-up years.
- A reduction in the rate of kidney enlargement. The rate is reduced by approximately 50%.

First round assessment of risks

The risks of tolvaptan in the treatment of ADPKD are:

- Hepatotoxicity and a risk of serious drug-induced liver injury (DILI). DILI events are likely to be rare, with an estimated incidence of 1 in 3,000 subjects, but will be serious, resulting in death or the need for liver transplantation;
- A number of adverse events associated with the drug's mechanism of action, such as thirst (incidence versus placebo 55.3% versus 20.5%), polydipsia (10.4% versus 3.5%), polyuria (38.3% versus 17.2%), pollakiuria (23.2% versus 5.4%) and nocturia (29.1% versus 13.0%). While most subjects are able to tolerate these effects, approximately 5% of subjects will discontinue therapy because of them;

- Increased serum uric acid concentrations with a possible increased risk of gout. Adverse events of gout occurred in 2.9% of subjects on tolvaptan compared with 1.4% of subjects on placebo.
- Hyponatraemia: AEs of hyponatraemia occurred in 2.8% of subjects on tolvaptan compared with 1.0% of subjects on placebo.
- Fatigue (13.6% versus 9.7%).

First round assessment of benefit-risk balance

- ADPKD is a serious condition for which no effective therapies are currently available. It would therefore be highly desirable for effective and safe treatments to be made available for subjects with the disease. However, the benefit-risk balance of tolvaptan in the treatment of ADPKD is considered borderline.
- The main clinical benefit of the drug is preservation of renal function. However, the magnitude of this benefit is modest, with an average benefit in terms of GFR of approximately 1 mL/min/1.73m² per year. This effect will need to be maintained for many years before clinically important outcomes are achieved (that is a delay or reduction in the need for renal replacement therapy). The only other efficacy benefit demonstrated for the drug was a reduction in the occurrence of events of severe renal pain, an effect which was also modest.
- Apart from DILI, the risks of tolvaptan use in the treatment of ADPKD appear acceptable, especially as ADPKD is a serious disease. Discontinuation due to AEs occurred in 15.0% of subjects treated with tolvaptan compared with 4.3% of subjects treated with placebo. This indicates that the majority of subjects are able to tolerate the drug's adverse effects (most commonly polyuria, polydipsia, thirst, nocturia etc.). The incidence of serious AEs was comparable in the two treatment groups.
- DILI is the major safety issue associated with tolvaptan in the treatment of ADPKD. No cases of fatal hepatic failure or hepatic failure requiring liver transplant were reported in the submitted studies. However, three cases meeting Hy's law criteria were observed and it is therefore likely that the drug will cause cases of hepatic failure resulting in death or liver transplantation.

First round recommendation regarding authorisation

On balance this evaluator is inclined to recommend rejection of the application on the grounds that the modest efficacy benefits (some preservation of renal function and a small decrease in the incidence of severe renal pain events) are outweighed by the risk of severe DILI.

It is noted that in 2013, the FDA requested an additional efficacy study, to be conducted in ADPKD subjects with more advanced renal impairment. The benefits of tolvaptan may be greater in such a population and the sponsor should be requested to provide details of the progress of this study. Any post-marketing data that might better define the risk of severe DILI should also be requested.

Clinical questions and second round evaluation of clinical data submitted in response to questions

For details of the clinical questions, the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Having considered the benefits, risks and uncertainties, and having given consideration to the unmet clinical need in the patients with ADPKD the benefit-risk balance of tolvaptan, given the proposed usage, is marginal and only just favourable. This assessment is provided the recommendations regarding the PI are implemented. It is noted that Study 156-13-210 is underway and that this will provide additional information about ADPKD patients with CKD stages 2 to early stage 4. It is noted this study is due to concluded in 2017. The provision of this study, in addition to information provided in the submission, would have provided a more complete data set.

Although the incremental benefit over 3 years is modest ADPKD is a slow progressive disease. Benefit was demonstrated for both the primary and secondary endpoints. Two of the four components of the key secondary endpoint drove the positive outcome but none of the endpoints demonstrated poorer outcomes for the respective variable.

The patients in the TEMPO 3:4 study were relatively young with a median age of 27.4 years. It may be considered that a reduction in deterioration of renal function of a modest 26% may be meaningful in this group whereas in advanced disease it may not to be so.

The PKPD modelling suggests a more favourable effect with poorer renal function. To further investigate the effects in patients with stage 2 and stage 3 CKD a study is underway to provide data on the use of tolvaptan in later stages of the disease. There is insufficient information about the progression of disease, delay of end stage renal disease (ESRD), delay of dialysis or renal transplant from the long term use of tolvaptan. There are no data to determine the optimal stage of disease at which treatment should commence; however the sponsor has proposed to restrict the indication to patients with evidence of rapidly progressive disease.

Although there is some experience with tolvaptan with its indication for the treatment of clinically significant hypervolaemic or euvolaemic hyponatraemia the doses are larger raising the possibility of dose-related toxicity. In the ADPKD clinical programme the most common adverse effects were thirst, polyuria, nocturia, pollakiuria, and dry mouth. While these symptoms are manageable, thirst and frequent urination have significant lifestyle restrictions and may have implications for compliance with tolvaptan. Careful fluid balance is required, particularly in patients with more advanced disease and may become problematic as renal function deteriorates.

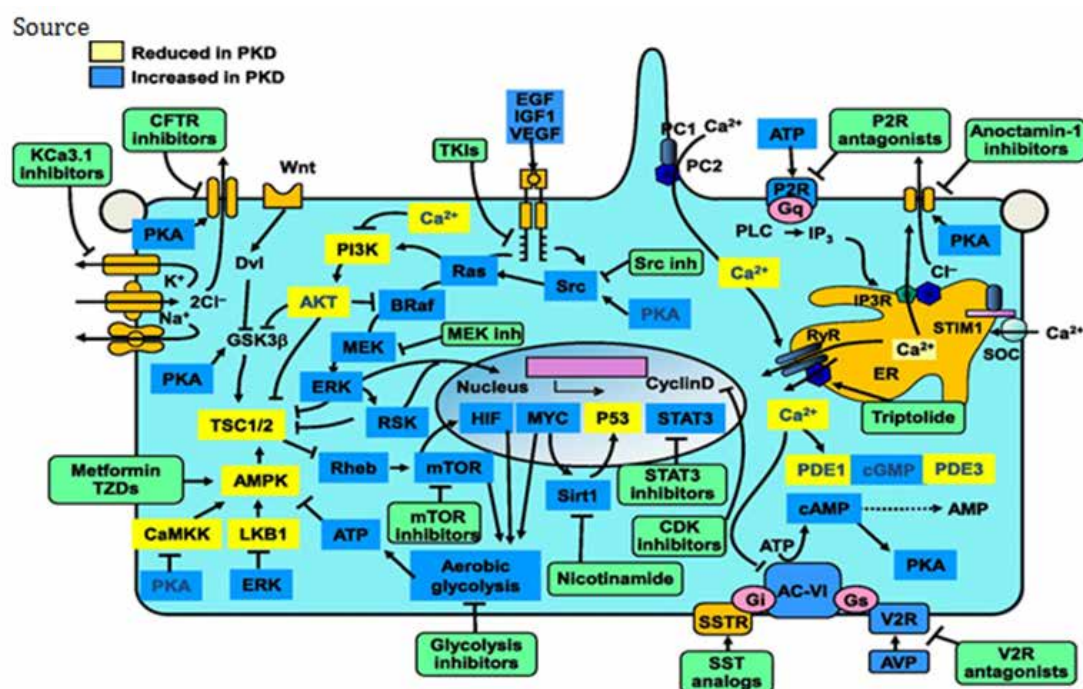
Idiosyncratic hepatic failure is a major cause for concern. The sponsor has estimated 1 in 4,400 patients will have severe idiosyncratic hepatic toxicity while taking tolvaptan. The risk of hepatic events appears to be greater in the ADPKD population than for hyponatraemia but that may be related to the dose. Of the three cases of DILI that have occurred in clinical trials none have been fatal or required transplant but this observation may be tempered by the occurrence of the events in clinical trials, with frequent monitoring and prompt action by the trial investigators. The numbers of events is small, and wider exposure may reveal more severe reactions. The sponsor has proposed risk minimisation activities in the form of a controlled distribution system, a boxed warning and extensive warnings throughout the PI. Frequent monitoring is recommended, and although the usefulness of frequent monitoring to detect idiosyncratic hepatic disease with other medicines has been recently questioned, but abnormalities of liver enzymes that will be detected by the laboratory tests. The sponsor has proposed recommendations for discontinuation of therapy based on the results of liver function tests in the PI to guide the prescriber.

There are a number of uncertainties in the efficacy and safety data. The placebo controlled duration of exposure is for only three years, and although acceptable for a submission for long term therapy in general, limits the conclusions that can be drawn because ADPKD is a slowly progressive disease. Of particular concern is uncertainty about the durability of the

tolvaptan effect. Historical controls have been used by the sponsor, but they are potentially confounded by advances in the management of other risk factors for renal disease. Data were missing from 23% of the tolvaptan subjects and 14% of the placebo patients) and the disproportionate number of discontinuations due to adverse events occurred in the tolvaptan group, adding to the uncertainty.

There is an unmet clinical need for a treatment for ADPKD, which is a progressive condition requiring in renal replacement therapy in the majority of patients by the age of 60 years. This is a major factor in concluding a positive benefit-risk balance for tolvaptan for the proposed indication. While Figure 2 shows signalling pathways that are potential targets for therapies for ADPKD there are no other medicines approved in Australia to halt or modify the progression of this disease. Tolvaptan has a demonstrated modest effect in slowing the progression of the disease, this is balanced against significant safety concerns that will require careful patient selection and vigilant clinical and laboratory monitoring by the treating physician. It will also require meticulous compliance by the patient not only in following the hydration recommendations but also for attendance for follow-up. It will therefore not be suitable for all adult patients with CKD stages 1 to 3.

Figure 2: Renal tubular cell signalling pathways found to be increased or decreased in PKD. (From Antignac C et al 2015)¹²



Source: Peters DJM in Antignac et al 2015

Second round recommendation regarding authorisation

The second round evaluation concludes Jinarc (tolvaptan) is recommended for authorisation for the sponsor's proposed indication. This recommendation is provided subject to the following:

- The PI is updated as requested.
- The sponsor provides Study 156-13-210 for evaluation as soon as it becomes available.

¹² Antignac C, Calver JP, Germino GC et al The Future of Polycystic Kidney Disease Research – As Seen By the 12 Kaplan Awardees J Am Soc Nephrol ePub 10.61681/ASN.2014121192

- The provision of all clinically relevant information from the ongoing studies listed in the pharmacovigilance plan.

The RMP team will evaluate the details of the restricted access programme but this programme is considered a most important aspect of the mitigation of the risks, and integral to the recommendation for authorisation.

VI. Pharmacovigilance findings

Risk management plan

- Otsuka Australia Pharmaceutical Pty Ltd has applied to extend the indications of tolvaptan, under a new brand (Jinarc) with new strengths (45 mg, 60 mg and 90 mg). Tolvaptan (Samsca) 15 mg and 30 mg tablets are currently approved for the treatment of clinically significant hypervolemic or euvolemic hyponatremia including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH). The current submission seeks to extend the indications to include adults with ADPKD.
- The sponsor has submitted EU-RMP version 12.6 (30 November 2015; DLP 18 May 2013) and Australian Specific Annex (ASA) version: (not stated), February 2016, in support of this extension of indication. The most recently evaluated EU-RMP was version 1, August 2010.
- The sponsor has submitted ASA (no version specified dated September 2016) in its response to questions in the first round evaluation.
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below:

Table 13: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Volume depletion and dehydration	Ü	Ü	Ü	–
	Dehydration associated renal dysfunction	Ü	Ü	Ü	–
	Too rapid rise of serum sodium and neurologic sequelae (encephalopathy, osmotic demyelination)	Ü	Ü	Ü	*? Ü
	Hyper - / hypoglycemia	Ü	Ü	Ü	–
	Hyperuricemia, gout	Ü	Ü	Ü	–
	Hyponatremia in heart failure patients	Ü	–	Ü	–
	Hyperkalemia in heart	Ü	–	Ü	–

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	failure patients				
	Interaction with CYP3A4 Inhibitors	Ü	Ü	Ü	-
	Interaction with CYP3A4 Inducers	Ü	Ü	Ü	-
	Interaction with vasopressin receptor agonists	Ü	Ü	Ü	-
	Pharmacodynamic Interaction tolvaptan and combined administration of diuretics leading to dehydration and renal dysfunction	Ü	-	Ü	-
	Liver injury in ADPKD patients	Ü	Ü	Ü	Ü
	Anaphylaxis	Ü	Ü	Ü	-
Important potential risks	Acute urinary retention (in patients with urinary outflow	Ü	Ü	Ü	-
	Allergic skin reactions	Ü	Ü	Ü	-
	Raised intraocular pressure / glaucoma	Ü	-	Ü	-
	Interaction tolvaptan and combined administration of warfarin and antiplatelet agents in heart failure patients	Ü	-	Ü	-
	Interaction tolvaptan and serum potassium concentration-increasing substances	Ü	Ü	Ü	-
	Pharmacodynamic Interaction tolvaptan and combined administration ACE-I possibly leading to dehydration and renal dysfunction	Ü	-	Ü	-

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	Pharmacodynamic Interaction tolvaptan and combined administration ARB possibly leading to dehydration and renal dysfunction	Ü	–	Ü	–
	Cardiac arrhythmias secondary to electrolyte shifts in Heart Failure patients	Ü	–	Ü	–
	Post-treatment myocardial ischemia in worsening Heart Failure patients	Ü	–	Ü	–
	Dyspnea in Heart Failure patients	Ü	–	Ü	–
	Hypercoagulability (stroke, myocardial infarction) in Heart Failure patients	Ü	–	Ü	–
	Gastrointestinal bleeding in cirrhotic patients	Ü	–	Ü	–
	Skin Neoplasms (basal cell carcinoma) in ADPKD patients	Ü	Ü	Ü	–
	Teratogenicity	Ü	Ü	Ü	–
Missing information	Pediatric data	Ü	–	Ü	–
	Pregnancy outcome data	Ü	Ü	Ü	–
	Breast-feeding data	Ü	–	Ü	–
	Off-label use	Ü	Ü	Ü	–
	Usage in hepatic impaired patients	Ü	–	Ü	–
	Use in ADPKD patients with renal function other than stage 1-3 kidney disease	Ü	–	Ü	–
	Use of Jinarc in patients	Ü	Ü	Ü	–

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	over 50 years				
	Long term use of Jinarc in clinical practice	Ü	Ü	Ü	–

*Table 3.1-1 in the ASA 'How risk minimisation activities will be implemented in Australia' states that additional risk management activities are planned for 'too rapid rise in serum sodium' for the EU-RMP but none are planned for Australia for Jinarc. However, the EU-RMP Table 5.3 Summary of Risk Minimisation Measures states that there is additional risk minimisation activity for Samsca only (a direct healthcare professional communication (DHPC)). The sponsor has clarified in its Section 31 response that no additional risk minimisation activities are planned in Australia for the Safety Concern 'too rapid rise in serum sodium,' which is acceptable.

- Additional pharmacovigilance activities include post-authorisation safety studies, a drug use survey and a Phase I pharmacokinetic/pharmacodynamic open label trial.
- Additional risk minimisation activities for liver injury include prescriber's education, certification in the prescriber's registry, patient education brochure and Patient Alert Card. In its response to issues raised, the sponsor agreed to develop pharmacist and nurse safety information as an additional risk minimisation activity for the safety concern 'liver injury' as requested by the RMP Evaluator. This should be provided to the TGA for evaluation prior to registration.

Advice to the delegate regarding the PI/CMI (from round 1)

1. In the PI/CMI, the RMP evaluator recommends that the Delegate consider adding information regarding the risk of hyperkalemia.

RMP Evaluator comment (Round 2): The wording is now consistent with the Canadian PI under PRECAUTIONS. The CMI has also been updated with wording regarding high levels of potassium under "Tell your doctor if you have or have had any of the following medical conditions".

2. Recommendation 20 The RMP evaluator recommends to the Delegate that a boxed warning be added about liver injury in the PI and also highlight the liver injury risk in the CMI.

RMP Evaluator comment (Round 2): The PI and CMI have been satisfactorily updated to highlight the risk of liver injury.

3. Recommendation 21 The RMP evaluator recommends the Delegate consider revising the wording in the CMI with regard to 'older patients' not taking tolvaptan and replace with the following "or patients older than 50 years".

RMP Evaluator comment (Round 2): The RMP evaluator recommends the sponsor revise the wording in the CMI with regard to 'older patients' not taking tolvaptan and replace with the following "or patients older than 50 years".

Sponsor's response: Otsuka will provide a revised PI and CMI after receiving advice from the Delegate and will take into consideration the recommendation made above by the RMP Evaluator

RMP Evaluator Post Round 2: The response is satisfactory.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

After consideration of the sponsor's Round 2 response the wording for conditions of registration is as follows:

Implement EU-RMP version 12.6, (dated 30 November 2015, data lock point 18 May 2013), with Australian Specific Annex (dated September 2016), and any future updates, as a condition of registration.

VII. Overall conclusion and risk/benefit assessment

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

Background

Tolvaptan is an antagonist of the vasopressin V2 receptor. Tolvaptan is currently registered in Australia under the trade name Samsca, for the treatment of clinically significant hyponatremia.

ADPKD is an inherited disorder characterised by the formation of multiple fluid filled cysts in the kidneys. The cysts develop from mutated tubular epithelial cells scattered throughout the kidney. It is caused by a mutation in one of two genes (PKD1 or PKD2) which encode transmembrane proteins (polycystin 1 and polycystin 2 respectively) involved in the regulation of tubular and vascular development in the kidneys and other organs. Mutations in PKD1 are more common, accounting for 85% of ADPKD cases.

Clinical manifestations of ADPKD are highly variable. Common features include hypertension, flank pain, haematuria, pyelonephritis and renal cyst infections. Renal failure requiring dialysis develops in approximately 50% of subjects, usually between the ages of 30 and 60 years. Adverse prognostic factors for disease progression include PKD1 mutation, increased age, male sex, impaired renal function and higher total kidney volume. Extrarenal manifestations include polycystic liver disease, cysts in other organs (for example pancreas, seminal vesicles), intracranial and coronary artery aneurysms and mitral valve prolapse.

In ADPKD, cAMP is known to promote abnormal cyst cell proliferation and secretion of fluid into the cysts, and vasopressin is a potent activator of renal adenylyl cyclase, the enzyme responsible for conversion of ATP to cAMP. ADPKD is also associated with upregulation of the vasopressin V2 receptor and increased circulating levels of vasopressin. The rationale for the clinical development of tolvaptan as a treatment for ADPKD is therefore based on the drug's ability to inhibit the effects of vasopressin through inhibition of the vasopressin V2 receptor.

There are currently no drugs registered in Australia for the treatment of ADPKD.

At the time of lodgement of the application in Australia (February 2016), similar applications had been lodged in the USA (March 2013), Europe (November 2013), Canada (March 2014) and Switzerland (November 2014). The application in the United States was deferred in August 2013; the FDA had concerns about the magnitude of the efficacy benefit and about hepatotoxicity. Approval was granted in Canada in February 2015 and in Europe in May 2015, with the following indications and dosage regimens:

Europe

Jinarc is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease (see Section 5.1).

Jinarc is to be administered twice daily in split dose regimens of 45 mg + 15 mg, 60 mg + 30 mg or 90 mg + 30 mg. The morning dose is to be taken at least 30 minutes before the morning meal. The second daily dose can be taken with or without food. According to these split dose regimens the total daily doses are 60, 90, or 120 mg.

Canada

Jinarc (tolvaptan) is indicated to slow the progression of kidney enlargement in patients with autosomal dominant polycystic kidney disease (ADPKD). In ADPKD, kidney enlargement reflects renal cyst burden.

Jinarc is to be administered twice daily in split tolvaptan dose regimens of 45+15 mg, 60+30 mg, or 90+30 mg. According to these split-dose regimens, the total daily tolvaptan doses are 60, 90, or 120 mg, respectively.

Tolvaptan (Samsca) was considered at the 2012/1 meeting of ACPM as a new chemical entity for the treatment of hyponatraemia.

Quality

The same manufacturing process has been used for the 45, 60, and 90 mg tablets as for the currently approved (Samsca) 15 and 30 mg tablets. The new tablet strengths are quantitatively proportional to each other. In vivo bioequivalence has been demonstrated between the 30 mg and 90 mg tablets. Bioequivalence between the 15, 30, and 60 mg tablets has previously been shown. No bioavailability data for the 45 mg tablet was provided, which was considered acceptable. The manufacturing process involves the production of an intermediate product, tolvaptan spray dried powder. The proposed shelf life when stored below 25°C is 48 months for the 15, 30, and 60 mg tablets; and 36 months for the 45 and 90 mg tablets. With tolvaptan doses above 30 mg, a high-fat meal significantly increases C_{max} . Therefore the dosing advice that morning (higher) dose is taken at least 30 minutes before food, but the second dose may be taken with or without food, is acceptable. This is consistent with European dosing instructions.

The quality evaluator considers that there is one remaining issue to be addressed which precludes registration, namely provision of GMP clearance for a manufacturing site in Japan.

Nonclinical

The nonclinical evaluator has no objections to the registration of Jinarc. Primary pharmacology studies demonstrated that tolvaptan decreases renal cAMP, urine osmolality, kidney weight, kidney volume, cyst volume, fibrosis volume, apoptotic index and mitotic index, and thus supports the proposed indication. Adverse findings in the repeat-dose toxicity studies were confined to effects attributable to exaggerated pharmacology or general stress. There was no evidence of histopathological changes directly caused by tolvaptan in dogs at a high margin of the human exposure (up to 41 times the clinical AUC at 120 mg/day). While the mouse and rat carcinogenicity studies were negative, these studies suffer from the inability to obtain high multiples of the clinical exposure to tolvaptan in rodent species. The AUC values for tolvaptan at the highest dose in the mouse and rat studies were only about 0.5 and 1.9 to 5.1 times that of patients at the maximum recommended human dose. Tolvaptan is unlikely to pose a

particular risk of carcinogenicity in patients as there were universally negative findings in the assays for genotoxicity, no pre-neoplastic lesions in the rodent carcinogenicity studies, and no hyperplastic changes observed in the 52 week dog study (AUC relative exposure of ≤ 41). Findings of embryofetal lethality and teratogenicity in rabbits at low or relatively low exposure margins (2.6 to 7.4), albeit in conjunction with maternotoxicity, warrant placement of tolvaptan in Pregnancy Category D (this is the current pregnancy category of tolvaptan).

Clinical

The first round clinical evaluator recommended rejection of the application on the grounds that the modest efficacy benefits (some preservation of renal function and a small decrease in the incidence of severe renal pain events) are outweighed by the risk of severe DILI. The evaluator noted that the FDA requested an additional efficacy study (Study 156-13-210), to be conducted in ADPKD subjects with late Stage 2 to early Stage 4 chronic kidney disease. The benefits of tolvaptan may be greater in such a population and the sponsor will be requested to provide details of the progress of this study. Any post-marketing data that might better define the risk of severe DILI will also be requested.

The second round clinical evaluator recommended authorisation for the sponsor's proposed indication. This recommendation is provided subject to the following:

- The PI is updated as requested.
- The sponsor provides Study 156 -13-210 for evaluation as soon as it is available.
- The provision of all clinically relevant information from the ongoing studies listed in the pharmacovigilance plan.
- Finalisation of an agreed risk management plan.

The clinical dossier included the following data:

- 10 clinical pharmacology studies
- 1 population pharmacokinetic study (156-11-296)
- 1 pivotal efficacy/safety study (156-04-251)
- 5 open label long-term extension studies: three Phase III (156-08-271, 156-09-003, 156-10-003) and two Phase II (156-05-002, 156-04-250)
- 1 pooled efficacy analysis from two extension studies (156-09-283)
- 2 studies providing safety data from subjects with other indications not previously reviewed by the TGA (156-03-002, 156-04-247)

Pharmacology

The pharmacokinetics of tolvaptan are similar in ADPKD patients and hyponatremia patients. Tolvaptan is rapidly absorbed with C_{max} occurring about 2 hours after dosing. The absolute bioavailability of tolvaptan is about 56%. Steady state concentrations of tolvaptan are obtained after the first dose.

Tolvaptan is extensively metabolised in the liver almost exclusively by CYP3A4. In vitro studies indicated that tolvaptan has no inhibitory activity for CYP3A. Fourteen metabolites have been identified in plasma, urine and faeces; all metabolites have little to no contribution to the pharmacological effect of tolvaptan.

Tolvaptan binds reversibly (98%) to plasma proteins. Tolvaptan is only a minor component in plasma (3%). Less than 1% of intact active substance is excreted unchanged

in the urine. Radiolabelling studies showed that 40% of the radioactivity was recovered in the urine and 59% was recovered in the faeces, where unchanged tolvaptan accounted for 32% of radioactivity. The terminal elimination half-life is about 8 hours.

Renal impairment increases the systemic exposure to tolvaptan. In the population PK analysis, baseline estimated glomerular filtration rate (eGFR) was a significant covariate affecting tolvaptan clearance.

Tolvaptan is associated with an increase in urine volume and free water clearance, and a decrease in urine osmolality. In a study in ADPKD patients, mean 24 hour urine volume increased from 1,982 mLs at baseline to 6,533 mLs at 21 days after titration to tolvaptan 120 mg daily.

Efficacy

In the Phase II Study 156-04-250, the minimum effective dose was 60 mg daily (45 + 15), and the maximum tolerated dose was 90 mg daily (60 + 30), although this was tolerated by fewer than 50% of subjects.

Study 156-04-251

This was a Phase III, randomised, double blind trial with two parallel treatment groups (tolvaptan versus placebo, randomised 2:1, N=961 versus 484). The study enrolled patients aged 18 to 50 years with a diagnosis of ADPKD based on imaging, a total kidney volume of at least 750cm³, and an estimated GFR \geq 60mL/min using the Cockcroft-Gault formula (that is, CKD stage 1 or 2). After randomisation, subjects underwent an initial 3 week titration phase where treatment was commenced at the 45 + 15 split dose level and then increased weekly as tolerated up to a maximum dose of 90 + 30 mg. Randomised treatment was then continued for 36 months. During the treatment phase subjects were reviewed at 4 monthly intervals. At the end of the treatment phase there were two follow-up visits; Follow-Up 1 occurred 7 to 21 days after the 36 month visit and Follow-Up 2 occurred a further 7 to 21 days later. The primary efficacy outcome was the rate of kidney volume change from baseline (total, for both kidneys). The key secondary efficacy outcome was a composite endpoint consisting of time to four events representing clinical progression of ADPKD (hypertension, severe renal pain, albuminuria, and worsening renal function).

The original sample size required was estimated to be approximately 1,200 subjects. Based on previous data the average increase in renal volume in the placebo arm was assumed to be 7% per year. A reduction of 20% to 5.6% per year was assumed for the tolvaptan group. With a power of 85%, a 2:1 randomisation and an alpha of 0.049, it was calculated that a total of 504 subjects would be required. This was increased to 600 to allow for a 20% rate of withdrawal. This number was doubled, to enable a power equivalent to two independent studies. After discussions with the FDA the sample size was re-estimated after 1,000 subjects had been enrolled, without unblinding of the data. The FDA considered that the primary endpoint of TKV was of uncertain clinical significance, and that therefore the sample size should be based on the composite secondary endpoint. As this was to be the only comparative trial, an alpha of 0.01 was used. The recalculation estimated that a total of 1400 subjects would be required.

The median age of the population was 39.0 years (range 18 to 51). 84.3% of subjects were Caucasian, 12.7% were Asian, 1.5% were Hispanic, 1.3% were black and 0.2% were from other races. Renal function was reasonably well preserved, with 74.3% of subjects having a creatinine clearance > 80 mLs/min. Mean TKV was 1692.3 \pm 905.31 mLs. CKD stages at baseline using the eGFRCKD-EPI formula were (tolvaptan versus. placebo): Stage 1 – 34.5% versus. 35.9%; Stage 2 – 48.5% versus. 46.5%; Stage 3 – 17.0% versus. 17.4%. A history of hypertension was present in 80.0% of subjects in the tolvaptan arm and 80.2% of subjects in the placebo arm. 76.9% of subjects in each arm were using anti-hypertensive

medication. The proportion of subjects using medication for renal pain at baseline was comparable in the two arms (5.1% versus 5.8%).

For the primary endpoint, rate of kidney growth over three years in the placebo arm was 5.51% per year, whereas in the tolvaptan arm, it was 2.80% per year, a reduction of 49.2%. The absolute difference between treatment arms was 2.71% per year (95%CI 2.15% to 3.27%; $p < 0.0001$).

For the secondary endpoint, in the placebo arm, clinical progression events occurred at a rate of 50.0 per 100 follow-up years. In the tolvaptan arm, the rate was 43.9 per 100 follow-up years (hazard ratio 0.87; 95%CI: 0.78 to 0.97; $p = 0.0095$). In terms of individual components of the secondary endpoint, the risk of experiencing a worsening renal function event (defined as a 25% reduction from baseline in the reciprocal of serum creatinine) was reduced by 61.4% (hazard ratio 0.39; 95% CI: 0.26 – 0.57; $p < 0.0001$); the risk of experiencing a severe renal pain event was reduced by 35.8% (hazard ratio 0.64; 95% CI: 0.47 – 0.89; $p < 0.0071$); there was no significant reduction in the risk of experiencing a worsening hypertension event or a worsening albuminuria event.

The rate of decline of eGFR in the tolvaptan group was -2.72 mL/min/1.73 m²/year compared with -3.81 mL/min/1.73 m²/year in the placebo group ($p < 0.0001$).

Study 156-04-250

This was a Phase II open label US trial that enrolled 46 patients who had participated in two clinical pharmacology studies but were ineligible to be enrolled in the pivotal efficacy trial. The aim of the study was to identify a dose at which urine osmolality was maintained below 300 mOsm/L over 24 hours. An initial titration period resulted in two doses (60 mg and 90 mg daily) being compared in a 12 month fixed dose extension period. Efficacy and safety were similar between the two dose regimens.

Studies 156-05-002, 156-09-003

These were a Phase II open label study and Phase III open label extension which enrolled patients in Japan who had participated in a previous clinical pharmacology study. 17 subjects were treated with tolvaptan 15 mg twice daily (BD) for up to three years. Results suggested this dose is unlikely to be effective.

Studies 156-10-003, 156-08-271

These are ongoing open label extension studies enrolling around 1,000 patients who had participated in a previous study, including the pivotal trial. Interim study reports have so far not provided significant efficacy data.

Safety

A total of 1,581 subjects received at least one dose of tolvaptan, including 1,432 subjects with ADPKD. 1,275 subjects received tolvaptan 60 to 120 mg for at least 6 months, and 1,002 subjects for at least 12 months. In the pivotal study, 80.9% of subjects in the tolvaptan arm were titrated up to 120 mg per day at the end of the 3 week titration period, however the proportion of subjects tolerating this dose decreased over time. At Month 36, only 54.4% of subjects in the tolvaptan arm had a dose of 120 mg per day; average daily dose was around 100 mg per day.

In the pivotal study, adverse events occurred in 97.9% of subjects in the tolvaptan arm, compared to 97.1% in the placebo arm. Serious adverse events occurred in 18.4% versus 19.7%, and treatment related adverse events (adverse drug reactions) in 88.6% versus 62.5%. No single serious adverse event occurred in more than 1.0% of subjects in either arm. There were no deaths in the pivotal study; two deaths in other studies (one self-inflicted gunshot wound; one subarachnoid haemorrhage) were judged to be unrelated to treatment.

In the pivotal study, adverse events more common with tolvaptan included thirst (55% versus 21%), polyuria (38% versus 17%), nocturia (29% versus 13%), gout (2.9% versus 1.4%), constipation (8.4% versus 2.5%) and rash (4.2% versus 1.9%). Renal adverse events less common in the tolvaptan group were renal pain (27% versus 35%), haematuria (7.8% versus 14%), nephrolithiasis (1.6% versus 2.9%), and urinary tract infection (8.4% versus 13%).

15% subjects in the tolvaptan arm discontinued due to an adverse event versus 4.3% in the placebo arm, most commonly due to urinary adverse events (polyuria, pollakiuria, nocturia, thirst).

There was an increased incidence of elevated hepatic transaminases in the tolvaptan arm of the pivotal study (aspartate transaminase (AST) or alanine transaminase (ALT) > 3 x upper limit of normal (ULN): 4.9% versus 1.7% for placebo), including two subjects meeting the “Hy’s law” criteria for severe DILI (AST or ALT elevation; elevated bilirubin; no evidence of cholestasis; and exclusion of other explanations). A third “Hy’s law” case occurred in a long-term extension study. Events were not dose related but were more common in subjects with lower creatinine clearance at baseline. Serious hepatic adverse events were more common in the tolvaptan arm (2.1% versus 1.0%). There were no reports of liver failure or liver transplant and no fatal hepatic adverse events. An independent Hepatic Adjudication Committee concluded that “tolvaptan has the potential to cause liver injury capable of progression to liver failure”, with an estimated incidence of liver failure among patients receiving long-term treatment of around 1 in 3,000.

A review of PSURs for Samsca covering a three year period 2009 to 2012 revealed five reports of hepatic adverse events. These were reviewed by the Hepatic Adjudication Committee and judged to be unlikely related to tolvaptan. Estimated exposure during this period was 3,790 patient-years. The PSURs revealed additional safety signals for rapid increases in serum sodium and for raised intraocular pressure / glaucoma.

Tolvaptan was associated with an increased incidence of clinically significant hyponatremia (> 150 mEq/L; 4.0% versus 1.4% for placebo) and potentially clinically significant elevations in serum uric acid (6.2% versus 1.7%). The incidence of potentially clinically significant increases in serum creatinine was lower in the tolvaptan arm (16.7% versus 21.0%).

Post-market experience from Europe and Canada, involving an exposure of 9,447 patient-years and 799 adverse event reports, revealed no new safety signals. There were 223 reports of hepatobiliary disorders, with 88 assessed as serious.

Risk management plan

The Pharmacovigilance and Special Access Branch (PSAB) has accepted the EU Risk management Plan for Jinarc (tolvaptan) (version 12.6), with ASA (version September 2016).

Additional proposed studies are two post-authorisation safety studies (Study 156-09-101 and Study 156-12-299); two interaction studies (involving CYP 3A4 inhibitors and P-gp inhibitors); and a liver injury study in Japan.

There are additional risk management activities planned for the safety concern of liver injury, comprising prescriber education, certification of prescribers, and registration of patients. Potential prescribers would be required to undertake an educational activity provided by the sponsor in order to be included in the prescriber’s registry. Proposed educational materials provided with the EU RMP include a ‘Healthcare Professional Educational Guide’, ‘Mandatory Prescribing Checklists’ for treatment initiation and

monitoring, a patient education brochure and patient alert card. Distribution of Jinarc will be through a single distribution channel. Prescribing will be restricted to nephrologists.

The PI contains the following boxed warning:

Tolvaptan has been associated with idiosyncratic elevations of blood alanine and aspartate aminotransferases (ALT and AST), rarely associated with concomitant elevations in bilirubin-total (BT). To help mitigate the risk of liver injury, blood testing for hepatic transaminases is required prior to initiation of Jinarc, then continually monthly for 18 months, then every 3 months thereafter during treatment with Jinarc (See PRECAUTIONS).

The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised in Table 13 above.

The risk mitigation strategy implemented in Canada additionally involves prescribers certifying that patients' ALT and AST levels will be $< 3 \times$ ULN before prescribing tolvaptan.

Risk-benefit analysis

Dosage

Current:

Due to the need for a dose titration phase with close monitoring of serum sodium and volume status, **treatment with Samsca should be initiated and re-initiated in hospital.**

Treatment with Samsca should be initiated at a dose of 15 mg, orally, once daily. The dose may be increased to a maximum of 60 mg once daily as tolerated to achieve the desired level of serum sodium. Increase from the starting dose should be done incrementally (first to 30 mg and then to 60 mg if required) at intervals ≥ 24 hours. During titration, patients should be monitored for serum sodium and volume status.

Proposed:

The proposed dosage regimen for Jinarc is a twice-daily regimen, with the first dose taken upon waking and the second dose 8 hours later. Three dose levels are proposed:

- 45 mg + 15 mg (total 60 mg/day);
- 60 mg + 30 mg (total 90 mg/day);
- 90 mg + 30 mg (total 120 mg/day).

The morning dose is to be taken at least 30 minutes before the morning meal. The second dose can be taken with or without food.

The proposed starting dose is the 45 + 15 regimen. The dose is then titrated upwards (with at least weekly intervals between titrations) through the two higher regimens. Patients are maintained on the highest dose regimen tolerated. Treatment is to continue indefinitely.

The currently approved regimen for Samsca is a starting dose of 15 mg once daily, increasing up to a maximum of 60 mg once daily. Administration for more than 30 days is not recommended due to the risk of hepatic toxicity.

Efficacy

Data comes principally from a single randomised controlled trial. Tolvaptan was associated with a significant reduction in the rate of increase of TKV (2.80% per year

versus 5.51% per year for placebo). The validity of TKV as an efficacy endpoint in ADPKD has been questioned; however TKV has been shown to be predictive of the rate of decline of GFR. TKV is accepted as valid indicator of disease progression.

Tolvaptan was associated with a statistically significant reduction in clinical progression events (43.9 per 100 years versus 50.0 for placebo), due to a reduction in renal pain and worsening renal failure events. Tolvaptan was not associated with a reduction in risk of hypertension or microalbuminuria. Tolvaptan was associated with a statistically significant but small reduction in the rate of decline of renal function. The sponsor provided evidence that the reduction in rate of decline of renal function seen with tolvaptan in ADPKD is similar to that seen with angiotensin receptor blockers in hypertensive nephropathy. It is accepted that this represents a clinically meaningful effect. ACMS advice is requested on this matter.

Patient population

The pivotal trial specifically excluded patients with stage 3 (moderate) CKD, although at the commencement of the study approximately 250 patients with CKD stage 3 were enrolled, of whom 166 were randomised to receive tolvaptan. Because of the deterioration of renal function in both patient groups, the CKD stage 3 group increased in size to a total of 253 in the tolvaptan group and 122 in the placebo group by the third year of the study. In a published post-hoc analysis, the reduction in decline in renal function in the CKD stage 3 group was 1.66 mL/min/1.73 m²/year compared to 0.9 mL/min/1.73 m²/year in the CKD stage 1 group. An additional efficacy study (Study 156-13-210), is underway, conducted in subjects with CKD stage 2 to 4. Because of the existence of some data in this patient group, it seems acceptable to specifically include stage 3 CKD patients in the indication for Jinarc, as in Europe. ACMS advice is requested on this matter.

Safety

Exposure was adequate across the full range of doses. Over 1,000 patients were treated for at least 12 months in clinical trials. The most common adverse events were those expected from the mechanism of action of tolvaptan (such as thirst, polyuria, nocturia); these were also the most common events leading to discontinuation. Tolvaptan was also associated with an increased incidence of gout, constipation, rash, and hyponatremia.

Hepatotoxicity

Tolvaptan was associated with a doubling in risk of serious hepatic adverse events with the potential to progress to liver failure. Additional risk management activities are planned to address this risk, including prescriber education and certification, and a single distribution channel. The draft PI contains a boxed warning referring to the need for regular liver function monitoring; monthly for the first 18 months, then 3 monthly thereafter; this is consistent with recommendations in the European and Canadian PIs. An additional requirement in Canada is that prescribers must certify that patients' AST and ALT values are < 3 x ULN before prescribing tolvaptan. ACSOM provided advice that a more restrictive access model, similar to the Canadian model, would be appropriate in Australia. However ACSOM also noted that prescribing will be done by a nephrologist, with hepatic function monitoring usually a part of routine care. The PI warnings and prescriber education program appear adequate to ensure appropriate patient monitoring; ACMS advice is requested on this matter.

Indication

The sponsor requests the following indication:

Jinarc is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease (see PHARMACOLOGY).

This is similar to the European indication, whereas the Canadian indication is:

Jinarc (tolvaptan) is indicated to slow the progression of kidney enlargement in patients with autosomal dominant polycystic kidney disease (ADPKD). In ADPKD, kidney enlargement reflects renal cyst burden.

The Dosage and Administration section of the PI recommends against use in children and adolescents. A suggested wording for the indication is as follows:

Jinarc is indicated to slow the progression of kidney enlargement in adults with autosomal dominant polycystic kidney disease (ADPKD) with CKD stage 1 to 3.

Data deficiencies

There are limited data in patients with more severe chronic kidney disease (stages 3 and above).

Conditions of registration

The following are proposed as conditions of registration and the sponsor is invited to comment in the Pre-ACM response:

- The implementation of the EU Risk management Plan for Jinarc (tolvaptan) (version 12.6), with Australian Specific Annex (version September 2016).
- The results of Study 156-13-210 to be submitted to the TGA as soon as available.

Questions for the sponsor

The sponsor is requested to address the following issues in the Pre-ACM response:

1. Please provide an update on the progress of study 156-13-210
2. Please provide any available post-marketing data, particularly in regard to the incidence of hepatic adverse effects
3. Please provide an update on the regulatory status of Jinarc in the USA
4. Please provide an update on an update on the progress of post-authorisation studies 156-09-101 and 156-12-299, as well as the CYP 3A4 inhibitor and P-gp inhibitor interaction studies.
5. Please comment on the significance of raised intraocular pressure / glaucoma seen in post-market reports for Samsca, and the need for intraocular pressure monitoring in patients taking Jinarc.
6. Please comment on the significance of the signal for rapid increase in serum sodium seen in post-market reports for Samsca.

Delegate's considerations

The primary issues with this submission are as follows:

1. The clinical significance of the primary endpoint (total kidney volume) in the pivotal study.
2. The significance of the effect of tolvaptan on renal function.

3. The intended patient group in terms of CKD stage.
4. The safety concerns around hepatic adverse events.

Proposed action

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

Request for ACPM advice

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

1. Is the reduction in TKV increase clinically significant?
2. Does tolvaptan have a clinically significant effect on renal function in ADPKD patients
3. Should the indication include patients with CKD stage 3?
4. Is the proposed risk mitigation strategy sufficient to mitigate the risk of severe liver injury? In particular, should routine liver function monitoring be mandated?

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

Response from sponsor

Otsuka Australia Pharmaceutical Pty Ltd refers to the Delegate's Overview and Request for ACM's advice (dated 3 January 2017), and concurs with the Delegate's preliminary assessment that there is "no reason to say, at this time, that Jinarc should not be approved for registration".

We note the Delegate's questions to the ACM regarding clinical significance of the reduction in TKV, the clinical significance of tolvaptan on renal function, whether CKD Stage 3 should be included in the indication and if the risk mitigation strategy for liver injury is sufficient. Otsuka's response to the questions and additional comments raised by the Delegate are provided below.

Response to questions raised by the delegate

1. *Please provide an update on the progress of Study 156-13-210.*

Sponsor's response:

An update on the progress of Study 156-13-210 was provided. This response advised that the aforementioned study is ongoing with the last patient visit planned for April/May 2017. A study report will be provided to the TGA as a condition of registration by approximately May 2018. No interim data has been collected or analysed for this study and as such not further details are available.

2. *Please provide any available post marketing data, particularly in regard to the incidence of hepatic adverse effects.*

Sponsor's response:

The following information has been provided previously in the response to first round issues raised:

- A post marketing report covering the period 24 March 2014 to 18 May 2016.
- An analysis of any Hy's Law cases.

The next available PSUR for the period 19 May 2016 to 18 November 2016 will be available on the 20 January 2017. An analysis of this data was not available at the time of preparation of this response.

3. *Please provide an update on the regulatory status of Jinarc in the USA.*

Sponsor's response:

The regulatory status of Jinarc in the USA remains as "deferred, pending complete response letter". Otsuka expects to resubmit the NDA in the fourth quarter of 2017.

4. *Please provide an update on the progress of post authorisation Studies 156-09-101 and 156-12-299, as well as the CYP 3A4 inhibitor and P-gp inhibitor interaction studies.*

Sponsor's response:

- Study 156-09-101 (Samsca PASS) is complete. CSR is available.
 - Study 156-12-299 (Jinarc PASS) is initiated; the first patient was enrolled on 31 Oct 2016. As of 01 Jan 2017 two patients are enrolled. Expected End of Trial is in 2022.
 - Study 156-14-216 (Drug-Drug Interaction: fluconazole, CYP 3A4 inhibitor) is complete. CSR is available.
 - Study 156-01-234 (Drug-Drug Interaction: digoxin) is complete. CSR is available.
 - Study 030998 (Drug Interaction: P-gp inhibitor) is complete. CSR is available.
5. *Please comment on the significance of raised intraocular pressure/ glaucoma seen in post market reports for Samsca, and the need for intraocular pressure monitoring in patients taking Jinarc.*

Sponsor's response:

Raised intraocular pressure / glaucoma is an important potential risk for tolvaptan. Intraocular pressure / glaucoma is not an identified risk for ADPKD patients and was not included in the product's reference safety information (including the company core data sheet (CCDS) and the European summary of product characteristics (EU-SmPC)). No direct evidence of causal association between the use of tolvaptan and glaucoma has been identified. The sponsor therefore does not believe that monitoring in patients taking Jinarc is required.

6. *Please comment on the significance of the signal for rapid increase in serum sodium seen in post-market reports for Samsca.*

Sponsor's response:

Samsca patients are at greater risk of a rapid rise in serum sodium. In the adult population with hyponatremia secondary to SIADH, it was observed that patients with very low baseline sodium concentrations may be at greater risk for too rapid correction of serum sodium, when treated with Samsca. The precaution section of the Jinarc PI states that, "Pre-treatment sodium abnormalities (hyponatraemia or hypernatremia) must be corrected prior to initiation with tolvaptan therapy."

Thus, an overcorrection of a low serum sodium is not expected to occur in a patient receiving Jinarc for ADPKD.

Sponsors comments on the revised indication

The Delegate has proposed the following suggested revised wording for the indication:

Jinarc is indicated to slow progression of kidney enlargement in adults with autosomal dominant polycystic kidney disease (ADPKD) with CKD stage 1-3.

Sponsor's response:

Otsuka have requested approval of the following indication for Jinarc:

Jinarc is indicated to slow the progression of cyst development and renal insufficiency of ADPKD in adults with CKD stage 1 to 3 at initiation of treatment with evidence of

The use of “cyst development” has been used interchangeably with “kidney enlargement”. However cyst development is the target of therapy, whereas kidney enlargement is the means by which this is measured in a very complicated dysmorphic organ. Although they appear to be used interchangeably it is important that the indication stipulates the intent of the therapy as opposed the way it is measured. It is for this reason that the sponsors has applied for the indication as proposed above.

As discussed (in point 2 below) TKV and renal function were primary and key secondary endpoint for the pivotal clinical trial, a description of the effects of tolvaptan on these clinically relevant signs of progression for ADPKD is believed to be important and should be included in the indication statement.

Including the important limitation of “rapidly progressing disease” in the indication statement is critical to establishing the proper benefit/risk formula for treatment with tolvaptan. By restricting the indication to patients likely to suffer the end consequences of this disorder (ESRD) prior to suffering from a competing mortality hazard (that is cardiac arrest), one can improve the degree of benefit and reduce exposing those unlikely to need those benefits.

Delegates request for advice from ACPM***1. Is the reduction in TKV increase clinically significant?****Sponsor's response:*

The clinical evaluator initially accepted TKV as a valid indicator of disease progression and that the measure of TKV reduction in Study 156-04-251 was statistically significant, however questioned the clinical significance of the result. Because renal function declines over decades, often before it can be measured, reductions in TKV or TKV growth rate contributes to and can predict the decline in renal function. Declining renal function is the cause of ESRD, which has significant clinical impacts on ADPKD patients, ultimately requiring renal replacement therapy. The clinical impact of kidney enlargement can vary from person to person. In some cases the tremendous cyst growth can result in abdominal protrusion, discomfort and pain. In Study 156-04-251 there were associations of TKV growth with the likelihood of experiencing events of renal pain and renal function decline. The likelihood of experiencing a composite event of renal function decline increased by 10 to 12% for every 1% increase in TKV growth during the trial regardless of treatment arm. These outcomes, which are reasonably associated with cystic growth and pressure, may be directly impacted by the acute reduction in size, and overall slowing in TKV growth. A reduction in TKV increase can ease the burden of these factors in ADPKD patients. To the individual this result can be clinically significant.

2. Does tolvaptan have a clinically significant effect on renal function in ADPKD patients?*Sponsor's response:*

As discussed in point one above Study 156-04-251 demonstrated a clinically significant effect by reducing TKV growth in patients taking tolvaptan. However to further support this finding Study 156-04-251 was designed to also measure renal function in two ways. The first was a 25% decline in the inverse of serum creatinine level, as part of a composite endpoint. The second was the slope in eGFR decline. This endpoint, which was also met with statistical significance, showed a relative reduction in renal function decline of

approximately 30% and an absolute benefit of approximately 1mL/min/1.73m²/year in eGFRCKD-EPI¹³. This treatment effect, if sustained over the years (as was the case for 3 years in the Study 156-04-251 trial, extended to 5 years in the Study 156-08-271 trial, preliminary results) is such that for approximately 4 years of treatment, ESRD will be delayed by 1 year. As discussed (in point 1 above), this demonstrates a clinically meaningful delay in the need for dialysis and renal transplant.

The effect size on the decline of renal function is comparable to that seen for inhibitors of the renin angiotensin aldosterone system (RAAS), in hypertensive and diabetic nephropathy. Several pivotal trials examining these agents' effects on deteriorating renal function have demonstrated effects on renal function slope which are comparable to the approximately 30% reduction in slope seen in the Study 156-04-251 trial. In these trials, slope changes as small as 0.8 to 1.2 mL/min/1.73m²/y were associated with significant delays in time to ESRD for these patients, and hence were clinically significant.

The Delegate has concurred that the decline in renal function reduction observed with tolvaptan represents a clinically meaningful effect.

3. *Should the indication include patients with CKD Stage 3?*

Sponsor's response:

The sponsor would like to bring ACMs attention to the fact that while subjects with CKD 3 represented only 17% of the overall treatment population of the pivotal trial (Study 156-04-251), the effects of tolvaptan, which were predicted to wane in later CKD stages, actually remained robust. The design of this trial was not aimed at evaluating each of the first three stages of CKD; however the post-hoc analysis published by Torres et al¹⁴ found the effects to be most prominent in CKD stages 2 and 3. Effects on eGFR were less prominent and non-significant in the subjects with a baseline eGFR in the CKD stage 1 range, likely due to slow eGFR decline and compensatory hyperfiltration. Effects on TKV were consistently seen in all three CKD stages, including CKD stage 1 subjects where TKV is believed to be a more reliable marker of treatment response (see response 1). On this basis there is strong evidence to support the use of tolvaptan in CKD Stage 3 patients, as well as CKD stage 1 and 2.

4. *Is the proposed risk mitigation strategy sufficient to mitigate the risk of severe liver injury? In particular should routine liver function monitoring be mandated?*

Sponsor's response:

The sponsor refers the ACM to the proposed Australian PI where detailed routine liver function monitoring is described as per the following: "To mitigate the risk of significant and/or irreversible liver injury, blood testing for hepatic transaminases and bilirubin is required prior to initiation of Jinarc, continuing monthly for 18 months and at regular 3 monthly intervals thereafter. Concurrent monitoring for symptoms that may indicate liver injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, dark urine or jaundice) is recommended." Furthermore, it states that "During the first 18 months of treatment, Jinarc can only be supplied to patients whose physician has determined that liver function supports continued therapy." Additionally, guidance of when to interrupt or discontinue therapy in response to abnormal liver transaminases and bilirubin are specifically described in the Jinarc PI.

Risk minimisation measures for Jinarc, such as prescriber's education, certification in the prescriber's registry, reassurance of prescriber's certification prior to the dispensation of

¹³ eGFRCKD-EPI an equation for estimating glomerular filtration rate (GFR) from serum creatinine from the chronic kidney disease epidemiology collaboration.

¹⁴ Torres VE et al. Effect of Tolvaptan in Autosomal Dominant Polycystic Kidney Disease by CKD Stage: Results from the TEMPO 3:4 Trial *Clin J Am Soc Nephrol.* 2016; 11:803

Jinarc (in accordance with local legislation), patient education brochure and patient alert card, have been implemented to mitigate the risk of severe liver injury. To assess the effectiveness of these risk minimisation activities, cases of liver injury are continuously monitored, and reviewed and adjudicated by a panel of independent experts in the Hepatic Adjudication Committee (HAC). This panel of independent experts reviews liver injury cases to assess causality and determine if the guidance for monitoring liver function tests and stopping tolvaptan administration is effective. The latest annual report from the HAC which was received on 1 July 2016 did not identify any new Hy's Law cases. This finding is consistent with other HAC reports covering cases received from 1 April 2012.

Advisory committee considerations

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

The ACM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Jinarc, immediate release tablets, containing 15, 30, 45, 60 and 90 mg. of tolvaptan to have an overall positive benefit-risk profile for the amended indication;

Jinarc is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 3A at initiation of treatment with evidence of rapidly progressing disease.

In making this recommendation the ACM:

- noted that the outcome of this submission should not be delayed by waiting for the REPRIS study for which the sponsor is expecting to submit data in mid-2018
- noted that no interventions have been shown to slow the rate of disease progression in ADPKD
- noted that toxicity of drug is important, with the drug being poorly tolerated because of intense polyuria.

Proposed conditions of registration

The ACM agreed with the Delegate on the proposed conditions of registration and advised on the inclusion of the following:

- Subject to satisfactory implementation of the Risk Management Plan most recently negotiated by the TGA.

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

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

- A statement in the PI highlighting that the drug could be used in patients with stage 3 chronic kidney disease (CKD) and in particular stage 3a.

Specific advice

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

1. *Is the reduction in total kidney volume (TKV) increase clinically significant?*

The ACM advised that the reduction in total kidney volume was statistically significant, and though the clinical benefit to the patient was small it was useful.

2. *Does tolvaptan have a clinically significant effect on renal function in ADPKD patients?*

ACM advised that there was a high withdrawal rate with the studies submitted, however the effects and measures were significant.

3. *Should the indication include patients with CKD Stage 3?*

The ACM advised that the indication should include patients with Chronic Kidney Disease (CKD) stage 3 and especially stage 3A.

4. *Is the proposed risk mitigation strategy sufficient to mitigate the risk of severe liver injury? In particular, should routine liver function monitoring be mandated?*

The ACM noted that the appearance of liver injury in trial subjects indicates that there is likely to be a higher level of liver toxicity in general treatment populations.

The ACM advised that regular monitoring of liver function made reversal of liver toxicity possible and while the proposed monitoring is adequate the ACM advised that baseline liver function testing should be conducted.

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

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of:

- Jinarc tolvaptan 15 mg tablet blister pack
- Jinarc tolvaptan 30 mg tablet blister pack
- Jinarc tolvaptan 15 mg + 45 mg tablet blister composite pack
- Jinarc tolvaptan 30 mg + 60 mg tablet blister composite pack
- Jinarc tolvaptan 30 mg + 90 mg tablet blister composite pack

Indicated for:

Jinarc is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with chronic kidney disease (CKD) stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease (see PHARMACOLOGY).

Specific conditions of registration applying to these goods

- The Jinarc EU-Risk Management Plan (EU-RMP), version 12.6, (dated 30 November 2015, data lock point 18 May 2013), with Australian Specific Annex (dated September 2016), included with submission PM-2015-04368-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- The following study reports must be submitted to the TGA as soon as possible after completion, for evaluation as a Category 1 submission: Study 156-13-210.

Attachment 1. Product Information

The PI for Jinarc approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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