Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Olaparib

Proprietary Product Name: Lynparza

Sponsor: AstraZeneca Pty Ltd

October 2019

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
~	Approximately
ACM	Advisory Committee on Medicines
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ARTG	Australian Register of Therapeutic Goods
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_{0-t}	Area under plasma concentration-time curve from zero to the last measurable time point
AUC_{ss}	Area under plasma concentration-time curve during the dosing interval following multiple dosing to steady state
AZD2281	Olaparib
BICR	Blinded independent central review
BID	Twice daily (*Latin*: bis in die)
BRCA	Breast cancer susceptibility gene/protein
BRIP1	BRCA1 interacting protein C-terminal helicase 1
CA-125	Cancer antigen-125
CHMP	Committee for Medicinal Products for Human Use (EU)
CI	Confidence interval
CL/F	Apparent plasma clearance
C_{max}	Maximum observed plasma concentration of a therapeutic drug
$C_{max,ss}$	Maximum plasma concentration of a therapeutic drug at steady state
CMI	Consumer Medicines Information

Abbreviation	Meaning
C_{min}	Minimum observed plasma concentration of a therapeutic drug
$C_{min,ss}$	Minimum plasma concentration of a therapeutic drug at steady state
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CYP	Cytochrome oxidase P450
DDI	Drug-drug interaction
DFS	Disease free survival
DoR	Duration of response
EC_{50}	Concentration which causes 50% maximum induction
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report forms
EMA	European Medicines Agency (EU)
E_{max}	Maximum induction
ENGOT	European Network of Gynaecological Oncological Trial Groups
EU	European Union
FACT-O	Functional Assessment of Cancer Therapy-Ovarian Cancer
FDA	Food and Drug Administration (USA)
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GLP	Good laboratory practice
Hb	Haemoglobin
HR	Hazard ratio
HRD	Homologous recombination deficiency
HRR	Homologous recombination repair

Abbreviation	Meaning
IC_{50}	Half maximal inhibitory concentration
IC_{90}	90% inhibitory concentration
ICH	International Council for Harmonisation
IVRS	Interactive Voice Response System
K_a	Absorption rate constant
M…	Major human olaparib metabolite
MATE1	Multi-drug and toxin extrusion protein-1
MCID	Minimal clinically important differences
MDS	Myelodysplastic syndrome
MRI	Magnetic resonance imaging
nM	Nanomolar
NR	Not reached
OCT2	Organic cation transporter-2
ORR	Overall response rate
OS	Overall survival
PARP	Poly adenosine diphosphate ribose polymerase
PARylation	Poly adenosinediphosphate ribosylation
PBMCs	Peripheral blood mononuclear cells
PBS	Pharmaceutical Benefits Scheme
PD	Pharmacodynamic
PFI	Platinum free interval
PFS	Progression free survival
PFS2	Time from randomisation to second progression or death
PI	Product information
PK	Pharmacokinetic
PO	By mouth/oral (*Latin:* per os)

Abbreviation	Meaning
PT	Preferred Term
QoL	Quality of life
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia correction
RAD51B	Rad51 paralog B
RBC	Red blood cells
RECIST	Response Evaluation Criteria in Solid Tumours
RMP	Risk management plan
SAE	Serious adverse event
SOC	System Organ Class
$t_{1/2}$	Half life
TFST	Time from randomisation to first subsequent therapy or death
t_{max}	Time to reach maximum observed concentration following drug administration
TOI	Trial Outcome Index
TSST	Time from randomisation to second subsequent therapy or death
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
WBC	White blood cells
wt	Wild type
µM	Micromolar

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications and major variation (strength and dosage form)
Decision:	Approved
Date of decision:	18 May 2018
Date of entry onto ARTG:	23 May 2018
ARTG numbers:	288613, 288614
, *Black Triangle Scheme*	No
Active ingredient:	Olaparib
Product name:	Lynparza
Sponsor's name and address:	AstraZeneca Pty Ltd PO Box 131 North Ryde NSW 1670
Dose form:	Film coated tablet
Strengths:	100 mg and 150 mg
Container:	Blister pack
Pack sizes:	56 tablets
Approved therapeutic use:	*Olaparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum- sensitive relapsed high grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) after platinum-based chemotherapy. Prior treatment must have included at least 2 courses of platinum-based regimens.*
Route of administration:	Oral
Dosage:	Two 150 mg tablets taken twice daily (daily total dose of 600 mg). 100 mg tablet is available for dose reductions only. For further details please refer to the Product Information.

Product background

This AusPAR describes the application by AstraZeneca Pty Ltd (the sponsor) to register a new strength and dosage form of Lynparza (olaparib) as a 100 mg and 150 mg tablet formulation for the following extension of indication:

> *Olaparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed high grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.*

Ovarian cancer is a leading cause of death from gynaecological cancer and approximately 75% of cases present with advanced disease. The 5 year overall survival of ovarian cancer patients is about 50% across all stages and < 30% in patients with advanced or metastatic disease (stage III/IV). Most women have primary debulking surgery, followed by adjuvant platinum based chemotherapy. Response rates are high in the first line setting (depending on the extent of post-surgical residual disease), but most women experience disease recurrence within 2 years and die within 3 to 4 years of diagnosis (that is, recurrent ovarian cancer is incurable, with currently available treatments), as such, new treatments are needed.

Olaparib is an orally active, specific poly adenosine diphosphate ribose polymerase (PARP) inhibitor approved for use as maintenance therapy in platinum sensitive, advanced ovarian cancer. Olaparib prolongs progression free survival (PFS) with acceptable toxicity in patients with breast cancer susceptibility gene1 and 2 (BRCA1 and BRCA2) mutations. In this submission the sponsor sought to extend the indications to patients without known deleterious or suspected deleterious BRCA mutations.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) under ARTG registration 234008 on 7 January 2016 (under Submission PM-2014-04684-1-4) with for a 50 mg capsule with the following indications:

> *Olaparib is indicated as monotherapy for the maintenance treatment of patients with platinum-sensitive relapsed BRCA-mutated (germline or somatic) high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) after platinum-based chemotherapy. Prior treatment must have included at least 2 courses of platinum-based regimens.*

In the current application, the sponsor has sought to register a new formulation of olaparib; 100 and 150 mg tablet formulation, with the following extension of indications:

> *Olaparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed high grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.*

At the time the TGA considered this application, a similar application to register the 100 mg and 150 mg tablet formulations had been approved in the United States of America (USA) on 17 August 2017 and was under consideration in Canada, the European Union (EU), New Zealand and Switzerland, with plans to submit an application in Singapore (see Table 1).

Table 1: Overseas regulatory status of Lynparza 100 mg and 150 mg tablet formulations as of 6 March 2018

Region	Submission date	Approval status	Indication
USA	22 February 2017	Approved 17 August 2017	*Lynparza is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy.* and *Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.*
Canada	5 May 2017	Under review	Under review
European Union (EU)	6 April 2017	Under review	Positive Committee for Medicinal Products for Human Use (CHMP) opinion issued 22 February 2018 for the following proposed indication. *Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.*
New Zealand	8 December 2017	Under review	Submission includes data to support indications in ovarian cancer and breast cancer consistent with Australian submissions PM-2017-01451-1-4 and PM-2017-03113-1-4.
Switzerland	18 August 2017	Under review	Submission includes data to support indications in ovarian cancer and breast cancer consistent with Australian submissions PM-2017-01451-1-4 and PM-2017-03113-1-4.
Singapore	Plans to submit		

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 time line

Table 2 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2017-01451-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	31 May 2017
First round evaluation completed	7 February 2018
Sponsor provides responses on questions raised in first round evaluation	22 February 2018
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	26 February 2018
Sponsor's pre-Advisory Committee response	2 March 2018
Second round evaluation completed	18 May 2018
Registration decision (Outcome)	18 May 2018
Completion of administrative activities and registration on ARTG	23 May 2018
Number of working days from submission dossier acceptance to registration decision*	231

*Statutory timeframe for standard applications is 255 working days

Evaluations included under Quality findings and Nonclinical findings incorporate both the first and second round evaluations.

III. Quality findings

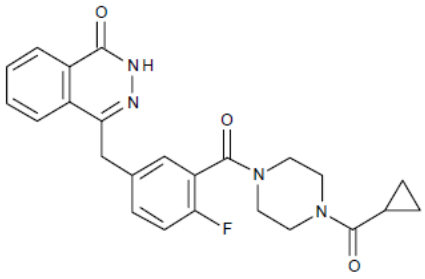
Introduction

The sponsor has applied to register olaparib 100 mg and 150 mg film coated tablets under the trade name Lynparza in blister packs containing 56 tablets and 112 tablets (2 cartons of 56). The sponsor has previously registered 50 mg hard capsules in bottles under the same trade name.

Drug substance (active ingredient)

The structure of olaparib, 4- ((3- ((4-(cyclopropylcarbonyl)-1-piperazinyl) carbonyl)-4-fluorophenyl) methyl)-1(2H)-phthalazinone, is shown in Figure 1.

Figure 1: Olaparib chemical structure



Olaparib is synthetic, manufactured as the free base. [Information redacted]. The synthetic route provided appears to be the same as that used in the manufacture the active ingredient for the 50 mg capsules, previously provided. The controls of critical steps and in-process controls appear adequate.

Drug product

The proposed 100 mg and 150 mg tablets are immediate release film coated tablets packed in blister packs. The proposed pack sizes for the blister presentations are 56 tablets and 112 tablets (2 cartons of 56).

The presentations are made by compression from a common formulated blend (and the manufacturing process is therefore identical up to the compression stage) of milled olaparib extrudate blended with post-extrusion excipients.

The cores common formulated blend is made using conventional mixing, hot melt extrusion, milling, followed by compression, and the tablet cores are film coated and packed. The tablet core strength is achieved by altering the compression weight of the blended material. The composition of the coating has a minor difference in the colourants between the 100 and 150 mg strengths (100 mg tablet coat contains no black iron oxide). [Information redacted].

The tablets are not scored. The tablet appearances are:

- 100 mg tablets: yellow to dark yellow, oval, bi-convex tablet, 14.5 mm by 7.25 mm, debossed with ‘OP 100’ on one side and plain on the reverse.
- 150 mg tablets: green to green/grey, oval, bi-convex tablet, 14.5 mm by 7.25 mm, debossed with ‘OP 150’ on one side and plain on the reverse.

The stability data provided is sufficient to support the proposed shelf life of 3 years when stored below 30°C with the conditions; protect from moisture, store in original container.

The data indicates that the manufacturing process has been adequately developed and optimised to ensure consistent manufacture.

Biopharmaceutics

The proposed tablets are immediate release. Solubility of the active ingredient is not pH dependent across the physiological pH range. Olaparib has low aqueous solubility and poor bioavailability. 50 mg capsules are registered and use active ingredient with crystalline form. [Information redacted]. The proposed 100 mg and 150 mg tablets have

been developed. [Information redacted] using hot melt extrusion with improved bioavailability leading to a reduction of the number of dosage units that patients would need in dosing. Olaparib tablets and capsules are not interchangeable.

Following oral administration of olaparib via the tablet formulation (2 times 150 mg), absorption is rapid with peak plasma concentrations typically achieved between 1.5 hours after dosing.

Few clinical studies have been conducted on olaparib in man. The lack of overall studies is largely due to the nature of the active ingredient (chemotherapeutic) and unsuitability for investigation in healthy subjects.

Bioavailability aspects of olaparib 50 mg capsules were reviewed previously under submission PM-2014-04684-1-4. The present submission is to register 100 mg and 150 mg tablets. The sponsor has demonstrated that registered capsules are not bioequivalent to the proposed tablets.

The following studies address bioavailability of capsules versus tablets, and food effect on tablets.

- Study D0816C00004; A 'randomised, open label, three-part, Phase I study to determine the effect of food on the pharmacokinetics of olaparib and to provide data on the effect of olaparib on QT interval following oral dosing of a tablet formulation in patients with advanced solid tumours.'
  - The study used olaparib 150 mg tablets, dosed at 300 mg (2 times 150 mg tablets) comparing the fasted and fed (high fat meal) states.
  - It is stated that the study was undertaken with appropriate ethical standards.
  - Following multiple oral administration of olaparib (2 times 150 mg tablets) on Day 5, the maximum observed plasma concentration (C_{max}) increased by approximately 36% compared to a single dose in fasting conditions. The area under the plasma concentration-time curve (AUC) increased approximately 1.5 fold on Day 5 compared with Day 1, geometric mean temporal change parameter was 1.454. There was evidence of some accumulation for olaparib, geometric mean accumulation index (AUC) was approximately 1.7 (range 0.888 to 4.68).

A previously evaluated bioavailability study was also provided for the capsules. This was:

- Study D081AC00001; 'A two part, randomised, open label, multicentre, Phase I study to determine the effect of food on the pharmacokinetics of olaparib following single 400 mg doses of the capsule formulation in patients with advanced solid tumours'.
  - The study used 50 mg capsules, dosed at 400 mg (8 times 50 mg capsules) comparing the fasted and fed (high fat meal) states.

Patient pharmacokinetic and initial tolerability study reports were also provided and included:

- Study D0810C00024; 'A Phase I, randomised, 2 period cross over study to determine the comparative bioavailability of two different oral formulations of AZD2281 in cancer patients with advances solid tumours.'
  - This was a Phase I, randomised, 2 period cross over study originally intended to determine the comparative bioavailability of two different oral formulations of olaparib in cancer patients with advanced solid tumours. This study has been previously reviewed. The evaluator for this submission concluded that the tablet formulations are not bioequivalent to the capsule formulation.
- Study D081BC00001; 'A Phase I, open label study to assess the safety and tolerability of doses of olaparib tablet in Japanese patients with advanced solid malignancies'.

  - In this study, the dose for Cohort 1 was 200 mg twice daily (BID) and for Cohort 2 was 300 mg BID, single oral dosing and at steady state after BID dosing of oral tablet formulation of olaparib.
- Study D081CC00001; 'An open label, non-randomised, parallel group, multicentre, Phase I study to assess the safety and the effect of olaparib at steady state on the pharmacokinetics of the anti-hormonal agents anastrozole, letrozole and tamoxifen at steady state, and the effect of the anti-hormonal agents on olaparib, following administration in patients with advanced solid cancer'.

Population pharmacokinetic study reports were also included for tablets and capsules.

Conclusion

Given that bioequivalence of the capsules and tablets is not claimed, it has been decided, on risk management grounds, not to review these studies in the context of the current submission.

Quality summary and conclusions

The application and the supporting data relating to the composition, development, manufacture, quality control, stability and bioavailability of the product have been assessed and checked for compliance, as applicable, with Australian legislation and requirements for new medicines and in accordance with pharmacopoeial standards and the technical guidelines adopted by the TGA. Some outstanding issues will be finalised separately.[1]

Registration is recommended on chemistry, quality control and bioavailability grounds.

IV. Nonclinical findings

Introduction

Olaparib (Lynparza) is registered in Australia (on 7 January 2016; ARTG R 234008) by the sponsor as a 50 mg capsule formulation, for the following indication:

> *Olaparib is indicated as monotherapy for the maintenance treatment of patients with platinum-sensitive relapsed BRCA-mutated (germline or somatic) high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) after platinum-based chemotherapy. Prior treatment must have included at least 2 courses of platinum-based regimens.*

In the current application, the sponsor has sought to register a 100 mg and 150 mg tablet formulation of olaparib with the following extension of indication:

> *Olaparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed high grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy*.

The sponsor also proposed various changes to nonclinical statements under the headings 'Pharmacological actions' and 'Pharmacokinetics' under 'Pharmacology' and 'Interactions with Other Medicines' in the PI document.

[1] All issues were subsequently resolved.

The proposed dosing regimen involves oral administration of 300 mg (2 times 150 mg tablets or 3 times 100 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg, which is lower than the recommended dose (400 mg twice daily) for the already approved indication.

Pharmacology

Two new pharmacology studies provided in this submission showed that olaparib inhibited PARP in a non BRCA1 mutated breast cancer cell line (HCC1806) *in vitro* (half maximal inhibitory concentration (IC_{50}) approximately (~) 1 nanomolar (nM)), cell proliferation of a BRCA1 mutant cell line *in vitro* (IC_{50} 1.6 nM), and PARP and tumour growth inhibition in a mice implanted with BRCA mutant breast cancer cells (HBCx-10). A pharmacodynamic (PD)/pharmacokinetic (PK) analysis of data from the mouse study showed correlation of PARP inhibition with free plasma olaparib concentration, and tumour regression was associated with time above IC_{50} > 13 hours and time above 90% inhibitory concentration (IC_{90}) > 6 hours. These findings are consistent with results of previously evaluated studies in the new chemical entity submission. Nonclinical pharmacology studies in animal models with cancer cells without BRCA mutation were not provided in this submission to support the new indication. Previously evaluated studies showed some efficacy in animal models with non BRCA mutant cancer cells, but anti-tumour activity of olaparib was significantly less against cells with functional BRCA than against BRCA mutant cells.

The pharmacological activity of three major human metabolites (M12, M15 and M18) was compared with the parent drug *in vitro*. The anti-PARP and anti-proliferative activities of M12 and M15 (~ 14% of parent in human plasma) are markedly lower that the activity of olaparib (≥ 20 fold lower), and the pharmacological activity of M18 (~ 20% of olaparib in human plasma) was 4 to 7 fold lower than that of the parent. Thus, the metabolites are unlikely to have a significant contribution to the pharmacological activity of olaparib.

Pharmacokinetics

Similar to the parent compounds, the extent of protein binding to its major metabolites M12, M15 and M18 was moderate to high in mice and in human plasma. For M12, no concentration dependence was observed in mouse plasma (free fraction ~ 45%), but protein binding appeared to be concentration dependent in human plasma over the range 1 to 100 micromolar (μM), free fraction 7% at 1 μM and 47% at 100 μM. For M15, no concentration dependence was observed in both mouse and human plasma (free fraction ~ 60% in plasma of both species). For M18, there was a trend for lower binding fraction at 100 μM (free fraction 24 to 32% in mouse plasma, 12 to 14% at 0.1 to 10 μM and 23% at 100 μM in human plasma).

Pharmacokinetic drug interactions

The sponsor re-analysed the cytochrome oxidase P450 3A4 (CYP3A4) induction data from a previously evaluated study. Olaparib induced CYP3A4 mRNA expression, but did not increase the activity of this enzyme in cultured human hepatocytes. The concentration which causes 50% maximum induction (EC_{50}) for mRNA induction in hepatocytes from 3 donors ranged from 6 to 18 μM, compared with the clinical free C_{max} of 3.8 μM (300 mg twice daily (BID) tablet);[2] or 1.8 μM (400 mg BID capsule). The induction of CYP3A4 by olaparib was 18 to 40% of that by the positive control rifampicin. iven that olaparib inhibits CYP3A4 (albeit at high concentrations) and the relatively low to moderate

[2] Based on steady state total C_{max} 21 μM (9.1 μg/mL) and 18% free fraction.

induction of mRNA (relative to the positive control) without an increase in CYP3A4 activity, the induction of CYP3A4 is not expected to occur during the clinical use.

Toxicology

Repeat-dose toxicity

It was concluded in the previous assessment that two species (rat and dog) were appropriate models based on pharmacokinetic parameters however the exposures to olaparib in longer term studies in rats and dogs were subclinical. With this submission, two repeat dose rat studies with higher oral doses (up to 1000 in males and 100 mg/kg/day in females) were provided, compared with the doses (up to 40 mg/kg/day in pivotal studies) used in previously evaluated studies. The exposures were below the anticipated clinical level. In the pivotal Good Laboratory Practice (GLP) compliant repeat dose toxicity study, olaparib was orally administrated to male and female rats for 3 months. Group sizes were adequate and the clinical route (by mouth (PO)) was used in this study. The animals were dosed only once daily (compared with the proposed clinical dosing regimen of BID), and the exposures to olaparib based on plasma $AUC_{0\text{-}24hours}$ were below the level achieved clinically in patients receiving 400 mg capsules BID or 300 mg tablets BID (see Table 3). Doses were selected based on the data obtained from a preliminary one month study where the dose levels of 1000 and 250 mg/kg/day in males and females were associated with reductions in weight gain (34 to 45%) and food consumption. Significant effects on body weight gain (~ 45% lower than the control group in both sexes), together with organ toxicity, were also observed in the 3 month study, suggesting adequate doses.

Table 3: Relative exposure in repeat dose toxicity study

Species	Study duration	Dose (mg/kg/day PO)		$AUC_{0\text{-}24hours}$ (µmol.hour)		Exposure ratio[#]			
						Tablet		Capsule	
		M	F	M	F	M	F	M	F
Rat	13 weeks	100	25	6.74	24.1	0.03	0.09	0.04	0.13
		250	50	15.3	41.0	0.06	0.15	0.08	0.22
		1000	100	36.6	70.6	0.13	0.26	0.2	0.4
Human (patients)	steady state (Population PK report MS-02, 2016)	300 mg twice a day tablet		275[##]		-		-	
	steady state (Population PK report MS-01, 2014)	400 mg twice a day capsule		186[###]		-		-	

The exposure ratios were calculated separately for male and female animals because the exposure in female animals is significantly higher than in males. [#] = animal: human plasma $AUC_{0\text{-}24hours}$, [##] $AUC_{ss(0\text{-}t)}$ 59.7 µg.hour/mL (137.4 µM.hour) times 2. [###] $AUC_{ss(0\text{-}t)}$ 40.4 µg.hour/mL (93 µM.hour) times 2. M = male, F = female.

The pivotal three month rat study generally showed similar toxicological findings as the previously evaluated studies, including decreased body weight gain as all dose levels (≥ 27 to 35% comparing to the control), and hypocellularity of bone marrow (and decreased red blood cells (RBC), white blood cells (WBC) and related parameters, for example haemoglobin (Hb), neutrophil, lymphocyte), lymphoid depletion and increased extramedullary haematopoiesis at 1000 mg/kg/day in males and ≥ 50 mg/kg/day in females. Epithelial degeneration of small intestines occurred in males at 1000 mg/kg/day.

Nonclinical summary and conclusions

Summary

- Olaparib (Lynparza) is currently registered to the sponsor as a 50 mg capsule, for monotherapy in the maintenance treatment of patients with platinum sensitive relapsed BRCA mutated (germline or somatic) high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) after platinum based chemotherapy. In the current application, the sponsor has applied to register two tablet formulations (100 mg and 150 mg) for olaparib and extend the indication to remove the requirement for a patient to have a BRCA mutation. The maximum proposed tablet dose is 300 mg BID, compared to 400 mg BID for the capsule formulation.
- Limited new nonclinical data was submitted to support these changes.
- Olaparib and three of its major metabolites (M12, M15 and M18) inhibited poly adenosinediphosphate ribosylation (PARylation) in a HCC 1806 breast cell line (with wild type BRCA), and inhibited the growth of MDA-MB-436 cell line (with BRCA 1 mutation) at nanomolar concentrations. The anti-PARP and anti-proliferative activities of M12 and M15 are markedly lower than the activity of olaparib (≥ 20 fold lower), and the pharmacological activity of M18 was 4 to 7 fold lower than that of the parent. Thus, the metabolites are unlikely to have a significant contribution to the pharmacological activity of olaparib. The anti-tumour efficacy of olaparib was also demonstrated in a mouse xenograft/allograft BRCA deficient model *in vivo*.
- *In vitro*, the extent of protein binding to olaparib and metabolites M12, M15 and M18 was moderate to high in mouse and human plasma.
- A previously evaluated study showed marked induction of CYP3A4 mRNA, but not enzyme activity. A re-analysis of the mRNA induction data showed that olaparib induced CYP3A4 mRNA expression with EC_{50} 6 to 18 μM and maximum induction (E_{max}) 18 to 40% of that by the positive control rifampicin.
- GLP compliant repeat dose toxicity studies were conducted in rats (up to 13 weeks) given oral olaparib once daily. Maximum olaparib exposure levels achieved in the three month study were below that anticipated clinically in patients. No new toxicity findings were identified in these studies, with the main target organs for toxicity being the haematopoietic system (including the bone marrow (myelosuppression and effects on erythroid differentiation), spleen/liver and thymus (secondary to reductions in circulating blood cells)), lymphoid organs (lymphoid depletion), and/or small intestine (epithelial degeneration in duodenum, jejunum, ileum).

Conclusions and recommendation

- The pharmacology studies support the use of olaparib to treat tumours with a mutated BRCA background. However, there is insufficient nonclinical information supporting the use of olaparib to treat tumours with wild type BRCA.

- The animal toxicity studies provided in the current submission did not identify any new toxicity findings at exposures higher than exposures in previously evaluated studies but below the clinical exposure. Toxicity studies demonstrated myelosuppression and haematological toxicity (including anaemia and lymphopenia), lymphoid depletion and epithelial degeneration of small intestines.
- In humans, the tablet 300 mg BID dosing achieves higher level of systemic exposure ($AUC_{0\text{-}t\ ss}$ 59.7 µg.hour/mL) than the capsule 400 mg BID dosing ($AUC_{0\text{-}t\ ss}$ 40.4 µg.hour/mL). Thus, toxicity findings in animal species are more likely to occur in patients taking the tablets than those taking the capsules.
- There are no objections on nonclinical grounds to the proposed registration of two tablet formulations (100 mg and 150 mg) for olaparib provided efficacy has been adequately demonstrated by clinical data.

V. Clinical findings

A summary of the clinical findings is presented in this section.

Introduction

Information on the condition being treated

Ovarian cancer is a leading cause of death from gynaecological cancer and approximately 75% of cases present with advanced disease. It is estimated that in 2017, 1,580 new cases of ovarian cancer will be diagnosed in Australia, representing 2.5% of all new cancers in females.[3] There will be an estimated 1,047 deaths from ovarian cancer, representing 5.1% of all female deaths from cancer. There were 3,980 women living with ovarian cancer in 2012. Advanced ovarian cancer is incurable. However, drug treatment can significantly prolong survival and the chance of surviving at least 5 years was 44.4% from 2009 to 2013.

BRCA1 and BRCA2 are genes which produce tumour suppressor proteins which help repair damaged DNA.[4] Mutated BRCA genes result in poorly functioning DNA repair leading to several cancers, particularly breast and ovarian cancer. Specific inherited mutations of BRCA1 and BRCA2 are implicated in approximately 15% of ovarian cancers, particularly in younger women, and in women of Ashkenazi Jewish descent. Not all mutations are associated with cancers, and these are classified as genetic variants of unknown significance (present in approximately 10% of women with mutations). Because BRCA1 and BRCA2 genes are involved in DNA repair, it has been suggested that harmful mutations may increase the sensitivity of tumours to anticancer therapies which act by damaging DNA (for example, cisplatin).

Current treatment options

The treatment of choice for advanced ovarian cancer is platinum based chemotherapy (most commonly paclitaxel/carboplatin) given as first and second line therapy.[5] However,

[3] Statistics from Cancer Australia, Australian Government.
[4] *BRCA* mutations have been classified in accordance with the American College of Medical Genetics and Genomics.
[5] Aebi, S. and Castiglione, M. on behalf of the EMSO Working Group (2008), Epithelial ovarian carcinoma: ESMO clinical recommendations for diagnosis, treatment and follow-up, *Ann Oncol*, 2008; 19: ii14-16.

new treatments are needed as progression free intervals are often short after treatment.[6] The vascular endothelial growth factor (VEGF) inhibitor bevacizumab is commonly used in patients who do not respond to platinum based chemotherapy. Details of other therapies, including PFS hazard ratios, are shown in Table 4.

Table 4: Current treatment options in platinum sensitive relapsed ovarian cancer

Phase III trial number/name	Agent(s)	N	Line of therapy	PFS HR (95% CI)	Median PFS months	OS HR (95% CI)	Median OS months	Reference	Comments
ICON4/ AGO-OVAR 2.2	Platinum/paclitaxel	392	92% 2nd line	0.76 (0.66-0.89)	13[a]	0.82 (0.69-0.97)	29	Parmar et al 2003	Platinum therapy: 84% carboplatin; 16% cisplatin
	Platinum	410			10[a]		24		
Not specified	Gemcitabine/carboplatin	178	2nd line	0.72 (0.58-0.90)	8.6	0.96 (0.75-1.23)	18	Pfisterer et al 2006	Not powered for OS
	Carboplatin	178			5.8		17.3		
OCEANS	Bevacizumab + gemcitabine/carboplatin	242	2nd line	0.48 (0.39-0.61)	12.4	0.96 (0.76-1.21)	33.4	Aghajanian et al 2012, Avastin EPAR 2012	Subsequent bevacizumab use was 39% in the chemotherapy alone arm vs 22% in the bevacizumab arm
	Gemcitabine/carboplatin	242			8.4		33.7		
GOG0213	Bevacizumab + paclitaxel/carboplatin	374	2nd line	0.61 (0.52, 0.72)	13.8	0.83 (0.68, 1.01)	42.2	Coleman et al 2015a	
	Paclitaxel/carboplatin	374			10.4		37.3		
OVA-301	Trabectedin + PLD	218	2nd line	0.73 (0.56-0.95)	9.2	0.83 (0.67-1.04)	27.0	Monk et al 2010, Monk et al 2012	PSR subgroup described here constituted 64% of the overall population
	PLD	213			7.5		24.1		
Not specified	PLD	109	2nd line	No HR stated p=0.037	6.7	No HR stated p=0.008	24.9	Gordon et al 2001	PSR subgroup described here constituted 46% of the overall population
	Topotecan	111			5.4		16.4		
CALYPSO	PLD + carboplatin	466	2nd/3rd line	0.82 (0.72-0.94)	11.3	0.99 (0.85-1.16)	30.7	Pujade-Lauraine et al 2010, Wagner et al 2012	Imbalance in post progression use of PLD, 68% in CP arm vs 43% in CD arm
	Paclitaxel + carboplatin (CP)	507			9.4		33		
D0810C00019 (Study 19)	Olaparib	74	Maintenance treatment ≥2nd line	0.18 (0.10-0.31)	11.2	0.62 (0.42-0.93)	34.9	Ledermann et al 2014 and Study 19 CSR Addendum 3 (DCO 09 May 2016), Module 5.3.5.1	*BRCAm* subgroup data described here
	Placebo	62			4.3		30.2		
ENGOT-OV16/ NOVA	***gBRCAm* cohort:**		Maintenance treatment ≥2nd line					Mirza et al 2016	OS data immature, overall 95/553 (17.2%) patients had died (60/372 [16.1%] patients in the niraparib group and 35/181 [19.3%] in the placebo group)
	Niraparib	138		0.27 (0.17-0.41)	21.0	NR	NR		
	Placebo	65			5.5				
	Non-*gBRCAm* cohort:								
	Niraparib	234		0.45 (0.34-0.61)	9.3	NR	NR		
	Placebo	116			3.9				

a Median PFS is reported as 13 vs 10 months in the abstract of Parmar et al 2003, whereas in the main results section of this publication median PFS is reported as 12 vs 9 months, in favour of platinum/paclitaxel in both cases.

BRCA Breast cancer susceptibility gene; *BRCAm gBRCA* or *sBRCA* mutated; CD Paclitaxel plus doxorubicin (pegylated liposomal); CI Confidence interval; CP Paclitaxel plus carboplatin; CSR Clinical study report; DCO Data cut-off; *gBRCA* Germline *BRCA*; *gBRCAm* Germline *BRCA* mutated; HR Hazard ratio; NR Not reported; OS Overall survival; PFS Progression-free survival; PLD Pegylated liposomal doxorubicin; PSR Platinum-sensitive relapsed; *sBRCA* Somatic tumour *BRCA*; vs Versus

Clinical rationale

The aim of treatment for advanced ovarian cancer is to maintain PFS and quality of life for as long as possible. Drug treatments should have acceptable toxicities and should be easily administered. Olaparib is an orally active, specific PARP inhibitor approved for use as maintenance therapy in platinum sensitive, advanced ovarian cancer. PARP inhibitors block the enzyme PARP, which acts to repair DNA damage. This action may prevent malignant cells from repairing themselves when they have been damaged by chemotherapy. Olaparib prolongs PFS with acceptable toxicity in patients with BRCA1 and BRCA2 mutations. It is hoped that olaparib will also prolong PFS in patients without known deleterious BRCA mutations.

[6] Ozols, R.F. et al. (2003), Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected Stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol*, 2003; 21:3194-3200.

Guidance

The studies were designed in accordance with the following:

- The CHMP guidelines on evaluation of anticancer medicinal products in man;[7] and methodological considerations for using PFS or disease free survival (DFS) in confirmatory trials.[8]
- The Food and Drug Administration (FDA) guidance to industry on clinical trial endpoints for the approval of cancer drugs and biologics.[9]
- Scientific advice was sought from the regulatory authorities of Sweden (Medical Product Agency), the Netherlands (Medicines Evaluation Board) and France (French National Agency for Medicines and Health Products Safety).

Contents of the clinical dossier

The clinical dossier contains the following clinical study reports:

- PK/PD studies
  - One comparative bioavailability study (Study D081OC00024).
  - One drug metabolism study (Study D0810C00010).
  - Four special population studies (Studies D081BC00001, D081OC00001, D0816C00007 and D0816C00007).
  - Three drug-drug interaction (DDI) studies (Studies D0816C00007, D0816C00008 and D081CC00001).
  - One food/QT interval corrected for heart rate (QTc) study (Study D0816C00004).
  - Four population PK/PD studies (Studies MS01, MS02, MS03 and MS04).
- Efficacy/Safety studies
  - Two dose ranging studies (Studies 09 and 12).
  - One pivotal Phase III study (Study 02 (also known as the SOLO-2 trial)).
  - One pivotal Phase II study (Study 19).
  - Four supportive Phase II studies (Studies 020, 041, 042 and08).

Paediatric data

No paediatric data was submitted.

Good clinical practice

All studies were conducted in accordance with the principles of the International Council for Harmonisation (ICH) Good Clinical Practice (GCP).

[7] European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), 11 January 2013, Guidelines on evaluation of anticancer medicinal products in man, EMA/CHMP/205/95/Rev.4.
[8] European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), 11 January 2013, Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man - methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials, CHMP/27994/2008 Rev. 1.
[9] Food and Drug Administration (FDA) Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, May 2007, Guidance for Industry on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.

Pharmacokinetics

Studies providing pharmacokinetic data

See Table 5.

Table 5: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID
PK in patients with solid tumours	PK- Single dose	D0810C00002
	Metabolism	D0810C00010
	- Multi-dose	D0810C00002
	Bioequivalence †- Single dose	D0801C0024
	- Multi-dose	
	Food effect	D081AC00001
	Food effect	D0816C00004
PK in special populations	Target population §- Single dose	
	- Multi-dose	D0810C00002
	Hepatic impairment	D0816C00005
	Renal impairment	D0816C00006
	Japanese patients (capsule formulation)	D0810C00001
	Japanese patients (tablet formulation)	D081BC00001
PK interactions	Drug anastrozole, letrozole tamoxifen	D081CC00001
	Drug itraconazole	D0816C00007
	Drug rifampicin	D0816C00008
Population PK analyses	Target population	MS-02
	Target population	MS-03

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

No PK results were excluded from consideration.

Evaluator's conclusions on pharmacokinetics

The sponsor has provided a reasonably comprehensive set of studies on the PK of olaparib, for the most part conducted in patients for whom the drug is intended to be used. These studies have adequately addressed the main PK issues to inform the clinical use of the medication.

Most studies have used an appropriate design and were powered to meet a priori objectives. In particular, the bioequivalence of the tablet formulation and the capsule formulation has been investigated with the tablet providing higher bioavailability than the capsule.

Some aspects of the DDI profile of olaparib, in particular the potential for interactions with transporter molecules, have been derived from model studies rather than *in vivo* studies in patients. The sponsors have made an adequate case that these model studies satisfactorily represent the outcome of any likely *in vivo* situations. Studies in renal and hepatic impairment can be considered as partial information as some cohorts usually included (for example severe renal impairment, Child-Pugh Class B) have not been examined. Consequently, dosing in such patients, based on potential PK effects should be conservative and has been adequately addressed in the proposed PI.

As all of the PK data presented in the clinical dossier, for the most part, conducted in the intended patient population, the difficulty of finding sufficient numbers of patients with such co morbidities probably explains this lack of clinical data.

The PK data in the PI and Consumer Medicines Information (CMI) adequately reflect the findings of the studies presented in the applications.

Population PK

Rationale for the evaluation

Previously, the sponsor received marketing approval in Australia for the use of olaparib capsules (400 mg BID) as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed BRCA mutated ovarian cancer (including fallopian tube or primary peritoneal) who are in complete or partial response to platinum based chemotherapy. In this extension application, the sponsor is seeking to register the olaparib tablet formulation (300 mg BID) as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed high grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are completely or partially responsive to platinum based chemotherapy.

The evaluation reviews two reports of the population PK and Exposure-Response (E-R) for olaparib. One report is entitled 'Population Pharmacokinetic (PK) and Exposure–Adverse Event Response Analysis for Phase I Olaparib Studies Following Dosing of Olaparib Tablet Formulation to Cancer Patients (Studies; D0816C00004, D0816C00007, D0816C00008, D0810C00024 and D081BC00001)' and the other is entitled 'Population Pharmacokinetic and Exposure–Response Analysis of Olaparib Tablet Formulation in Patients: SOLO-2 Study (D0816C00002)'. The reports were evaluated to determine the validity of the analysis methods and results presented and to assess the clinical implications of their findings.

The evaluation comprised:

- Replication of the key population PK analysis of five Phase I studies to confirm the results submitted by the sponsor.
- A detailed review of the population PK analysis of five Phase I studies using the Guideline on Reporting the Results of Population Pharmacokinetic Analyses.[10]
- A review of the E-R information included in the population PK report of five Phase I studies including validity of study design and implications for dosing.

[10] European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), 21 June 2007, Guideline on reporting the results of population pharmacokinetic analyses, CHMP/EWP/185990/06.

- A review of the PK/E-R report of the Phase III study the SOLO-2 trial, including validity of study design and implications for dosing.
- Comment on the consequences or implications, if any, of the results of this review on first-round benefit-risk assessment and relevant sections of the proposed Australian PI.

Summary of findings: PK report

The purpose of the analysis was to identify and quantify sources of PK variability for olaparib in five Phase I studies and to evaluate E-R analyses for selected safety endpoints.

On the basis of this evaluation, the following points were summarised:

- The PK model comprised a 2 compartment disposition model with sequential zero and first order absorption and different elimination rates for the first dose and all subsequent doses.
- The base and final PK models were successfully replicated verifying the models and the reported PK parameters in the report.
- The modelling methods described, including choice of software and analysis, modelling assumptions, model building methods, model evaluation methods, were appropriate and consistent with the requirements of the EMA guidelines. Model applications were relevant to understanding the clinical relevance of covariate effects and for subsequent exposure safety analyses.
- PK modelling was executed in accordance with EMA guidelines. The results may be deemed adequate for estimating individual exposures for subsequent exposure-safety analyses. However, covariate evaluations to characterise sources of PK variability for olaparib were incomplete as trends were evident in plots of random effect variable for inter-individual variability (ETA) apparent clearance (CL/F) for a subset of covariates in the final model.
- The only statistically significant covariate effect was an effect of tablet strength on absorption rate constant (K_a). Race (including Asian/Japanese), gender, age and weight were not selected as covariates in the PK analysis.
- Mean predicted exposures (AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$) for 300 mg BID tablet were in good agreement with those obtained by non-compartmental analysis. It was noted that exposures for 300 mg tablet BID were increased compared to exposures for 400 mg capsule BID.
- In the E-R analyses of adverse events (AEs), no relationships with olaparib exposure were identified for any of the AEs included in the graphical exploratory analysis, with the exception of the effect of olaparib on Hb.
- An indirect E-R model with olaparib AUC inhibiting synthesis of Hb described the reduction in Hb during olaparib treatment. Simulations showed that Hb concentrations decreased by mean values of 1.3 to 1.7 g/dL at the typical exposure for 300 mg tablet BID and by 2 to 3.2 g/dL when olaparib exposure was doubled relative to the typical exposure for 300 mg tablet BID. However, the effect of tablet strength (3 times 100 mg compared with 2 times 150 mg) on change in Hb concentration was small (0.3 to 0. 6 g/dL).

Summary of findings: SOLO-2 trial report

The purpose of the analysis was to evaluate the predictive ability of the previously developed population PK model in the SOLO-2 trial, a Phase III study of olaparib maintenance monotherapy in platinum sensitive relapsed BRCA mutated ovarian cancer patients and to examine E-R relationships between olaparib plasma exposure and selected efficacy and safety variables based on data from Study SOLO-2.

- Limitations of analysing sparse PK and E-R data at a single dose level in the SOLO-2 Study alone should have been addressed.
- The previously developed population PK model over predicted olaparib plasma concentrations in the SOLO-2 Study. Given the sparse nature of the data in SOLO-2, it would have been expected that the SOLO-2 data would have been added to the previous data set to explore the source of the misfit. Instead, the model was fit to the SOLO-2 data alone and parameters not supported by the data were fixed or removed so that remaining parameters could be precisely estimated. Diagnostic plots revealed misfit of the structural model to the data that was not explored in the SOLO-2 report. Nevertheless, the visual predictive check showed reasonable predictive ability of the model.
- No exposure-efficacy relationships were identified for PFS, time from randomization to second progression (PFS2) and overall survival (OS) in the analysis.
- An indirect E-R model was developed for Hb similar in structure to that developed previously. Model predictions were consistent with those in the previous analysis, such that Hb concentrations decreased by a mean of 1.3 g/dL and 2.7 g/dL, respectively for typical exposure and double the typical exposure associated with 300 mg tablet BID.
- A model was also developed to describe the relationship between olaparib exposure and fatigue. The relationship was not very strong since the predicted probability of experiencing fatigue on a day without prior fatigue was 0.258% for high exposures corresponding to the 97.5th percentile of predicted exposure for a 300 mg BID dose.

Implications of findings

References to these analyses in the Australian PI were deemed to accurately reflect the findings of this evaluation.

No assessment of benefit-risk was possible based on the evaluated analyses.

Pharmacodynamics

Studies providing pharmacodynamic data

See Table 6.

Table 6: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on PARP-1 activity	D0810C00001
	Effect on PARP-1 activity, efficacy	D0810C00002
	Effect on PARP-1 activity	D0810C00007
Secondary Pharmacology	Effect on QTc Interval	D0816C00004
	Effect on efficacy	D0810C00008
Gender other genetic and	Effect of gender	

PD Topic	Subtopic	Study ID
Age Related Differences in PD Response	Effect of genetic characteristic	
	Effect of age	
	Drug itraconazole on QTc	D0816C00007
PD Interactions	Combined QTc interval	MS-04
Population PD and PK-PD analyses	Target population	MS-02

No PD results were excluded from consideration.

Evaluator's conclusions on pharmacodynamics

The inhibition of PARP-1 was evaluated in clinical samples using peripheral blood mononuclear cells (PBMC). Inhibition after single and repeated doses showed high variability, between 20 and 80%. These studies did not demonstrate a dose response relationship for the extent of PARP inhibition. Studies of the effect of olaparib on QTc intervals showed that the drug caused minimal clinically meaningful changes even when co administered with itraconazole a CYP3A4 inhibitor. There was no simple relationship between olaparib concentrations and side effects.

The studies that were presented were appropriately designed. Data presented in the PI and CMI adequately reflect the results of the studies presented.

Dosage selection for the pivotal studies

Pharmacokinetics and pharmacodynamics: dose finding studies

The 300 mg BID tablet dose was selected as the dose/schedule for Phase III on the basis of having similar efficacy in terms of tumour shrinkage in advanced germline BRCA mutated ovarian cancer patients to the 400 mg BID capsule (D0801C0024) and having an acceptable tolerability profile.

The dose selection was supported by the nonclinical PK/PD modelling conducted in mice and based on the IC_{50} and IC_{90} PARP inhibition threshold and cover which identified the olaparib tumour IC_{50} of PARP as being 24.3 ng/mL (56 nM) and the IC_{90} of PARP as being 165.1 ng/mL (380 nM). Retrospective evaluation of the clinical exposure data has been conducted to compare the geometric mean free steady state trough plasma concentration (± 90% confidence interval (CI)) with the estimated nonclinical IC_{90} value (and its 95% CI). This analysis has shown a 300 mg BID tablet would be expected to maintain plasma concentrations above the IC_{90} (and its upper 95% CI) across the full dosing interval, that is, 12 hours. In contrast, a dose of 100 mg BID capsule results in plasma concentrations in the majority of patients lower than the IC_{90}.

The inhibition of PARP-1 was also evaluated in clinics but using the PBMC in blood (D0801C0024 with capsule and tablet formulations and in Japanese Study D0810C00001 with olaparib capsule). There was no evidence of any dose relationship in the extent of inhibition achieved in those two studies.

Phase II dose finding studies

Study 09 was a Phase II, open label comparison of two doses of olaparib capsules in patients with advanced ovarian. The overall response rates were clearly superior in the group given 400 mg BID (33.3%), compared with the group given 100 mg BID (12.5%). Study 12 was a Phase II, open label comparison of two doses of olaparib capsules versus liposomal doxorubicin in patients with advanced ovarian cancer. PFS in the olaparib 400 mg BID group was numerically superior to the 200 mg BID group but the difference was not statistically significant.

Phase III pivotal studies investigating more than one dose regimen

In the pivotal Phase II Study 19, patients with advanced ovarian cancer were treated with olaparib given as capsules 400 mg BID. In the pivotal Phase III SOLO-2 trial, patients with advanced ovarian cancer were treated with olaparib given as tablets 300 mg BID. Only one dose was investigated in each study.

Evaluator's conclusions on dose finding for the pivotal studies

Tablet and capsule are not strictly bioequivalent. At doses of up to 100 mg, the capsule and tablet had similar extent of absorption. At higher doses, the tablet formulation had consistently higher relative bioavailability than the capsule. Tablet doses of 300 mg BID and 400 mg BID delivered mean steady state $C_{max,ss}$, AUC_{ss} and minimum observed plasma concentration ($C_{min,ss}$) values which were all in excess (approximately 1.5 and 2.0 fold higher) of those delivered by the 400 mg BID capsule dose.

Dose finding for the pivotal studies is satisfactory. Dose finding studies in patients with advanced disease are limited by ethical constraints. In exploratory Phase II studies, the efficacy of the approved dose of 400 mg BID for the capsule formulation was clearly superior to 100 mg BID, and marginally superior to 200 mg BID. The efficacy of the 300 mg BID tablet formulation was investigated in the Phase III SOLO-2 trial.

Efficacy

Studies providing efficacy data

Two pivotal studies were conducted in patients with advanced ovarian cancer:

- The SOLO-2 trial was a Phase III study conducted in patients with a BRCA mutation.
- Study 19 was a Phase II study conducted in patients with or without a BRCA mutation.

Four supportive Phase II studies were conducted in patients with advanced ovarian cancer:

- Studies 020, 09, 12 and 041.

One exploratory Phase II study was conducted in patients with advanced cancers with a BRCA mutation (Study 042).

One study was conducted in patients with colorectal cancer (Study 08).

Table 7: Studies with evaluable efficacy data

Type of study	Study identifier, status	Objective(s) of the study	Study design/type of control	Test product, dosage regimen, route of administration	No. of subjects randomised /treated	Patient population	Location of Study Report
Efficacy, safety, PK	D0816C00002 (SOLO2) **Ongoing; primary PFS and interim OS analysis completed**	Determine the efficacy (assessed by PFS) of olaparib compared to placebo in *BRCAm* patients	Ph III, randomised, double-blind, placebo-control, multicentre	Olaparib 300 mg bd tablet (oral) Matching placebo	295/294	Patients with *BRCA* mutated platinum-sensitive high-grade serous ovarian or endometrioid cancer following treatment with ≥2 platinum-containing regimens	Module 5.3.5.1
Efficacy, safety	D0810C00019 (Study 19) **Completed: primary PFS and final OS analysis completed**	Determine the efficacy (assessed by PFS) of olaparib compared to placebo in overall population	Ph II, randomised, double-blind, placebo-control, multicentre	Olaparib 400 mg bd capsule (oral) Matching placebo	265/264	Patients with platinum-sensitive serous ovarian cancer following treatment with ≥2 platinum-containing regimens	Module 5.3.5.1

bd Twice daily; *BRCA* Breast cancer susceptibility gene; *BRCAm* *BRCA* mutated; OS Overall survival; PFS Progression-free survival; Ph Phase; PK Pharmacokinetics.

Evaluator's conclusions on efficacy

Two pivotal studies have been submitted to support the draft PI for olaparib tablets. Data has been provided to support the new olaparib tablet formulation given as 300 mg BID, compared with the approved capsule formulation given as 400 mg BID. The approved indication for the capsule formulation restricts the use of olaparib to patients with known BRCA mutations. The proposed amendment for the tablet formulation removes this restriction, to permit use in patients with or without BRCA mutations.

In the placebo controlled, Phase III SOLO-2 trial, the efficacy of long term, maintenance olaparib monotherapy using the proposed tablet formulation in patients with advanced ovarian cancer with known BRCA mutations has been demonstrated. The study was well conducted using endpoints generally recognised in regulatory guidelines and by professional bodies. The primary endpoint was PFS, measured by objective radiological assessments of tumour progression using Response Evaluation Criteria in Solid Tumours (RECIST) criteria. PFS was assessed by investigators, but confirmed by blinded central reviewers. Compared with placebo, there was a statistically significant and clinically meaningful 70% reduction in the risk of disease progression or death (hazard ratio (HR) 0.30, $p < 0.0001$). A survival benefit could not be established. The data was immature at the time of the primary analysis, and patients in the placebo group were offered other therapies when disease progression occurred. The study did not include patients without BRCA mutations so the efficacy of the tablet formulation in this population has not been established.

In the placebo controlled, Phase II Study 19 (evaluated previously by the TGA), the efficacy of maintenance olaparib monotherapy using the capsule formulation in patients with advanced ovarian cancer with unknown BRCA status has been demonstrated. The study conduct was sub optimal with a high number of important protocol deviations, mainly randomisation errors. Compared with placebo, there was a statistically significant and clinically meaningful 65% reduction in the risk of disease progression or death (HR 0.35, $p < 0.00001$). In a recent analysis (not evaluated previously by the TGA), BRCA status was retrospectively established in approximately 80% of the original patient population. In patients without BRCA mutations, there was a benefit in favour of olaparib compared with placebo in the subgroup of patients without BRCA mutations. There was a statistically significant 46% reduction in the risk of disease progression or death (HR 0.5435, $p < 0.0075$). Compared with patients with a BRCA mutation, the benefit was less marked but still clinically meaningful.

While Studies 02 and 19 are not directly comparable, the efficacy of the new tablet formulation can be considered comparable to that of the approved capsule formulation. The efficacy of the capsule formulation appears less in patients without BRCA mutations

compared with patients with BRCA mutations. Nonetheless, olaparib treatment offers a clinically meaningful benefit in patients without BRCA mutations who have few other therapeutic options. Patients without BRCA mutations have not been investigated in clinical studies with the new tablet formulation. However, efficacy in patients with BRCA mutations was comparable in Studies 02 and 19 using the tablet and capsule formulations, respectively. On this basis, it is reasonable to assume comparable efficacy with the tablet and capsule formulations in patients without BRCA mutations. There are no data to support retreatment with olaparib as maintenance following subsequent relapse.

Safety

Studies providing safety data

Pivotal and/or main efficacy studies

- Study 19 provided safety data for the capsule formulation.
- The SOLO-2 trial provided safety data for the tablet formulation.

Other efficacy studies

Safety data in other efficacy studies was pooled according to the formulation.

The 400 mg capsule pool comprised Study 19 and 11 additional studies:

- Four Phase I studies (Studies D0810C00001; D0810C0002; D0810C00007; D081A00001).
- Five Phase II studies (Studies D0810C00009; 1 D0810C00012; D0810C00020; D0810C00024; D0810C00042).
- Two Phase II studies in breast cancer (Study D0810C00008); and colorectal cancer (D9010C00008). These studies have not been evaluated for efficacy as they did not include patients with ovarian cancer.

The 300 mg tablet pool comprisedthe SOLO-2 trial and seven Phase I studies (Studies D0810C00024; D0816C00004; D0816C00007; D0816C00008; D081BC00001; D081CC00001; D0816C00006).

Studies with evaluable safety data: dose finding and pharmacology

None submitted.

Patient exposure

As of December 2016, 6558 patients in the total clinical trial program had received at least one dose of olaparib. Exposure has been calculated for the olaparib 300 mg tablet and 400 mg capsule pooled sets. Most patients in the pooled data sets had ovarian cancer (64.7% tablet; 68.1% capsule). The pooled data included all patients who had received at least one dose of olaparib as monotherapy (n = 482 tablet; n = 766 capsule). In the 300 mg tablet pool, 231 patients (47.9%) had 6 months exposure to olaparib; and 145 patients (30.1%) had 12 months exposure. In the 400 mg capsule pool, 325 patients (42.4%) had 6 months exposure to olaparib; and 140 patients (18.3%) had 12 months exposure. The median total treatment duration was more than three times longer in the olaparib group compared with the placebo group (19.4 months versus 5.6 months).

All adverse events (irrespective of relationship to study treatment)

The safety profiles of the placebo controlled, pivotal studies are assessed individually and compared. In addition, integrated safety analyses for the pooled 400 mg BID capsule

studies (Study 19 (n = 136), and supporting studies (n = 766)) are compared with the pooled 300 mg BID tablet studies (Study SOLO-2 (n = 195), and supporting studies (n = 482)).

Integrated safety analyses

The pattern of AEs was broadly comparable in each of the four groups. A comparison of the most common AEs (≥ 10%) by System Organ Class (SOC) and Preferred Term (PT) for the pivotal and pooled studies showed comparable AE profiles for the tablet and capsule formulations, and in keeping with the known adverse drug reactions (ADRs) associated with olaparib. Anaemia, dysgeusia, and asthenia were notably more common in patients treated with the tablet formulation, while fatigue was more common with the capsule formulation. Overall, severe AEs were marginally less common in the tablet pool compared with the capsule pool.

Pivotal and/or main efficacy studies

Study 19: In the overall population, at least one AE was reported in 95.1% of patients (olaparib 97.1%; placebo 93.0%), but most AEs were mild to moderate in severity. For AEs occurring in more than 10% of patients, the most common AEs were nausea (olaparib 70.6%; placebo 35.9%); fatigue (52.2% versus 39.1%); vomiting (33.8% versus 14.1%); and anaemia (21.3% versus 5.5%). Other AEs reported with 5% greater frequency in the olaparib group compared with placebo were constipation (20.6% versus 10.9%); decreased appetite (20.6% versus 13.3%); headache (20.6% versus 12.5%); upper abdominal pain (17.6% versus 7.8%); cough (17.6% versus 10.2%); dyspepsia (17.6% versus 8.6%); back pain (16.2% versus 6.3%); dysgeusia (16.2% versus 6.3%); dizziness (13.2% versus 7.0%); dyspnoea (11.8% versus 6.3%); and upper respiratory tract infection (11.8% versus 6.3%). AEs reported with 5% to 10% greater frequency in the olaparib group compared with placebo were muscle spasms (9.6% versus 3.9%); pyrexia (9.6% versus 3.1%); peripheral neuropathy (8.8% versus 2.3%); and stomatitis (8.8% versus 3.1%). Severe AEs (common terminology criteria for adverse events (CTCAE) Grade ≥ 3) were reported in more patients in the olaparib group (40.4%) compared with the placebo group (21.9%). The most common severe AEs were fatigue (7.4% versus 3.1%), and anaemia (5.1% versus 0.8%).

Safety in the subgroup of patients with BRCA mutations was comparable to the overall group. The most common AEs were nausea (73.0% versus 32.3%); fatigue (54.1% versus 37.1%); vomiting (36.5% versus 8.1%); diarrhoea (29.7% versus 19.4%); and anaemia (25.7% versus 4.8%). For AEs reported by SOC and PT, there were no meaningful differences compared with the overall population.

SOLO-2 trial: In the overall population, nearly all patients reported at least one AE (olaparib 98.5%; placebo 94.9%), but most AEs were mild to moderate in severity. For AEs occurring in more than 10% of patients reported by SOC and PT, the most common AEs in the olaparib group were nausea (olaparib 75.9%; placebo 33.3%), anaemia (43.1% versus 7.1%), fatigue (37.9% versus 15.2%), vomiting (37.4% versus 19.2%), diarrhoea (32.8% versus 20.2%) and asthenia (31.3% versus 27.3%). Other AEs reported with 5% greater frequency in the olaparib group compared with placebo were dysgeusia (26.7% versus 7.1%), headache (25.1% versus 13.1%), decreased appetite (22.1% versus 11.1%), cough (16.9% versus 5.1%), dizziness (13.3% versus 5.1%), pyrexia (13.3% versus 6.1%), dyspnoea (11.8% versus 1.0%), neutropenia (11.8% versus 5.1%), increased blood creatinine (10.8% versus 1.0%) and leukopenia (10.3% versus 1.0%). For severe AEs, severe events (Grade ≥ 3) were reported in 36.9% of the olaparib group compared with 18.2% in the placebo group. The most common severe AE in the olaparib group was anaemia (19.5% versus 2.0%), although discontinuation of treatment occurred in only 3.1% of patients.

Note: In the SOLO-2 trial, the median total exposure to olaparib was over three times longer than for placebo (19.4 months versus 5.6 months).

Treatment related adverse events (ADRs)

Integrated safety analyses

No integrated analyses of ADRs were performed.

Pivotal and/or main efficacy studies

Study 19: ADRs were reported in 90.5% and 72.6% of the olaparib and placebo groups, respectively. Severe ADRs (Grade 3 or higher) were reported in 21.6% and 8.1% of the respective groups.

SOLO-2 trial: ADRs were reported in 92.3% and 62.6% of the olaparib and placebo groups, respectively. Most ADRs were Grade ≤ 2 in severity (29.7% versus 7.1%). The most common severe ADR in the olaparib group was anaemia (19.5% versus 2.0%).

Deaths and other serious adverse events

Integrated safety analyses

The great majority of deaths were related to the underlying disease, and they occurred more than 30 days after the last treatment dose. Fewer deaths were reported in the tablet group compared with the capsule group. Serious adverse events (SAEs) were generally comparable between groups although they were marginally less frequent in the pooled tablet studies compared with the capsule studies. The most common SAE in each group was anaemia.

Pivotal and/or main efficacy studies

Study 19: In the overall population, 56.6% of the olaparib group died before the data cut off compared with 60.2% in the placebo group. Most deaths were due to disease progression (50.0% versus 55.5%), but there was only one death related to AEs with an outcome of death (0.7% versus 0%). SAEs were reported in 18.4% and 8.6% of the respective groups, most commonly anaemia (2.2%).

In the subgroup of patients with a BRCA mutation, 50.0% of the olaparib group died before the data cut off compared with 54.8% in the placebo group. Most deaths were due to disease progression (41.9% versus 48.4%), but there were few deaths related to AEs with an outcome of death (1.4% versus 0%). SAEs were reported in 21.6% and 9.7% of the respective groups. No single event by PT was reported in more than one patient.

SOLO-2 trial: In the olaparib group, 23.0% of patients died up to the data cut off compared with 27.3% in the placebo group. Most deaths were due to disease progression occurring at least 30 days after the last treatment dose (21.4% versus 25.3%). There were no deaths related to AEs in either treatment group. SAEs were reported in 17.9% and 8.1% of the respective groups, most commonly anaemia (2.2%).

Discontinuations due to adverse events

Integrated safety analyses

Overall, withdrawals due to AEs were infrequent and comparable in the capsule and tablet pooled sets. Anaemia was the most common reason for withdrawal, most notably in the patients treated with the tablet formulation (3.1% in Study 02).

Pivotal and/or main efficacy studies

Study 19: Overall, discontinuations due to AEs occurred more commonly in the olaparib group compared with the placebo group (5.1% versus 1.6%). The most commonly reported AEs were nausea, vomiting, fatigue and diarrhoea; however, these events rarely led to discontinuation. In patients with a BRCA mutation, there were no discontinuations

due to AEs in the placebo group. Discontinuations occurred in 8.1% of the olaparib group, but no single AE by PT was reported by more than one patient.

Study 02: AEs leading to drug discontinuation occurred more commonly in the olaparib group compared with the placebo group (10.8% versus 2.0%). The most common event leading to discontinuation was anaemia (4.1% versus 1.0%).

Safety issues with the potential for major regulatory impact

Liver function and liver toxicity

Note: AEs related to liver function are reported differently in the different studies in the clinical study reports and clinical summary. However, all significant events have been identified and reported in detail.

Integrated safety analyses

No cases of potential disease induced liver injury were identified in analysis of alanine aminotransferase (ALT) and bilirubin in any capsule or tablet treatment groups. In the tablet pool of 482 patients, there were eight events of aspartate aminotransferase (AST) or ALT ≥ 3 times upper limit normal (ULN) and total bilirubin ≥ 2 times ULN. Each event had a plausible explanation, including biliary obstruction, cancer disease progression, and disease progression in the liver. Maximal ALT/AST elevations > 3 times ULN to ≤ 5 times ULN were reported in 3.1% of patients; and ALT/AST elevations > 5 times ULN to ≤ 10 times ULN were reported in 1.9% of patients. No pooled analysis of the capsule population was performed.

Pivotal and/or main efficacy studies

Study 19: AST/ALT elevations remained < 3 times ULN in 95% of patients in the olaparib and placebo groups. The pattern of maximal AST/ALT elevations was comparable in each group; however, two patients in the olaparib group (both with a BRCA mutation) had AST/ALT elevations > 10 times ULN to ≤ 20 times ULN. One patient had fatal cholestatic jaundice after 1014 days of olaparib treatment. It was considered unrelated to study treatment by the investigator. The second patient developed AST/ALT elevations without increased bilirubin after 431 days of olaparib treatment. The study drug was stopped and the patient died of progressive disease on Day 869.

Study 02: Overall, AEs of Grade 1, 2, 3 and 4 related to ALT elevations were comparable in the olaparib and placebo groups. Grade 3 elevations were reported in 1% of each group. There was a single Grade 4 event in the olaparib group. The patient developed and ALT elevation ≥ 20 times ULN with bilirubin ≥ 2 times ULN on Day 337 and treatment was stopped. The abnormalities met the criteria for Hy's law;[11] however, the event was attributed to biliary obstruction by progressive lymph node metastases at the liver hilum.

Renal function and renal toxicity

Integrated safety analyses

There was no evidence of renal toxicity related to olaparib assessed by serum creatinine, blood urea, and urinalysis in the pooled capsule and tablet analyses. Increased serum creatinine is a known common ADR associated with olaparib. Mild transient increases were observed in the majority of patients in the olaparib groups but not in the placebo group, in keeping with the known inhibitory effects of olaparib on organic cation transporter 2 (OCT2) and multidrug and toxin extrusion 1 (MATE1). No meaningful changes in blood urea were reported.

[11] Hy's law: ALT > 3 times ULN and total bilirubin > 2 times ULN

Pivotal and/or main efficacy studies

Study 19: In the first week of olaparib treatment, there was a small increase in mean and median serum creatinine in the olaparib group (median 71 µmol/L at baseline; and 85 µmol/L on Day 8). Median levels returned to Baseline at the Day 30 follow up visit. No similar changes were observed in the placebo group. With the exception of raised serum creatinine, renal AEs were reported in 12.5% and 9.4% of the olaparib and placebo groups, respectively. Only one patient in the olaparib group had a Grade 4 AE related to renal function.

Study 02: More patients in the olaparib group had Grade 1 elevations in serum creatinine (39.5%) compared with the placebo group (28.3%). Grade 2 creatinine elevations were observed in 4.6% and 1.0% of the respective groups but no Grade 3 or 4 elevations were seen in either group. Renal and urinary disorders were reported in 9.2% and 11.1% of the respective groups.

Other clinical chemistry

Integrated safety analyses

Changes in clinical chemistry were assessed by changes in mean values over time, changes in individual patients over time, and individually important AEs. The only notable difference in clinical chemistry between the pooled groups was serum creatinine.

Pivotal and/or main efficacy studies

Study 19: In the overall population, there were no clinically meaningful changes from Baseline or changes over time for any clinical chemistry parameter with the exception of serum creatinine.

Study 02: With the exception of serum creatinine, there were no meaningful differences between the olaparib and placebo groups.

Haematology and haematological toxicity

Integrated safety analyses

Leukopenia, neutropenia, and thrombocytopenia are known important ADRs associated with olaparib. Anaemia is very common with an incidence of ≥ 10% of patients. The incidence of anaemia in the tablet pool (35.1%) was higher than in the capsule pool (28.5%). The incidence of Grade 3 events was higher in Study 02 (19.5%) than in Study 19 (7.4%). However, the incidence of events in the tablet pool (14.1%) was comparable to the capsule pool (13.6%).

Pivotal and/or main efficacy studies

Study 19: In the overall population, there was a decrease from Baseline in mean Hb in the olaparib group, and a slight rise from Baseline in the placebo group. AEs related to haematology were mostly mild to moderate in severity. However, Grade 3 AEs related to anaemia were reported more commonly in the olaparib group (5.1%) compared with the placebo group (0.8%). Grade 4 events were reported only in the olaparib group (1.5% versus 0.0%). Severe AEs related to lymphocytes, neutrophils and platelets were also reported more commonly in the olaparib group.

Study 02: The incidence of anaemia AEs was notably higher in the olaparib tablet group (43.6%) compared with the placebo group (8.1%). Most events were mild to moderate in severity; however, there was a high incidence of severe AEs in the olaparib group (19.5% versus 2.0%). Most anaemia was observed in the first 6 months of treatment. Other haematological events were reported more commonly in the olaparib group compared with the placebo group. AEs related to leukopenia were reported in 15.9% and 2.0% of the respective groups; neutropenia AEs were reported in 19.5% and 6.1% of the respective

groups; and thrombocytopenia AEs were reported in 13.8% and 3.0% of the respective groups. The incidence of severe AEs related to other haematological parameters was low.

The incidence of anaemia in Study 02 was notably higher than in Study 19, although the incidence of anaemia in the pooled tablet and capsule populations was similar.

Electrocardiograph findings and cardiovascular safety

Integrated safety analyses

For ethical and safety reasons, a thorough QTc study cannot be performed. In Studies 04 and 07, a pooled analysis of 119 patients showed a treatment effect on QT interval corrected for heart rate using Fridericia correction (QTcF) of < 10 ms at all time points. No safety issues related to olaparib were identified for cardiovascular AEs by SOC or PT.

Pivotal and/or main efficacy studies

Study 19: Cardiac disorder AEs (most commonly palpitations and tachycardia) were reported in 5.9% and 3.9% of the olaparib and placebo groups, respectively.

Study 02: Cardiac disorder AEs (most commonly palpitations) were reported in 5.1% and 4.0% of the olaparib and placebo groups, respectively. There was a single SAE of pericarditis in the olaparib group. No clinically significant ECG changes were reported during the study.

Vital signs and clinical examination findings

Integrated safety analyses

No pooled analyses were performed.

Pivotal and/or main efficacy studies

Studies-19 and 02: No clinically important changes in vital signs were identified. Mean blood pressure, heart rate and weight did not change significantly in the olaparib group during the study. Significant changes in individuals were reported as AEs.

Immunogenicity and immunological events

Integrated safety analyses

No pooled analyses were performed.

Pivotal and/or main efficacy studies

Study 19: There were few AEs related to immunological events, and no meaningful differences between the treatment groups.

Study 02: There were few AEs related to immunological events, and no meaningful differences between the treatment groups. Immunological disorders were reported in 3.1% and 3.0% of the olaparib and placebo groups, respectively.

Serious skin reactions

Integrated safety analyses

No pooled analyses were performed.

Pivotal and/or main efficacy studies

Study 19: Skin AEs were reported in 29.4% and 27.3% of the olaparib and placebo groups, respectively. Most were mild to moderate in intensity and no SAEs were reported.

Study 02: Skin AEs were reported in 29.7% and 26.3% of the olaparib and placebo groups, respectively. No SAEs were reported.

Adverse events of special interest

Integrated safety analyses

No pooled analyses were performed.

Main/pivotal studies that assessed safety as the sole primary outcome

Study 19: There were no defined events of special interest.

Study 02: There were four cases of myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML) in each treatment group (olaparib 2.1% versus 4.0% placebo). New primary, non-haematological malignancies were reported in one patient in each treatment group. Three cases of pneumonitis were reported, all in the olaparib group. No other events of special interest were defined in the study.

Post marketing data

The tablet formulation of olaparib has not yet received marketing approval.

Evaluator's conclusions on safety

No new safety concerns have been identified for the new olaparib tablet formulation. Nausea, vomiting, fatigue, asthenia, anaemia, diarrhoea, dyspepsia, dysgeusia, dizziness and headache are common ADRs documented in the olaparib capsule PI. The safety profiles of the pooled tablet and capsule data sets were comparable. In the pivotal studies, the safety profile of the tablet formulation in Study 02 was comparable to that of the capsule formulation in Study 19. In Study 02, the incidence of AEs was significantly higher in the olaparib group compared with the placebo group. However, most AEs were of mild to moderate severity, intermittent and manageable with dose interruptions or reductions. Of note, exposure was over three times higher in the olaparib group (19.4 months versus 5.6 months). The most common severe AE was anaemia, reported in 36.9% and 18.2% of the olaparib and placebo groups, respectively. Nearly all deaths were related to the underlying disease, and only one death (AML) was attributed to olaparib during treatment. Study drug was discontinued due to AEs in 10.8% and 2.0% of the olaparib and placebo groups, respectively.

No new AEs of regulatory interest or special interest were identified. Minor serum creatinine elevations without renal impairment were reported (a known ADR). Haematological toxicity was reported in line with the documented olaparib ADR profile. No hepatic events suggestive of drug induced liver injury were reported with the tablet formulation. The safety profile of the olaparib tablet formulation was comparable in all age groups. There was no evidence for racial differences although the majority of patients were White.

First round benefit-risk assessment

First round assessment of benefits

Table 8 summarises the assessment of benefits of Lynparza for the proposed indication at the first round evaluation.

Table 8: First round assessment of benefits

Benefits	Strengths and Uncertainties
In patients with advanced ovarian cancer, maintenance olaparib given as tablets reduced the risk of disease progression or death by 70% compared with placebo. PFS was 19.1 months in patients treated with olaparib tablets, compared with 5.5 months in patients given placebo.	The hazard reduction was highly statistically significant ($p < 0.0001$) and clinically meaningful. Efficacy with the new tablet formulation was comparable to that of the approved capsule formulation.
Platinum sensitive patients responded to olaparib irrespective of BRCA status.	The benefits of olaparib were less marked in patients without BRCA mutations with a risk reduction of 46%. However, the benefit is highly statistically significant ($p < 0.0075$) and clinically meaningful in a patient population with few other treatment options.
The tablet formulation offers simple BID oral treatment (two tablets BID).	

First round assessment of risks

Table 9 summarises the assessment of risks of Lynparza for the proposed indication at the first round of evaluation.

Table 9: First round assessment of risks

Risks	Strengths and Uncertainties
AEs are reported commonly in patients treated with the olaparib tablet formulation.	The risks of olaparib are well understood and documented in the approved PI for the capsule formulation. No new safety signals have been detected. Most AEs are mild to moderate, intermittent, and manageable with dosage interruption or reduction. Haematological toxicities are common, in particular anaemia. Severe AEs or SAEs can be expected infrequently, and deaths due to AEs are unlikely.
The efficacy of the tablet formulation has not been investigated in patients without BRCA mutations.	The capsule formulation has worthwhile efficacy in patients without BRCA mutations. It is unlikely that the tablet formulation will prove ineffective in this patient population.

First round assessment of benefit-risk balance

The benefit-risk balance is positive for the proposed indication:

> *Olaparib is indicated as monotherapy for the maintenance treatment of patients with platinum- sensitive relapsed high grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) after platinum-based chemotherapy. Prior treatment must have included at least 2 courses of platinum-based regimens.*

The tablet formulation has a comparable benefit-risk balance to that of the approved capsule formulation.

First round recommendation regarding authorisation

Subject to satisfactory responses to the outstanding comments and questions, authorisation is recommended for olaparib tablets used for the following indication:

> *Olaparib is indicated as monotherapy for the maintenance treatment of patients with platinum-sensitive relapsed high grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) after platinum-based chemotherapy. Prior treatment must have included at least 2 courses of platinum-based regimens.*

Clinical questions and second round evaluation

Question 1

There does not appear to be a study specifically addressing the bioequivalence of the 100 and 150 mg tablets. Does the sponsor have a post-hoc analysis of the PK following either single or multiple administrations of these tablet forms?

Apart from the population PK studies there is no consideration of the effect of age. Is there a report in which data were combined to examine any potential effect in more detail?

Is data from the on-going studies in hepatic and renal impairment now available?

Sponsor's response

[Information redacted]

The sponsor has undertaken a new analysis of non-compartmental kinetic data stratified by age for both single dose and steady state data. Stratification of C_{max} and AUC data by different age cohorts did not show any effect of age. This is concordant with the population PK analysis which also showed no effect of age on single or repeated dose PK. Age was not found to be a significant covariate in the E-R models for the decline in Hb or increase in fatigue with increasing olaparib exposure.

The sponsor does not plan studies in severe renal or hepatic impairment. Due to slow recruitment, a final report on moderate hepatic impairment is not available at this time.

Evaluation of response

The sponsor's response is satisfactory.

Question 2

In Study 19, 29.8% of patients recorded important protocol deviations relating to Interactive Voice/Web Response System (IVRS) stratification errors with imbalance between the arms (olaparib 35.3%, placebo 24.0%). The clinical study report states simply that the errors were corrected in the database by source data verification before the statistical analyses were performed. Please provide details of what stratification errors were made; how the errors were allowed to occur; and provide a more detailed description of the corrective actions taken.

Sponsor's response

[Information redacted]

Evaluation of response

The sponsor's response is satisfactory.

Second round benefit-risk assessment

Second round assessment of benefits

No change to the first round assessment.

Second round assessment of risks

No change to the first round assessment.

Second round assessment of benefit-risk assessment

No change to the first round assessment.

VI. Pharmacovigilance findings

A risk management plan (RMP) evaluation report was not produced since this was a product with an existing, previously evaluated RMP. Wording for an RMP condition of registration was provided separately.

Risk management plan

Proposed wording for conditions of registration

The Lynparza Core RMP (version 5.0, dated 12 July 2017, data lock point 15 December 2016), with Australian Specific Annex (version 5.0, dated 11 August 2017) that was included with a concurrent submission, to be revised to the satisfaction of the TGA, must be implemented.

VII. Overall conclusion and risk/benefit assessment

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

Background

Condition

The 5 year overall survival of ovarian cancer patients is about 50% across all stages and < 30% in patients with advanced or metastatic disease (Stage III/IV). Ovarian cancer is predominantly a disease of postmenopausal women. The majority of women in various clinical trials have had high grade epithelial (usually serous) ovarian cancer. About 70% of women with ovarian cancer have advanced or metastatic disease (which includes local pelvic extension) at diagnosis.

Most women have primary debulking surgery, followed by adjuvant platinum based chemotherapy. Response rates are high in the first line setting (depending on the extent of

post-surgical residual disease), but most women experience disease recurrence within 2 years and die within 3 to 4 years of diagnosis (that is, recurrent ovarian cancer is incurable, with currently available treatments). Women with ovarian cancer typically experience multiple recurrences and receive multiple lines of chemotherapy over the course of their disease.

The choice of subsequent therapies is based on the interval between the last platinum regimen and recurrence (platinum free interval: PFI). If PFI > 6 months, the woman's disease is called platinum sensitive and she receives further platinum based therapy.

Germline and somatic BRCA mutations

About 15% of women with ovarian cancer have a germline BRCA mutation. Perhaps another 5% have a somatic BRCA mutation.

Platinum sensitive, high grade, recurrent ovarian cancers are more likely to be BRCA positive. For example, in Study 19, 136 out of 265 (51%) of women were BRCA positive, including 18 (7%) with a somatic (tumour) mutation without a reported germline mutation.

Current treatment options

The proposed indication for olaparib is maintenance treatment for women with platinum sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in a complete or partial response to platinum based chemotherapy.

Bevacizumab is approved in a similar setting. However, the administration of bevacizumab differs from that of olaparib in that bevacizumab is administered in combination with chemotherapy, and is then continued as a single agent in patients who are in response (complete or partial) at the end of 6 to 8 cycles of chemotherapy, as maintenance.

Other PARP inhibitors (niraparib, rucaparib) are approved in some other countries for use in ovarian cancer. They do not currently have marketing approval in Australia. PARP inhibitors in clinical development include veliparib and talazoparib.

Because recurrent ovarian cancer is an incurable disease, the aim of management is to balance multiple lines of treatment with acceptable toxicity and quality of life.

Quality

Minor quality issues are being finalised separately but will not delay clinical consideration of the application.[12]

Nonclinical

The nonclinical evaluator had no objections to registration of the tablets.

Clinical

Pharmacology

Key issues were:

- Bioavailability of the tablet versus the capsule.

[12] These issues were subsequently resolved.

- Dose adjustment in women with renal or hepatic impairment.
- Dose adjustment due to DDI.

A tablet formulation was developed for the Phase III SOLO-2 trial. It is not unusual for capsules to be used in Phase I/II studies and tablets used in Phase III studies.

Study 24 was an adaptive Phase I study in patients with advanced solid tumours.[13] The mean steady state C_{max}, C_{min}, and AUC were 1.3 to 1.7 times higher with the 300 mg tablet BID than the 400 mg capsules BID.

An integrated population PK analysis (including data from the SOLO-2 trial) also showed higher bioavailability of the tablet versus the capsule.

The SOLO-2 trial showed that benefit-risk balance of the olaparib tablets (300 mg BID) was positive; similar to the results from Study 19, which used the capsules (400 mg BID); although there were more treatment discontinuations due to AEs in the SOLO-2 trial versus Study 19 (11% versus 4%), perhaps reflecting the higher bioavailability..

A dedicated hepatic impairment study showed that no dose adjustment is needed in patients with mild hepatic impairment (Child-Pugh A).

A dedicated renal impairment study showed that no dose adjustment is needed in patients with mild renal impairment. The dose should be reduced to 200 mg BID for moderate renal impairment.

The dose should be reduced to 100 mg BID if a strong CYP3A inhibitor must be co administered; 150 mg BID: moderate CYP3A inhibitor.

Strong or moderate CYP3A inducers should be avoided because they can cause decreased efficacy.

Efficacy

Study 19

Design

- Randomised, double blind, multicentre: 86 sites, 16 countries (US, Canada, Australia, Western Europe, Israel, Russia, and Ukraine).
- Recruitment: August 2008 to February 2010.
- Primary data cut off (for the primary endpoint of PFS): June 2010. RECIST data for PFS were not collected after this primary data cut-off.

[13] Mateo, J. et al. (2016), An adaptive study to determine the optimal dose of the tablet formulation of the PARP inhibitor olaparib*. Target Oncol,* 2016; 11: 401–415.

Table 11: Summary of Study 19 design

Patients	olaparib (n=136) placebo (n=129) Inclusion criteria • Recurrent ovarian (including fallopian tube, primary peritoneal) cancer • Grade 2 or 3, with serous features • Platinum-sensitive (no disease progression in the first 6 months after the last dose of the penultimate line of platinum-based chemotherapy) • 2+ previous lines of platinum-based chemotherapy • Complete or partial response to the most recent line of platinum-based chemotherapy Selected exclusion criteria • Grade 1 • Previous treatment with PARP inhibitors • Poor health (Eastern Cooperative Oncology Group (ECOG): 2+) Known mutated BRCA status was not required for eligibility, but was established via case report forms documenting previous local germline BRCA testing, or via retrospective germline BRCA testing (Integrated BRAC Analysis assay [Myriad Genetics, Salt Lake City, UT, USA]) or tumour BRCA testing (next generation sequencing [Foundation Medicine, Cambridge, MA, USA])
Intervention	Maintenance (median time from last platinum dose was 40 days) monotherapy; 400 mg (in eight 50 mg capsules) twice daily, until progression. Toxicities could be managed by dose reductions and treatment interruption.
Comparator	Placebo
Endpoints	Primary • PFS: investigator assessed by modified RECIST Secondary • OS • Time to first subsequent therapy • Time to second subsequent therapy • etc

Tumour assessments:

- Every 12 weeks until Week 72, then every 24 weeks.
- RECIST data were not collected after the primary data cut off (June 30, 2010).

Randomisation was stratified by:

- Certain Jewish ancestry (mutated BRCA is more common); about 15% of trial participants).
- Time to progression from completion of penultimate platinum based regimen (6 to 12 months versus > 12 months).
- Response to most recent platinum based regimen (complete response versus partial response).

Sample size (Phase II)

- The pre specified primary analysis was when at least 137 PFS events had occurred.
- Minimal clinically important differences (MCID): HR (PFS) = 0·75 (equivalent to a 33% increase in median (PFS) from 9 months to 12 months).
- Type I error: 20% (one sided test); Phase II.
- Power: 80%; Phase II.

Table 12: Baseline characteristics of patients in Study 19

	Olaparib N=136	Placebo N=129
Age		
mean	59 years	59 years
range	21, 89	33, 84
75+ years	12 (9%)	5 (4%)
ECOG		
0	110 (81%)	95 (74%)
1	23 (17%)	30 (23%)
2	1 (1%)	2 (2%)
missing	1 (1%)	2 (2%)
Prior bevacizumab	8 (6%)	7 (5%)
Response to last platinum		
CR	57 (42%)	63 (49%)
PR	79 (58%)	66 (51%)
Interval from penultimate platinum to progression:		
6-12 months	53 (39%)	54 (42%)
12+ months	83 (61%)	75 (58%)
Mutation status		
BRCA1	40 (29%)	30 (23%)
BRCA2	13 (10%)	13 (10%)
Prior chemo regimens		
Median (range)	3 (2, 11)	3 (2, 8)
Prior platinum regimens		
Median (range)	2 (2, 7)	2 (2, 8)

Baseline characteristics were also well balanced across the BRCA mutant (n = 136) and the BRCA wildtype (n = 118) subgroups. Bevacizumab use was low and this was expected, given the dates of recruitment: 2008 to 2010.

Results

Primary endpoint, PFS, investigator assessed

- Data cut off point for the PFS analysis was June 2010 (154 events had occurred; 137 were expected; see sample size in Table 13).
- RECIST data were not collected after this date.
- These PFS results were provided in the dossier for the registration of the capsules for BRCA mutant women in December 2015/January 2016.[14]

Table 13: Primary endpoint Study 19 (PFS), intention to treat

Primary endpoint (PFS)	Olaparib N = 136	Placebo N = 129
Events (%)	60 (44%)	94 (73%)
Median (PFS)	8.4 months	4.8 months
HR (PFS)	0.35 (0.25, 0.49); p < 0.00001	

The median improvement for the intention to treat population for PFS (3.6 months) is similar to that reported for bevacizumab in this setting (for example, from GOG-0213).

[14] Ledermann, J.A. et al. (2014), Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised Phase II trial, *Lancet Oncol*, 2014; 15: 852–861.

Table 14: Primary endpoint Study 19 (PFS), BRCA mutant population

Primary endpoint (PFS)	Olaparib N = 74	Placebo N = 62
Events (%)	26 (35%)	46 (74%)
Median (PFS)	11.4 months	4.3 months
HR (PFS)	0.18 (0.10, 0.31); p < 0.00001	

Includes somatic BRCA mutations.

Table 15: Primary endpoint Study 19 (PFS), BRCA wild type population

Primary endpoint (PFS)	Olaparib N = 57	Placebo N = 61
Events (%)	32 (56%)	44 (72%)
Median (PFS)	7.4 months	5.5 months
HR (PFS)	0.54 (0.34, 0.85); p < 0.007	

Secondary endpoint, OS

- These are the new results for Study 19, submitted in this current dossier.
- Data cut off point: May 2016; 210 (79%), of the 265 trial participants, had died (follow up: 6 years).
- The published data;[15] are for data cut off point: September 2015; 203 (77%) of the 265 had died.

Table 16: Secondary endpoint Study 19 (OS), intention to treat population

Secondary endpoint (OS)	Olaparib N = 136	Placebo N = 129
Deaths (%)	98 (72%)	112 (87%)
Median (OS)	29.8 months	27.8 months
HR (OS)	0.73 (0.55, 0.95); p = 0.021[a]	

a) Not statistically significant: Phase II study; no pre-specified rules for dealing with statistical multiplicity for subgroups or secondary endpoints.

[15] Ledermann, J.A. et al. (2016), Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, Phase II trial, *Lancet Oncol*, 2016; 17: 1579–1589.

Table 17: Secondary endpoint Study 19 (OS), BRCA mutant population

Secondary endpoint (OS)	Olaparib N = 74	Placebo N = 62
Deaths (%)	49 (66%)	50 (81%)
Median (OS)	34.9 months	30.2 months
HR (OS)	0.62 (0.42, 0.93); p = 0.021[a]	

a) Not statistically significant: Phase II study; no pre-specified rules for dealing with statistical multiplicity for subgroups or secondary endpoints.

Table 18: Secondary endpoint Study 19 (OS), BRCA wild type population

Secondary endpoint (OS)	Olaparib N = 57	Placebo N = 61
Deaths (%)	45 (79%)	57 (93%)
Median (OS)	24.5 months	26.6 months [a]
HR (OS)	0.84 (0.57, 1.25); p = 0.397	

a) Not an error, the curves were close together near the median.

Subsequent treatments

Formal cross over was not part of the study design. After discontinuation of the study treatment, the woman's clinician was responsible for selecting further treatment.

Subsequent cancer treatments had been received by 89 (65%) of 136 patients from the olaparib group (45 (61%) of 74 patients with BRCA mutations) and 111 (86%) of 129 patients from the placebo group (55 (89%) of 62 patients with BRCA mutations). From the placebo group, 17 (13%) of 129 patients had received post-discontinuation PARP inhibitor treatment, of whom 14 (23%) of 62 patients had BRCA mutant. No patients from the olaparib group had received subsequent PARP inhibitor treatment.

Exploratory endpoints: time to subsequent treatments

Analyses on the exploratory endpoints of time to first subsequent therapy (or death) and similarly for second subsequent therapy were done. For all study participants, first subsequent therapy: HR = 0.39, median (15.6 versus 6.2 months); second subsequent therapy: HR = 0.41, median (22.0 versus 15.3 months). Improvements were larger in BRCA mutant group than the BRCA wildtype group, but were seen for both groups (not definitive, subgroup comparisons for exploratory endpoints).

Improvement in time to second subsequent therapy or death can show continued benefit, beyond the next line of treatment, and this intermediate endpoint can therefore support other efficacy endpoints when assessing the long term effect of investigational treatments; and perhaps can address the concern that PARP inhibitors could affect the efficacy of subsequent treatments.

SOLO-2 trial

Design

- Phase III, double blind, placebo controlled, multicentre (123 sites), multinational (16 countries: Australia, EU, US, UK, Canada, Poland, Russia, Brazil, South Korea, and Japan).
- Recruitment: Aug 2013 to Nov 2014.
- Data cut off for this analysis: Sep 2016.
- 187 PFS events in 295 patients.

Table 19: Summary of SOLO-2 trial study design

Patients	olaparib (n=196) placebo (n=99); 2:1 randomisation Inclusion criteria • High-grade serous or endometrioid • 2+ lines of platinum-based chemotherapy (relapsed) • Currently in CR or PR (RECIST or CA-125) • Platinum sensitive: disease progression at least 6 months after the penultimate regimen. • Germline or somatic BRCA1/2 (all enrolled patients were positive for germline BRCA1/2) • 18+ years • ECOG: 0 or 1 Selected exclusion criteria • Brain metastases • Recent drainage of ascites
Intervention	Maintenance monotherapy; 300 mg (in two 150 mg tablets) twice daily, until progression toxicities could be managed by dose reductions and treatment interruptions
Comparator	placebo
Endpoints	Primary PFS: investigator assessed by modified RECIST; blinded independent central review (BICR) as a sensitivity analysis Secondary PFS2, OS, overall response rate (ORR),duration of response (DoR)

Patients were assessed using computed tomography (CT) or magnetic resonance imaging (MRI) scans every 12 weeks until Week 72, and then every 24 weeks thereafter until objective disease progression. The scans were also sent to a clinical research organisation for blinded independent central review. After disease progression, patients were followed every 12 weeks for second progression. Crossover to olaparib was not permitted within the design of the study but patients were able to access PARP inhibitors outside of the study. That is, when the woman finished the study treatment, further treatment was selected by their doctor.

Table 20: Baseline characteristics, SOLO-2 trial

	Olaparib N=196	Placebo N=99
Age, median (interquartile range)	56 years (51, 63)	56 years (49, 63)
ECOG		
0	162 (83%)	77 (78%)
1	32 (16%)	22 (22%)
Missing	2 (1%)	-
Primary tumour location		
Ovary	164 (84%)	86 (82%)
Fallopian tube or peritoneal	31 (16%)	13 (13%)
Missing	1 (1%)	-
Histology		
Serous	183(83%)	86(87)
Endometrioid	9(5%)	8(8%)
Mixed	3(2%)	5(5%)
Missing	1(1%)	-
>2 cm lesions	30 (15%)	18 (18%)
Germline BRCA[a]		
BRCA1	132 (67%)	61 (62%)
BRCA2	58 (30%)	35 (35%)
Both	-	-
Missing	6 (3%)	3 (3%)
Response to platinum therapy		
Complete	91 (46%)	47 (47%)
Partial	105(54%)	52 (53%)
Number of platinum-based regimens		
2	110 (56%)	62 (63%)
3	60 (31%)	20 (20%)
4	18 (9%)	12 (12%)
5+	7 (4%)	5 (5%)
Platinum-free interval		
6-12 months	79(40%)	40 (40%)
>12 months	117 (60%)	59 (60%)
Prior bevacizumab	33(17%)	20(20%)

a) Women with somatic BRCA mutations were eligible to enrol in the study, but none were identified during the recruitment process.

Results

Primary endpoint, PFS, investigator assessed[16]

See Table 21.

Table 21: Primary endpoint results (PFS), SOLO-2 trial

Primary endpoint (PFS)	Olaparib N = 196	Placebo N = 99
Events # (%)	107 (55%)	80 (81%)
Median (PFS)	19.1 months	5.5 months
HR (PFS)	0.30 (0.22, 0.41); p < 0.00001	

Sensitivity/supportive analysis using BICR-assessed PFS: HR = 0.25 (0.18, 0.35).

Secondary and exploratory endpoints

See Tables 22 to 24.

[16] Pujade-Lauraine, E. et al. (2017), Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO-2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, Phase 3 trial, *Lancet Oncol*, 2017; 18: 1274-1284

Table 22: Secondary and exploratory endpoints; PFS2

Secondary endpoint (PFS2)	Olaparib N = 196	Placebo N = 99
Events # (%)	70 (36%)	80 (81%)
Median (PFS2)	NR	18.4 months
HR (PFS2)	0.50 (0.34, 0.72); p = 0.0004	

Table 23: Secondary and exploratory endpoints; OS

Secondary endpoint (OS)	Olaparib N = 196	Placebo N = 99
Deaths # (%)	45 (23%)	27 (27%)
Median (OS)	NR	NR
HR(OS)	0.80 (0.50, 1.29); p = 0.86	

Further analyses on OS are planned, with longer follow up.

Table 24: Secondary and exploratory endpoints; ORR, DoR

Secondary endpoint (ORR and DoR)	Olaparib N = 196	Placebo N = 99
Complete + partial response (%)	17 + 21 (19%)	5 + 4 (9%)
Median (DoR)	13.6	5.6

Quality of life (QoL)

Patient reported health related QoL was assessed with the Trial Outcome Index (TOI) derived from the Functional Assessment of Cancer Therapy-Ovarian Cancer (FACT-O). The mixed model for repeated measures showed no material difference in quality of life for patients receiving olaparib compared with those receiving placebo. However, this analysis was exploratory.

Subgroup analyses

All the subgroup analyses (for example, response to last platinum; platinum free interval; age; prior lines of platinum, prior bevacizumab, BRCA 1 or 2, Asian, ECOG performance score) gave HRs < 0.5.

Safety

The main safety data were from SOLO-2, with updated data from Study 19.

Olaparib formulations and doses differed between Study 19 (eight 50 mg capsules = 400 mg BID) and SOLO-2 (two 150 mg tablets = 300 mg BID). [Information redacted].

Table 25: SOLO-2 trial safety overview

AEs	Olaparib N = 195	Placebo N = 99
Grade 1 to 4 AEs	192 (99%)	94 (95%)
Grade 3 to 4 AEs	72 (37%)	18 (18%)
Serious AEs	35 (18%)	8 (8%)
AEs leading to death within 30 days	0	0

Table 26: SOLO-2 trial, dose discontinuations and modifications

Dose discontinuations and modifications	Olaparib N = 195	Placebo N = 99
AEs leading to discontinuation	21 (11%)	2 (2%)
AEs leading to dose interruption	84 (44%)	17 (17%)
AEs leading to dose reduction	53 (27%)	3 (3%)

The most common specific events leading to discontinuation of olaparib in the SOLO-2 trial were:

- Anaemia (n = 6)
- Neutropaenia (n = 3)
- Thrombocytopaenia (n = 2)
- MDS/AML (n = 2)

Placebo:

- Thrombocytopaenia (n = 1)
- Breast cancer (n = 1)

Table 27: SOLO-2 trial, specific AEs leading to dose reduction or interruption

Specific AEs	Olaparib N = 195	Placebo N = 99
Anaemia	42 (22%)	0
Neutropaenia	17 (9%)	3 (3%)
Fatigue	16 (8%)	1 (1%)
Vomiting	14 (7%)	1 (1%)
Nausea	12 (6%)	4 (4%)
Thrombocytopaenia	8 (4%)	0

Table 28: Study 19; dose discontinuations and modifications

Dose discontinuations and modifications	Olaparib N = 136	Placebo N = 128
AEs leading to discontinuation	6 (4%)	2 (2%)
AEs leading to dose interruption	41 (30%)	12 (9%)
AEs leading to dose reduction	31 (23%)	6 (5%)

Table 29: Study 19; specific AEs leading to dose reduction or interruption

Specific AEs	Olaparib N = 136	Placebo N = 128
Nausea	14 (10%)	1 (1%)
Vomiting	14 (10%)	3 (2%)
Fatigue	12 (9%)	3 (2%)
Anaemia	11 (8%)	1 (1%)

Comparing the SOLO-2 trial with Study 19, there were more discontinuations on olaparib in the SOLO-2 trial (11% versus 4%) and more interruptions (44% versus 30%). This could be because of the greater bioavailability of the tablet versus the capsule. Medical oncologists would be experienced with managing the AEs leading to discontinuations or interruptions (for example, anaemia, thrombocytopaenia, nausea, vomiting).

MDS/AML

MDS/AML was reported with PARP inhibitors. This may be related to the genetic limitation of DNA repair and prior exposure to cytotoxic chemotherapy. There were 3 cases in the olaparib group Study 19 (and 1 case in the placebo group); and 4 cases in the olaparib group in the SOLO-2 trial (and 4 cases in the placebo group). 21 cases have been reported from 1,680 patients involved in clinical trials for olaparib across various indications. This gives an incidence of about 1.5%. More cases have been identified from post marketing reports; incidence seems similar: 1 to 2%.

The development of therapy-related AML has a long latency (reported to be approximately 5 years in a Danish national population-based study of 3,055 unselected patients with AML).[17] This, along with confounding factors (as above, post chemotherapy patients and patients with BRCA may have a higher baseline risk) makes it difficult to provide a precise estimate of the increased risk (above the baseline risk).

Pneumonitis

The safety database included 10 cases of pneumonitis with the capsule (including the one in Study 19); and 6 cases with the tablet (including 3 in the SOLO-2 trial). Deaths have occurred following pneumonitis; although none with the tablet formulation. The risk may be higher in patients who have had radiation to the chest.

[17] Granfeldt Østgård, L.S. et al. (2015), Epidemiology and Clinical Significance of Secondary and Therapy-Related Acute Myeloid Leukemia: A National Population-Based Cohort Study, *J Clin Oncol*, 2015; 33:3641-3649.

Risk management plan

The summary of safety concerns are shown in Table 30.

Table 30: Summary of safety concerns from the RMP

Summary of safety concerns	
Important identified risks	• Anaemia • Thrombocytopenia • Neutropenia • Raised creatinine levels • Nausea/vomiting • DDI with CYP3A strong/moderate inducers and strong/moderate inhibitors
Important potential risks	• MDS/AML • Pneumonitis • New primary malignancies • Potential for off label use • Potential for medication errors • Effects on embryofetal survival and development
Missing information	• Interaction with substrates of CYP enzymes and transporter proteins • Exposure in patients with moderate/severe hepatic impairment • Exposure in patients with severe renal impairment and end-stage renal disease • Exposure in elderly (> 75 years) • Exposure in ethnically diverse groups • Long-term exposure to/potential toxicity to olaparib • Use in patients with ECOG performance status > 2

Safety concerns stemming from the introduction of the tablet formulation

The tablet formulation permits a significantly decreased pill burden to patients (two tablets twice daily as opposed to eight capsules twice daily for the recommended starting doses), but due to the difference in bioavailability, the two formulations are not interchangeable, and therefore the introduction of the new formulation poses a risk of medication error to patients currently receiving the capsule formulation.

The sponsor has provided the following information:

- Differences in packaging, strength, appearance and dose of the tablet and capsule presentations are expected to mitigate potential for most prescribing and dispensing errors. These differences will serve variously as check points for prescribers, pharmacists and patients to avoid instances of unintended errors in prescription, dispensing, or patient misunderstanding of the dosing instructions. There will also be different PIs.

- Prescribers and pharmacists will be advised, by the sponsor, in writing, that a tablet formulation of olaparib will be available. The differences in dose and strength of Lynparza tablets and capsules require that Lynparza tablets be listed on the Pharmaceutical Benefits Scheme (PBS) under different PBS item codes to those of Lynparza capsules. Also, Lynparza is listed on the PBS as an Authority Required restricted benefit. This differentiated and restricted PBS listing arrangement will serve to avoid both prescribing and dispensing errors.

Post-marketing studies

Post-marketing commitments (n = 3) in US:

- SOLO-3 trial: olaparib versus physician choice of single agent chemo for third line treatment of women with platinum-sensitive relapsed germline BRCA mutated ovarian cancer.
- Final OS report for SOLO-2 due in the second quarter of 2020.
- OPINION trial: maintenance olaparib treatment in women with germline BRCA wildtype relapsed ovarian cancer.

The OPINION trial is a Phase IIIb, single arm, open label, multicentre study to assess the efficacy and safety of single agent olaparib as a maintenance treatment in patients with relapsed high grade serous ovarian cancer or high-grade endometrioid cancer (including patients with primary peritoneal and/or fallopian tube cancer) who do not have known deleterious or suspected deleterious germline BRCA mutations (non-germline BRCA mutant) and who had responded following platinum based chemotherapy. The primary endpoint is PFS based on investigator recorded assessments according to modified RECIST v1.1. Secondary endpoints include assessment of PFS according to tumour homologous recombination deficiency (HRD) status as determined by the MyriadMyChoice HRD test, assessment of time to first subsequent therapy or death, time to treatment discontinuation or death, the chemotherapy-free interval and health-related QoL.

Risk-benefit analysis

Delegate's considerations

Summary

Tablet formulation

The SOLO-2 trial (a Phase III study) has established the safety and efficacy of the tablet formulation. It is not unusual for capsules to be used in Phase I/II studies and for a final tablet formulation to be tested in Phase III. The sponsor has proposed a series of risk mitigation measures during the transition from capsules to tablets.

Extension of indications

The initial approval of olaparib for ovarian cancer (in the EU and Australia) was based on a retrospectively defined subgroup (BRCA mutant) from the Phase II all comers trial (Study 19). The pre specified primary endpoint was PFS. At that time, data on OS were not mature.

This current submission includes data on OS, with about 6 years follow up. The mature OS results provide reassurance that there was no detrimental effect of maintenance olaparib on OS and that there probably was probably a benefit on OS.

The key question for this submission is whether the indication should be extended to women without a BRCA mutation; that is BRCA wildtype. A subgroup analysis from

Study 19, suggests that some BRCA wildtype women may benefit; although it is not currently possible to identify which ones; for example women with other HRD.

Benefit-risk summary

Benefits and associated uncertainties

Study 19

The Phase II trial, Study 19 (olaparib n = 136; placebo n = 129) reported a benefit on the intention to treat analysis for the primary endpoint of PFS (investigator assessed) for all-comers (that is, BRCA agnostic). Larger benefits were reported for the BRCA mutation (germline and somatic) group. There also appeared to be a benefit (albeit smaller) in the BRCA wildtype group.

- All-comers (that is, intention to treat, BRCA agnostic): HR (PFS) = 0.35 (0.25, 0.49); gain in median (PFS) = 3.6 months.
- BRCA mutation: HR (PFS) = 0.18 (0.10, 0.31); gain in median (PFS) = 7.1 months.
- BRCA wildtype: HR (PFS) = 0.54 (0.34, 0.85); gain in median (PFS) = 1.9 months.

The results for the secondary endpoint of OS (~ 6 years follow up) provided reassurance that there was no detrimental effect of olaparib on OS and that there probably was probably a benefit on OS. (Interpretation of OS for recurrent ovarian cancer is problematic because of possible confounding due to differential use of post discontinuation treatments and long post progression survival).

- All-comers (that is, intention to treat, BRCA agnostic): HR (OS) = 0.73.
- BRCA mutation: HR (OS) = 0.62.
- BRCA wild-type: HR (OS) = 0.84.

These results should be interpreted cautiously because they are for secondary endpoints, and for subgroups, (from a Phase II study); CIs and p-values are given, but not provided in this summary because they are subject to statistical multiplicity.

Results for other endpoints from Study 19, such as 'time to first subsequent treatment', were consistent with those for the primary endpoint of PFS.

SOLO-2 trial

The Phase III trial, SOLO-2 (olaparib n = 196; placebo n = 99), which only enrolled germline BRCA mutation patients, confirmed the benefit on PFS (the pre-specified primary endpoint) in the BRCA mutation group: HR (PFS) = 0.30 (0.22, 0.41); gain in median (PFS) = 13.6 months. There was also a benefit on the secondary endpoint of time to second progression: HR (PFS2) = 0.50. Data OS are currently immature (about one quarter of the women have died, with nearly 2 years follow up): HR (OS) = 0.80 (0.50, 1.29).

Harms and associated uncertainties

The most common AEs leading to discontinuation of olaparib treatment were anaemia, thrombocytopenia, neutropenia, nausea/vomiting, and fatigue.

Comparing the SOLO-2 trial (tablets) with Study 19 (capsules), there were more discontinuations on olaparib in SOLO-2 (11% versus 4%) and more interruptions (44% versus 30%). This could be because of the greater bioavailability of the tablet versus the capsule.

A known complication of PARP inhibitors (perhaps exacerbated by genetic limitations of DNA repair and prior exposure to cytotoxic chemotherapy) is MDS/AML. Incidence for patients on PARP inhibitors is about 1 to 2%. The excess risk over the background risk is difficult to determine because development of therapy related MDS/AML has a median

latency of about 5 years; and post chemotherapy and BRCA mutation patients have a higher background risk.

More recent data on pneumonitis are reassuring, but it should remain as a precaution/warning in the PI.

Risk management

- Olaparib is intended to be prescribed by oncologists.
- Oncologists will be familiar with the identification and management of the toxicities associated with olaparib: anaemia, thrombocytopenia, fatigue, nausea, and vomiting.
- MDS/AML and pneumonitis are uncommon, but serious, AEs that prescribers should be aware of.
- Measures are needed (for example, prominent labelling, Dear Health Care Professional Letters) to ensure no confusion between the (non-interchangeable) tablet and capsule that might lead to dosing errors; during the period when the capsules remain on the market.

Post market studies

- SOLO3 trial: olaparib versus physician choice of single agent chemo for third line treatment of women with platinum sensitive relapsed germline BRCA mutated ovarian cancer.
- Final OS report for the SOLO-2 trial, due second quarter of 2020.
- OPINION trial: maintenance olaparib treatment in women with germline BRCA wildtype relapsed ovarian cancer (to identify which BRCA wildtype women benefit from olaparib).

Benefit-risk balance

Recurrent ovarian cancer is a life threatening condition; and, for many women, it is incurable.

In this setting, the reported benefit on PFS (the pre-specified primary endpoint for the two randomised controlled trials: Study 19, SOLO-2 trial) is clinically meaningful: the delay in progression means that exposure to subsequent cytotoxic chemotherapy and its associated toxicities is delayed.

It can be difficult to establish benefit on OS for ovarian cancer: multiple line of post study (post discontinuation) treatment; long post recurrence/progression survival.

Extension of indications to all-comers (agnostic to BRCA status)

In this application, the new data from Study 19 is that, for all-comers (regardless of BRCA mutation status), HR (OS) = 0.73 (0.55, 0.95); p = 0.021 (however, this result should not be regarded as statistically significant because there was no formal pre-specified adjustment for multiplicity). Along with the well characterised toxicity profile of olaparib, and the previously reported results from Study 19 for PFS (pre specified primary endpoint) these results provide the evidential basis for extending the indication to be agnostic for BRCA status.

Study 19 (subgroup analysis of BRCA mutated women) and the SOLO-2 trial (only BRCA mutated women eligible) showed that (as expected from the mechanism of action) the benefit is greater in BRCA mutated women: Study 19 subgroup analysis HR (PFS) = 0.18 (0.10, 0.31), improvement in median (PFS) = 7 months; SOLO-2 trial intention to treat analysis: HR (PFS) = 0.30 (0.22, 0.41), improvement in median (PFS) = 14 months.

Based on a subgroup analysis from Study 19, it seems that some women with BRCA wildtype ovarian cancer do benefit from olaparib (HR (PFS) = 0.54, improvement in

median (PFS) = 2 months). These are possibly patients with other HRD. There is currently no way to identify BRCA wildtype women who might benefit from olaparib. For example, there are no commercially available tests to identify HRD patients. About 12% (7 out of 57) of BRCA wildtype women in Study 19 took olaparib for > 5 years, with no relapse (BRCA mutated: 11 out of 74 (15%); placebo: 1 out of 128 (1%)). These BRCA wildtype women would be restricted from receiving olaparib if the indication was restricted to BRCA mutated, only. Also, it is not standard regulatory practice to separate out a subgroup from an overall positive trial, unless there was a clear detrimental effect in that subgroup; or there is a clear reason based on the mechanism of action.

Tablet

The SOLO-2 trial showed that benefit-risk balance of the olaparib tablets (300 mg BID) was positive; similar to the results from Study 19, which used the capsules (400 mg BID); although there were more treatment discontinuations due to AEs in the SOLO-2 trial, perhaps reflecting the higher bioavailability.

Request for independent expert clinical advice

The Delegate required independent expert advice on the following question:

> Is the evidence from Study 19 sufficient to extend the indication to women without a BRCA mutation (that is, BRCA wildtype)?

Three independent Australian medical oncologists were consulted.[18] All three advised that the indication should be extended to BRCA wildtype, thereby aligning with the FDA and EMA.

Proposed action

Based on the independent expert advice, the Delegate was of a mind to approve the application to extend the indications for Lynparza to women without a BRCA mutation.

Response from sponsor

The sponsor welcomes the opportunity to provide comments in response to the Delegate's request for advice and the evaluation of the application proposing to register Lynparza (olaparib) tablets for the proposed indication:

> *Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) after platinum-based chemotherapy. Prior treatment must have included at least 2 courses of platinum-based regimens.*

The sponsor acknowledges the comments of the clinical evaluator recommending authorisation of the proposed indication.

The sponsor seeks approval of olaparib for the maintenance treatment for ovarian cancer patients with platinum sensitive disease irrespective of BRCA mutation status on the basis of the intention to treat analyses of 2 independent, large randomised controlled trials in this setting, namely the SOLO-2 trial (n = 295) and Study 19 (n = 265). Both studies met their primary endpoints with highly significant and clinically meaningful effects on PFS (HRs of 0.30 and 0.35, respectively) with supportive secondary and exploratory endpoints. Both studies also show a trend towards benefit in OS. In Study 19 a clinically relevant benefit was observed across all subgroups irrespective of BRCA mutation status, including

[18] TGA does not routinely release the names of its independent specialist medical advisors.

the BRCA wild type/variant of uncertain significance subgroup. Additionally, the consistency of effect for the PARP inhibitor class across multiple clinical trials as shown by the efficacy results for olaparib in Study 19 and the SOLO-2 trial, niraparib in the NOVA trial and rucaparib in the ARIEL3 trial increases our understanding of the identification of patients with sensitivity to this therapeutic target and provides context and confidence in the clinical benefit of olaparib.

In a setting of relapsed incurable disease with limited treatment options and where patients will ultimately succumb to their disease, olaparib has a distinct safety profile with demonstrated efficacy and duration of benefit as seen with the follow up of > 6 years in Study 19 in patients with and without a deleterious BRCA mutation. The sponsor, therefore, believes patients with platinum sensitive relapsed ovarian cancer, irrespective of BRCA status, should be provided access to olaparib.

The sponsor considers the proposed indication in the overall population (that is including women without a BRCA mutation) is supported by the body of evidence as described below.

Established biological rationale that identifies patient populations beyond mutated BRCA sensitive to PARP inhibition

Olaparib, as a PARP inhibitor, has a distinct mechanism of action compared with other biomarker driven oncology drugs. The mechanism of action of olaparib is based on the concept of synthetic lethality, where an underlying HRD in tumour cells makes cells highly susceptible to PARP inhibition. When cells with HRD are treated with a PARP inhibitor there is massive and unsustainable DNA damage, resulting in cell death. This mechanism of action is quite distinct from the more common situation where drugs are designed to target very specific driver mutations (oncogenes) or products thereof (such as tyrosine kinase inhibitors that directly inhibit mutated, constitutively activated tyrosine kinases). In such instances, physicians can select for responding patients by directly screening for the genetic aberration synonymous with the mechanism of action. By contrast, the anti-tumour effects of olaparib and other PARP inhibitors are not dependent on a direct interaction with a mutated gene/protein, but rather on an underlying defect in a cancer cell's DNA damage repair mechanisms.

Sensitivity to platinum agents correlates significantly with sensitivity to olaparib. The most profound deficit in the homologous recombination repair (HRR) pathway is seen in tumours with BRCA mutations. However, in the absence of BRCA mutations, the HRR pathway may be compromised by other mechanisms, examples of which include loss of function mutation in other HRR genes, including BRCA1 interacting protein C-terminal helicase 1(BRIP1) and Rad51 paralog B (RAD51B), and epigenetic inactivation of BRCA1. The relationship between sensitivity to olaparib and DNA repair deficiency is therefore likely to be more akin to a continuous rather discrete variable; for example patients with a BRCA mutation are highly sensitive to PARP inhibition but the lack of a BRCA mutation does not preclude sensitivity to olaparib.

The platinum sensitive relapsed ovarian cancer landscape has evolved significantly in the past few years. While multiple randomised controlled trials have demonstrated that platinum sensitive BRCA mutation patients have profound response to maintenance treatment with PARP inhibitors, consistent with the mechanism of action of PARP inhibition, clinically relevant benefit has also been seen in patients whose tumours do not harbour BRCA mutations (Study 19 (olaparib), NOVA trial (niraparib), and ARIEL3 trial (rucaparib)). While not fully elucidated it is likely that these responders have defects in other components of HRR pathways. HRR is a complex system involving many overlapping and complementary pathways and currently available diagnostic technology to identify patients with defects in this system lags behind the clinical benefit being demonstrated in these patients by PARP inhibitors as a class. Instead, these data from clinical trials with

PARP inhibitors support the hypothesis that platinum sensitivity itself is a clinical selection biomarker for HRD.

Clinical selection based on platinum sensitivity outperforms current diagnostics. Currently there is no comprehensive method for identifying patients with HRD. While the sponsor has active clinical studies exploring a range of HRD based patient selection hypotheses, there are no beyond BRCA diagnostics in routine clinical use or that have received regulatory approval. The clinical evidence of olaparib benefit in patients with non BRCA mutated platinum sensitive relapsed ovarian cancer together with mechanistic linkage indicate that platinum sensitivity and response to platinum containing therapy are appropriate clinical selection factors to identify patients likely to benefit from olaparib treatment.

Robustness of Study D0810C00019 (Study 19) design and data

Study 19, a pivotal study in this application, was a large (n = 265), randomised, double blind, placebo controlled, multicentre study of olaparib maintenance treatment for patients with platinum sensitive relapsed serous ovarian cancer. Patients were randomised 1:1 to receive either olaparib (136 patients) or placebo (129 patients). The full analysis set included all randomised patients, irrespective of BRCA mutation status, representing the intent to treat population.

In Study 19, 51% of patients (136 out of 265) were identified to be BRCA mutated in either the germline and/or the tumour. The rest of the patients were classified as BRCA wildtype/unknown (n = 118, which included patients with a variant of uncertain significance), or BRCA missing (n = 11, for whom there were insufficient data to allow classification of mutation status). At study entry, germline BRCA status was known for 98 patients (60 patients were reported as having germline BRCA mutation and 38 patients were BRCA wildtype).

The proportion of patients identified as harbouring a BRCA mutation in Study 19 is larger than might have been predicted based on figures for newly diagnosed ovarian cancer patients. However, the clinical selection of platinum sensitive patients who are also in response to platinum containing chemotherapy is considered to have enriched for HRD tumours, of which BRCA mutated tumours are the most common in an ovarian cancer population. To the sponsor's knowledge, Study 19 is the first and only large randomised control trial of a PARP inhibitor in the platinum sensitive relapsed setting unselected for BRCA mutation and the patient population is considered representative of the intended population.

Study 19 met its primary endpoint of significantly prolonging investigator assessed PFS (58% maturity) in the full analysis set for patients treated with maintenance olaparib versus placebo (PFS HR 0.35; (95% CI 0.25 to 0.49); $p < 0.00001$; median 8.4 versus 4.8 months). The Kaplan Meier plot for PFS showed early and consistent separation in favour of olaparib treated patients. The primary analysis of PFS by investigator assessment was confirmed by all sensitivity analyses, including blinded independent central review. While the greatest benefit of effect with olaparib was observed in the BRCA mutant subgroup (PFS HR 0.18; (95% CI 0.10 to 0.31)), the clinically relevant treatment benefit observed in the BRCA wildtype subgroup (PFS HR 0.54; (95% CI 0.34 to 0.85)) indicates the overall treatment effect is not driven by a single subgroup.

The data from all the secondary endpoints are highly consistent with the primary PFS analysis and demonstrate a large, meaningful benefit for olaparib using efficacy endpoints that have been recommended by the ovarian clinical community and provide a high degree of confidence in the overall efficacy observed (see Table 31).

Table 31: PFS, OS, TFST and TSST data in subgroups across Study 19 and the SOLO-2 trial

	Study 19 (*gBRCA*wt/VUS[a])		Study 19 (*gBRCA* unknown[a])		Study 19 (*gBRCA*m)[a]		SOLO2[a] (*gBRCA*m)[a]	
	Olaparib capsule	Placebo	Olaparib capsule	Placebo	Olaparib capsule	Placebo	Olaparib Tablet	Placebo
Number of Patients	50	64	33	22	53	43	196	99
PFS			DCO 30 June 2010				DCO 19 Sep 2016	
Median PFS (months)	8.3	5.5	7.4	4.5	11.2	4.1	19.1	5.5
HR (95% CI)	0.50 (0.30-0.82)		0.43 (0.21-0.87)		0.17 (0.09-0.31)		0.30 (0.22-0.41)	
P-value (2-sided)	p=0.00572		p=0.001970		p<0.00001		p<0.0001	
OS			DCO 9 May 2016				DCO 19 Sep 2016 (interim)	
Number of events: total number of patients (%)	38:50 (76.0)	57:64 (89.1)	25:33 (75.8)	21:22 (95.5)	35:53 (66.0)	34:43 (79.1)	45:196 (23.0)	27:99 (27.3)
Median OS (months)	29.7	28.9	25.4	25.9	32.9	27.3	NR	NR
HR (95% CI)	0.83 (0.54-1.26)		0.57 (0.31-1.05)		0.68 (0.42-1.10)		0.80 (0.50-1.31)	
Nominal P-value (2-sided)	p=0.38278		p=0.06932		p=0.11363		p=0.4267	
TFST			DCO 9 May 2016				DCO 19 Sep 2016	
Number of events: total number of patients (%)	41:50 (82.0)	62:64 (96.9)	27:33 (81.8)	21:21 (100)	38:53 (71.7)	41:43 (95.3)	92:196 (46.9)	79:99 (79.8)
Median TFST (months)	12.9	6.9	12.9	5.7	15.6	6.2	27.9	7.1
HR (95% CI)	0.43 (0.28-0.66)		0.55 (0.30-1.01)		0.32 (0.20-0.51)		0.28 (0.21-0.38)	
Nominal P-value (2-sided)	p=0.00010		p=0.05384		p<0.00001		p<0.0001	
TSST			DCO 9 May 2016				DCO 19 Sep 2016	
Number of events: total number of patients (%)	41:50 (82.0)	61:64 (95.3)	26:33 (78.8)	20:21 (95.2)	37:53 (69.8)	38:43 (88.4)	68:196 (34.7)	60:99 (60.6)
Median TSST (months)	19.1	15.2	16.3	13.0	19.3	15.3	NR	18.2
HR (95% CI)	0.61 (0.40-0.92)		0.56 (0.31-1.04)		0.44 (0.28-0.71)		0.37 (0.26-0.53)	
Nominal P-value (2-sided)	p=0.01826		p=0.06715		p=0.00086		p<0.0001	

a Study 19 and SOLO2 investigator assessment of PFS data presented

BICR Blinded independent central review; *BRCA* Breast cancer susceptibility gene; *BRCA*wt/VUS *BRCA* wild type/variant of uncertain significance; CI Confidence interval; DCO Data cut-off; *gBRCA* Germline *BRCA*; *gBRCA*wt/VUS *gBRCA* wild type/variant of uncertain significance; HR Hazard ratio; NR Not reached; OS Overall survival; PFS Progression-free survival; TFST Time to first subsequent therapy or death; TSST Time to second subsequent therapy or death

The final OS analysis with a median duration of follow up for OS of 6.5 years represents the most comprehensive dataset with longest follow up for patients treated with a PARP inhibitor. The final analysis showed a favourable prolongation of OS for olaparib treated patients compared to placebo treated patients. The reduced risk of death in olaparib treated patients is reflected by an HR of 0.73 (95% CI 0.55 to 0.95, nominal p = 0.02138; statistical significance not reached). The separation in the Kaplan Meier curves in favour of the olaparib arm became most apparent for patients still at risk at 36 months, with flattening of the olaparib curve following this time point. The proportion of patients still alive at 60 months was 29% on olaparib versus 20% on placebo and at 72 months was 26% on olaparib and 12% on placebo. No new safety signals or long term toxicity was observed with the long term follow up.

An unprecedented duration of clinical benefit is observed in Study 19, with more than 10% of patients continuing to receive durable benefit from olaparib maintenance treatment for at least 6 years (15 patients (11%) on olaparib versus 1 patient (1 %) on placebo). Moreover, the long-term benefit from olaparib was not confined to BRCA mutated patients. Of the 15 patients who received olaparib maintenance treatment for ≥ 6 years, 9 are now known to have a BRCA mutation in their tumour or blood sample with 1 of the remaining 6 patients not evaluable for tumour BRCA status. Hence 5 out of 15 patients treated with olaparib for more than 6 years had no detectable BRCA mutation. Tumours tested negative for additional candidate biomarkers (HRR wildtype or BRCA wildtype/HRD negative) were found amongst the patients who remained on olaparib for over 6 years.

This shows unprecedented benefit in a disease setting where the median PFS with platinum based doublet chemotherapy at first or second relapse is approximately 12 months from the start of chemotherapy and median survival is approximately 3 years.

With the prolonged duration of follow up that exceeds that of any other PARP inhibitor; olaparib has a well characterised and distinct safety profile. In Study 19, almost a quarter of patients stayed on olaparib treatment for over 2 years, with > 10% of patients staying on for over 6 years, supporting the statement that olaparib is a well-tolerated drug that is appropriate for prolonged administration.

Limited treatment options

Current standard of care for patients with platinum sensitive relapsed ovarian cancer is platinum based chemotherapy given for 6 cycles, followed by a period of observation when patients are monitored for the inevitable disease recurrence. In platinum sensitive relapsed ovarian cancer, the pattern of recurrence and response followed by further recurrence means that patients can receive multiple lines of chemotherapy during the course of their disease. Given the toxicities of platinum chemotherapy, the number of treatment cycles is generally limited. As the number of relapses increases, the duration of any response diminishes leading to a shorter time before further chemotherapy is required, a shorter time to recover from chemotherapy associated toxicities and an increased likelihood of chemotherapy related cumulative toxicity. Following multiple relapses, patients will ultimately succumb to their disease. Treatment with olaparib extends the duration of time before a patient must undergo another course of chemotherapy treatment. For patients with terminal cancer, this extended period without cytotoxic chemotherapy and frequent, time consuming visits to the chemotherapy clinic gives them an improved quality of life.

Treatment options for relapsed ovarian cancer in the Australia include bevacizumab (Avastin), either in combination with carboplatin and gemcitabine for the treatment of patients with first recurrence of platinum sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF-targeted angiogenesis inhibitors for 6 to 8 cycles and is then continued as a single agent in patients who are in response. This requires patients to present every 3 weeks for an intravenous infusion, with the associated inconvenience to patients and burden on the health system. The pivotal study showed a 4 month improvement in median PFS (HR 0.48 (95% CI 0.38 to 0.61)) and was supported by a non-statistically significant favourable trend in OS (HR 0.95 (95% CI 0.77 to 1.18)) in platinum sensitive relapsed ovarian cancer when bevacizumab was added to chemotherapy followed by maintenance bevacizumab, compared to standard of care platinum based chemotherapy. Bevacizumab treatment is associated with some significant toxicity, including but not limited to gastrointestinal perforation and fistulae, arterial and venous thromboembolic events, haemorrhage, proteinuria, hypertension, and posterior reversible encephalopathy syndrome.

Olaparib (capsule formulation) is currently the only approved personalised treatment option in the maintenance setting for women with BRCA mutated platinum sensitive relapsed high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial response) to platinum based chemotherapy available in Australia. The safety profile for olaparib (capsule formulation) is consistent with that observed in the SOLO-2 trial with the tablet formulation.

Olaparib (tablet formulation) as a maintenance treatment for women with platinum sensitive relapsed ovarian cancer provides patients who may have received multiple lines of chemotherapy the opportunity to receive olaparib earlier in the course of their disease, before platinum resistance develops which may limit the effectiveness of PARP inhibition. The tablet formulation of olaparib provides a more convenient, simpler, efficacious, tolerable dosing for patients compared with other currently available treatments for platinum sensitive relapsed ovarian cancer and meaningfully delays the requirement for further such therapies.

Benefit-risk assessment of olaparib

Data from Study 19 demonstrates that olaparib has a positive benefit risk profile with a clinically meaningful and statistically significant improvement in PFS in platinum sensitive relapsed ovarian cancer patients. This is supported by evidence from a range of relevant clinical endpoints, including clear evidence of no detriment and a trend towards benefit for OS. Safety data confirm that olaparib is suitable for long term use in the maintenance setting, with long term follow up of patients receiving the capsule formulation in the maintenance treatment setting demonstrating that up to 24% of platinum sensitive relapsed ovarian cancer patients remain on olaparib and thereby avoid further therapy for ≥ 2 years and up to 11% for ≥ 6 years.

Interpretation of overall benefit risk should take into account the biology, science, and existing clinical data available across the field. In the case of olaparib, the target enzyme PARP is present in all tumour cells, not just those of patients with BRCA mutations, and the sensitivity to PARP inhibition has been clearly demonstrated in both biomarker positive and negative subgroups for patients with platinum sensitive relapsed ovarian cancer. In this regard, the totality of the evidence for olaparib in platinum sensitive relapsed ovarian cancer, including olaparib's mechanism of action, safety profile and data supporting its benefit from primary and supportive secondary endpoints, form the basis for its approval as a maintenance treatment in an unselected platinum sensitive relapsed ovarian cancer population.

The presence of a BRCA mutation appears to represent the strongest known molecular determinant of the magnitude of benefit of olaparib compared to placebo, however, BRCA mutation is a functional marker but not the sole determinant of the HRD phenotype. While BRCA mutated patients experienced the greatest magnitude of benefit in Study 19, the data demonstrate that BRCA wildtype patients also derived benefit. Although, the benefit in BRCA wildtype patients is of a lesser magnitude, it remains clinically meaningful as evidenced by 50% reduction in the risk of progression at any point in time for olaparib versus placebo. Based on the totality of data, the sponsor believes the level of benefit observed across biomarker defined subgroups in Study 19 supports the extension of the proposed indication to include all patients who are in response to a platinum based chemotherapy. Additionally, the different level of benefit observed between the subgroups is presented in the proposed PI thus allowing physicians to make the decision regarding which patients to treat as opposed to limiting olaparib availability to one subgroup.

The sponsor considers that the clinical selection markers of platinum sensitivity and response to platinum chemotherapy are the most appropriate tools to identify all patients with high grade recurrent ovarian cancer who are sensitive to olaparib, thus supporting the proposed indication. The availability of olaparib as a maintenance treatment in the platinum sensitive relapsed ovarian cancer setting would provide physicians another treatment option for all patients who are in response to a platinum based chemotherapy, thereby allowing physicians an additional treatment option in platinum sensitive relapsed ovarian cancer whereby they are able to optimise treatment for each patient based on clinical judgement and experience managing cancer patients.

Advisory Committee Considerations[19]

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the extension of indications of new dosage form Lynparza tablets containing olaparib (100 mg and 150 mg) to:

> *Olaparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) after platinum-based chemotherapy. Prior treatment must have included at least 2 courses of platinum-based regimens.*

Specific conditions of registration applying to these goods

1. Submit the results of the following post-marketing studies, when they become available.
   a. SOLO3: olaparib versus physician choice of single agent chemo for third line treatment of women with platinum sensitive relapsed germline BRCA mutated ovarian cancer;
   b. Final OS report for SOLO-2; and
   c. OPINION trial: maintenance olaparib treatment in women with germline BRCA wildtype relapsed ovarian cancer.
2. An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

Attachment 1. Product Information

The PI for Lynparza 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>.

[19] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au