



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for irinotecan (as sucrosofate)

Proprietary Product Name: Onivyde

Sponsor: Baxalta Australia Pty Ltd

October 2017

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.

Copyright

© Commonwealth of Australia 2017

This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the *Copyright Act 1968* or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the TGA Copyright Officer, Therapeutic Goods Administration, PO Box 100, Woden ACT 2606 or emailed to <tga.copyright@tga.gov.au>.

Contents

Common abbreviations	5
I. Introduction to product submission	8
Submission details	8
Product background	8
Regulatory status	13
Product Information	16
II. Quality findings	16
Introduction	16
Drug substance (active ingredient)	16
Drug product	17
Biopharmaceutics	17
Quality summary and conclusions	18
III. Nonclinical findings	18
Pharmacology	18
Pharmacokinetics	19
Toxicology	20
Nonclinical summary and conclusions	25
IV. Clinical findings	26
Introduction	26
Pharmacokinetics	29
Pharmacodynamics	30
Dosage selection for the pivotal studies	30
Efficacy	30
Safety	32
First round benefit-risk assessment	34
First round recommendation regarding authorisation	35
Clinical questions	35
Second round evaluation	35
Second round benefit-risk assessment	35
Second round recommendation regarding authorisation	35
V. Pharmacovigilance findings	35
Risk management plan	35
VI. Overall conclusion and risk/benefit assessment	39
Quality	39
Nonclinical	39

Clinical	40
Risk management plan	45
Risk-benefit analysis	45
Outcome	53
Attachment 1. Product Information	54
Attachment 2. Extract from the Clinical Evaluation Report	54

Common abbreviations

Abbreviation	Meaning
5-FU	5-fluorouracil
ACPM	Advisory Committee on Prescription Medicines
AE	Adverse Event
AEOSI	Adverse event of special importance
ALKP	Alkaline Phosphatase
ALT	Alanine Transaminase
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
AST	Aspartate Transaminase
AUC	Area under the curve
CBR	Clinical benefit response
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
Cmax	Maximum concentration
CMI	Consumer Medicines Information
CL	Clearance
CPT-11	Irinotecan
CR	Complete Response
CT	X-Ray Computed Tomography
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
DHCP	Dear Healthcare Professional
DILI	Drug-induced liver injury
DLT	Dose limiting toxicity
DoR	Duration of Response

Abbreviation	Meaning
ECG	Electrocardiograph
EMA	European Medicines Agency
ER	Exposure ratio
ESMO	European Society of Medical Oncology
EORTC	European Organisation for Research and Treatment of Cancer
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GIT	Gastrointestinal tract
ICH	International Conference on Harmonisation
ITT	Intention to Treat
IV	Intravenous
KPS	Karnofsky performance scale
LDH	Lactate Dehydrogenase
LFTs	Liver function tests
LV	Leucovorin (folinic acid)
MEDRA	Medical dictionary for regulatory activities
MM-398	Onivyde
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
ORR	Objective response rate
OS	Overall Survival
PD	Pharmacodynamics
PFS	Progression free survival
PI	Product Information

Abbreviation	Meaning
PK	Pharmacokinetics
PP	Per Protocol
PR	Partial Response
PRO	Patient reported outcome
QoL	Quality of Life
RMP	Risk management plan
SAE	Serious adverse event
TEAE	Treatment emergent adverse event
TTF	Time to Treatment Failure
TMR	Tumour Marker Response
UGT1A1	Uridine diphosphate-glucuronyl transferase 1A1

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New chemical entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	13 December 2016
<i>Date of entry onto ARTG</i>	19 December 2016
<i>Active ingredient:</i>	Irinotecan (as sucrosofate)
<i>Product name:</i>	Onivyde
<i>Sponsor's name and address:</i>	Baxalta Australia Pty Ltd 1 Baxter Drive Old Toongabbie NSW 2146
<i>Dose form:</i>	Concentrated liposomal solution for infusion
<i>Strength:</i>	43 mg/10 mL
<i>Container:</i>	Type 1 glass vial with a rubber stopper and a flip off seal
<i>Pack size:</i>	1 vial/carton
<i>Approved therapeutic use:</i>	Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and folinic acid (leucovorin) in adult patients who have been previously treated with gemcitabine-based therapy.
<i>Route of administration:</i>	Intravenous (IV)
<i>Dosage:</i>	70 mg/m ² IV over 90 minutes (proposed)
<i>ARTG number:</i>	263184

Product background

This AusPAR describes the application by the sponsor, Baxalta Australia Pty Ltd, to register a new chemical entity, irinotecan (as the sucrosofate salt), as a concentrated nanoliposomal-solution for infusion under the trade name Onivyde.

The chemical substance irinotecan is included on the ARTG as, for example, Camptosar (irinotecan hydrochloride, supplied as an aqueous solution). In Onivyde, within the liposome, irinotecan is present as the sucrosofate salt. Schedule 9 of the *Therapeutic Goods Regulations 1990* defines a new chemical entity as (amongst other things):

*(b) an isomer, mixture of isomers, complex of, derivative of or **salt of**, a registered chemical substance that, having previously been included in the Register, differs from the registered substance in having different safety or efficacy properties*

Onivyde has been viewed as a new chemical entity for the purpose of this application. The sponsor, in its pre-submission planning documentation, also indicated that this was a new salt/ester/isomer/complex/derivative of an existing active ingredient having different safety or efficacy properties.

The proposed indications are:

Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and folinic acid (leucovorin) in adult patients who have been previously treated with gemcitabine-based therapy.

Regarding dosing, the proposed PI states:

Onivyde, LV and 5-fluorouracil (5-FU) should be administered sequentially. The recommended dose and regimen of Onivyde is 70 mg/m² intravenously over 90 minutes, followed by LV 400 mg/m² intravenously over 30 minutes, followed by 5-FU 2400 mg/m² intravenously over 46 hours, administered every 2 weeks.

*A reduced starting dose should be considered of Onivyde 50 mg/m² for patients known to be homozygous for the UGT1A1*28 allele as they may have an increased risk for developing neutropenia based on experience with non-liposomal irinotecan therapy. In the clinical study evaluating Onivyde in combination with 5-FU and LV, patients homozygous for the UGT1A1*28 allele did not experience a greater incidence of Grade 3 or 4 neutropenia than those not homozygous.*

Recommendations are also made regarding dose adjustments (escalation and also reduction for Grade 3-4 toxicity). Regarding escalation, the following recommendation is made:

*Patients who are known to be homozygous for UGT1A1*28 and without drug related toxicities during the first cycle of therapy (reduced dose of 50 mg/m²) may have the dose of Onivyde increased to a total dose of 70 mg/m² in subsequent cycles based on individual patient tolerance.*

NB: some TGA evaluation reports and sponsor documents may refer to dosing as initially proposed (80 mg/m² Q2wk), which reflects the salt base of irinotecan. The current approved dose (70 mg/m²) reflects the amount of the free base of irinotecan.

Pancreatic cancer

The sponsor writes in their application cover letter:

Pancreatic cancer is a malignant neoplasm of the pancreas. About 90-95% of exocrine pancreatic cancers are infiltrating ductal adenocarcinomas. The remaining 5% include adenosquamous carcinomas, signet ring cell carcinomas, hepatoid carcinomas, colloid carcinomas, undifferentiated carcinomas, and undifferentiated carcinomas with osteoclast-like giant cells. Exocrine pancreatic tumours are far more common than pancreatic endocrine tumours, which make up about 1% of total cases.

Pancreatic cancer has a low survival rate as it is most often diagnosed at an advanced stage. In Australia, it is the 5th most common cause of cancer death despite being the 10th most common form of cancer.¹

Therapeutic landscape

The sponsor continues:

¹ Australian Institute of Health and Welfare 2014. Australia's health 2014. Australia's health series no. 14. Cat. no. AUS 178. Canberra: AIHW.

The current treatment options available to patients diagnosed with pancreatic cancer are limited. For patients with early disease (stage I and some in stage II), radical surgery may be effective. In more advanced stages, chemotherapy may be offered but primarily for the palliation of symptoms as overall survival is improved for very few patients (see above). The two most commonly used antineoplastic agents are gemcitabine (Gemzar) and 5-fluorouracil. Other agents recently approved include erlotinib (Tarceva) and nanoparticle albumin-bound paclitaxel (Abraxane).

EviQ includes three chemotherapy protocols for metastatic pancreatic cancer:

- Folfirinox (Modified), which is relatively aggressive chemotherapy and which incorporates fluorouracil, leucovorin, irinotecan and oxaliplatin as follows in Table 1 (all on – or starting on – day 1, and all IV).

Table 1: Treatment schedule summary.

Drug	Dose
Oxaliplatin	85 mg/m ²
Irinotecan	180 mg/m ²
Calcium folinate (Leucovorin)	50 mg
Fluorouracil	400 mg/m ²
Fluorouracil	2400 mg/m ² over 46 hours

Frequency: 14 days

Cycles: Continuous until disease progression or unacceptable toxicity (up to 12 cycles)

Neither irinotecan nor oxaliplatin are approved for use in pancreatic cancer, that is, such use is off-label.

- Folfox6 (Modified), which incorporates fluorouracil, leucovorin and oxaliplatin, and which is recommended after failure of gemcitabine therapy

EviQ commented about evidence for m-Folfox as follows:

A search of the literature did not find strong evidence to support the use of Folfox in the treatment of advanced pancreatic cancer after failure of first line gemcitabine based chemotherapy ... The committee was most strongly influenced by the Phase II trial by Yoo et al.²

- The combination of gemcitabine and nab-paclitaxel.

NCCN guidelines³ for metastatic disease give emphasis to performance status. With good performance status, and previous gemcitabine based therapy, the endorsed second line therapies are:

- Clinical trial
- 5-FU + LV + Onivyde (as proposed in this application)
- Other fluoropyrimidine based chemotherapies
- Radiotherapy for severe pain

ESMO guidelines⁴ note regarding second line therapy:

A first randomised trial (168 patients) has shown, in patients with advanced gemcitabine refractory pancreatic cancer, that second line 5-FU, folinic acid and oxaliplatin, significantly extend the duration of OS when compared with 5-FU, folinic

² Yoo C, et al. A randomised phase II study of modified FOLFIRI.3 vs modified FOLFOX as second-line therapy in patients with gemcitabine-refractory advanced pancreatic cancer. *Br J Cancer* 101: 1658-1663 (2009).

³ Version 1.2016.

⁴ Ducreux M, et al. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 26 Suppl 5: v56-68 (2015).

acid alone.⁵ These results have not been confirmed by a more recent Canadian trial.⁶ Very recently, combination of MM-398, a nanoliposomal encapsulation of irinotecan, and 5-FU, folinic acid has shown an improvement of OS (6.1 versus 4.2 months), PFS and ORR in the intent-to-treat population over 5-FU/LV alone. Second-line therapy of pancreatic cancer has to be considered in terms of risk benefit for the patient. If the general status remains correct, considering the conflicting results on the use of oxaliplatin, MM-398 when available in all countries may be the best option for second-line treatment of these patients [II, B].

Ryan⁷ noted that more emphasis has been given lately to gauging clinical benefit and symptom improvement, than previously.

In a first line setting, Ryan⁸ uses Folfirinox ahead of gemcitabine based doublets in less frail patients, but gemcitabine based doublets such as gemcitabine + nab-paclitaxel or gemcitabine + capecitabine for more frail patients. In those who might have received gemcitabine based doublets but who have liver impairment, Folfox is offered. In the very frail, gemcitabine monotherapy, or gemcitabine + capecitabine, or gemcitabine + S-1 are options. NCCN and ESMO guidelines also endorse gemcitabine monotherapy for poor performance status patients.

In a second line setting, the optimal regimen is not established. Ryan⁹ reserves therapy for patients with a good performance score after first line therapy, and endorses:

- A gemcitabine-based regimen (gemcitabine + Abraxane, or gemcitabine + capecitabine) for those patients refractory to or intolerant of first line Folfirinox
- For patients initially treated with Folfox because of elevated bilirubin, who continue to have elevated bilirubin, options include Onivyde + FU, or single agent gemcitabine
- For patients initially treated with a gemcitabine-containing regimen, options include a regimen including FU + oxaliplatin, or Onivyde + FU.

Ryan¹⁰ states that in second line, a fluoropyrimidine **alone** may be appropriate – but notes oxaliplatin based combinations “appear to be superior to best supportive care alone or a fluoropyrimidine alone (in most studies)”.

Conventional irinotecan has been used in this second line setting, for example, in combination with oxaliplatin.¹¹

⁵ Oettle H, et al. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. *J Clin Oncol.* 32: 2423-2429 (2014).

⁶ Ciliberto D, et al. Role of gemcitabine-based combination therapy in the management of advanced pancreatic cancer: a meta-analysis of randomised trials. *Eur J Cancer* 49: 593-603 (2013).

⁷ Ryan DP. Chemotherapy for advanced exocrine pancreatic cancer. Up-to-date; Topic 2475 Version 63.0; last updated 30 Jun 2016.

⁸ Ryan DP. Chemotherapy for advanced exocrine pancreatic cancer. Up-to-date; Topic 2475 Version 63.0; last updated 30 Jun 2016.

⁹ Ryan DP. Chemotherapy for advanced exocrine pancreatic cancer. Up-to-date; Topic 2475 Version 63.0; last updated 30 Jun 2016.

¹⁰ Ryan DP. Chemotherapy for advanced exocrine pancreatic cancer. Up-to-date; Topic 2475 Version 63.0; last updated 30 Jun 2016.

¹¹ Ryan DP. Chemotherapy for advanced exocrine pancreatic cancer. Up-to-date; Topic 2475 Version 63.0; last updated 30 Jun 2016.

Onivyde

Mechanism of action

Irinotecan is a camptothecin analogue with cytotoxic and antineoplastic properties. It acts through inhibition of topoisomerase I, an enzyme that reduces torsional stress in supercoiled DNA to allow DNA to become untangled and commence replication.

The sponsor makes the following claims regarding the liposomal formulation:

The major benefit of a liposome formulation is that it can prolong the blood circulation time, thereby achieving a longer half-life, larger AUC, slower clearance, and very small volume of distribution of the drug, resulting in a longer tissue exposure than free drug. For liposome anti-cancer drugs, the prolonged circulation can also result in greater passive accumulation of drug in tumour tissue through the leaky neovasculature of the tumour.

The sponsor also claims that there is increased conversion of irinotecan to SN-38 in tumours. Non-liposomal irinotecan is converted to the active metabolite SN-38 primarily by esterases in the liver.

It is stated that SN-38 is 100 to 1,000 fold more active than irinotecan. In one Onivyde study, irinotecan concentrations were ~250 fold higher than SN-38 in tumours. This raises the possibility that SN-38 makes a large contribution to activity.

Based on EviQ, conventional irinotecan is generally given once every 2-3 weeks. In the Folfirinox regime for pancreatic cancer, dose is 180 mg/m², once every 2 weeks (and irinotecan is given in 250-500 mL glucose 5% over 90 minutes). In the modified Folfoxiri regimen for metastatic colorectal cancer, dose is 165 mg/m² Q2W. Dosing for a Q3W regimen may be 240 mg/m² (for example, Xeliri in colorectal metastatic cancer), or as high as 350 mg/m² (for example, colorectal metastatic irinotecan Q3W, that is, monotherapy), or in the case of SCLC with cisplatin, 65 mg/m² on days 1 and 8 of a 21 day cycle.

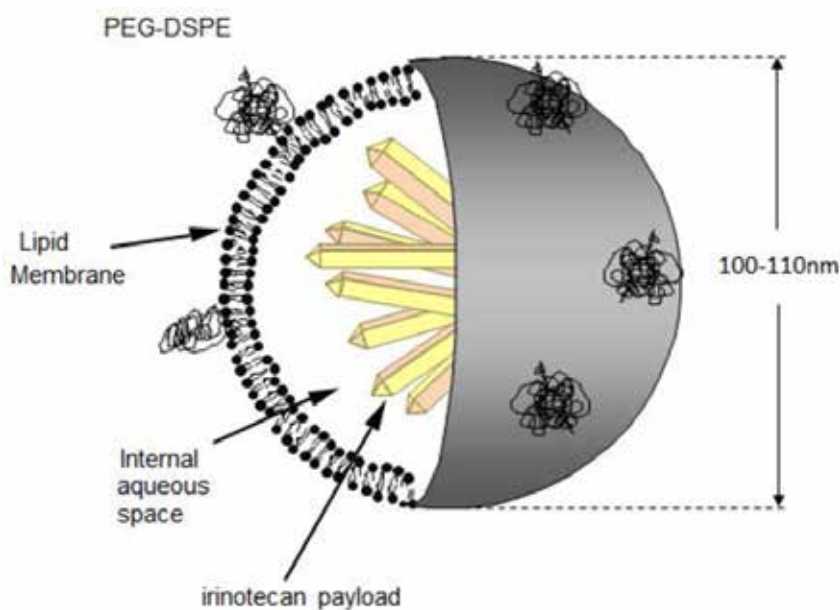
Clinical development programme

Onivyde trials have been conducted in cervical cancer, gastric/gastro oesophageal junction cancer and pancreatic cancer patients.

Regulation

Onivyde has not been designated as an orphan medicine in Australia.

Irinotecan hydrochloride trihydrate has been approved for use in Australia since 1997 as the hydrochloride trihydrate. The current formulation differs from the approved formulations due to the encapsulation of an irinotecan payload into liposome nanoparticles (Figure 1). The Onivyde liposome is a small unilamellar lipid bilayer vesicle (SUV) approximately 110 nm in diameter that encapsulates an aqueous space which contains irinotecan in a precipitated state as the sucrosolate salt. The lipid membrane is composed of phosphatidylcholine, cholesterol, and a polyethyleneglycol-derivatised phosphatidyl-ethanolamine in the amount of approximately one polyethyleneglycol (PEG) molecule for 200 phospholipid molecules. For clarity, the liposomal bound irinotecan has been referred to as MM-398 and the free irinotecan formulation referred to as CPT-11, as used by the sponsor. Formulation did not change during the clinical development programme.

Figure 1: Schematic of Onivyde (MM-398).**Regulatory status**

The following section is current at dates noted.

US: FDA (as of 20 July 2016)

Onivyde received a new drug application (NDA) approval letter on 22 October 2015. The currently approved indication is:

Onivyde is indicated, in combination with fluorouracil and leucovorin, for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

Limitation of Use: Onivyde is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas [see Clinical Studies (14)].

Several relevant aspects of the US Onivyde PI include:

- Boxed warnings related to severe neutropenia and severe diarrhoea;
- A recommendation against substituting Onivyde for other drugs containing irinotecan HCl.

EU: EMA (as of 1 September 2016)

An application similar to that seen in Australia had been lodged in Europe in May 2015. According to the EMA website:

On 21 July 2016, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Onivyde, intended for the treatment of metastatic adenocarcinoma of the pancreas. Onivyde was designated as an orphan medicinal product on 9 December 2011. The applicant for this medicinal product is Baxalta Innovations GmbH.

Onivyde will be available as a concentrate for solution for infusion (5.0 mg/ml Irinotecan HCl Trihydrate). The active substance of Onivyde is irinotecan, a

topoisomerase I inhibitor (ATC code: L01XX19) which binds reversibly to the topoisomerase I DNA complex and induces single strand DNA lesions blocking the DNA replication fork. Onivyde contains irinotecan in a pegylated liposomal formulation.

When added to 5-fluorouracil (5-FU) 2,400 mg/m² and leucovorin (LV) 400 mg/m², Onivyde improved survival compared with 5-FU 2,000 mg/m² and LV 200 mg/m². The most common side effects are diarrhoea, nausea, vomiting, decreased appetite, neutropenia, fatigue, asthenia, anaemia, stomatitis and pyrexia.

The full indication is:

Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil (5-FU) and leucovorin (LV), in adult patients who have progressed following gemcitabine based therapy.

It is proposed that Onivyde be prescribed by physicians experienced in the use of anti-cancer therapies.

Detailed recommendations for the use of this product will be described in the summary of product characteristics (SmPC), which will be published in the European public assessment report (EPAR) and made available in all official EU languages after the marketing authorisation has been granted by the European Commission.

Overall international regulatory status

The overall international regulatory status at time of the current submission to TGA is shown in Table 2.

Table 2: International regulatory status.

Country / region	Submission date	Approval date	Status	Indications (approved or requested)
US	24 Apr 2015	22 Oct 2015	Approved	Onivyde is a topoisomerase inhibitor indicated, in combination with fluorouracil and leucovorin, for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.
EU - centralised procedure	30 Apr 2015		CHMP positive opinion	Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil (5-FU) and leucovorin (LV), in adult patients who have progressed following gemcitabine based therapy.
Switzerland	5 Nov 2015		Under review	Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin in patients who have been previously treated with gemcitabine.
Canada	18 Dec 2015		Under review	Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin in patients who have been previously treated with gemcitabine-based therapy.
New Zealand	25 Mar 2016		Under review	Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin in patients who have been previously treated with gemcitabine.
Singapore	31 May 2016		Under review	Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin in patients who have been previously treated with gemcitabine.

The sponsor confirms that an application for Onivyde has not been rejected, withdrawn, or repeatedly deferred in the US or Canada.

Product Information

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

II. Quality findings

Introduction

There are currently numerous irinotecan immediate release injections. For example, Pfizer's innovator Camptosar irinotecan concentrated solution for infusion contains 5 mg/mL of irinotecan hydrochloride trihydrate and is indicated as a component of first line therapy for patients with metastatic carcinoma of the colon or rectum. It is also indicated for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial therapy. The concentrated injection is always diluted prior to use and may be used in combination with 5-FU and LV or as monotherapy. For monotherapy, the maximum recommended dosage is 350 mg/m² and for combination therapy the recommended dosage is 180 mg/m².

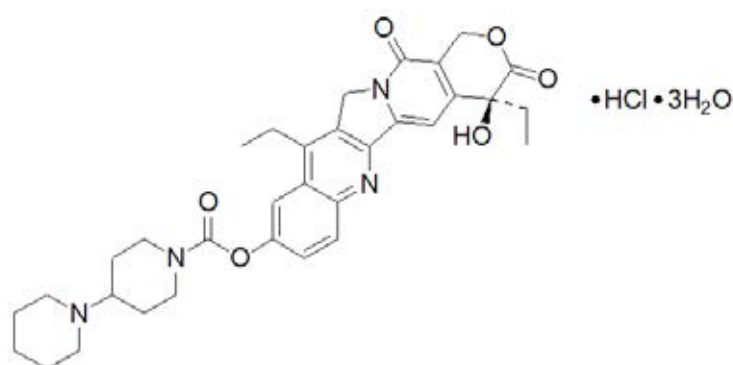
The proposed drug product is a sterile, white to slightly yellow opaque isotonic liposomal dispersion for intravenous infusion. Each millilitre of the drug product contains 5 mg of irinotecan drug substance reported on the hydrochloride trihydrate basis, which is equivalent to 4.3 mg/mL irinotecan anhydrous base. The product is intended for single use administration only.

The formulation was designed to have a combination of long circulation lifetimes and stable retention encapsulated irinotecan, allowing the drug time to accumulate selectively in solid tumours. The product is indicated for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-FU and LV in adult patients who have been previously treated with gemcitabine-based therapy. The recommended dose is 70 mg/m² intravenously over 90 minutes, followed by LV 400 mg/m² IV over 30 minutes, followed by 5-FU 2400 mg/m² intravenously over 46 hours, administered every 2 weeks.

The application has not been referred to the Pharmaceutical Subcommittee (PSC) of the ACPM.

Drug substance (active ingredient)

Irinotecan hydrochloride trihydrate (Figure 2) is a yellowish to yellow crystalline powder that is freely soluble in DMSO and anhydrous acetic acid and slightly soluble in ethanol. The drug substance melts at 250-256°C and is produced as a single polymorphic form. The molecular formula is C₃₃H₃₈N₄O₆•HCl•3H₂O and molecular weight is 677.18.

Figure 2: Structure of irinotecan hydrochloride trihydrate.**Drug product**

The active ingredient in the drug product is derived from irinotecan hydrochloride, which is precipitated as the sucrosolate salt and encapsulated and retained inside a small unilamellar lipid bilayer of approximately 110 nm in diameter.

The lipid membrane is composed of 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethylene glycol-2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE) in the amount of approximately one polyethyleneglycol (PEG) molecule for 200 phospholipid molecules (Figure 1). The liposomal excipients encapsulate and retain the drug substance until it is passively delivered to the tumour site.

The liposome encapsulated drug substance is dispersed in a formulation buffer consisting of 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid (HEPES) and sodium chloride (NaCl). The pH of the formulation buffer (7.2) is critical to controlling the degradation of DSPC to LysoPC by drug substance catalysed hydrolytic degradation.

The vial product may be stored for a maximum of 24 months (from the date of manufacture of the bulk product) at 2-8°C.

Biopharmaceutics

The pharmacokinetics of the proposed formulation were evaluated using PK sampling across 6 studies (PEP0201, PEP0203, PEP0206, PIST-CRC-01, MM-398-01-01-02 and NAPOLI-1). Both non-compartmental analysis and population pharmacokinetic analysis were used.

Analytes measured included total irinotecan (which includes encapsulated and un-encapsulated irinotecan), its active metabolite SN-38 and its inactive glucuronidated form SN-38G.

Encapsulated irinotecan was measured in Study PEP0201; the results showed that encapsulated and total irinotecan were indistinguishable. Un-encapsulated irinotecan was not measured because of this finding and SN-38 was used as the surrogate to measure the unencapsulated (released) form of irinotecan.

The direct comparison of the pharmacokinetics of irinotecan and SN-38 in patients administered the proposed formulation at 120 mg/m² Q3w or un-encapsulated irinotecan (Campto/Camptosar) 300 mg/m² Q3w was evaluated in Study PEP0206. Compared to the administration of un-encapsulated irinotecan at 300 mg/m² Q3w, administration of the proposed formulation at 120 mg/m² Q3w resulted in:

- Higher exposure of total irinotecan [C_{max} 13.4 fold, half-life(t_{1/2}) 2.0 fold]

- $AUC_{0-\infty}$ 46.2 fold (comparison values were not dose normalised) for total irinotecan
- Higher SN-38 $t_{1/2}$ (3.0 fold), and $AUC_{0-\infty}$ (1.4 fold); however,
- Reduced SN-38 C_{max} (0.19 fold).

The plasma protein binding of the proposed formulation is low (<0.44% of the irinotecan API). By comparison immediate release irinotecan injection displays moderate plasma protein binding (65% bound). SN-38 is highly bound to human plasma proteins (approximately 95% bound). Direct measurement of liposomal irinotecan shows that 95% of irinotecan remains liposome encapsulated during circulation.

The volume of distribution (V_d) estimates in patients administered the proposed product were approximately 2 L/m², which suggests that the proposed product is confined mostly to the vascular fluid volume. This value is almost two orders of magnitude smaller than the V_d for unencapsulated irinotecan administration (157 L/m²).

The metabolism of the phospholipids constituting the liposome has not been studied.

Quality summary and conclusions

There are no major objections to the chemistry and quality aspects of the proposed product.

III. Nonclinical findings

Pharmacology

Primary pharmacology

Irinotecan is a topoisomerase I (topo I) inhibitor. Topo I is a nuclear enzyme involved in DNA replication. Inhibition of this enzyme causes reversible single strand DNA breaks, which progress to double strand damage as DNA is synthesized during the S phase of the cell cycle, and as a consequence results in apoptosis of mammalian cells. Irinotecan is converted by carboxylesterases into the 100 to 1000 fold more active metabolite, SN-38. SN-38 and to a lesser extent, irinotecan, inhibits the supercoiled DNA relaxation activity of topo I.

Anti-tumour efficacy and cellular uptake of MM-398 and conversion to SN-38 were assessed in vitro in macrophages and cancer cell lines as well as in animal cancer models including pancreatic cancer. Liposomes were internalised by tumour cell lines and macrophages. Conversion to SN-38 was demonstrated in colon, pancreatic, lung and ovarian cell lines with high variability within and between cell lines. This suggests potential for heterogeneity in response to MM-398. Murine and human macrophage cells showed significantly greater uptake of liposomes than tumour cell lines in vitro (10-40x), and in murine colon and lung cancer models.

In murine and human macrophages loaded with MM-398, the lipids were retained longer in macrophage cells than irinotecan. Unexpectedly, the release of free irinotecan from MM-398-loaded macrophages was faster than CPT-11 loaded cells, suggesting rapid release of irinotecan from liposomes within the macrophage. The uptake of irinotecan by macrophages for CPT-11 was greater than that of MM-398 in vitro; however, in vivo studies showed longer retention of irinotecan and SN-38 in animals dosed with MM-398 than CPT-11 (see below).

The anti-tumour activity of MM-398 was investigated in multiple tumour models in mice and was compared to CPT-11. The *in vivo* studies collectively demonstrated increased anti-tumour activity for MM-398 compared to CPT-11. MM-398 was effective across different tumour cell lines to varying extents, including pancreatic cell lines. In pancreatic tumour models, MM-398 at weekly IV doses of 10-20 mg/kg significantly inhibited tumour growth in orthotopic and ectopic (subcutaneous) tumour xenopants. One study comparing anti-tumour activity of MM-398 with CPT-11 showed significantly greater anti-tumour activity for MM-398 than CPT-11, associated with higher tumour tissue irinotecan and SN-38 levels (at 24 h). In a study where plasma and tumour tissue drug concentrations were measured,¹² improved anti-tumour activity of MM-398, relative to free irinotecan, was correlated with increased retention of SN-38 in tumour tissues in a murine colon cancer model. The authors also showed that MM-398 administered at doses 5 fold lower than free irinotecan achieved similar intratumoural exposure of SN-38 but with superior antitumour activity. In a tissue distribution study in mice carrying colon cancer xenograft, concentrations (AUC values) of irinotecan and SN-38 in tumour tissues were 20 and 5 fold, respectively, higher for 398-MM than for CPT-11 at the same IV dose. While MM-398 demonstrated significantly improved anti-tumour activity compared to CPT-11, tumour regression was often transient and demonstrated regrowth after cessation of treatment.

There was no drug combination study in pancreatic cell models. In a colon cancer xenograft model, combination of 5-FU and MM-398 yielded significantly better inhibition of tumour growth than either MM-398 or 5-FU alone.

Taken together, the nonclinical data collectively indicate that MM-398 is comparatively more efficacious than CPT-11 in inhibiting xenograft tumour growth.

Secondary pharmacodynamics and safety pharmacology

No secondary pharmacodynamic studies were performed. In a single dog safety pharmacology study, no cardiovascular, hemodynamic, electrocardiographic, or respiratory effects were observed at doses up to 21 mg/kg. No specific CNS safety pharmacology studies were conducted. Low brain distribution was detected in rats dosed with MM-398, although the brain level was slightly higher for MM-398 than for CPT-11. In repeat dose toxicity studies, signs of CNS effects (tremors, uncoordinated gait and salivation) were noted in CPT-11 administered rats at 75 mg/kg, but no such observations were seen in the MM-398 treated rats or in dogs.

Pharmacokinetics

Pharmacokinetics of MM-398 were studied in mice, rats and dogs, and compared with that of the free formulation, CPT-11 by IV infusion. Encapsulation of irinotecan in MM-398 achieved higher C_{max} and AUC values, longer elimination half-life, lower clearance (8.4 compared with 631 mL/h/kg in rats, 5.3 compared with 679 mL/h/kg in dogs) and smaller volume of distribution (42 compared with 1620 mL/kg in rats, 191 compared with 2707 mL/kg in dogs) compared to CPT-11. Increases in C_{max} and AUC, relative to CPT-11, were also noted for the active metabolite SN-38. After repeated dosing, the elimination t_{1/2} of irinotecan and SN-38 in rats dosed with MM-398 were similar to that in humans (~20 h for irinotecan and ~50 h for SN-38), while the t_{1/2} in dogs was highly variable, ranging from 3 to 40 h for irinotecan and 2-30 h for SN-38.

Encapsulated and total irinotecan in blood circulation was investigated in dogs after a single dose of MM-398. In plasma, encapsulated irinotecan accounted for ~80% of total

¹² Kalra AV, et al. Preclinical activity of nanoliposomal irinotecan is governed by tumor deposition and intratumor prodrug conversion. *Cancer Res.* 74: 7003-7013 (2014).

irinotecan over 168 h, suggesting good stability of the liposome capsules and slow release of irinotecan from liposomes. In all other pharmacokinetic and toxicokinetic studies, total irinotecan was measured.

Binding of liposomes in MM-398 to human plasma protein in vitro was negligible (<1%), compared to the moderate plasma protein binding (30-68%) for free irinotecan (Camptosar PI). Tissue distribution of MM-398 was examined in one mouse study (with colon cancer xenograft) and two rat studies. The mouse study showed significantly higher tissue distribution of both irinotecan and the active metabolite, SN-38 for MM-398 than CPT-11 in tumour, liver, kidney and intestines (only tissues collected for analysis in the study). The rat studies with radiolabelled MM-398 and CPT-11 demonstrated considerably higher distribution to spleen and lungs for MM-398 than CPT-11, probably due to uptake by mononuclear cells in these organs. Higher levels were also detected in liver, bile, renal cortex, heart and adrenal for MM-398 than for CPT-11. Distribution to bone marrow was comparable between MM-398 and CPT-11, suggesting liposome encapsulation would not increase bone marrow toxicity of irinotecan. Surprisingly, much higher levels were seen in GIT contents and urine, as well as salivary gland, Harderian gland and uveal tract for CPT-11 than for MM-398. Generally, the elimination of radioactivity from tissues was longer for MM-398 than for CPT-11. Relatively high levels of radioactivity were still present in spleen and uveal tract in rats dosed with MM-398 7 days after dosing (high levels were also detected in uveal tract in rats dosed with CPT-11 3 days after dosing, the last sampling time).

No metabolism studies were performed for MM-398. Once irinotecan is released from liposomes, it is expected to be metabolised by the same pathway as the free formulation. The active metabolite, SN-38 was detected in animal species used in pharmacology and toxicology studies.

Excretion of MM-398 and/or its metabolites in rats was predominantly via faeces (~80% of the dose), with ~20% excreted in urine. In bile duct cannulated rats, 57% of the dose was recovered in bile, suggesting significant biliary excretion.

Pharmacokinetic drug interactions

The sponsor did not submit specific studies investigating pharmacokinetic drug interactions. Since irinotecan and SN-38 are metabolised to inactive metabolites via CYP3A4 and UGT1A1, respectively, co-administration of MM-398 with inhibitors or inducers of CYP3A4 or UGT1A1 could increase or decrease systemic exposures to irinotecan or SN-38.

Toxicology

Acute toxicity

Single dose toxicity studies were conducted in mice, rats and dogs using the clinical route of administration. One rat study and 2 dog studies were GLP compliant. In a non-GLP study in mice, deaths occurred at all dose levels (200-800 mg/kg MM-398 and 200 mg/kg CPT-11, equivalent to 600 mg/m²). In rats, the maximum non-lethal dose was 720 mg/kg MM-398 (4320 mg/m²), while the lowest dose of CPT-11 (200 mg/kg) caused 50% mortality (2 out of 4 male rats). In dogs deaths occurred at ≥ 30 mg/kg MM-398 (no deaths at 15 mg/kg, 300 mg/m²) and 30 mg/kg CPT-11 (lowest dose tested). In all species toxicity of the GI tract was noted at most doses, with discoloured soft, mucoid or liquid faeces, emesis (dogs) as common clinical signs and corresponding necropsy findings (dark or gelatinous GIT contents and mottled/discoloured GIT wall). Decreased blood WBC (and differentials), RBC parameters and platelets (dogs only) were also apparent in rats and

dogs, consistent with bone marrow toxicity observed in repeat dose studies. The maximum non-lethal dose of MM-398 in rats and dogs were 54 and ~4 times, respectively, the clinical dose (80 mg/m²).

Repeat dose toxicity

Repeat dose toxicity of MM-398 was investigated in rats and dogs with weekly dosing for 4 weeks and every 3 weeks dosing for 18 weeks (a total of 6 doses). All studies were GLP-compliant, used the clinical route of administration and included a group dosed with CPT-11 for comparison. The 4 week studies incorporated a recovery period of 2 weeks and the 18 week studies a recovery period of 6 weeks. The repeat dose toxicity studies were not well designed. The dosing schedule (either weekly or every 3 weeks) of the repeat dose toxicity studies differ from that in patients (every 2 weeks).

Relative exposure

Relative exposures are calculated based on AUC_{0-t} after the last dose in the rat and dog repeat dose toxicity studies. Human reference AUC_{0-t} values are from the Summary of Clinical Pharmacology. The rat studies with MM-398 achieved high exposure ratios (ER) for both total irinotecan and the active metabolite, SN-38 (Table 3). The ERs in the dog studies were low and the ERs for SN-38 were subclinical.

Table 3: Relative exposure in repeat-dose toxicity studies.

Study	Dose formulation	Dose (mg/kg)	AUC _{0-t}		Exposure Ratio*	
			Irinotecan (µg.h/mL)	SN-38 (ng.h/mL)	Irinotecan	SN-38
Rat [4 weeks, weekly dosing]	MM-398	65	41906	142420	81	277
		130	49324	35627	96	69
		260	105226	64201	204	125
	CPT-11	130	82.9	437	0.16	0.85
Rat [18 weeks, dosed every 3 weeks]	MM-398	30	30990	230650	20	149
		75	80250	301364	52	195
		190	236411	327277	153	212
	CPT-11	75	82.8	7550	0.05	4.89
Dog [4 weeks, weekly dosing]	MM-398	4	662	16.6	1.29	0.03
		8	735	77.6	1.43	0.15
		16	4775	184	9.27	0.36
	CPT-11	16	38.5	44.2	0.07	0.09
Dog [18 weeks, dosed every 3 weeks]	MM-398	9	2046	127	1.32	0.08
		15	4394	268	2.84	0.17
		21	8775	419	5.68	0.27
		36 [^]	11431	558	7.40	0.36
	CPT-11	21	59.6	182.5	0.04	0.12
		36 [^]	119.7	233	0.08	0.15

* Animal AUC/human AUC based on human AUC_{0-t} values of 1030 µg.h/mL irinotecan and 587 ng.h/mL SN-38 at 80 mg/m² every 2 weeks (*Summary of Clinical Pharmacology*); for the 4-week studies with weekly dosing, the exposure ratio was calculated by animal AUC_{0-t} x 2/human AUC_{0-t}, and for the 18-week studies with dosing every 3 weeks, the exposure ratio was calculated by animal AUC_{0-t} x 2/human AUC_{0-t} x 3. [^] Data after the first dose since all animals were euthanised by day 23 due to severe toxicity.

Major toxicities

The toxicity of MM-398 was consistent with that of un-encapsulated irinotecan. Main toxicity findings were GIT effects (dogs only), bone marrow suppression, lymphoid atrophy/necrosis, and reproductive organ toxicity in both rats and dogs. Generally, MM-

398 was more toxic, associated with higher exposure to irinotecan and SN-38 (based on AUC), than CPT-11 at the same dose. No NOAEL was established in rats since leukopenia and lymphopenia were observed in all female groups and increased extramedullary haematopoiesis in both sexes treated with MM-398 in the 18 week study, and decreased body weight gain and thymic atrophy at all doses in the 4 week study. The NOAEL in dogs was 9 mg/kg every 3 weeks in the 18 week study and 4 mg/kg/week in the 4 week study. Most effects were fully or partially reversed after recovery.

GIT toxicity was probably the main cause of mortalities in dogs at high doses (16 mg/kg/week or ≥ 21 mg/kg every 3 weeks). Histological lesions included mucosal atrophy, congestion and haemorrhage and epithelial necrosis/regeneration throughout the intestinal tract. The dogs also showed decreased appetite and activity, decreased body weight gain, and soft dark faeces. The GIT lesions were not completely reversed after a 6-week recovery. There was no clear evidence of GIT toxicity in rats.

Bone marrow suppression, described as bone marrow hypocellularity, was seen in rats and dogs. Anaemia, leukopenia, neutropenia, and lymphopenia were evident in rats, which also had reticulocytosis (indicating increased regeneration of erythrocytes as a result of anaemia). Increased extramedullary haematopoiesis in spleen and/or liver, which was still evident after recovery, were observed in both species.

Lymphoid atrophy/necrosis of thymus, spleen, lymph nodes and Peyer's patch was observed mainly in dogs treated with MM-398. Thymus atrophy was reported in rats receiving weekly doses of MM-398 for 4 weeks.

Reproductive organs were affected in rats and dogs. Seminiferous tubule degeneration/necrosis, atrophy and mineralisation of testes, and/or aspermia of epididymides were noted in a single rat at 190 mg/kg and dogs at 36 mg/kg in the 18 week studies, atrophy of prostate, seminal vesicle and testes in rats at 260 mg/kg in the 4 week study. Reduced follicles in ovaries and uterine transmural atrophy and endometrial inflammation were observed in dogs at ≥ 21 mg/kg in the 18-week study.

Liver toxicity was apparent in rats at 190 mg/kg (no effect at 75 mg/kg), characterised by hepatocellular necrosis and increased plasma total bilirubin. There was no increase in plasma aminotransferases.

Other findings included renal interstitial inflammation in rats at ≥ 75 mg/kg/3 weeks, and hypertrophy of renal medulla in rats at 260 mg/kg/week. Adrenal neutrophil infiltration and cortical vacuolation/haemorrhage, pancreas acinar atrophy and salivary gland acinar atrophy were observed only in dogs that either died or sacrificed after a non-tolerated, high dose of 36 mg/kg in the 18 week study.

Accumulation of foamy histiocytes/macrophages was evident in multiple organs (lymph nodes, spleen, adrenal, ovaries, uterus, heart, lungs and liver) in rats and dogs. In rats, this finding was mainly observed in the liposome placebo and high dose MM-398 groups in the 18-week and 4-week studies (190 and 260 mg/kg, respectively). Low incidences in a small number of organs (kidney, lymph node and spleen) were also reported in the 4 week rat study at lower doses (65 and 130 mg/kg/week). In dogs, the lesions were seen at all dose levels of MM-398 and in the liposome placebo group. The lesions were reversed in some tissues but were still present in most tissues of both species after recovery. The intracellular foamy material was most likely liposomes taken up by the mononuclear phagocyte system (MPS). While no other abnormalities were observed in the liposome placebo groups, the effect of liposome accumulation on functions of macrophages and other MPS cells (for example, antigen presentation, pathogen killing) was not specifically studied.

Genotoxicity

No specific genotoxicity studies were submitted for MM-398. The genotoxicity potential of irinotecan and SN-38 has been studied previously. Irinotecan and SN-38 caused chromosomal damage to cultured Chinese hamster cells and irinotecan gave positive results in the mouse micronucleus test. The genotoxicity of encapsulated irinotecan, i.e. MM-398, is not expected to be different from the free drug.

Carcinogenicity

No carcinogenicity studies were submitted for MM-398, which is acceptable. A previous study with irinotecan showed a dose related increase in the incidence of mammary gland adenocarcinoma and acinar proliferation in female rats after 13 weeks of dosing followed by observation for 91 weeks (Camptosar PI).

Reproductive toxicity

No specific reproductive toxicity studies were performed, which is acceptable. Adverse effects on male and female reproductive organs were observed in repeat dose toxicity studies in rats and dogs, similar to study findings for un-encapsulated irinotecan. Embryofoetal toxicity was demonstrated in rats and rabbits dosed with un-encapsulated irinotecan (Camptosar PI).

Local tolerance

While no specific local tolerance studies were conducted, reddening and/or swelling, oedema, or turgor of the injection site were noted at MM-398 doses ≥ 21 mg/kg in repeat dose toxicity studies in rats and dogs. Similar reactions were also noted for the reference CPT-11. An in vitro assay showed that MM-398 was not haemolytic at concentrations up to 500 $\mu\text{g/mL}$

Immunotoxicity and phototoxicity

No immunotoxicity or phototoxicity studies were provided by the sponsor. This is acceptable.

Excipients

Three excipients in Onivyde are new or to be administered by a new route for pharmaceutical products in Australia. Sucrostate potassium (sucrose octasulfate, SOS) is a novel excipient. Distearoylphosphatidylcholine has been approved for use in an inhalation product, but not in any IV product. The buffer, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), is also new by IV administration.

Distearoylphosphatidylcholine (DSPC)

DSPC is the major component of the liposome bilayer, comprising 74.4% by weight percentage and 59.8% by molar percentage. The concentration in the finished product is 6.81 mg/mL. In all toxicity studies, animals in the vehicle control group received the liposome placebo (without irinotecan), while those in the treatment groups were given the liposome formulation containing irinotecan. Liposome doses in the repeat dose toxicity studies are compared with the clinical dose in the table below (Table 4). The Quality evaluator advised that the liposome formulation had minimal changes over the development stages of the drug product.

Table 4: Relative exposure to liposomes in repeat-dose toxicity studies

Study	Irinotecan dose (mg/kg)	Liposome dose		Exposure ratio*
		($\mu\text{mol/kg}$)	($\mu\text{mol/m}^2$)	
Rat [4 weeks, weekly dosing]	0	447	2682	33.5
	65	112	672	8.4
	130	224	1344	16.8
	260	447	2682	33.5
Rat [18 weeks, dosed every 3 weeks]	0	340.5	2043	8.5
	30	51	306	1.9
	75	126	756	4.7
	190	329	1974	12.3
Dog [4 weeks, weekly dosing]	0	26	520	6.5
	4	6.8	136	1.7
	8	13.6	272	3.4
	16	27.2	544	6.8
Dog [18 weeks, dosed every 3 weeks]	0	60	1200	5.0
	9	15	300	1.3
	15	25	500	2.1
	21	35	700	2.9
	36 [^]	60	1200	5.0

* Animal exposure ($\mu\text{mol/m}^2$)/human exposure ($160 \mu\text{mol/m}^2$, based on the irinotecan/liposome ratio of 500 mg irinotecan/mmol phospholipids in MM-398 and clinical dose of irinotecan at 80 mg/m² every 2 weeks). For the 4-week studies with weekly dosing, the animal exposure was multiplied by 2, and for the 18-week toxicity studies with dosing every 3 weeks, the animal exposure was multiplied by a factor of 2/3. [^]36 mg/kg High Dose (HD) contains same phospholipid concentration as the vehicle-only group.

As discussed above, in the repeat dose toxicity studies accumulation of foamy histiocytes/macrophages observed in multiple organs (lymph nodes, spleen, adrenals, ovaries, uterus, heart, lungs and liver) was associated with the liposomes. The findings were still present in some organs after a recovery period of 2 or 6 weeks. No other abnormalities were observed in the liposome placebo groups.

Sucrosfate potassium

The sponsor provided a safety review of SOS in the submission. SOS is a trapping agent for irinotecan. It was stated that SOS (and triethylamine, TEA) was first encapsulated into the liposome before loading with irinotecan, and the encapsulated TEA and SOS were largely replaced by irinotecan, leaving only low levels in the final drug product. The finished product contains 2.02 mg/mL SOS. The safety of SOS was assessed in the toxicity studies, where the vehicle control group received the liposome placebo containing SOS. All findings in the liposome placebo group appear to be related to phospholipids of the liposome formulation. According to the SOS safety review, rats and dogs of the vehicle control group in the 4 week toxicity studies received up to 57.9 and 1.6 mg/kg/week (equivalent to 347 and 32 mg/m²/week), respectively, compared to the exposure of 32.3 mg/m² every 2 weeks in patients based on the proposed clinical irinotecan dose of 80 mg/m² and the concentration of irinotecan (5 mg/mL) and SOS (2.02 mg/mL) in the finished product. Animals in the 18 week repeat dose toxicity studies most likely received SOS as well, but the SOS doses in these studies are unknown. The genotoxicity and reproductive toxicity potential of SOS is expected to be low.

HEPES is used as a buffering agent since pH of the formulation is critical to controlling the degradation of DSPC to LysoPC by drug substance catalysed hydrolytic degradation. HEPES is added to the formulation at the drug loading step of the manufacturing process. The final concentration in the drug product is 4.05 mg/mL. In the response to pre-submission questions, the sponsor claimed that HEPES was present in the placebo formulation, and thus the safety was assessed in the toxicity studies. However, according to the manufacturing process, HEPES does not appear to be added to the liposome

formulation before drug loading. In response to questions, the sponsor confirmed that HEPES buffer was used for the drug containing liposomes and placebo material at Step 3 (formulation with HEPES buffer) resulting in identical concentrations of HEPES in the two preparations.

The safety of sucrosfate potassium, DSPC and HEPES has been adequately assessed by the toxicity studies provided in the submission. There are no toxicological objections to the use of these excipients in the drug product.

Paediatric use

No specific studies in juvenile animals were submitted in relation to MM-398. Onivyde is not indicated in paediatric patients.

Nonclinical summary and conclusions

Summary

- Nonclinical studies compared the efficacy, pharmacokinetics and toxicity of MM-398 with the un-encapsulated irinotecan (referred to as CPT-11). All pivotal safety-related studies were GLP compliant.
- *In vitro* and *in vivo* pharmacology studies showed that MM-398 is more efficacious than CPT-11 in inhibiting xenograft tumour growth including pancreas cancer. Uptake of MM-398 by and conversion to the active metabolite, SN-38 in tumour cells were demonstrated. While it is proposed that MM-398 be administered in combination with 5-fluorouracil (5-FU) and leucovorin, this combination was not tested. In a colon cancer xenograft model, combination of 5-FU and MM-398 yielded significantly better inhibition of tumour growth than either MM-398 or 5-FU alone.
- Safety pharmacology studies assessed effects on the cardiovascular and respiratory systems; no adverse effects were noted. No CNS safety pharmacology studies were conducted. Low brain distribution was detected in rats dosed with MM-398. In repeat dose toxicity studies, signs of CNS effects were noted in CPT-11 administered rats, but not in MM-398-treated rats or dogs.
- Compared with CPT-11, MM-398 showed a reduced clearance and volume of distribution and prolonged elimination half-life. Exposures (based on plasma AUC) in animals after repeated dosing with MM-398 were 600-1040/~135 fold (total irinotecan, rats/dogs) and 40-80/2-4 fold (SN-38, rats/dogs) higher than exposures for CPT-11 at the same dose. In plasma, encapsulated irinotecan accounted for ~80% of total irinotecan over 168 h in dogs, suggesting good stability of the liposome capsules and slow release of irinotecan from liposomes. As a result of liposome uptake by mononuclear cells, drug levels in tumour and other tissues, particularly in tissues of the mononuclear phagocytic system were significantly higher for MM-398 than CPT-11. Faecal excretion was the major route of excretion, similar to that for un-encapsulated irinotecan.
- MM-398 demonstrated a high acute toxicity in dogs, moderate acute toxicity in mice and low order of acute toxicity in rats.
- Repeat dose toxicity studies were conducted in rats and dogs by weekly or every 3 weeks dosing, differing from the proposed clinical dosing schedule of every 2 weeks. The animal/human exposure ratios (based on AUC) in the rat studies were high (≥ 20 for both irinotecan and SN-38) but low in dogs (< 10 for irinotecan and < 0.5 for SN-38). The toxicity of MM-398 was consistent with that of un-encapsulated irinotecan, but it was more toxic, associated with high tissue and plasma levels of irinotecan and SN-38,

than un-encapsulated irinotecan. Main toxicity findings were GIT effects (dogs only), bone marrow suppression, lymphoid atrophy/necrosis, and reproductive organ toxicity in both species. Accumulation of foamy histiocytes/macrophages (uptake of liposomes by mononuclear phagocytic cells) was evident in multiple organs of rats and dogs dosed with the liposome placebo or MM-398.

- No genotoxicity, carcinogenicity and reproductive studies were conducted with MM-398.
- No significant local tolerance issues were identified in the repeat dose toxicity studies or in an *in vitro* haemolysis assay.

Conclusions and recommendation

- Tumour inhibitory activity of MM-398 was demonstrated *in vitro* and in animal cancer models including pancreatic cancer. MM-398 is more efficacious than un-encapsulated irinotecan, associated with increased uptake and retention of liposomes and higher concentration of irinotecan and SN-38 in tumour cells.
- The toxicity profile of MM-398 was consistent with that of un-encapsulated irinotecan, but it was more toxic, associated with higher tissue and plasma levels of irinotecan and SN-38, than un-encapsulated irinotecan at equivalent doses.
- The toxicity of MM-398 in combination of 5-FU and leucovorin was not investigated in animal studies.

IV. Clinical findings

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

Introduction

Clinical rationale

Adenocarcinoma of the pancreas is a malignant tumour arising from epithelium lining the pancreatic ducts.¹³ According to Cancer Australia, it was projected that 3030 new cases of pancreatic cancer would be diagnosed in Australia in 2015, with 2710 deaths.¹⁴ Incidence increases with increasing age, peaking during the seventh and eighth decades of life and is approximately equal in the sexes.¹⁵

Early stage disease is usually clinically silent. With more advanced disease typical symptoms and signs include abdominal pain, nausea, asthenia, anorexia, weight loss, hyperglycaemia and obstructive jaundice. Less common manifestations include pancreatitis, venous thrombosis, gastric outlet obstruction, gastrointestinal bleeding, panniculitis and depression.¹⁶

Progression of the disease is associated with local invasion of tissues surrounding the pancreas, spread to regional lymph nodes and distant metastases (usually to the liver, peritoneum and lung). The current staging system for pancreatic adenocarcinoma is

¹³ Hidalgo M. Pancreatic cancer. *N Engl J Med*. 362: 1605-1617 (2010).

¹⁴ Cancer Australia. Pancreatic cancer statistics. Accessed 13 January 2016.

¹⁵ National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology – Pancreatic Adenocarcinoma. Version 2.2015. Accessed 11 January 2016.

¹⁶ Vincent A, et al. Pancreatic cancer. *Lancet* 378: 607-620 (2011).

summarised. Patients who present with early stage disease can be treated surgically. However, most patients present with late stage disease. The prognosis for patients diagnosed with pancreatic cancer is poor with a 5 year survival rate of only 5%.¹⁷ For subjects with metastatic disease typical median overall survival is the range of 6-11 months. Adverse prognostic factors in pancreatic cancer include lymph node metastases, high tumour grade, large tumour size, elevated levels of the serum biomarker CA 19-9 and positive resection margins following surgery.¹⁸

The mainstay of treatment for metastatic disease is chemotherapy. Available chemotherapy regimens include the following.

First line therapy

- The FOLFIRONOX regimen. This regimen combines oxaliplatin, irinotecan and 5-fluorouracil/leucovorin. In a randomised controlled trial,¹⁹ this regimen was shown to produce a significant overall survival benefit when compared to the then standard therapy of gemcitabine monotherapy (median overall survival 11.1 versus 6.8 months). In Australia, neither oxaliplatin nor irinotecan is registered for the treatment of pancreatic cancer.
- Nanoparticle albumin-bound paclitaxel (Nab-paclitaxel) combined with gemcitabine. In a randomised controlled trial,²⁰ this combination was also shown to produce a significant overall survival benefit when compared to gemcitabine monotherapy (median overall survival 8.5 versus 6.7 months). The combination is registered for the first-line treatment of pancreatic cancer in Australia.
- Erlotinib combined with gemcitabine. In another randomised controlled trial,²¹ this combination demonstrated a significant survival advantage compared to gemcitabine monotherapy (median overall survival 6.2 versus 5.9 months). This combination is also registered in Australia.
- Gemcitabine monotherapy. In a randomised controlled trial published in 1997,²² this regimen was shown to produce a significant overall survival benefit when compared to the then standard therapy of 5-fluorouracil monotherapy (median overall survival 5.7 versus 4.4 months). Gemcitabine monotherapy is approved for the treatment of pancreatic cancer in Australia.

There are two recently published clinical practice guidelines on the management of pancreatic cancer. These were produced by the NCCN²³ and the ESMO.²⁴ Both guidelines recommend FOLFIRONOX or Nab-paclitaxel/gemcitabine as the preferred regimens for first line treatment of patients with good performance status. Gemcitabine monotherapy is recommended for subjects with poor performance status.

¹⁷ Ducreux M, et al. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 26 Suppl 5: v56-68 (2015).

¹⁸ Hidalgo M. Pancreatic cancer. *N Engl J Med*. 362: 1605-1617 (2010).

¹⁹ Conroy T, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 364: 1817-1825 (2011).

²⁰ Von Hoff DD, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 369: 1691-1703 (2013).

²¹ Moore MJ, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. 25: 1960-1966 (2007).

²² Burris HA, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol*. 15: 2403-2413 (1997).

²³ National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology – Pancreatic Adenocarcinoma. Version 2.2015. Accessed 11 January 2016.

²⁴ Ducreux M, et al. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 26 Suppl 5: v56-68 (2015).

Second line therapy

There is currently no standard of care for second-line treatment. A randomised controlled trial (CONKO-003) published in 2014²⁵ compared the combination of oxaliplatin and 5-fluorouracil/leucovorin (OFF regimen) with 5-FU/LV alone in subjects who had disease progression after gemcitabine monotherapy. The OFF regimen was associated with a significant improvement in overall survival (median overall survival 5.9 versus 3.3 months). However, another trial, the PANCREOX study,²⁶ compared a similar regimen of oxaliplatin and 5-FU/LV (the mFOLFOX6 regimen) with 5-FU/LV alone and found a detrimental effect on overall survival (median overall survival 6.1 versus 9.9 months).

The NCCN guideline recommends the use of fluoropyrimidine based chemotherapy for subjects who have received prior gemcitabine based chemotherapy, and gemcitabine based chemotherapy for subjects who have received prior fluoropyrimidine based treatment. The ESMO guidelines do not make any specific recommendations for second line therapy but suggest that Onivyde may become the best option in the future. Neither of these guidelines specifically recommends the OFF regimen for second line therapy. In Australia, the “eviQ” site of the Cancer Institute of NSW provides a protocol for the OFF regimen for subjects who have failed gemcitabine.²⁷ However, it is not clear whether the results of the PANCREOX trial have been considered.

In Australia, 5-FU and mitomycin are grandfathered drugs that have a broad indication for pancreatic cancer that would not exclude use in the second line setting.

The rationale for the development of Onivyde was therefore to address an unmet clinical need for second line (or later) therapy in subjects who have already failed gemcitabine based chemotherapy.

According to the sponsor, the liposomal formulation of irinotecan was designed to combine the following characteristics:

- Prolong circulation in plasma and in tumour through the protection provided by the liposomal encapsulation;
- Increase delivery in tumours to take advantage of the compromised vasculature of tumours; and
- Increase conversion of irinotecan to SN-38 in tumours.

Liposomal encapsulation of cytotoxic agents is not a novel approach. Liposomal doxorubicin has been marketed in Australia for many years.

Guidance

The following EMA guidelines, which have been adopted by TGA, are considered relevant to the current submission:

- Guideline on the evaluation of anticancer medicinal products;²⁸
- Points to consider on application with 1. Meta-analyses; 2. One pivotal study.²⁹

²⁵ Oettle H, et al. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. *J Clin Oncol.* 32: 2423-2429 (2014).

²⁶ Gill S, et al. PANCREOX: A randomized phase 3 study of 5FU/LV with or without oxaliplatin for second-line advanced pancreatic cancer in patients who have received gemcitabine-based chemotherapy. *ASCO Meeting Abstracts* 32: 4022 (2014).

²⁷ Cancer Institute of NSW. EviQ – Protocols – Medical Oncology – Upper Gastrointestinal - Pancreas Metastatic FOLFOX6 (Modified) (Fluorouracil Leucovorin Oxaliplatin). Accessed 12 January 2016.

²⁸ European Medicines Agency, “Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95/Rev.4)”, 13 December 2012.

Contents of the clinical dossier

The submission contained the following clinical information:

- 4 Phase I dose escalation studies designed to examine maximum tolerated dose, dose limiting toxicity and pharmacokinetics (PEP0201, PEP0202, PEP0203 and PIST-CRC);
- 1 other Phase I study which generated pharmacokinetic data (MM-398-01-01-02);
- 1 population PK and exposure-response analysis;
- 1 pivotal efficacy/safety study (MM-398-07-03-01);
- 2 supportive Phase II studies using Onivyde as monotherapy (PEP0206 and PEP0208);
- Literature references.

Paediatric data

The submission did not include paediatric data. As metastatic pancreatic cancer is a disease of adults, the absence of paediatric data is acceptable.

Good clinical practice

The reports for the clinical studies in the submission included assurances that they were conducted in accordance with the ethical principles of GCP as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

Pharmacokinetics

Studies providing pharmacokinetic data

Summaries of the pharmacokinetic studies are presented. Table 5 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 5: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in oncology subjects	General PK - Single dose	PEP0201	*
		PIST-CRC-01	*
		PEP0203	*
		MM-398-01-01-02	*
		PEP0206	
		MM-398-07-03-01 (NAPOLI-1)	
Population PK analyses	Oncology subjects	-	*

* Indicates a primary aim of the study.

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

Evaluator's conclusions on pharmacokinetics

Overall the submitted studies are considered adequate for defining the pharmacokinetics of irinotecan and SN-38 after administration of Onivyde.

²⁹ European Medicines Agency, "Points to consider on application with 1. Meta-analyses; 2. One pivotal study (CPMP/EWP/2330/99)", 31 May 2001.

Compared with conventional irinotecan, Onivyde administration results in a prolonged irinotecan half-life with reduced clearance and volume of distribution. AUC and C_{max} values for irinotecan are increased. AUC values for the active metabolite SN-38 are also increased but C_{max} values are decreased. The clinical data do not provide any evidence that concentrations of irinotecan or SN-38 are increased in tumour tissue compared to conventional irinotecan.

Although the PK comparisons with conventional irinotecan are of interest, they are of limited clinical relevance, as conventional irinotecan is not used as a single agent in the treatment of pancreatic cancer.

Pharmacodynamics

There were no clinical pharmacodynamic studies in the submission.

Dosage selection for the pivotal studies

In the pivotal study two dosage regimens of Onivyde were tested:

- Monotherapy using a dose of 120 mg/m² every 21 days; and
- Combination with 5FU/LV using 80 mg/m² every 14 days.

120 mg/m² every 21 days was determined to be the maximum tolerated dose (MTD) for monotherapy in Study PEP0201. This dose had also been used in a Phase II study (PEP0208) in subjects with pancreatic cancer.

The dose of 80 mg/m² every 14 days in combination with 5-FU/LV was based on the findings of an investigator initiated Phase II study in subjects with colorectal cancer (the PEPCOL study). The safety data from this study apparently indicated that the toxicity of this combination was similar to that of Onivyde monotherapy.

Efficacy

Studies providing efficacy data

Pivotal efficacy study

The pivotal efficacy study was MM-398-07-03-1 (NAPOLI-1).

This study was a randomised open label, Phase III trial with three parallel groups.

The primary objective of the study was to compare overall survival following treatment with Onivyde, with or without 5-FU/LV, versus 5-FU/LV, in patients with metastatic pancreatic cancer that had progressed on gemcitabine based therapy.

Secondary objectives were to:

- Compare the following between the experimental and control arms: Progression-free survival (PFS); Time to treatment failure (TTF); Objective Response Rate (ORR); Tumour marker response of CA 19-9; Clinical Benefit Response (CBR) rate; and Patient-reported outcomes (PROs) using the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life core questionnaire (EORTC-QLQC30).
- Compare the safety and AE profile between the treatment arms;
- Determine the pharmacokinetic properties of Onivyde, as a single agent and in combination with 5-FU and LV, in this population.

The study was conducted at 76 sites in 15 countries (Argentina, Australia, Brazil, Canada, Czech Republic, France, Germany, Hungary, Italy, South Africa, South Korea, Spain, Taiwan, UK and US).

The trial commenced in January 2012. The date of data cut-off for inclusion in the study report was 14 February 2014. The study report itself was dated 13 March 2015. The study has been published.³⁰

Other efficacy studies

Study PEP0208

Study PEP0208 was a single arm, open label, Phase II trial of Onivyde monotherapy in subjects with metastatic pancreatic cancer. It was conducted between 2009 and 2012 in three centres in Taiwan and the US. The primary objective of the study was to assess the 3 month survival rate.

The study enrolled subjects with metastatic adenocarcinoma of the exocrine pancreas who had documented disease progression after gemcitabine based therapy. Subjects were required to have a KPS \geq 70.

Study PEP0201

This was the first-in-man study of Onivyde. The product was administered as monotherapy. Two of the 11 subjects had pancreatic cancer.

Study PEP0203

This was a Phase I, open dose escalation study of Onivyde in combination with 5-FU and LV in subjects with advanced solid tumours.

Evaluator's conclusions on efficacy

The pivotal study in the submission was well designed and executed. The design generally complied with the requirements of the EMA guideline on anticancer agents.³¹

Treatment with the combination of Onivyde + 5-FU/LV resulted in a statistically significant improvement in overall survival compared with 5-FU/LV alone. Median survival was improved by approximately 2 months. Given that the median survival with 5-FU/LV alone was only 4.2 months, an additional 2 months is considered clinically significant.

The finding of an overall survival benefit was supported by improvements in secondary endpoints such as PFS and TTF. There was also a small improvement in objective response rate and in the rate of response based on the biomarker CA19-9. The Onivyde + 5-FU/LV combination did not produce significant improvements in symptoms (as assessed by the CBR rate) or quality of life, compared to 5-FU/LV alone.

The submission to register Onivyde is based on a single pivotal study and the TGA has adopted an EMA guideline that deals with this situation.³² This guideline sets out certain 'prerequisites' that must be met for approval of such a submission. In the opinion of this reviewer, the design and results of the pivotal study allow the conclusion that these prerequisites have been met.

³⁰ Wang-Gillam A, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. *Lancet* 387: 545-557 (2016).

³¹ European Medicines Agency, "Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95/Rev.4)", 13 December 2012.

³² European Medicines Agency, "Points to consider on application with 1. Meta-analyses; 2. One pivotal study; (CPMP/EWP/2330/99)", 31 May 2001.

The Phase II monotherapy study in pancreatic cancer (PEP0208) provided some supportive evidence for efficacy in that a response rate of 7.5% was observed.

There are currently no established treatments for patients with metastatic pancreatic cancer who have failed gemcitabine based therapy. Given the demonstrated survival benefit and lack of alternative treatments, the evidence to support the efficacy of Onivyde in combination with 5-FU/LV is considered acceptable.

Safety

Studies providing safety data

The submission did not include an analysis of pooled safety data. Hence, safety data from each study are reviewed separately. The following studies provided evaluable safety data:

Pivotal efficacy study

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

- General AEs. Information on AEs was collected at each study visit through open-ended questioning. AEs were graded (grades 1-5) according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.0. They were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.1.
- A number of AEs of special importance (AESI) were identified by the sponsor.
- Vital signs were recorded at most study visits. Physical examinations were performed regular intervals.
- Laboratory tests were performed at most study visits. Parameters tested were:
 - § Complete blood count (CBC): white blood count (WBC) and differential, haemoglobin, haematocrit and platelet count;
 - § Serum chemistry: electrolytes (sodium, potassium, chloride and bicarbonate), BUN, serum creatinine, glucose, direct and total bilirubin, AST, ALT, alkaline phosphatase, LDH, uric acid, total protein, albumin, calcium, magnesium, and phosphate
- ECGs were performed at screening and at the end of the study.

Phase II studies

There were two Phase II studies:

- Study PEP0208, which was a single arm study of Onivyde as monotherapy in subjects with pancreatic cancer who had failed gemcitabine treatment.
- Study PEP0206, which compared Onivyde monotherapy with conventional irinotecan as monotherapy and docetaxel as monotherapy in subjects with gastric cancer. Safety data from this study are of interest as they enable a comparison of the toxicities of Onivyde and conventional irinotecan.

The safety data collected in these studies were comparable to those collected in the pivotal study.

Phase I studies

There were five Phase I studies in the submission. Safety data from these studies are reviewed separately.

Patient exposure

A total of 634 subjects were treated in the studies. Of these, 412 received Onivyde either as monotherapy or in combination with other chemotherapy agents.

Safety issues with the potential for major regulatory impact

Liver toxicity

The current PI for conventional irinotecan solution states that liver enzyme abnormalities have been reported with the drug, but usually in patients with known hepatic metastases. It also states that increases in AST and ALT in the absence of progressive liver metastasis have been reported rarely.³³

The submission did not provide a discussion of any patients that met 'Hy's law' criteria for liver toxicity. However, in the pivotal study, approximately 70% of subjects had hepatic metastases at baseline. The incidence of grade 3/4 abnormalities of ALT was increased in the combination arm compared to the comparator arm. However, abnormalities of other LFTs were not notably increased. There were 2 reported cases of hepatic failure in the 5-FU/LV control arm and none in the two Onivyde arms.

Comment: Irinotecan does not appear to have been associated with severe irreversible drug-induced liver injury (DILI). The submitted data do not suggest this is a risk for Onivyde.

Haematological toxicity

Haematological toxicity is a known adverse reaction associated with irinotecan. In the pivotal study, Onivyde was associated with a significantly increased risk of grade 3/4 neutropaenia and leukopaenia. There were two cases of pancytopenia reported in the Onivyde monotherapy arm.

Serious skin reactions

According to the current PI for conventional irinotecan solution, alopecia is a common adverse effect. Rashes have also been reported but these did not result in discontinuation of treatment.

In the pivotal study in this submission, the incidence of dermatological adverse events was 28.2% in the combination arm and 29.1% in the 5-FU/LV comparator arm. There were no serious dermatological reactions reported.

In Study PEP0202, in which Onivyde was administered in combination with cisplatin, there was 1 case of Stevens-Johnson syndrome that was assessed as being unrelated to Onivyde.

Cardiovascular safety

The current PI for conventional irinotecan solution lists vasodilation (due to irinotecan's anti-cholinesterase activity) and thromboembolic events as potential cardiovascular toxicities.

Combination treatment was associated with an increased incidence of hypotension (6.0% versus 1.5%) compared to 5-FU/LV. Otherwise there was no suggestion of increased cardiovascular toxicity due to Onivyde. There was no increase in the incidence of serious cardiovascular AEs in the combination arm.

³³ PI for irinotecan hydrochloride (CAMPTOSAR).

Unwanted immunological events

The current PI for conventional irinotecan solution indicates that hypersensitivity reactions including severe anaphylactic and anaphylactoid reactions have been observed with the drug.

In the pivotal study, infusion reactions (defined using a standardised MedDRA query for hypersensitivity type events) and acute infusion reactions (those occurring on the day of treatment) occurred with similar frequency in the two treatment arms. There were no reports of anaphylaxis in any of the submitted studies.

Post marketing data

There were no post marketing data included in the submission.

Evaluator's conclusions on safety

The addition of Onivyde to 5-FU/LV for the treatment of metastatic pancreatic cancer results in an increase in toxicity. The incidence of drug related AEs was notably increased (91.5% versus 69.4%), as was the incidence of grade ≥ 3 AEs (76.9% versus 56.0%). However, the incidence of serious AEs was only slightly increased (47.9% versus 44.8%). There was no apparent increase in the incidence of AEs leading to death, and in any event the drug has beneficial effect on overall survival.

The pattern of adverse events associated with the increased toxicity was consistent with the known safety profile of irinotecan: mainly GIT toxicity (diarrhoea, vomiting, nausea), myelotoxicity (mainly neutropaenia) and infections. No novel toxicities associated with Onivyde treatment were identified.

The toxicities appeared to be manageable with dose delays and dose reductions, as evidenced by the proportion of patients having to discontinue treatment due to AEs being only slightly higher in the combination arm than in the 5-FU/LV arm (11.1% versus 7.5%).

Metastatic pancreatic cancer is a life threatening condition and subjects who have already failed treatment with gemcitabine have a very poor prognosis. Although the proposed combination of Onivyde with 5-FU/LV has significant toxicity, it is considered acceptable given the proposed patient population.

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

The benefits of Onivyde in the proposed usage are:

- An increase in OS with a prolongation of median survival of approximately 2 months.

The drug was not associated with any improvement in symptoms or quality of life.

First round assessment of risks

The risks of Onivyde in the proposed usage are:

- A toxicity profile similar to that seen with conventional irinotecan solution (mainly gastrointestinal toxicity and myelotoxicity).

First round assessment of benefit-risk balance

The benefit-risk balance of Onivyde, given the proposed usage, is favourable. This assessment takes into consideration the very poor prognosis of the proposed patient group and the lack of established alternative therapies.

First round recommendation regarding authorisation

It is recommended that the application for registration be approved.

Clinical questions

There are no clinical questions.

Second round evaluation

Details of sponsor's responses to clinical questions and evaluator's subsequent comments are contained in Attachment 2.

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

No new clinical information was submitted. Accordingly, the benefits of Onivyde are unchanged from those identified in the first round evaluation.

Second round assessment of risks

No new clinical information was submitted. Accordingly, the risks of Onivyde are unchanged from those identified in the first round evaluation.

Second round assessment of benefit-risk balance

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

Second round recommendation regarding authorisation

It is recommended that the application for registration be approved.

V. Pharmacovigilance findings**Risk management plan**

The sponsor submitted an EU RMP Version 1.0 (dated 21 April 2015, DLP 17 April 2015) with Australian Specific Annex (ASA) Version 1.0 (dated 2 November 2015), which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 6.

Table 6: Ongoing safety concerns.

Summary – Ongoing Safety Concerns	
Important identified risks	Diarrhoea
	Leukopaenia/Neutropaenia
	Anaemia
	Cholinergic reactions
	Acute infusion reactions
	Thromboembolic events
Important potential risks	Drug interactions
	Embryotoxicity/teratogenicity
	Hypersensitivity reactions
	Medication error related to drug/dose confusion with irinotecan
	Interstitial lung disease
Missing information	Use in patients with hepatic impairment
	Use in patients with renal impairment
	Use in the paediatric population
	Use in breastfeeding women

RMP reviewer comment

The following Precautions and reported Adverse Effects are advised in the PI:

- ‘No studies to assess the mutagenic potential have been performed with Onivyde.’
- ‘Carcinogenicity studies with Onivyde were not conducted.’
- ‘There are no clinical data on fertility.’
- Thrombocytopenia, in addition to leukopaenia, neutropaenia and anaemia, is also listed as a ‘Very Common’ adverse effect with use of Onivyde.
- There are a number of metabolic and nutrition disorders identified as ‘Very Common’ or ‘Common’ with use of Onivyde, including hypokalaemia, hypomagnesemia, dehydration, hypophosphatemia, hyponatremia, hypoglycaemia.
- Acute kidney injury is listed as a ‘Common’ adverse effect with use of Onivyde.

However, notwithstanding to the evaluation of the non-clinical and clinical aspects of the SS, the summary of safety concerns is considered appropriate in the context of this application. The missing data on mutagenicity, carcinogenicity and fertility may reasonably be excluded from the Summary given the nature of the medical condition being treated and chemotherapy regimen. The electrolyte disturbances and kidney effects may reasonably be associated with the condition, the chemotherapy regimen as a whole, and/or the known risk of potentially severe diarrhoea.

The sponsor should provide comment on why thrombocytopenia is not included in the Summary.

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance³⁴ for safety concerns.

³⁴ Routine pharmacovigilance practices involve the following: (a) All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner; (b) Reporting to regulatory authorities; (c) Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling; (d) Submission of Periodic Safety Update Reports (PSURs); and (e) Meeting other local regulatory agency requirements.

RMP reviewer comment

There is no definite objection to the pharmacovigilance plan proposed by the sponsor in the context of this application, i.e. routine pharmacovigilance only.

Risk minimisation activities

The sponsor proposes routine risk minimisation activities³⁵ for all safety concerns.

RMP reviewer comment

The sponsor's general conclusions with regards to proposed risk minimisation activities are considered acceptable in the context of this submission. However, to enhance safe use of the liposomal irinotecan formulation, it is recommended that the sponsor considers additional risk minimisation in the form of healthcare professional education.

Reconciliation of issues outlined in the RMP report

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

Recommendation #1 in RMP evaluation report

Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated Section 31 request and/or the nonclinical and clinical evaluation reports, respectively. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

Sponsor response

The comment is noted. We will ensure any safety considerations raised by the nonclinical and clinical evaluators that concern the RMP will be addressed appropriately in an updated RMP.

Evaluator's comment

The sponsor's response to the comment is acceptable.

Recommendation #2 in RMP evaluation report

Thrombocytopaenia, in addition to leukopaenia, neutropaenia and anaemia, is listed as a 'Very Common' adverse effect with use of Onivyde. The sponsor should provide comment on why thrombocytopaenia is not included in the Summary of Safety Concerns.

Sponsor response

Leukopenia/neutropenia and anemia are considered important identified risks for Onivyde. Thrombocytopenia is an identified risk, however, it is not considered an important identified risk and therefore excluded in the summary of safety concerns in the RMP. Due to the lower incidence of grade 3 or higher thrombocytopenia compared with neutropenia, leukopenia, and anemia in the pivotal Phase III NAPOLI-1 study, thrombocytopenia was not considered an important identified risk and therefore, not reflected in the summary of safety concerns within the Onivyde risk management plan.

Evaluator's comment

The incidence of Grade 3 or higher (<50,000/microL) thrombocytopenia reported in the NAPOLI -1 study was 2.6% in combination with 5-FU/LV. The incidence of any grade

³⁵ Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the PI or by careful use of labelling and packaging.

thrombocytopenia in NAPOLI-1 was 12.8% in combination with 5-FU/LV. In the context of the illness and population treated and the standard of care routine in oncology treatment facilities the RMP evaluator finds that sponsor's conclusion that thrombocytopenia is an identified, but not an important identified risk is acceptable. The identified risk of 'Thrombocytopenia' is adequately described and mitigated by routine risk minimisation content in the PI.

Recommendation #3 in RMP evaluation report

The sponsor should propose an additional risk minimisation activity to enhance safe use of the liposomal irinotecan formulation considering the history of use of the non-liposomal formulation. For example, the sponsor could provide a Dear Healthcare Professional (DHCP) letter to oncologists with a table comparing formulations with respect to indication, presentation and dosage.

Sponsor response

An educational DHCP letter on the proper use of Onivyde and preventing/minimizing medication errors will be provided to medical professionals as an additional risk minimization activity to enhance safe use of Onivyde. In addition, Baxalta has improved the prominence of the current caution: "Do not use interchangeably with other formulations of irinotecan" on the carton label by placement in a green banner. An updated mock-up is provided.

Evaluator's comment

The DHCP should be listed as an additional risk minimisation activity in the ASA and provided for review before distribution.

Summary of recommendations

Outstanding issues

Issues in relation to the RMP

The sponsor must submit the updated EU-RMP at the outcome of the European Marketing Authorisation Application (MAA) with a revised ASA containing the agreed changes.

The DHCP letter should be submitted with the ASA for review.

Comments on the safety specification of the RMP

Clinical evaluation report

- Round 1: "The Safety Specification in the draft RMP is satisfactory."
- Round 2: "No changes to the RMP were recommended in the first round clinical evaluation. A revised RMP was not submitted."

Nonclinical evaluation report

The nonclinical evaluator recommended changes to the nonclinical part of the safety specification of the EU-RMP v1.0 in the nonclinical evaluation report and 'Nonclinical evaluator's comments on sponsor's response to NGER'. It is noted that the nonclinical evaluator has not recommended any change to the Summary of Safety Concerns.

As the European MAA is ongoing, the sponsor proposes to submit, when it becomes available, an approved EU-RMP for review to TGA before the requested changes (agreed in the sponsor's response) are proposed to the EMA by the sponsor. The outstanding issues remaining with the EU-RMP safety specification should be resolved to the satisfaction of the nonclinical evaluator and Delegate before the RMP can be deemed acceptable. The changes do not affect the consideration of the safety profile in the context of the RMP evaluation.

Key changes to the updated RMP

No revision to the RMP was submitted.

The changes agreed to by the sponsor below will be submitted in a revised ASA annexed to the approved EU-RMP (if it is approved), when available.

Table 6: Summary of agreed changes to be included in a revised EU-RMP and ASA.

Safety specification	<ul style="list-style-type: none"> Revised content in the EU-RMP 'Part II: SII Non clinical part of the safety specification' to the satisfaction of the non-clinical evaluator
Pharmacovigilance activities	<ul style="list-style-type: none"> n/a
Risk minimisation activities	<ul style="list-style-type: none"> Dear Healthcare Professional Letter: additional risk minimisation to mitigate the risk of medication error related to drug/dose confusion with irinotecan.
ASA	<ul style="list-style-type: none"> Non-SI Units in all documents converted to SI units. DHCP letter listed as an additional risk minimisation measure

Suggested wording for conditions of registration**RMP**

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

A suggested wording for the RMP condition of registration cannot be provided until a revised risk management plan consisting of the most recent approved EU-RMP and ASA containing the agreed changes is submitted for evaluation.

VI. Overall conclusion and risk/benefit assessment

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

Quality

The ACPM summary states:

There are no major objections to the chemistry and quality aspects of the proposed product. A few minor issues remain outstanding, including ensuring all the proposed manufacturers have appropriate GMP clearances and tightening the limits for LysoPC in the bulk drug product.

This is expanded upon in the Clearance Note as follows:

A couple of issues remain unresolved: The expiry limit for LysoPC in the bulk drug product should be tightened to 1.0 mg/mL, in line with the release limit for LysoPC in the drug product. In addition, GMP clearance for several of the proposed manufacturing sites remains outstanding.

Nonclinical

There were no nonclinical objections to registration.

Intracellular foamy material accumulated in rat and dog histiocytes/macrophages in multiple organs, most likely liposomes taken up by the mononuclear phagocyte system. No other abnormalities were seen in the liposome placebo group, but:

the effect of liposome accumulation on functions of macrophages and other MPS cells (for example, antigen presentation, pathogen killing) was not specifically studied.

The nonclinical evaluation report noted three excipients in Onivyde that are new or to be administered by a new route, but no objections were raised.

Unresolved issues impacting on the nonclinical safety specification in the RMP are:

- whether a NOAEL was observed in an 18 week rat study (the sponsor arguing that NOAEL was at 30 mg/kg, the TGA toxicologist considering that no NOAEL was established); and
- whether elevated bilirubin in a rat study is toxicologically relevant

The final form of the nonclinical part of the safety specification will need to be resolved before the RMP can be considered acceptable. However, a decision about registration is not necessarily contingent on this.

Clinical

The clinical evaluator recommends approval of the proposed use. A second round report was not commissioned; the sponsor's Section 31 responses have been taken into account in this overview.

The clinical evaluator described the scope of the sponsor's dossier as:

- 4 Phase I dose escalation studies designed to examine maximum tolerated dose, dose limiting toxicity and pharmacokinetics:
 - PEP0201
 - PEP0202
 - PEP0203
 - PIST-CRC-01
- 1 other Phase I study which generated pharmacokinetic data (MM-398-01-01-02);
- 1 population PK and exposure response analysis;
- 1 pivotal efficacy/safety study (MM-398-07-03-01);
- 2 supportive Phase II studies using Onivyde as monotherapy (PEP0206 and PEP0208);
- Literature references.

Pharmacology

General comments about PK

Pharmacology aspects are well described.

Because irinotecan is converted into the active metabolite SN-38, the measurement of SN-38 becomes an important goal of PK studies. Parameters generally measured were total irinotecan, SN-38 and SN-38G (the inactive metabolite of SN-38).

There were no PK data gathered after multiple doses of Onivyde.

Study PEP0206 allowed direct comparison of Onivyde (PEP02) and conventional irinotecan. The following conclusions were drawn (amongst others):

- Following PEP02 administration, systemic exposure to **total irinotecan** was significantly greater than after conventional irinotecan (dose normalised C_{max} 35.7-fold, dose normalised $AUC_{0-\infty}$ 173-fold)
- Systemic exposure to active metabolite **SN-38** was also increased (dose-normalised $AUC_{0-\infty}$ 4.99-fold). However, C_{max} for SN-38 was *decreased* with PEP02 (dose-normalised C_{max} ratio = 0.498). Similar results were observed for SN-38 glucuronide
- Mean AUC values for total irinotecan and SN-38 were significantly greater in Caucasian subjects compared to Asian subjects (2-3 fold) after PEP02. This difference was less marked after irinotecan.

Study MM-398-01-01-02 considered tumour levels of total irinotecan and SN-38:

- In plasma, mean peak concentration of total irinotecan was approximately 12500 fold higher than that of SN-38.
- In tumour, concentration of total irinotecan was approximately 247 fold higher than that of SN-38.

This study did not allow direct comparison with conventional irinotecan. The clinical evaluator notes:

There were no clinical data to establish that tumour concentrations of SN-38 were higher after Onivyde administration than after administration of conventional irinotecan hydrochloride.

Population PK model

It is the source of recommendations about use in: *UGT1A1*28* homozygosity; hepatic impairment; renal impairment; advanced age; and patients given concomitant 5-FU.

Deficiencies in PK characterisation

There was no PK characterisation of multiple dosing.

Drug-drug interactions were not well characterised. For context, the Caelyx PI states no formal drug interactions have been studied with Caelyx. The interactions section of the Onivyde PI leverages off knowledge about conventional irinotecan.

EviQ notes that patients with Gilbert's syndrome should have their dose of irinotecan reduced. There is no clear dosing strategy; based on the area under the concentration-time curve of SN-38, Innocenti et al. recommend 20% dose reduction.³⁶

Efficacy

Study MM-398-07-03-1 (NAPOLI-1)

This was an open label study where patients with metastatic pancreatic cancer that had progressed on gemcitabine based therapy (in a locally advanced or metastatic setting) were randomised into 3 arms – Onivyde; 5-FU/LV; or both Onivyde+5-FU/LV. The primary objective was to compare OS across the 3 arms. The data cut-off was 14 February 2014. Dose finding for the study is discussed.

Inclusion and exclusion criteria

The clinical evaluator observes that:

³⁶ Innocenti F, Ratain MJ. Pharmacogenetics of irinotecan: clinical perspectives on the utility of genotyping. *Pharmacogenomics* 7: 1211-1221 (2006).

Enrolment in the study was limited to subjects with good performance status (Karnofsky score ≥ 70). In practice, many patients with progressive disease after first line chemotherapy are too sick to receive further treatment.

There is some suggestion that in a real world setting, patients who receive gemcitabine-based first line therapy for metastatic disease are those too frail to receive Folfirinox. However, enrolment in the study was limited to those with good performance status, so it is unclear how representative of 'frail subjects' the cohort within NAPOLI-1 is. As the clinical evaluator observes, subjects with metastatic pancreatic cancer who are too frail may not receive a second line agent at all. This emphasises the need for the PI to clearly describe the patient population under study.

It is noted that inadequate hepatic function was a common reason for screening failure (64/577 screened); inadequate performance (KPS <70) was also a reason (29/577).

Randomisation and interventions

Randomisation was stratified by baseline albumin, Karnofsky performance score, and ethnicity. The three study treatments were:

- Arm A: Onivyde 120 mg/m² IV over 90 minutes Day 1 of a 21 day cycle;
- Arm B: 5-FU 2000 mg/m² IV over 24 hours Days 1, 8, 15, 22 of a 42 day cycle;
LV 200 mg/m² IV over 30 minutes Days 1, 8, 15, 22 of a 42 day cycle;
- Arm C: Onivyde 80 mg/m² IV over 90 minutes Day 1 of a 14 day cycle;
5-FU 2400 mg/m² IV over 46 hours Day 1 of a 14 day cycle;
LV 400 mg/m² IV over 30 minutes Day 1 of a 14 day cycle.

There were 151 patients randomised to Onivyde (Arm A), n = 149 to 5-FU/LV (Arm B) and 117 to Onivyde + 5-FU/LV (Arm C; this arm was added in Protocol Version 2.1, after some patients had already been enrolled; this also explains the presence of four arms in many data presentations, for example, Arm B subjects enrolled after Arm C was initiated were used in the comparison with Arm C).

The clinical evaluator considered that the **choice of comparator** (5-FU + LV) was acceptable, in the context of there being no standard therapy, for the following reasons:

- According to NCCN guidelines, fluoropyrimidine based regimens are appropriate in this situation;
- 5-FU/LV has been used as the comparator arm in other recent phase 3 studies of 2nd line chemotherapy in pancreatic cancer;
- ...trials of more intensive fluoropyrimidine-based regimens (for example, 5-FU with oxaliplatin) have given conflicting results
- In Australia, 5-FU has a broad grandfathered indication for the treatment of pancreatic cancer that does not exclude use as a second-line agent.

Regarding the first dot point (endorsement of fluoropyrimidine based therapies), this might be taken to mean regimens such as mFOLFOX, rather than FU/LV alone, but this is not explicit in the NCCN guideline. ESMO does not strongly endorse Folfox, noting the conflicting trial results discussed by the evaluator. EviQ endorses modified Folfox. Overall, the control regimen is considered relevant, though perhaps not the preferred choice for every patient in this setting.

Demographic and baseline characteristics

Mean age was 63 years. 12% had only one prior line of treatment for advanced/metastatic disease; 56% had two prior lines; and 32% had 3+ prior lines. 5-10% of subjects were *UGT1A1*28* homozygotes across arms.

One inclusion criterion in NAPOLI-1 was a requirement for a Karnofsky performance score of 70+. The clinical evaluator suggested that patients with a KPS of <70 should not be prescribed Onivyde. The sponsor responded:

While patients enrolled in the NAPOLI-1 study were required to have a performance status of KPS \geq 70, the physician should not be prevented from treating patients with lower performance status as this is not the case for non-liposomal irinotecan. To address the evaluator's concern, we have therefore agreed to include a precaution that patients in the clinical trials had a performance status of KPS \geq 70.

This approach is acceptable.

Efficacy assessment methodology

The primary endpoint was OS; other endpoints such as PFS and ORR were secondary. The study was open label; tumour responses were assessed unblinded by investigators, which allows for bias.

The study made an attempt to gauge clinical benefit using a composite endpoint based on pain, performance status and weight, and this approach is considered relevant for a study in advanced pancreatic cancer, though the endpoint's construction is fairly complex, and only certain patients were included in the CBR evaluable population.

Efficacy outcomes

Overall survival

The hazard ratio for OS was 0.67 (95% CI 0.49-0.92); median OS was 4.2 months in the control arm, 6.1 months in the Onivyde+5-FU/LV arm. Probability of survival at 9 months increased from 24% to 35%. In subgroup analysis, those previously treated with irinotecan did not have a survival benefit, though the number of such patients was small.

Secondary endpoints

Onivyde+5-FU/LV also resulted in PFS benefit relative to 5-FU/LV. Of note, there was no statistically significant difference in clinical benefit rate. There was no improvement in quality of life, with emphasis on change from baseline at 6 then 12 weeks. The sponsor also argued that despite addition of Onivyde, there was no appreciable deterioration in symptoms or quality of life.

Onivyde monotherapy arm did not confer any advantage over 5-FU/LV.

Other studies

Study PEP0208 was a single arm study in 40 patients with metastatic adenocarcinoma of the pancreas after gemcitabine based therapy. Only Onivyde monotherapy was studied. Median OS was 5.1 months. ORR was 7.5%.

Neither PEP0201 nor PEP0203 provided strong evidence supporting the proposed use.

Safety

Exposure

There were 412 Onivyde treated patients, but only 123 of these received Onivyde 80 mg/m² + 5-FU / LV (117/123 patients were from NAPOLI-1). In NAPOLI-1, median duration of Onivyde exposure was 8.7 weeks (range 2-65 weeks), the mean duration higher at 15 weeks.

Study PEP0206 was of tangential interest. It enrolled patients with gastric cancer but it allowed comparison with conventional irinotecan.

In Study PEP0202 in cervical cancer, Onivyde 80 mg/m² Q3W + cisplatin was dangerous (2/3 patients died after AEs) and the study was terminated.

Safety issues

Deaths

In the pivotal study, AEs leading to death were reported in 10.2% (Onivyde) versus 1.7% (Onivyde+5-FU/LV) versus 7.5% (5-FU/LV). Treatment related deaths were reported in 2.7% versus 0.9% versus 0%, respectively. The one patient in the Onivyde 5-FU/LV arm died of neutropenic sepsis after one dose. In the NAPOLI-1 Onivyde monotherapy arm and in other supportive studies, there were four other treatment related deaths from infection in subjects given Onivyde. In Phase I studies, several further such deaths occurred.

Serious AEs

In the pivotal study, serious AEs were seen in 48% of the Onivyde+5-FU/LV arm and 45% of the 5-FU/LV arm (and 61% of the Onivyde monotherapy arm). The pattern of events was consistent with common AEs, discussed below. The increase in Onivyde dose in the monotherapy arm translated to an increase in toxicity relative to Onivyde + 5-FU/LV, for example, diarrhoea and febrile neutropenia.

Discontinuations

In the pivotal study, AEs leading to treatment discontinuation were seen in 11.1% in the Onivyde+5-FU/LV arm (versus 7.5% in the 5-FU/LV arm).

Common AEs

The clinical evaluator writes of the pivotal study:

Compared to the 5-FU/LV arm the combination arm was associated with notable increases the incidence of the following toxicities:

- § *Gastrointestinal toxicity: diarrhoea, nausea, vomiting, decreased appetite and stomatitis/mucosal inflammation;*
- § *Myelotoxicity: anaemia, leukopaenia, neutropaenia and decreased platelet count;*
- § *Constitutional symptoms: fatigue, pyrexia and decreased weight.*

The incidence of diarrhoea was even higher in the Onivyde monotherapy arm, where a higher dose of Onivyde was used.

The higher incidence of diarrhoea with higher dose Onivyde was reflected in many parameters, including the relatively insensitive change in median QOL symptom scale score.

Neutropenia was prominent with Onivyde+5-FU/LV, for example, severe neutropenia was reported in 14.5% (along with febrile neutropenia in 1.7%). Grade 3+ sepsis was also reported more often than in the 5-FU / LV arm (3.4% vs 0.7%). Grade 3+ neutropenia was more prominent in Asians (24%) than Whites (12%).

In Study PEP0206, the incidence of common AEs was comparable for Onivyde and conventional irinotecan.

Interestingly, significant weight loss (>5%) occurred more frequently with Onivyde+5-FU/LV than with 5-FU/LV (53% versus 25%), perhaps related to the increased levels of GI disturbance with addition of Onivyde. (Onivyde monotherapy, with its higher dose, had more diarrhoea and also more significant weight loss than Onivyde in combination.) It is noted that weight gain was a 'secondary' measure of clinical benefit in NAPOLI-1.

Risk management plan

The RMP evaluator considered that all issues identified in the initial RMP Evaluation had been addressed adequately. There was a recommendation that the sponsor provide revised versions of the EU-RMP and ASA prior to registration.

A recommendation was made that the nonclinical part of the RMP's safety specification be revised to the satisfaction of the nonclinical evaluator.

It was noted that a DHCP letter is planned, to mitigate the risk of medication error related to drug/dose confusion with (conventional) irinotecan.

Recommended conditions of registration

The RMP evaluator noted:

A suggested wording for the RMP condition of registration cannot be provided until a revised risk management plan consisting of the most recent approved EU-RMP and ASA containing the agreed changes is submitted for evaluation.

Risk-benefit analysis

Delegate's considerations

There was one pivotal study supporting the proposed use. NAPOLI-1 was an open label study that compared Onivyde+5-FU/LV against 5-FU/LV (there was also an Onivyde monotherapy arm). The Delegate's preliminary view is that 5-FU/LV is a relevant comparator, but the ACPM's advice on this issue is requested. With the caveat that choice of 5-FU/LV as a comparator is subject to ACPM's advice, the addition of Onivyde appeared to provide a survival advantage, with an impressive hazard ratio (0.67) although the absolute gain in survival as measured by comparison of median survival was only ~2 months. Quality of life was assessed and there was no evidence that addition of Onivyde lowered quality of life for patients, although it did increase the burden of drug-related adverse events. The proposed use appears to have a positive benefit-risk balance, but the ACPM's advice on this issue is requested.

Summary of issues

Onivyde is a liposomal formulation of irinotecan, proposed for use in metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and folinic acid (leucovorin) in adult patients who have been previously treated with gemcitabine-based therapy.

Onivyde is not being proposed as a substitute for irinotecan in any established protocol for second or later line metastatic pancreatic cancer. That is, the sponsor is proposing a new regimen. It resembles Folfiri (irinotecan [180 mg/m²], leucovorin, fluorouracil, all on day 1 Q2wk) – but according to EviQ, Folfiri is not used in metastatic pancreatic cancer.

There are no manufacturing, quality control or nonclinical issues with the submission.

There was one pivotal study supporting the proposed use. NAPOLI-1 was an open label study that compared Onivyde+5-FU/LV against 5-FU/LV (there was also an Onivyde monotherapy arm). The Delegate's preliminary view is that 5-FU/LV is a relevant comparator, but the ACPM's advice on this issue is requested. With the caveat that choice of 5-FU/LV as a comparator is subject to ACPM's advice, the addition of Onivyde appeared to provide a survival advantage, with an impressive hazard ratio (0.67) although the absolute gain in survival as measured by comparison of median survival was only ~2 months. Quality of life was assessed and there was no evidence that addition of Onivyde

lowered quality of life for patients, although it did increase the burden of drug related adverse events. The proposed use appears to have a positive benefit-risk balance, but the ACPM's advice on this issue is requested.

Proposed action

The Delegate's preliminary view is that there is a positive benefit-risk balance for Onivyde in its proposed use. This view is subject to possible change, based on the advice of ACPM.

Request for ACPM advice

- Is the choice of comparator (5-FU/LV) in NAPOLI-1 relevant?
- The proposed use is:

Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and folinic acid (leucovorin) in adult patients who have been previously treated with gemcitabine-based therapy.

Is the benefit-risk balance of Onivyde in combination with 5-FU + LV positive for the proposed use?

- Should there be specific advice to check for *UGT1A1*28* allele homozygosity prior to starting treatment, given that dosing is different in this group? Currently, the PI only implies this should be done, via recommending consideration of a reduced starting dose in this group.
- Is a boxed warning required about neutropenia, diarrhoea, use as monotherapy, use as a substitute for conventional irinotecan, or any other aspect?

Questions for sponsor

- For Onivyde, to what extent do different sites contribute to conversion of irinotecan to SN-38? For example, liver; tumour; other sites. Does this differ appreciably compared to Camptosar? Does this have any implications for clinical use, for example, in patients with organ dysfunction, such as hepatic dysfunction?
- Should there be a recommendation in the PI regarding dose adjustment in Gilbert's Syndrome? It is noted that there is already acknowledgement that such patients may be at greater risk of myelosuppression when receiving therapy with Onivyde.

Response from sponsor

Introduction

The sponsor would firstly like to acknowledge the Delegate's view that Onivyde has a positive benefit-risk balance for the indication proposed:

Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and folinic acid (leucovorin) in adult patients who have been previously treated with gemcitabine-based therapy.

Product background

Onivyde, also known as MM-398, is a novel liposomal formulation of irinotecan (as sucrosfate salt). The major benefit of Onivyde is that as a liposomal formulation of irinotecan, it prolongs the blood circulation time, thereby achieving a longer half-life,

higher AUC and slower clearance resulting in a longer tumour exposure of SN-38 compared to non-liposomal irinotecan.³⁷

Disease background

In Australia, a total of 2,825 new cases of pancreatic cancer were diagnosed in 2012, which is estimated to increase to 3,123 in 2016. The mortality from pancreatic cancer is also increasing – there were 2,558 deaths in 2012 and estimated deaths is 2,823 in 2016 – taking pancreatic cancer from 6th most common cause of death from cancer in 2012 to 5th most common in 2016.³⁸ The 5 year survival is also low (7%). Poor survival despite advancement of first line gemcitabine based therapies in the last two decades³⁹ indicates an imperative need for second line treatment options for patients with metastatic pancreatic cancer.

The Delegate has requested advice from the ACPM on a number of issues and we would like to provide our comments.

Delegate's advice sought from ACPM

1. Is the choice of comparator (5-FU/LV) in NAPOLI-1 relevant?

The Delegate's preliminary view is that 5-FU/LV is a relevant comparator used in the pivotal Phase III study, NAPOLI-1;⁴⁰ however, advice from the ACPM is sought. The sponsor would like to provide some context to the decision of comparator.

In the absence of standard of care, approved agents were considered preferable as a control arm for the NAPOLI-1 study. 5-FU has been approved as first-line therapy for the treatment of pancreatic cancer for many years, and was one of the mainstays of therapy until the approval of gemcitabine in 1995 (5-FU was the control in the initial approval study for gemcitabine).⁴¹ The addition of LV to 5-FU is now standard, as there is evidence that it may decrease toxicity and increase efficacy of 5-FU.⁴² In addition, the original study design of NAPOLI-1 was to determine the effect of Onivyde as a single agent; therefore, a single agent needed be chosen as control, so as to reasonably assess the impact of Onivyde (5-FU/LV is considered a single agent, as the 5-FU is the basis of the anticancer activity).

Non-liposomal irinotecan was considered in the control arm regimen, but it is not approved for the treatment of pancreatic cancer, nor is it standard of care. There are no adequate well controlled studies of single agent irinotecan in this population. Although irinotecan is now often used as part of the FOLFIRINOX regimen (oxaliplatin, irinotecan, 5-FU/LV) in the front line setting of advanced pancreatic cancer therapy;⁴³ combinations of

³⁷ Drummond DC et al. Development of a highly active nanoliposomal irinotecan using a novel intraliposomal stabilization strategy. *Cancer Res.* 66: 3271-3277 (2006); Kalra AV, et al. Preclinical activity of nanoliposomal irinotecan is governed by tumor deposition and intratumor prodrug conversion. *Cancer Res.* 74: 7003-7013 (2014).

³⁸ Australian Institute of Health and Welfare 2017. Australian Cancer Incidence and Mortality (ACIM) books: Pancreatic cancer. Canberra: AIHW.

³⁹ Burris HA III, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J. Clin. Oncol.* 15: 2403-2413 (1997); Moore MJ, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J. Clin. Oncol.* 25: 1960-1966 (2007); Von Hoff DD, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med.* 369: 1691-1703 (2013).

⁴⁰ Wang-Gillam A, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. *Lancet* 387: 545-557 (2016).

⁴¹ Burris HA III, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J. Clin. Oncol.* 15: 2403-2413 (1997).

⁴² Moran RG. Leucovorin enhancement of the effects of the fluoropyrimidines on thymidylate synthase. *Cancer* 63: 1008-1012 (1989).

⁴³ Conroy T, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med.* 364: 1817-1825 (2011).

irinotecan are not routinely used for treatment of pancreatic cancer worldwide and limited to patients with good performance status (ECOG 0-1) and bilirubin level <1.5x ULN.⁴⁴ Since the NAPOLI-1 study was a global registration study in post-gemcitabine metastatic pancreatic cancer setting, the control arm needed to be accepted by most countries.

In support of the choice of 5-FU/LV as the comparator in the NAPOLI-1 study, the historical precedent of CONKO-001 study⁴⁵ and two contemporary ongoing studies in advanced pancreatic cancer patients with prior gemcitabine based chemotherapy that used 5-FU/LV as the control arm were also taken into consideration. The CONKO-003 study (evaluating the combination of 5-FU/LV with oxaliplatin versus 5-FU/LV) suggested that its control arm (same 5-FU/LV regimen used in NAPOLI-1) was effective in locally advanced or metastatic pancreatic cancer patients previously treated with gemcitabine.⁴⁶ The PANCREOX study also evaluated the efficacy of 5-FU/LV with or without oxaliplatin in a similar patient setting.⁴⁷ The use of 5-FU/LV in these three studies supports the fact that 5-FU/LV is a clinically accepted comparator in this indication.

The appropriateness of the pivotal Phase III NAPOLI-1 study design, including the choice of control group, was discussed with the FDA and EMA, and both the agencies considered the choice of 5-FU/LV as a comparator to be acceptable from a regulatory point of view.

2. Is the benefit-risk balance of Onivyde in combination with 5-FU + LV positive for the proposed use?

The Delegate's preliminary view is that Onivyde in combination with 5-FU/LV has a positive benefit-risk balance for the proposed indication; however, advice from the ACPM is sought. The sponsor would like to discuss the benefit-risk balance of Onivyde in terms of observed efficacy, safety, and quality of life.

A significant benefit has been demonstrated based on a large international multi-centre, randomised, open label, three arm, pivotal study (NAPOLI-1), which demonstrated that treatment with Onivyde+5-FU/LV significantly increased median OS (primary endpoint) by 1.9 months relative to the control 5-FU/LV treatment (6.1 versus 4.2 months, $p = 0.0122$; HR 0.67, 95% CI for HR 0.49-0.92). This observed survival benefit is important for patients with metastatic pancreatic cancer as, although some improvements have been shown for first line treatment, there are no approved or satisfactory methods of treatment in the second line setting. The efficacy analysis was further validated by the FDA and EU CHMP who concluded that an improved survival of median 2 months, or a 50% prolongation of median survival, is considered clinically and regulatory meaningful in patients with relapsed/refractory pancreatic cancer.

The safety profile of Onivyde has been characterized in the NAPOLI-1 study. The most common TEAEs with Onivyde observed in the NAPOLI-1 study are consistent with the known safety profile of non-liposomal irinotecan; that is, gastrointestinal adverse events

⁴⁴ Ducreux M, et al. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 26 Suppl 5: v56-68 (2015).

⁴⁵ Pelzer U, et al. Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase III-study from the German CONKO-study group. *Eur J Cancer* 47: 1676-1681 (2011).

⁴⁶ Oettle H, et al. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. *J Clin Oncol.* 32: 2423-2429 (2014).

⁴⁷ Gill S, et al. PANCREOX: A randomized phase 3 study of 5FU/LV with or without oxaliplatin for second-line advanced pancreatic cancer (APC) in patients (pts) who have received gemcitabine (GEM)-based chemotherapy (CT). ASCO 2014 Annual Meeting. Abstract number 4022; Gill S, et al. PANCREOX: A Randomized Phase III Study of 5-Fluorouracil/Leucovorin With or Without Oxaliplatin for Second-Line Advanced Pancreatic Cancer in Patients Who Have Received Gemcitabine-Based Chemotherapy. *J Clin Oncol.* 34: 3914-3920 (2016).

(AEs) and myelosuppression (for example, neutropenia). The safety results from the NAPOLI-1 study showed that most TEAEs observed in the Onivyde+5-FU/LV combination arm were manageable with supportive therapy, dose delays and/or reduction or both, as recommended in the PI for Onivyde.

The results of the health related QoL assessment (as measured by the EORTC-QLQ-C30 instrument) showed that the baseline median Global Health Status, Functional Scale and Symptoms Scale scores were similar among treatment arms in the NAPOLI-1 study. Patients with metastatic pancreatic cancer typically demonstrate deterioration in the symptoms and QoL due to the severity and natural progression of the disease. There was no appreciable deterioration of symptoms and QoL with Onivyde+5-FU/LV combination treatment compared to control arm despite the underlying disease burden and one additional cytotoxic agent (Onivyde) in the treatment regimen, and QoL was maintained. This view is also observed by the Delegate:

...there was no evidence that addition of Onivyde [to 5-FU/LV] lowered quality of life.

The survival benefit of Onivyde observed in the NAPOLI-1 study was not only accepted by the health care agencies, but also recommended by the scientific communities for their clinical practice guidelines. Onivyde in combination of 5-FU/LV is now included in the NCCN guidelines as a Category 1 second line treatment option for metastatic pancreatic cancer. In addition, the current ESMO clinical practice guidelines for pancreatic cancer state:⁴⁸

Second line therapy of pancreatic cancer has to be considered in terms of risk benefit for the patient. If the general status remains correct, considering the conflicting results on the use of oxaliplatin, MM-398 [Onivyde] when available in all countries may be the best option for second line treatment of these patients [II, B].

In summary, in the absence of approved methods of treatment for patients with metastatic pancreatic cancer who progressed on gemcitabine based therapy, a median OS improvement of 1.9 months, corresponding to approximately 50% prolongation of median survival with no appreciable deterioration of QoL, is considered clinically meaningful. In view of the survival benefit of Onivyde in combination with 5-FU/LV and the identified risks of irinotecan, which are manageable, the benefit-risk balance of Onivyde in patients with metastatic pancreatic cancer who failed previous gemcitabine-based therapy is positive.

3. Should there be specific advice to check for UGT1A1*28 allele homozygosity prior to starting treatment, given that dosing is different in this group?

The proposed PI for Onivyde includes the precaution:

*Consider a reduced starting dose of Onivyde of 50 mg/m² for patients known to be homozygous for the UGT1A1*28 allele. Patients without drug related toxicities during the first 2 weeks of therapy may have their dose of Onivyde increased to 70 mg/m² based on individual patient tolerance [see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY].*

Although testing all patients for UGT1A1*28 could have merit, it is not practical as such testing is not routinely performed in Australia,⁴⁹ with the major reasons listed as “lack of peer recognition of the tests” and “lack of clinical authority to use for interpretation”. Therefore, the sponsor recommends that where UGT1A1*28 status is unknown, all patients be initiated with the standard starting dose and any dose modification decisions

⁴⁸ Ducreux M, et al. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 26 Suppl 5: v56-68 (2015).

⁴⁹ Wu AHB, et al. Pharmacogenomic Testing in Current Clinical Practice. 2011. Humana Press; pp. 66-68.

made based on guidance provided in the PI if myelosuppression related adverse events are observed.

The sponsor would like to mention that the Camptosar (non-liposomal irinotecan) PI does not include any advice to check for *UGT1A1**28 allele homozygosity prior to starting treatment with non-liposomal irinotecan, and recommends that such patients should be administered the normally indicated irinotecan starting dose and monitored for haematological toxicities.

4. Is a boxed warning required about neutropenia, diarrhoea, use as monotherapy, use as a substitute for conventional irinotecan, or any other aspect?

Irinotecan has been registered in Australia since 1997; therefore, oncologists have had almost 20 years' experience with this agent, including managing the associated diarrhoea and neutropenia through appropriate dose reduction and treatment delay. The risk assessment of the clinical evaluator was that Onivyde had:

a toxicity profile similar to that seen with conventional irinotecan solution (mainly gastrointestinal toxicity and myelotoxicity).

Furthermore, the proposed PI already includes comprehensive discussion on diarrhoea and myelosuppression and their management in three sections (Precautions, Adverse Effects, and Dosage and Administration). Therefore, the sponsor believes there will be no additional benefit gained in including a boxed warning – particularly as myelosuppression and gastrointestinal effects are among the most common adverse reactions associated with antineoplastics. The delegate has made reference to the boxed warning in the US Onivyde prescribing information; however, it should be noted that the US prescribing information for non-liposomal irinotecan (Camptosar) also contains a similar boxed warning while no boxed warning appears in the Australian Camptosar PI. In addition, neither EU SPC for Onivyde or Camptosar contains such a boxed warning.

The delegate has also requested advice on the need for boxed warnings regarding use as monotherapy and substitution with conventional irinotecan. With regard to substitution, we should highlight the RMP evaluator is satisfied with the sponsor's response to issue a DHCP letter as well as improving the prominence of "Do not use interchangeably with other formulations of irinotecan" on the carton and vial label by placement in a green banner.

With regard to monotherapy, the sponsor wishes to highlight the proposed indication clearly defines the use of Onivyde:

...in combination with 5-fluorouracil and folinic acid (leucovorin)...

As previously discussed, the NAPOLI-1 study has demonstrated a clinically meaningful benefit for the combination of Onivyde +5-FU/LV over 5-FU/LV alone. Onivyde monotherapy did not show a statistically significant improvement in median OS over 5-FU/LV (4.9 versus 4.2 months, respectively; $p = 0.9416$; HR = 0.99). A boxed warning regarding Onivyde monotherapy would infer a significant safety risk; however, it should be noted that even though there was a higher incidence of AEs in the monotherapy arm, the Onivyde dose in this arm was 50% higher than in the combination arm (with treatment given Q3w versus Q2w) and therefore it is difficult to make a direct comparison of safety specifically based on whether Onivyde is used alone or in combination.

Questions to sponsor

1. For Onivyde, to what extent do different sites contribute to conversion of irinotecan to SN-38? For example, liver; tumour; other sites. Does this differ appreciably compared to Camptosar? Does this have any implications for clinical use, e.g. in patients with organ dysfunction, such as hepatic dysfunction?

Upon Onivyde (MM-398) administration, free irinotecan is converted to the active metabolite SN-38, primarily by the carboxylesterases enzymes (CES1, which is abundantly expressed in liver and monocytes/macrophages,⁵⁰ and CES2 which is commonly expressed in the tumour tissue).⁵¹ High concentrations of SN-38 are expected to be found in tumours and in the liver, the metabolite then being excreted with bile into the GI tract where high amounts are also expected to be found.

Deposition of irinotecan from the liposomes and subsequent conversion to SN-38 in both neoplastic cells and tumour associated macrophages were evaluated in a Phase I study (Study MM-398-01-01-02).⁵² Thirteen patients with refractory solid tumours received MM-398 at 80mg/m² Q2w. Levels of irinotecan and SN-38 averaged 3.73 mcg/g [0.13-12.75 mcg/g] and 14.67 ng/g [1.2-64.0 ng/g], respectively, at 72 h. SN-38 levels in tumour biopsies were 5 fold higher than in plasma at 72 h (p = 0.013), and these significantly higher SN-38 levels in tumour also suggest strong local conversion activity of liposomal irinotecan.

Several nonclinical studies have evaluated the potential for selective targeting of MM-398 to tumour tissues and organs (Study PEP02-NC-N-PK-005 in SCID mice and Study PEP02-NC-N-PK-002 in SD rats). In these studies, liposomalisation of irinotecan effectively increased the length of time irinotecan and SN-38 in the blood, resulting in increased concentrations of irinotecan and the SN-38 metabolite in healthy tissues as well as in tumour tissue. C_{max} for irinotecan was higher (160%) in tumour and slightly higher (10%) in liver of mice receiving MM-398 than irinotecan. In addition, in mice bearing human colorectal carcinoma xenograft, longer circulation of SN-38 in tumour vs plasma, longer circulation for MM-398 versus Camptosar, were observed.

Specific organ function-based eligibility criteria, precautions, and recommendations for dose modifications are described in the "Precaution" and "Dosage and Administration" sections of the PI for patients with organ dysfunction (for example, hepatic or renal impairment).

2. Should there be a recommendation in the PI regarding dose adjustment in Gilbert's Syndrome? There is already acknowledgement that such patients may be at greater risk of myelosuppression when receiving therapy with Onivyde.

The "Precaution" section of the proposed PI includes:

Patients with deficient glucuronidation of bilirubin, such as those with Gilbert's syndrome, may be at greater risk of myelosuppression when receiving therapy with Onivyde.

Instead of recommending any dose adjustment for all patients with Gilbert's syndrome, the sponsor is of the view that such patients may be initiated on the standard dose and that any dose modification decisions based on guidance provided in the PI should be left

⁵⁰ Needham LA, et al. Drug targeting to monocytes and macrophages using esterase-sensitive chemical motifs. *J. Pharmacol. Exp. Ther.* 339: 132-142 (2011).

⁵¹ Xu G, et al. Human carboxylesterase 2 is commonly expressed in tumor tissue and is correlated with activation of irinotecan. *Clin. Cancer Res.* 8: 2605-2611 (2002).

⁵² Ramanathan RK, et al. Lesion characterization with ferumoxytol MRI in patients with advanced solid tumors and correlation with treatment response to MM-398, nanoliposomal irinotecan (nal-IRI). *Eur J Cancer* 50: 87 (2014).

with the treating physician if any myelosuppression related AE is observed in such patients. This recommendation has now been added to the PI.

Other issues

Quality

The sponsor agrees to tighten the LysoPC bulk drug product stability specification from ≤ 2.0 mg/mL to ≤ 1.0 mg/mL as recommended. In addition, the bulk drug product hold time will be shortened from 24 months to 12 months.

Nonclinical/RMP

The only outstanding aspect in the RMP is the nonclinical specification. Although Baxalta agreed in principle to make modifications to the EU RMP, it should be remembered that all changes need to be approved by EMA. However, we note the Delegate's comment:

a decision on registration is not necessarily contingent on this [the nonclinical part of the safety specification].

Advisory Committee considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Onivyde concentrate for solution for infusion containing 10 mL vial containing 43 mg irinotecan anhydrous free base, which is the equivalent of 50 mg of irinotecan hydrochloride trihydrate, as a dispersion of liposomes of irinotecan (liposomal encapsulated) to have an overall positive benefit-risk profile for the proposed indication;

Onivyde is indicated in the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and folinic acid (leucovorin) in adult patients who have been previously treated with gemcitabine-based therapy.

In making this recommendation, the ACPM:

- Noted that the ITT analysis demonstrates a statistically significant increase in the overall survival of Onivyde+5-FU/LV (Q2W regimen) compared with 5-FU/LV.
- Noted that sensitivity analyses favour Onivyde+5-FU/LV overall survival across prognostic subgroups, tumour characteristics and most previous treatments.
- Noted that PP analysis demonstrates that the overall survival difference is maintained with the Onivyde+5-FU/LV combination regimen.
- Noted that the safety profile of the treatment was manageable, with the most frequent Grade ≥ 3 AEs including neutropenia, fatigue, and gastrointestinal events.

Proposed conditions of registration

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

Proposed PI/CMI amendments

ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- A boxed warning in the PI/CMI regarding the use as a substitute for conventional irinotecan.
- A recommendation in the PI about dose adjustment in Gilbert's syndrome.

Specific advice

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

- *Is the choice of comparator (5-FU/LV) in NAPOLI-1 relevant?*

ACPM agreed that the choice of comparator (5-FU/LV) in NAPOLI-1 is relevant. A current systematic review⁵³ suggests that median survival is longer with active treatment than with supportive care, but does not suggest any agreed standard second line agent.

- *The proposed use is:*

Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and folinic acid (leucovorin) in adult patients who have been previously treated with gemcitabine-based therapy.

Is the benefit-risk balance of Onivyde in combination with 5-FU/LV positive for the proposed use?

ACPM noted that there is a 1.9 months survival benefit with Onivyde+5-FU/LV over 5FU/LV (improvement of OS from 4.2 months to 6.1 months) that is clinically meaningful to oncologists and patients.

- *Should there be specific advice to check for UGT1A1*28 allele homozygosity prior to starting treatment, given that dosing is different in this group? Currently, the PI only implies this should be done, via recommending consideration of a reduced starting dose in this group.*

ACPM accepted the current wording of the PI, however recommends the adjustment to PI regarding dose adjustment in Gilbert's syndrome.

- *Is a boxed warning required about neutropenia, diarrhoea, use as monotherapy, use as a substitute for conventional irinotecan, or any other aspect?*

ACPM agreed that a boxed warning regarding the use as a substitute for conventional irinotecan is desirable.

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

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Onivyde (irinotecan [as sucrosfate]) 43 mg/10 mL (as a free base) concentrate solution for infusion indicated for:

Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and folinic acid (leucovorin) in adult patients who have been previously treated with gemcitabine-based therapy.

Specific conditions of registration applying to these goods

- The Onivyde EU-RMP, Version 1.0 (dated 21 April 2015, DLP 17 April 2015) with ASA Version 1.0 (dated 2 November 2015), along with the agreed modifications to those documents which include the provision of a DHCP letter, and any subsequent revisions that have been considered acceptable by the RMP evaluation section, will be implemented in Australia.

⁵³ Nagrial AM, et al. Second-line treatment in inoperable pancreatic adenocarcinoma: A systematic review and synthesis of all clinical trials. *Crit Rev Oncol Hematol*. 96: 483-497 (2015).

Attachment 1. Product Information

The PI approved for Onivyde at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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>