



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Docetaxel

Proprietary Product Name: Docetaxel-PF

Sponsor: Pfizer Australia Pty Ltd

May 2013

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, 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 <<http://www.tga.gov.au>>.

About AusPARs

- An Australian Public Assessment Record (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, in that it will provide 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 2013

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

I. Introduction to product submission	4
Submission details	4
Product background	4
Regulatory status	6
Product Information	7
II. Quality findings	7
Injection formulation	7
Micellar injections	9
Quality summary and conclusions	12
III. Nonclinical findings	12
Introduction	12
Toxicology	12
Nonclinical summary and conclusions	13
IV. Clinical findings	15
V. Pharmacovigilance findings	15
VI. Overall conclusion and risk/benefit assessment	15
Quality	15
Nonclinical	15
Clinical	16
Risk management plan (RMP)	16
Risk-benefit analysis	16
Outcome	27

I. Introduction to product submission

Submission details

<i>Type of Submission:</i>	New generic
<i>Decision:</i>	Withdrawn
<i>Date of Decision:</i>	18 December 2012
<i>Active ingredient:</i>	Docetaxel
<i>Product Name:</i>	Docetaxel-PF
<i>Sponsor's Name and Address:</i>	Pfizer Australia Pty Ltd 38-42 Wharf Road, West Ryde NSW 2114
<i>Dose form:</i>	Concentrated Injection
<i>Strengths:</i>	20 mg/2 mL, 80 mg/8 mL, 130 mg/13 mL, 200 mg/20 mL
<i>Container:</i>	polypropylene vial
<i>Pack sizes:</i>	1 and 5 Vial carton
<i>Approved Therapeutic use:</i>	Not applicable
<i>Route of administration:</i>	Intravenous (IV)
<i>Dosage:</i>	Same as for Taxotere ¹
<i>ARTG Number:</i>	Not applicable

Product background

Docetaxel belongs to a group of drugs called taxanes. Taxanes were originally derived from natural sources (from plants of the genus *Taxus* yews) but have since also been synthesised artificially. Taxanes are widely used as chemotherapy agents but present difficulties in formulation as medicines because they are poorly soluble in water.

This AusPAR describes the application by Pfizer Australia Pty Ltd to register Docetaxel-PF, a single vial presentation containing docetaxel (anhydrous) 10 mg/mL as a generic version of the currently registered two-vial presentation, Taxotere containing 10 mg/mL docetaxel trihydrate. Docetaxel-PF is proposed to be registered in strengths of 130 mg/13

¹ Administer intravenously (IV) over 1 hr every 3 weeks. Breast cancer (BC) locally advanced or metastatic: 60 mg/m² to 100 mg/m² single agent. BC adjuvant: 75 mg/m² administered 1 hour after doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m² every 3 weeks for 6 cycles. Non Small Cell Lung Cancer (NSCLC): after platinum therapy failure: 75 mg/m² single agent. NSCLC: chemotherapy-naïve: 75 mg/m² followed by cisplatin 75 mg/m². Refractory prostate Cancer (RPC): 75 mg/m² with 5 mg prednisone twice a day continuously. Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN): 75 mg/m² followed by cisplatin 100 mg/m² IV (day 1), followed by fluorouracil 1000 mg/m² per day as a 24-hr IV (days 1–4); for 3 cycles. For all patients:

- Premedicate with oral corticosteroids.
- Adjust dose as needed

mL and 200 mg/20 mL, in addition to the strengths of 20 mg/2 mL and 80 mg/8 mL already registered for Taxotere.

The innovator product Taxotere from Sanofi-Aventis Australia Pty Ltd has the active ingredient docetaxel (trihydrate) and is supplied as two vials: one containing docetaxel trihydrate 10 mg/mL and polysorbate 80 (circa 259 mg/mL) and the other containing ethanol (circa 95 mg/mL) in water, which are mixed prior to dilution in infusion solution. For example, after reconstitution of 2-vial presentation of Taxotere 80 mg/2 mL it forms 80 mg/8 mL.

Docetaxel-PF is a single vial presentation containing docetaxel anhydrous 10 mg/mL, polysorbate 80 (259 mg/mL), ethanol (circa 317 mg/mL), propylene glycol (374 mg/mL), disodium edetate (0.01 mg/mL) and citric acid (circa 3.5 mg/vial), which is added directly to infusion solution.

The indications and dosage and administration recommendations proposed by the sponsor for Docetaxel-PF are identical to those approved for Taxotere.

The indications proposed for Docetaxel-PF are the same as those for Taxotere; in breast cancer, non-small cell lung cancer, ovarian cancer, prostate cancer and head and neck cancer.²

There are numerous registered generic docetaxel products and numerous dose strengths.

² **Innovator Indications:**

Metastatic Breast Cancer

TAXOTERE is indicated for the treatment of patients with locally advanced or metastatic breast cancer in whom previous chemotherapy has failed. TAXOTERE in combination with capecitabine is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior anthracycline containing chemotherapy. TAXOTERE in combination with trastuzumab is indicated for the treatment of patients with metastatic breast cancer whose tumours overexpress HER2 and who previously have not received chemotherapy for metastatic disease.

Adjuvant Treatment of Breast Cancer

TAXOTERE in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with node-positive breast cancer. Doxorubicin and cyclophosphamide followed by TAXOTERE in combination with trastuzumab (AC-TH) is indicated for the adjuvant treatment of patients with operable breast cancer whose tumours overexpress HER2. TAXOTERE in combination with carboplatin and trastuzumab (TCH) is indicated for the adjuvant treatment of patients with operable breast cancer whose tumours overexpress HER2. TAXOTERE in combination with cyclophosphamide is indicated for the adjuvant treatment of operable breast cancer with a primary tumour of ≥ 1 cm and < 7 cm.

Non Small Cell Lung Cancer

TAXOTERE is indicated for the treatment of patients with locally advanced or metastatic non small cell lung cancer, including those who have failed platinum-based chemotherapy.

Ovarian Cancer

TAXOTERE is indicated for the treatment of metastatic carcinoma of the ovary after failure of first-line or subsequent chemotherapy.

Prostate Cancer

TAXOTERE is indicated for the treatment of patients with androgen independent (hormone refractory) prostate cancer.

Head and Neck Cancer

TAXOTERE, in combination with cisplatin and fluorouracil is indicated as induction treatment prior to chemoradiotherapy, for the treatment of patients with locally advanced, squamous cell carcinoma of the head and neck, who have low probability of surgical cure, require organ preservation or where the tumour is technically unresectable.

Relevant regulations and guidelines

The Therapeutic Goods Regulations 1990 provide the following definition for ‘generic medicine’:

<p>generic medicine means a medicine that, in comparison to a registered medicine:</p> <ol style="list-style-type: none"> has the same quantitative composition of therapeutically active substances, being substances of similar quality to those used in the registered medicine; and has the same pharmaceutical form; and is bioequivalent; and has the same safety and efficacy properties.

TGA guidelines

Impurities

Note for Guidance on Impurities in New Drug Products (CPMP/ICH/2738/99)

Generic medicines

Guideline on the Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98 Rev 1)
Adopted by TGA with notations (the notations are of no direct relevance here).

Australian Regulatory Guideline on Prescription Medicines

The Australian Regulatory Guidelines for Prescription Medicines (ARGPM) states in Section 4.3.1 (*‘Essentially similar medicines’*):

Definitions

The EC guidelines state that a product *is essentially similar* to another product if:

- it has the same qualitative and quantitative composition in terms of active principles/substances; and
- the same pharmaceutical form; and
- is bioequivalent

unless it is apparent in the light of scientific knowledge that it differs significantly from the original product as regards safety or efficacy.

Medicines that are *essentially similar* to an *innovator product* may be designated *generics*.

The Regulations ask for “the same” safety and efficacy properties, and this is interpreted in the ARGPM to mean that safety and efficacy properties cannot differ “significantly”.

Regulatory status

Table 1 provides a summary of the international regulatory status of Docetaxel.

Table 1. Summary of International Regulatory Status

Country	Submission Date	Approval Date	Indications
European Union (EU)	21 April 2011	5 July 2012	Approved indications are identical to those for Taxotere
United States	29 April 2011	Under evaluation	

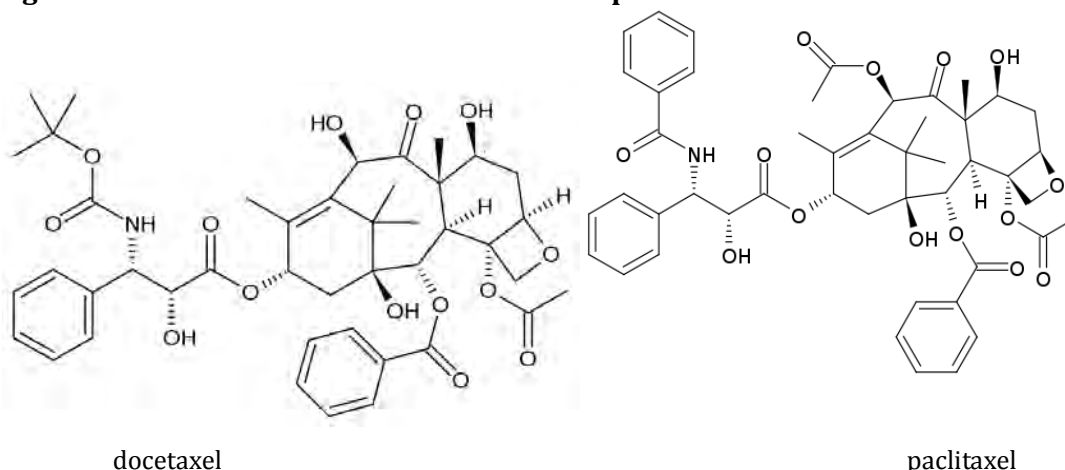
Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Docetaxel is a semi-synthetic analogue of paclitaxel; docetaxel is slightly more water soluble. Figure 1 shows the chemical structure of docetaxel and paclitaxel.

Figure 1. Chemical structure of docetaxel and paclitaxel.



There is a European Pharmacopeia (Ph.Eur.) monograph for Docetaxel Trihydrate and United States Pharmacopeia (USP) monographs for Docetaxel and for Docetaxel Injection. Control of the drug substance is considered acceptable.

The recommended dosing is complex (see Product Information), with doses of up to 100 mg/m² recommended. The proposed new 200 mg vial is larger than any currently registered. It could give a single dose for a patient with a body surface area (BSA) of 2 m². It is thus probably reasonable to not construe it as a multidose vial.

Injection formulation

Docetaxel injection products are currently registered as various 20, 80, 140 and 160 mg strengths in a confusing range of concentrations by different sponsors (20 mg powder, 20 mg/0.5 mL, 20 mg/1 mL, 20 mg/2 mL; 80 mg powder, 80 mg/2 mL, 80 mg/4 mL, 80 mg/8 mL; 140 mg/7 mL; 160 mg/8 mL and 160 mg/16 mL).

Like some other hydrophobic drugs, it is difficult to formulate intravenous docetaxel because of its very limited aqueous solubility. The innovator Taxotere concentrated

injection is formulated with polysorbate 80 ('Tween') and ethanol. That formulation was recently changed from a two-vial to a one-vial presentation, with an increase in the ethanol content.

Docetaxel is always administered after further dilution of the concentrate in either 0.9% sodium chloride solution or 5% glucose solution. This dilution causes the formation of small micelles dispersed in the injection solution (see further comments later). The infusion is administered over one hour.

Taxotere docetaxel infusion solution is supersaturated and drug crystallises from the infusion on storage with a marked temperature dependence. The solution is typically usable (that is, does not crystallise) for several hours. There are special Product Information directions to reduce the risk of crystallisation.

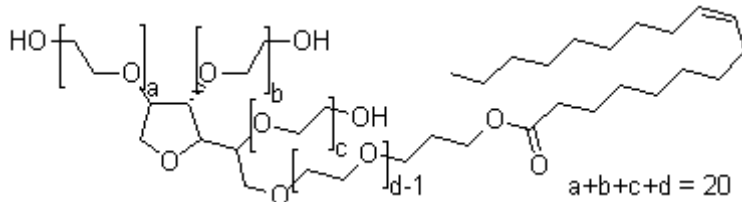
There are currently six sponsors of docetaxel injections in Australia, with Sandoz having two formulations registered.

Formulation of the injections is challenging because of solubility but also because some excipients are viscous and can lead to gelling or foaming.

The innovator (Taxotere) is only formulated with ethanol and polysorbate 80. Registered injections either copy this or use other solubilising agents, especially macrogol (polyethylene glycol). Citric acid and disodium edetate are used in some products as chelating antioxidants.

All formulations include polysorbate 80 (chemical structure shown in Figure 2) which is a sugar extensively modified by polyoxyethylene substitution and esterification. Polysorbate 80 is a non-ionic surfactant which forms micelles in water.

Figure 2. Polysorbate 80



Proposed Docetaxel-PF formulation

The formulation of the innovator and proposed Pfizer infusion solutions as administered (200 mg per 250 mL infusion bag) are compared below:

Table 2. Comparison of Taxotere and Docetaxel PF

	Taxotere [1-vial] (concentrate 80 mg/4 mL)	proposed Docetaxel PF (concentrate 80 mg/8 mL)
Docetaxel	200 mg (0.77 mg/mL)	200 mg (0.74 mg/mL)
Polysorbate 80	5.4 g (20.8 mg/mL)	5.18 g (19 mg/mL)
Ethanol	3.95 g (15.2 mg/mL)	6.44 g (58 mg/mL)
Propylene Glycol	-	7.48 g (28 mg/mL)
<i>Total Volume (approximately)</i>	<i>260 mL</i>	<i>270 mL</i>

[volume changes on dilution of ethanol ignored here]

The proposed Pfizer injection is thus formulated with a similar amount of polysorbate 80, a somewhat larger amount of ethanol (6.44 g versus 3.95 g per 200 mg dose) plus a

significant amount of propylene glycol (7.48 g per 200 mg dose). Propylene glycol is not used in the formulation of any other docetaxel injections in Australia.

As expected for a non-aqueous formulation diluted in an infusion solution, the aqueous pH of as administered is very similar to the innovator (pH 3.5). By contrast the osmolality of the Pfizer injection after dilution in either saline or 5% weight/volume (w/v) glucose is markedly higher (1300 mOsm/kg, compared to Taxotere 440 mOsm/kg).

Development

Pfizer's product development was apparently focussed on stability in use and "*a review of the literature indicated that a combination of polysorbate-80, ethanol and a glycol (such as propylene glycol) may enhance the solubility and stability of taxanes such as docetaxel.*"³ Unfortunately the Pfizer formulation does not appear to have a significantly lower risk of crystallisation in use.

The original submission provided a terse justification for the acceptability of the polysorbate-80, propylene glycol and ethanol "used as solvents", by comparing the total daily intakes with Taxotere (for polysorbate 80), Taxol (for ethanol) and phenytoin injection (for propylene glycol). Pfizer also, however, submitted a "blood compatibility" study and an animal tolerance study. These have been reviewed separately.

There are toxicological concerns with the proposed Pfizer formulation which are addressed separately.

Micellar injections

Concentrated docetaxel injections form unstable micellar injections on dilution, although this is not well explained in the innovator nor proposed generic Product Information documents. There has been some regulatory discussion of such products [for example, see *Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems (non-polymeric surfactants)*⁴]. Micellar injections are chiefly intended to allow intravenous administration; they are different from liposomal injections (such as Caelyx doxorubicin) which have markedly different pharmacokinetics.

Docetaxel thus will initially circulate *in vivo* in polysorbate micelles and then redistribute as protein bound drug.⁵ 'Polysorbate 80' is a mixture of components with different micellar effects.⁶ Pfizer uses a high purity grade which contains almost purely (>99%) oleate ester. It is likely that relevant polysorbate 80 micelles *in vivo* are rapidly cleared (within circa 2 h),⁷ perhaps due to rapid degradation by esterases.⁸ There is limited literature on the effects of added alcohols (such as ethanol or propylene glycol) on polysorbate 80 micelles.⁹

Macrogols (that is, polyethylene glycols) are used in some other formulations, always in combination with polysorbate 80. Macrogols alone will not form micelles (they do not

³ Chen H, Zhang Z, McNulty C, et al. A high-throughput combinatorial approach for the discovery of a cremophor EL-free paclitaxel formulation. *Pharm Res* 2003; 20 (8): 1302-8

⁴ <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/03/WC500124410.pdf>

For recent EU consideration see for example

<http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Docetaxel_Teva_Generics_29/WC500129345.pdf>

⁵ W. Loos, S. Baker, J. Verweij, J. Boonstra, A. Sparreboom *Clin Pharmacol Ther.* 2003 Oct;74(4):364-71.

⁶ G. Lafitte et al. *Langmuir.* 23(22):10933-9, 2007 Oct 23

⁷ L. Webster et al. *Cancer Chemotherapy & Pharmacology.* 39(6):557-60, 1997

⁸ O. van Tellingen et al. *Clin Cancer Res.* 5(10):2918-24, 1999

⁹ M. Ueda, T. Urahata, A. Katayama et al. *Colloid Polym Sci* 1980; 258(10):1202-3 and M. Rosen *Micelle formation by surfactants.* In: *Surfactants and interfacial phenomena.* 3rd ed. Hoboken, NJ: John Wiley & Sons, Inc; 2004: p. 105-77.

contain a separate hydrophobic moiety) but will change the characteristics of polysorbate micelles in the products in which they are used.

Different formulations can thus be administered *in vivo* as micelles with different characteristics, potentially affecting circulation, localisation and clearance of docetaxel.

The European *Guideline on the Investigation of Bioequivalence*¹⁰ states that generic micelle forming injection formulations could be registered without a bioavailability study ("eligible for a biowaiver") where:

- a. rapid disassembly of the micelle on dilution occurs and the drug product is not designed to control release or disposition;
- b. the method and rate of administration is the same as the currently approved product;
- c. the excipients do not affect the disposition of the drug substance.
- d. In these cases, the composition of the micelle infusion, immediately before administration, should be qualitatively and quantitatively the same as that currently approved and satisfactory data should be provided to demonstrate similar physicochemical characteristics, for example, the critical micelle concentration, the solubilisation capacity of the formulation (such as Maximum Additive Concentration), free and bound active substance and micelle size.

A bioequivalence study is required unless both products contain the same excipients in very similar quantity and it can be adequately justified that any difference in quantity does not affect the pharmacokinetics of the active substance.

In the original submission, Pfizer included some physicochemical data comparing the proposed and innovator injections. Pfizer argues (with respect to the Bioequivalence Guidance) that both Taxotere and Docetaxel-PF have same "composition of the micelle infusion, immediately before administration, (are) qualitatively and quantitatively the same as that currently approved and satisfactory data (are) provided to demonstrate similar physicochemical characteristics." This ignores the effect of ethanol and propylene glycol.

Pfizer claims that both its injection (with 5.18 g polysorbate 80, inter alia, per 80 mg drug) and the innovator Taxotere injection (5.4 g polysorbate 80) "contain essentially the same drug-to-surfactant ratio ... therefore micellar properties are expected to be similar".

A summary (only) of physicochemical analyses was provided.

Physicochemical characterisation of the micelles is thus limited to Critical Micelle Concentration (CMC) and size measurements. Micelle size is similar to Taxotere. Pfizer reports a CMC measured for Taxotere of 6.32×10^{-4} mg/mL and a clearly higher CMC for the Pfizer injection of 4.11×10^{-3} mg / mL. The difference is probably mostly due to the ethanol and propylene glycol. These CMCs are far smaller than the concentration of polysorbate in the diluted infusion solution (approximately 20 mg/mL). Alone that would suggest that the drug will be administered in stable micelles, however note that CMCs in plasma will be different, apparently significantly higher.

Similar pharmacokinetic profiles are claimed in a study of intravenous doses in dogs but the TGA reviewer notes that a pharmacokinetic study in dogs cannot be used to predict whether the two docetaxel formulations will have equivalent kinetic characteristics in humans because the dog has not been established as an equivalent model (see Nonclinical findings below).

¹⁰ <<http://www.tga.gov.au/pdf/euguide/ewp140198rev1.pdf>>

Advisory committee considerations

The application was considered at the 147th (2012/5) meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM), which recommended:

1. The PSC endorsed all the questions raised by the TGA in relation to pharmaceutical and biopharmaceutical aspects of the submission by Pfizer Australia Pty Ltd to register Docetaxel-PF concentrated injections containing 20 mg/2 mL, 80 mg/8 mL, 130 mg/13 mL and 200 mg/20 mL of docetaxel.
2. The PSC advised that all outstanding issues should be addressed to the satisfaction of the TGA.
3. The PSC advised that there should be data establishing the compatibility of the product with infusion bags and the issues raised in relation to impurity levels should be addressed.
4. In relation to the physicochemical comparison of micelles formed by the proposed products and the innovator product, the PSC advised that the data provided were inadequate given the absence of:
 - Data comparing the micelle characteristics (critical micelle concentration) in the 0.9% sodium chloride solution and in the 5% glucose solution proposed as diluents and extent of solubilisation of the docetaxel by the micelles.
 - Studies on the effects of variations in ethanol and propylene glycol levels on the micelles.
5. The PSC noted the sponsor's claim of similar total docetaxel pharmacokinetic profiles following intravenous doses of the proposed formulation (diluted in saline) and the innovator product in dogs. The PSC noted that the fate of the micelles *in vivo* had not been determined. The PSC agreed that a pharmacokinetic study in dogs cannot be used to predict whether the two docetaxel formulations will have equivalent kinetic characteristics in humans given that:
 - The dog has not been established as an equivalent model for humans
 - The study was not powered to detect differences between the formulations.
6. The PSC did not accept the sponsor's justification for not providing a clinical bioequivalence study between the proposed formulation and the innovator product.
7. In the Product Information (PI)
 - The "Description" section should be amended to include the partition coefficient of the drug substance as function of pH.
 - The "*Preparation for the Intravenous Administration*" section should be amended to include the pH or pH range of the reconstituted infusion solution. This section should also include a statement such as "Product is for single use in one patient only. Discard any residue" or words to this effect.
8. There is no requirement for this submission to be reviewed again by the PSC before it is presented for consideration by the Advisory Committee on Prescription Medicines (ACPM).

Data on compatibility of the proposed formulation with infusion bags (especially DEHP extraction from PVC) could be generated quickly. Data on solubilisation of docetaxel by the formulation, CMC data in both proposed diluents, and CMC effects of variation in the alcohol contents could also be measured quickly.

In vivo characterisation of the docetaxel micelles would require a new clinical study.

Quality summary and conclusions

Pfizer seeks to register a generic docetaxel injection with a markedly different formulation from that of the innovator. Some toxicological concerns have been raised about the proposed product.

Consistent with PSC advice, the characterisation of the product is considered inadequate. Registration is not recommended on chemistry and biopharmaceutic grounds.

III. Nonclinical findings

Introduction

Studies showing similar pharmacokinetic characteristics for docetaxel in dogs given Docetaxel-PF and Taxotere are not necessarily reassuring of bioequivalence between formulations in humans. While the dog has previously been established as an adequate model for toxicity testing of docetaxel, dogs and humans do not have identical pharmacokinetics with respect to docetaxel and therefore the findings in the dog cannot be used with certainty to predict the kinetics of various docetaxel formulations in humans. Further, the study involved very small numbers of animals (5/group) and is unlikely to be adequately powered to allow reliable comparisons to be made.

The *in vitro* studies showing similar plasma protein binding and micellar release characteristics of docetaxel in the proposed and innovator formulations would be supportive of more robust data showing formulation equivalence; however, they do not by themselves provide evidence of *in vivo* equivalence.

Overall, the nonclinical pharmacokinetic data cannot, by themselves, be used to support a claim of bioequivalence between Docetaxel-PF and Taxotere.

Toxicology

Formulation related toxicity

Docetaxel contains several excipients that are not present in Taxotere, which raises the question of whether the two formulations are toxicologically equivalent. Docetaxel-PF was shown to cause greater severity of local irritation, including tissue necrosis, than Taxotere after IV and PV injection in rabbits, probably because of the more irritant properties of the Docetaxel-PF vehicle. This difference is considered important as it suggests that Docetaxel-PF may be less safe than Taxotere. There were no studies comparing the systemic toxicity of the formulations.

Ethanol

The concentration of ethanol is about 3.5 times higher in Docetaxel-PF than in Taxotere. At the highest approved clinical dose of docetaxel, the amount of ethanol delivered to a patient via Docetaxel-PF would be about 6.4 g.

The sponsor has included a safety assessment to justify the concentration of ethanol in Docetaxel-PF. It is acknowledged that the blood concentration of alcohol that could be achieved via slow infusion of Docetaxel-PF would be similar to or less than that achieved after ingestion of a standard drink in healthy adults (10 g of alcohol, from the *NHMRC Australian Guidelines to reduce health risks from drinking alcohol*. 2009¹¹). While the

¹¹ <<http://www.nhmrc.gov.au/guidelines/publications/ds10>>

proposed dose of alcohol is considerably lower than that associated with toxicity and death in a healthy individual, a dose of 6.4 g has the potential to cause alcohol-associated impairment and this may be exacerbated in the proposed patient population particularly if renal and hepatic elimination mechanisms are impaired. Propylene glycol, also present in Docetaxel-PF also causes alcohol-like symptoms and therefore there is a high risk of alcohol-induced side effects with Docetaxel-PF.

Issues associated with monitoring patients during and after infusion possible of alcohol-associated impairment are not relevant with Taxotere but will arise with Docetaxel-PF. This raises significant doubts about whether the two formulations should be considered equivalent and interchangeable.

Propylene glycol

Docetaxel-PF contains 374 mg/mL propylene glycol, while none is present in Taxotere. At the highest recommended dose of docetaxel, patients could receive up to 7.5 g of propylene glycol with Docetaxel-PF, which is higher than the recommended (oral) daily intake of 1.25 g/day (see sponsor's justification below).

While propylene glycol is commonly used as an excipient in human medicines, particularly in oral formulations, it is associated with a range of toxicities (including fatal) at concentrations not dissimilar to those proposed for Docetaxel-PF, including cardiac, metabolic, renal and central nervous system (CNS) toxicities (refer to Poisindex® Summary and Poisindex® Management for propylene glycol¹²). See also, for example, *"Inactive" Ingredients in Pharmaceutical Products: Update (Subject Review) PEDIATRICS Vol. 99 No. 2 February 1997, pp. 268-278*¹³.

Potential toxicities associated with IV propylene glycol, particularly in association with the high ethanol content, must be taken into account if Docetaxel-PF is to be registered. Such issues are not relevant with Taxotere and therefore the two formulations cannot be considered equivalent or interchangeable.

Impurities

Proposed limits for five individual impurities and for total impurities are higher than those accepted without qualification according to current regulatory guidelines. Adequate justification was provided for 2 of these, on the basis that they comply with relevant compendial standards and/or are a docetaxel metabolite. The sponsor's justification for the remaining 3 impurities and for total impurities was based on *"a comparison with Taxotere as well as on a structure-based risk assessment"*. The latter argument is theoretically-based and insufficient by itself. The argument concerning formulation similarity cannot be evaluated on the basis of Module 4 (nonclinical) data because information is not available for the evaluator to compare the impurity profile of Docetaxel-PF with the approved profile of Taxotere. On this basis, the proposed limit for impurities three individual impurities and for total impurities is not acceptable.

Nonclinical summary and conclusions

- According to the sponsor, nonclinical data for this application were intended to "provide comparative pharmacokinetic and safety information with Taxotere and are submitted in support of a request for a human bioequivalence study waiver".
- The data were not Good Laboratory Practice (GLP) compliant but appeared to be of acceptable quality. Nevertheless, they are not, by themselves, adequate to support claims of bioequivalence between Docetaxel-PF and Taxotere in humans.

¹² <<http://micromedex.hcn.net.au/mdx-tga/>>

¹³ <<http://aappolicy.aappublications.org/cgi/content/full/pediatrics;99/2/268#B161>>

- Regardless of whether it was administered as Docetaxel-PF or Taxotere, docetaxel showed a similar pharmacokinetic profile in dogs after IV infusion; a similar degree of binding to human or dog plasma proteins; and a similar in vitro release profile from (polysorbate-based) micelles. Both formulations were compatible with human blood at a drug:blood ratio up to 1:2. The pharmacokinetic study in dogs cannot be used to predict whether the two docetaxel formulations will have equivalent kinetic characteristics in humans because the dog has not been established as an equivalent model in terms of docetaxel kinetics in humans. Further, the size of the groups (n = 5) is probably too small to allow reliable comparisons.
- In a rabbit vascular irritation study, the extent and severity of local irritation after IV or paravenous injection was greater with 10 mg/mL Docetaxel-PF or its vehicle than with Taxotere 10 mg/mL. The 1 mg/mL concentration of either formulation was no more irritant than saline.
- Issues regarding the safety of relatively high concentrations of ethanol and propylene glycol in Docetaxel-PF must be taken into account with the proposed formulation. Such issues do not apply for Taxotere, which highlights the fact that the two formulations are not equivalent and interchangeable.
- Docetaxel-PF and Taxotere have a different impurity profile. No nonclinical studies addressing impurities were provided, and according to the sponsor, *“nonclinical studies to evaluate the potential impact of the difference in impurity ratios in Pfizer Docetaxel Injection and Taxotere® have not been conducted”*.
- Specifications for Docetaxel-PF include several impurities at limits above those acceptable without qualification or justification. No impurity studies were provided in Module 4 (nonclinical dossier), with justification for the proposed limits based on a comparison of expected impurities in Taxotere as well as on structure-activity assessments.
- It is not possible to provide nonclinical comment on whether differences in the impurity profile might impact on criteria for establishing pharmaceutical bioequivalence between Docetaxel-PF and Taxotere. It is not possible to comment on whether the different impurity profile impacts on the safety of Docetaxel-PF when compared with Taxotere.
- The justification was not adequate to support proposed limits for three individual impurities or total impurities.

Conclusions and recommendation

Nonclinical data do not support the application to register Docetaxel-PF as a generic version of Taxotere (two-vial presentation) for the following reasons:

- The study comparing the pharmacokinetics of docetaxel after administration of Docetaxel-PF and Taxotere in dogs cannot be used to support claims for bioequivalence between these formulations.
- Nonclinical data indicate that Docetaxel-PF is associated with greater safety concerns than Taxotere. Specifically, the risk of local irritation is greater with Docetaxel-PF than with Taxotere; and there are risks of alcohol-associated impairment with Docetaxel-PF but not with Taxotere.

IV. Clinical findings

There were no clinical pharmacokinetic, pharmacodynamic, efficacy or safety studies. Published papers were provided amongst references. None of these addressed the safety of ethanol/propylene glycol.

V. Pharmacovigilance findings

There was no RMP for evaluation; one was not considered necessary by the TGA.

VI. Overall conclusion and risk/benefit assessment

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

Quality

The TGA's Pharmaceutical Chemistry Section did not recommend registration because characterisation of the product is considered inadequate.

The sponsor did not provide a clinical bioequivalence study for review but did provide a justification for not submitting any clinical bioequivalence study. The Pharmaceutical Chemistry Section has provided input into whether this justification is acceptable. The quality evaluator has reservations about the adequacy of the physicochemical comparison of micelles formed by Docetaxel-PF and Taxotere (see also PSC Recommendations 4-6 above). The issue relates directly to whether it is reasonable to waive the requirement for a bioavailability study.

Nonclinical

The nonclinical evaluation had objections to registration of Docetaxel-PF. Nonclinical data comparing Docetaxel-PF and Taxotere included:

- A single IV dose pharmacokinetics study in dogs (Study 0432-2010)
- Plasma protein binding studies (Study 0433-2010)
- A study on the release of docetaxel from micelles (Study 0433-2010)
- A vascular irritation study in rabbits (Study 10LJ041)
- A human blood compatibility study (Study 09LJ059)

In a comment taking into account the sponsor's response to the initial TGA nonclinical evaluation of Module 4 data, the TGA toxicologist notes that the dog study *"cannot be used to predict whether the two docetaxel formulations will have equivalent kinetic characteristics in humans because the dog has not been established as an equivalent model in terms of docetaxel kinetics in humans and the group sizes are too small to allow reliable comparisons"*.

The TGA toxicologist also states that *"the safety profile of the Docetaxel-PF formulation is expected to be different from Taxotere due to high concentrations of ethanol and propylene glycol"*.

Clinical

There were no clinical pharmacokinetic, pharmacodynamic, efficacy or safety studies. Published papers were provided amongst references. None of these addressed the safety of ethanol / propylene glycol.

Risk management plan (RMP)

There was no RMP for evaluation; one was not considered necessary by the TGA.

Risk-benefit analysis

Delegate considerations

Four requirements must all be met before declaring a product essentially similar to another (that is, a generic), according to the definition of a generic medicine in the *TG Regulations 1990* and the ARGPM. These are considered below.

1. Quantitative composition of therapeutically active substances

The proposed generic product and the reference product Taxotere have the same quantitative composition of docetaxel.

2. Pharmaceutical form

The proposed generic product and the reference product Taxotere have the same pharmaceutical form.

3. Bioequivalence

Clinical bioequivalence studies were not submitted in this application. The sponsor submitted a justification for this. There are circumstances, outlined in the TGA adopted European Union (EU) guideline on bioequivalence, where it is reasonable to accept bioequivalence of a 'micelle-forming injection' formulation and the innovator formulation without an *in vivo* bioavailability study. Note: the guideline indicates that bioequivalence must be shown in humans unless there are grounds to waive the requirement.

The Delegate's view is that the sponsor's justification for not submitting a clinical bioequivalence study is insufficient, that is, that in the absence of appropriate data, Docetaxel-PF and Taxotere cannot be considered bioequivalent.

4. Same safety and efficacy properties

Regardless of whether the two products are bioequivalent, the two products have to have the same efficacy and safety properties for Docetaxel-PF to be considered a generic version of Taxotere, that is, these properties cannot differ significantly. Of relevance is the risk of *worse* efficacy or safety with Docetaxel-PF relative to Taxotere.

The Delegate considered that a significant difference in efficacy and safety properties is signalled by either: different clinical management practices stemming from differences between the two products (for example, the need for additional risk mitigation measures); or clinically relevant differences in safety or efficacy outcomes.

In this submission, safety concerns arise from aspects of the Docetaxel-PF other than the active ingredient. These concerns are discussed below.

Ethanol and propylene glycol content

Differences between products

Docetaxel-PF includes ethanol and propylene glycol amongst its excipients. The TGA nonclinical evaluator states that the “*concentration of ethanol is about 3.5 times higher in Docetaxel-PF than in Taxotere*”. Also, at the maximum docetaxel dose, the propylene glycol dose from Docetaxel-PF is 7.5 g; Taxotere does not have propylene glycol as an excipient. The sponsor states:

“The total daily intake (TDI) of Docetaxel-PF is estimated to be 6.4 g ethanol and 7.5 g propylene glycol, as calculated from the maximum dose of the drug product (i.e., 100 mg docetaxel (anhydrous) per square metre, which equates to 200 mg docetaxel (anhydrous) in 20 mL solution, assuming a maximum body surface area of 2 square metres). Precedence [sic] to use intravenous drug products containing at least these levels of ethanol and propylene glycol includes Taxol (paclitaxel injection, TDI of 23.1 g ethanol) and phenytoin injection (TDI of 8.7 g propylene glycol).”

Other IV products may have the stated levels of ethanol and/or propylene glycol, however the issue not whether Docetaxel-PF is safe in this regard relative to medicines in general. The issue is whether Docetaxel-PF’s safety in this regard is comparable to Taxotere. Therefore, a key concern is whether the amounts of ethanol and propylene glycol in Docetaxel-PF lead to clinically significant safety issues that are not seen with Taxotere.

Text in proposed Product Information

The sponsor proposes the following text in the Docetaxel-PF PI that is not present in the Taxotere PI:

Excipients

This medicinal product contains 40% (v/v) ethanol (alcohol) and 36% (v/v) propylene glycol per mL of concentrate. The total daily intake from the use of this medicinal product is 3.2 g/m² of ethanol and 3.7 g/m² of propylene glycol if Docetaxel-PF is administered at the highest dose (i.e., 100 mg/m², which equates to 200 mg docetaxel per person, assuming a maximum body surface area of 2 m²). This may be harmful for those suffering from alcoholism and is to be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease or epilepsy.

The amount of alcohol in this medicinal product may alter the effects of other medicines. The amount of alcohol in this medicinal product may impair the ability to drive or use machines.

This text was apparently based on model text in “EMA¹⁴ Guideline: Volume 3B. Excipients in the label and package leaflet of medicinal products for human use; CPMP/463/00 Final”¹⁵. That guideline is not adopted for use by the TGA. Despite this, the sponsor considered it appropriate to include the above text. The guideline’s threshold for such text is 3 g ethanol/dose (see Table 4), considerably lower than the amount of ethanol (let alone ethanol plus propylene glycol) contained in Docetaxel-PF.

¹⁴ EMA=European Medicines Agency

¹⁵ <http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003412.pdf>

Table 4. Extracts from EMEA Guideline: Volume 3B. Excipients in the label and package leaflet of medicinal products for human use; CPMP/463/00 Final. Threshold

It is accepted that excipients may only show an effect above a certain 'dose'. Except where otherwise stated, thresholds are expressed as Maximum Daily Doses of the excipient in question, taken as part of a medicinal product. The threshold is a value, equal to or above which it is necessary to provide the information stated. A threshold of 'zero' means that it is necessary to state the information in all cases where the excipient is present in the medicinal product.

Ethanol	Oral and Parenteral	Less than 100 mg per dose	This medicinal product contains small amounts of ethanol (alcohol), less than 100mg per <dose>.	- - - This statement is to provide reassurance to parents and children concerning the low levels of alcohol in the product.
		100 mg – 3g per dose	This medicinal product contains ... vol % ethanol (alcohol), i.e. up to ... mg per dose, equivalent to ... ml beer, ... ml wine per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.	The package leaflet should give the equivalent volume of beer and wine, nominally calculated assuming 5 % vol and 12% vol ethanol respectively. Separate warning statements may be needed in different parts of the PL.
	Oral and Parenteral	3 g per dose	This medicinal product contains ... vol % ethanol (alcohol), i.e. up to ... mg per dose, equivalent to ... ml beer, ... ml wine per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease or epilepsy. The amount of alcohol in this medicinal product may alter the effects of other medicines. The amount of alcohol in this medicinal product may impair your ability to drive or use machines.	
Propylene glycol and esters	Topical	Zero	May cause skin irritation	
	Oral Parenteral	400mg/kg adults 200mg/kg children	May cause alcohol-like symptoms	

The innovator's ethanol content is below this threshold; it falls into the guideline's 100 mg–3 g range, which is accompanied by different model text (the Taxotere PI does not include such text; the EMA Guideline has not been adopted for use by the TGA). The *additional* text in the '3 g and above' bracket is as follows:

"The amount of alcohol in this medicinal product may alter the effects of other medicines.

The amount of alcohol in this medicinal product may impair your ability to drive or use machines."

The EMA guideline categorises risk using threshold amounts of alcohol. The true difference in risks is likely to be more dose-dependent, that is, correlate more with the extent of alcohol dose differences. Therefore, risks that are identified even in the '100 mg – 3 g' category (such as risk of harm in those suffering from alcoholism or from epilepsy) are likely to be more appreciable with Docetaxel-PF than with Taxotere.

General discussion of alcohol-related side-effects

Given that docetaxel infusion is generally 3 weekly, only acute effects are practically important. The foremost effect is neurological impairment, which would probably occur within the hospital setting during or just after infusion. Neurological symptoms of acute

low-dose alcohol ingestion include sedation, impaired co-ordination, disinhibition and euphoria.

Propylene glycol causes some ethanol-like effects so may contribute to neurological impairment caused by ethanol.

Ethanol ingested orally is subject to 8-9% first-pass metabolism.¹⁶ This will not happen when given intravenously, so intake of IV ethanol is not directly comparable to intake of oral ethanol. The same is presumably the case for propylene glycol, since it shares the same metabolism as ethanol (via alcohol dehydrogenase).

The exposed population may be somewhat debilitated and more likely to have increased systemic exposure to alcohol and increased vulnerability to its effects, relative to healthy subjects. There may also be people requiring treatment with docetaxel that have specific sensitivities, for example those with alcoholism, severe hepatic impairment and so on.

Symptoms of alcohol intoxication may be influenced by individual tolerance, rate and extent of exposure, individual expectations of the effects of alcohol and the environment in which alcohol is used. There is unlikely to be any pronounced peak of systemic exposure to alcohols with Docetaxel-PF because it is infused over 1 hour. The medical setting of Docetaxel-PF administration and the fact that patients will most likely not be expecting any 'alcoholic effects' may offset symptoms. Despite this, the range of individual tolerance to alcohol is large so there may be many exposed patients with low tolerance who do become symptomatic, in which case the lack of anticipation may make some symptoms more unpleasant.

It is difficult to predict blood alcohol level in patients given Docetaxel-PF. A published paper¹⁷ measured plasma kinetics of ethanol in 13 healthy subjects given 0.4 g/kg ethanol by IV infusion over 30 minutes (that is, 28 g to a 70 kg individual or about 4 fold more than in Docetaxel-PF given over half the time). Mean maximum arterial blood concentration was 0.95 g/L at the end of the infusion. This suggests that only people with low tolerance will have more than minor symptoms during or just after infusion of Docetaxel-PF.

In the context of Docetaxel-PF's use, some risks (such as impairment of driving ability) may be less clinically relevant than others. Patients given Docetaxel-PF will not be driving cars at or around the time of infusion. However, impairment of driving ability suggests impairment of other functions and impairment of these other functions could make an appreciable difference in some scenarios in the ward setting.

Drug interactions

There is potential for drug interactions between alcohols in Docetaxel-PF and other medications, for example drugs that are substrates of alcohol dehydrogenase or cytochrome P450 isozyme CYP2E1. Pharmacodynamic interactions seem relevant; ethanol in particular may cause sedation (etc) which could add to effects of other medications given around the time of infusion. Disulfiram should probably not be taken when Docetaxel-PF is being given.

Haemolysis

Propylene glycol can cause haemolysis at high doses. It seems less likely that clinically relevant haemolysis will be observed with Docetaxel-PF due to its propylene glycol content.

¹⁶ Ammon E et al. Disposition and first-pass metabolism of ethanol in humans: is it gastric or hepatic and does it depend on gender? Clin Pharmacol Ther 1996; 59 (5): 503-13

¹⁷ Jones AW, Norberg A and Hahn RG. Concentration-time profiles of ethanol in arterial and venous blood and end-expired breath during and after intravenous infusion. J Forensic Sci 1997; 42: 1088-1094

Conclusions regarding ethanol and propylene glycol content

The Delegate's current view is that because of higher alcohol content per dose, Docetaxel-PF will produce clinical safety issues that are not seen with Taxotere. This view is consistent with the sponsor's own statement in the proposed Product Information (PI), discussed above.

Symptoms are likely to be minor in most exposed people, but (a) even minor symptoms are in addition to those expected after Taxotere, (b) in some people symptoms may be more than minor, and (c) management of patients may become more difficult (the sponsor acknowledges that the Docetaxel-PF induced central nervous system effects may require "careful monitoring in the clinic").

Impurities

The Australian Regulatory Guidelines for Prescription Medicines (ARGPM) notes on page 51/64 that the *"comparative impurity profile of the two products will also be relevant to whether or not safety data are required on the essentially similar brand"*.

Docetaxel-PF and Taxotere have different impurity profiles. Nonclinical studies to evaluate the potential impact of the difference in impurity ratios in Docetaxel-PF and Taxotere have not been conducted.

The nonclinical evaluator noted that specifications for Docetaxel-PF include some impurities at limits above those considered 'acceptable without qualification' according to current regulatory guidelines.¹⁸ The nonclinical evaluator considered justification inadequate for three individual impurities and total impurities. Justifications were based on 'close structural similarity' to the parent drug docetaxel and on 'similar (predicted) total impurity content for [Docetaxel-PF] and Taxotere'.

Pfizer responded to this issue with a comparison of the Pfizer impurity specifications with the USP monograph for Docetaxel Injection.

Based on this information, the Delegate did not consider that the differing impurity profile of Docetaxel-PF and Taxotere will lead to substantially differing safety profiles of the two products.

Vascular irritation

Vascular irritation (in a rabbit model) was greater with Docetaxel-PF (10 mg / mL) than with Taxotere (10 mg / mL). It was considered that after dilution this would not be a safety concern by the nonclinical evaluator. The sponsor notes:

"Parenteral products containing up to 50% alcohol have been formulated. Concentrations of 5-10% are preferred due to pain associated with injection. [Docetaxel-PF] is administered at 3.0% v/v¹⁹, which is well below the concentration which may cause pain at the injection site."

The Delegate agreed that vascular irritation is not likely to differ appreciably between Docetaxel-PF and Taxotere once the two products are added to 250 mL solution for infusion.

Dog study

The Delegate did not consider that the presented dog study can meaningfully inform about the relative safety in humans of the two products. The nonclinical evaluator noted:

¹⁸ Note for Guidance on Impurities in New Drug Products (CPMP/ICH/2738/99).
<<http://www.tga.gov.au/pdf/euguide/ich273899enrev2.pdf>>

¹⁹ v/v=volume/volume

'Clinical signs of aggression, decreased activity, redness of eyes and ear flaps, emesis and soft stools/diarrhoea were observed in individual dogs given either formulation. Because of small animal numbers, it was not possible to assess whether the incidence or severity of these was formulation-dependent: in any case, this study was not designed for this type of assessment.'

Trade name

The quality evaluator noted the potential for docetaxel products with similar trade names to be registered. The Delegate has not considered this as an issue because the Delegate proposed to reject the Docetaxel-PF application.

Summary

Docetaxel-PF does not appear to be essentially similar to Taxotere because, in the light of scientific knowledge, (a) its bioequivalence to Taxotere is not established and (b) the two products have differing safety profiles in one significant regard (specifically, the ethanol and propylene glycol content of Docetaxel-PF may produce clinically appreciable symptoms of neurological impairment, absent in the case of Taxotere).

The Delegate proposed to reject the application.

The advice of the ACPM was requested on the following issues:

- What is the Committee's view regarding the bioequivalence of the two products?
- What is the Committee's view regarding the safety profile of Docetaxel-PF, relative to Taxotere? For example, will differing alcohol contents produce clinically meaningful differences in safety?

Response from sponsor

Pfizer appreciates the opportunity in this Pre-ACPM Response to address the issues raised by the Delegate. The issues being addressed are identified in bold text with Pfizer's response in normal text.

Issues

1. Bioequivalence

Delegate's Overview: ...the advice of the Pharmaceutical Subcommittee of ACPM was that there were inadequate data for a proper physicochemical comparison of micelles formed by each product:

PSC Recommendation (4): In relation to the physicochemical comparison of micelles formed by the proposed products and the innovator product, the PSC advised that the data provided were inadequate given the absence of:

- Data comparing the micelle characteristics (critical micelle concentration) in the 0.9% sodium chloride solution and in the 5% glucose solution proposed as diluents and extent of solubilisation of the docetaxel by the micelles.

The critical micelle concentration and the estimated percentage of surfactant expected to form micellar entities (that is, extent of solubilisation of docetaxel in micelles) is summarised in Table 5. Note that the comparative critical micelle concentrations were previously provided in the submission dossier, and have been reanalysed to calculate the extent of solubilisation.

Table 5. Estimated concentration of micellar entities in Taxotere and Docetaxel-PF (0.74 mg/mL)

Micellar Attribute	Taxotere	Docetaxel-PF
Critical Micelle Concentration	6.32×10^{-4} mg polysorbate per mL	4.11×10^{-3} mg polysorbate per mL
Concentration of polysorbate in admixture (0.74 mg per mL)	20.7 mg polysorbate per mL	19.6 mg polysorbate per mL
% free docetaxel	0.003	0.021
% docetaxel in micellar entities	99.997	99.979
% free polysorbate	0.002	0.011
% polysorbate as micellar entities	99.992	99.944

The test results indicated that the critical micelle concentration, and the extent (amount) of the micellar component in Taxotere is comparable to Docetaxel-PF when prepared at the target admixture infusion of 0.74 mg/mL, using 5% glucose in water for injection as a diluent.

The use of an ionic diluent, such as 0.9% sodium chloride solution, may ionise the active ingredient as well as the surface charge of the micelle, and as a consequence, alter the critical micelle concentration and the micelle characteristics. However, both docetaxel active ingredient and polysorbate-80 are non-ionic and the physicochemical properties of docetaxel and polysorbate-80 are not expected to be altered by the ionic strength of the aqueous solution. The micelle characteristics and extent of solubilisation (free and solubilised fractions of the drug) of Docetaxel-PF will be comparable to Taxotere, regardless of the choice of the aqueous diluent. In summary, the use of 5% glucose in water for injections is adequate as a model solution to determine the micelle characteristics and extent of solubilisation and is reflective of the characteristics when other aqueous diluents, such as 0.9% sodium chloride in water for injections, are used.

Delegate's Overview: The TGA's quality evaluator... also notes a clearly higher critical micelle concentration (CMC) for Docetaxel-PF than for Taxotere:

The critical micelle concentration estimates the threshold concentration at which polysorbate-80 forms micellar components which can solubilise the active ingredient. Pfizer acknowledges the critical micelle concentration for Docetaxel-PF (4 µg polysorbate/mL) is higher than Taxotere (0.6 µg polysorbate/mL; Table 5). However, the difference is small in the context of the overall dose administered (approximately 20,000 µg polysorbate/mL). As more than 99.9% of polysorbate 80 is present in micellar form in the two products, the slightly higher critical micelle concentration in Docetaxel-PF will not have a significant impact on fraction of the free and solubilised drug. Moreover, upon infusion, the micellar component formed by polysorbate rapidly disassembles and degrades from plasma dilution and serum carboxylesterases, respectively. The difference in the critical micelle concentration between Docetaxel-PF and Taxotere in the diluted admixture solution presents no pharmacokinetic significance regarding drug delivery.

PSC Recommendation (4): ...Studies on the effects of variations in ethanol and propylene glycol levels on micelles

It was previously established that the levels of polysorbate-80 for both drug products are adequate to solubilise the active ingredient in the dosing solution, that is, the critical micelle concentration is significantly below the levels of polysorbate-80 present in the drug product at the target admixture concentration of 0.74 mg active ingredient per millilitre (Table 5), and that stability of the micelles are only affected by alcohols when the levels of alcohols rises above 10%v/v.²⁰ In this regard, the ethanol concentration (3.0% v/v) and propylene glycol concentration (2.7% v/v) in Docetaxel-PF are well within these

²⁰ EMA/CHMP/QWP/799402/2011. Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems.

limits when the drug product is diluted as a 0.74 mg/mL infusion solution. As the proportion of ethanol and propylene glycol in Docetaxel-PF are controlled as part of the manufacturing process, any minor variations in the level of ethanol and propylene glycol on micelle characteristics will be clinically insignificant.

PSC Recommendation (5): ...The PSC noted that the fate of the micelles in vivo had not been determined. The PSC agreed that a pharmacokinetic study in dogs cannot be used to predict whether the two docetaxel formulations will have equivalent kinetic characteristics in humans given that:

- ***The dog has not been established as an equivalent model for humans***
- ***The study was not powered to detect differences between the formulations***

Surfactants exist in equilibrium between free and micellar polysorbate-80 in aqueous solution. Due to dilution with plasma and shifting of the equilibrium towards free surfactant, the micelles formed by polysorbate will disassemble upon intravenous administration. Furthermore, polysorbate is rapidly degraded by serum carboxylesterases.²¹ The dog study was not intended to predict human pharmacokinetic behaviour but rather to compare the two formulations with respect to potential differences in their impact on the pharmacokinetics of docetaxel in an *in vivo* model. It was demonstrated in this study model that the higher levels of ethanol and the presence of propylene glycol do not impact the pharmacokinetic clearance of docetaxel active ingredient. With respect to the power of the study, it was demonstrated that the 90% confidence intervals for the ratio of the geometric means for the AUC and C_{max} endpoints fall within the 80 to 125% target interval. There is adequate precision in the estimates to demonstrate equivalent pharmacokinetics based on these two endpoints. By assessing the expected power for a prospective study (to account for the uncertainty in the root mean-square error of the statistical model fits)²², it is also confirmed that such a study would have approximately the same sample size as the current study, that is, with 80% power.

PSC Recommendation (6): The PSC did not accept the Sponsor's justification for not providing a clinical bioequivalence study between the proposed formulation and the innovator product:

Polysorbate 80 is used primarily to solubilise docetaxel in the two products, and the pharmacokinetic behaviour may be impacted if the extent of free and solubilised drug is different as a result of different docetaxel to polysorbate 80 ratios. In this regard, the polysorbate-to-docetaxel ratio for Docetaxel-PF (approximately 1.8% v/v polysorbate) is very similar to Taxotere (approximately 1.9% v/v) when diluted to a 0.74 mg/mL infusion solution.

To further compare the micelle system present in Docetaxel-PF with Taxotere, Pfizer has investigated all the surrogate markers of bioequivalence, as established in the TGA adopted *Guideline on the Investigation of Bioequivalence*.²³ In addition, Pfizer demonstrated that inclusion of propylene glycol and an increased proportion of ethanol in the formulation does not affect the physical stability and comparative solubilising capacity of the infusion solutions, the characteristics of the micelle components (see Table 5) and free drug fraction (that is, the [free] versus [solubilised] fraction of the active ingredient), and rate and extent of release of the active ingredient from the micelles^{20, 23}. These data

²¹ Ten Tije AJ, Verweij J, Loos WJ, et al. Pharmacological effects of formulation vehicles : implications for cancer chemotherapy. Clin Pharmacokinet 2003; 42(7):665-85.

²² Julious SA, Owen RJ. Sample size calculations for clinical studies allowing for uncertainty about the variance. Pharm Stat. 2006 Jan-Mar;5(1):29-37.

²³ CPMP/EWP/QWP/1401/98 Rev1. Guideline on the investigation of bioequivalence.
<<http://www.tga.gov.au/pdf/euguide/ewp140198rev1.pdf>>

indicate that the different excipient profile does not affect the disposition of docetaxel, and the bioavailability of Docetaxel-PF will be comparable to Taxotere.

2. Formulation safety

Delegate's Overview: Therefore, a key concern is whether the amounts of ethanol and propylene glycol in Docetaxel-PF lead to clinically significant safety issues that are not seen with Taxotere.

As Docetaxel-PF contains more ethanol than Taxotere, patients administered with Docetaxel-PF at the highest clinical doses may have higher blood alcohol levels than patients administered with Taxotere at the end of infusion. However, any differences in blood alcohol levels are likely to be minimal and insufficient to produce clinically significant differences in the safety profile of Docetaxel-PF relative to Taxotere.

It has previously been reported that, upon the infusion of 0.4 g ethanol per kg body weight over 30 minutes (equivalent to 28 g ethanol for a 70 kg individual), the venous blood alcohol level is 84.7 mg/dL at the end of infusion.²⁴ A summary of this, and other similar studies assessing the blood alcohol levels after ethanol infusion, is presented below.

Table 6. Estimated blood alcohol concentration after intravenous infusion with ethanol

Study Author	Infusion Rate	Approximate total daily intake	Duration of infusion	Blood alcohol level at the end of infusion
Jones et al	0.4 g ethanol per kg body weight	28 g ethanol for a 70 kg individual	0.5h	84.7 mg/dL*
Jones et al ⁶	0.6 g ethanol per kg body weight	42 g ethanol for a 70 kg individual	1h	108 mg/dL*
Rangno et al ⁷	0.375 g ethanol per kg body weight	26.3 g ethanol for a 70 kg individual	0.5h	88 mg/dL†

* Venous blood alcohol level reported

† Plasma alcohol level reported

Jones et al. Concentration-time profiles of ethanol in arterial and venous blood and end-expired breath during and after intravenous infusion. J Forensic Sci. 1997 Nov;42(6):1088-94.

⁶Jones AW, Hahn RG, Stalberg HP. Pharmacokinetics of ethanol in plasma and whole blood: estimation of total body water by the dilution principle. Eur J Clin Pharmacol. 1992;42(4):445-8.

⁷Rangno RE, Kreeft JH, Sitar DS. Ethanol 'dose-dependent' elimination: Michaelis-Menten v classical kinetic analysis. Br J Clin Pharmacol. 1981 Nov;12(5):667-73.

It is well established that blood alcohol levels exceeding 100 mg/dL can result in impairment of motor function including ataxia and lack of co-ordination.²⁵ Subjects with lower blood alcohol levels, that is, less than 50 mg/dL, were reported to exhibit increased talkativeness, increased relaxation and impairment of some tasks requiring skill.

The total daily intake of ethanol from Docetaxel-PF (6.4 g, or 0.09 g/kg for a 70 kg individual) is approximately 3 times greater than Taxotere (2.2 g) when the drug product is administered at the maximum dose. As ethanol clearance is estimated to be between 0.10 g - 0.15 g ethanol per kg body weight, per hour^{26, 27}, it is expected that all the ethanol will be cleared within one hour given the zero order kinetics of ethanol, and based on the summary data detailed in Table 6. The modestly higher levels of ethanol in Docetaxel-PF are therefore considered unlikely to elicit clinically appreciable differences when compared to Taxotere.

²⁴ Jones AW, Norberg A, Hahn RG. Concentration-time profiles of ethanol in arterial and venous blood and end-expired breath during and after intravenous infusion. J Forensic Sci. 1997 Nov;42(6):1088-94.

²⁵ Vonghia L, Leggio L, Ferrulli A, et al. Acute alcohol intoxication. Eur J Intern Med. 2008 Dec;19(8):561-7.

²⁶ Adinoff B, Bone GH, Linnoila M. Acute ethanol poisoning and the ethanol withdrawal syndrome. Med Toxicol Adverse Drug Exp. 1988 May-Jun;3(3):172-96.

²⁷ Norberg A, Jones AW, Hahn RG, et al. Role of variability in explaining ethanol pharmacokinetics: research and forensic applications. Clin Pharmacokinet. 2003;42(1):1-31.

Propylene glycol is used as a solvent in Docetaxel-PF. With respect to the potential contribution of propylene glycol to clinical signs of intoxication, it has previously been reported that this excipient is only one-third as intoxicating as ethanol.²⁸ In addition, a significant proportion of propylene glycol (approximately 12-45%) is also eliminated unchanged in the urine.²⁹

In summary, the inclusion of propylene glycol and the modestly higher ethanol level in Docetaxel-PF versus Taxotere is not expected to produce clinically meaningful differences in safety.

A review of the current docetaxel products demonstrates another registered formulation (Docetaxel Sandoz) has higher levels of ethanol than either Taxotere or Docetaxel-PF (Table 7). Docetaxel Sandoz is deemed an equivalent brand with Taxotere on the Pharmaceutical Benefits Scheme (PBS) Schedule³⁰, and can be interchanged without difference in clinical effect. The PI for Docetaxel Sandoz does not contain any warning statement regarding alcohol-like symptoms due to ethanol. Accordingly, Pfizer also proposes to remove wording regarding alcohol-like symptoms from the Docetaxel-PF Product Information.

Table 7. Total Daily Intake of Ethanol from Docetaxel Injections drug products detailed in the ARTG

Product Name	Total Daily Intake of Ethanol [*]
Taxotere 2-vial (Sanofi)	2.0 g
Taxotere 1-vial (Sanofi)	4.0 g
Docetaxel-PF (Pfizer)	6.4 g
Docetaxel Sandoz (Sandoz)	11.8 g

^{*} Total Daily Intake assumes that the maximum dose of 200 mg docetaxel is administered.

Delegate's Overview: The Delegate's current view is that because of higher alcohol content per dose, Docetaxel-PF will produce clinically safety issues that are not seen with Taxotere. This view is consistent with the sponsor's own statement in the proposed Product Information (PI), discussed above.

There are currently no TGA Guidance documents, nor TGA adopted EU Guidance document which addresses warning statements on PIs for particular excipients. Therefore, reference is made to the EU (not adopted by TGA) Notice to Applicants, Volume 3B (July 2003), *Excipients in the label and package leaflet of medicinal products for human use*.³¹ The Delegate noted the additional PI text in relation to the ethanol content: "(the levels of ethanol) may be harmful for those suffering from alcoholism and is to be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease or epilepsy" and the "amount of alcohol in this medicinal product may alter the effects of other medicines. The amount of alcohol in this medicinal product may impact your ability to drive or use machines" was obtained from this guidance document.

Pfizer acknowledges these warning statements in the proposed PI for Docetaxel-PF are more extensive than those in the Australian PIs for Taxotere and other high-ethanol containing, intravenously-administered drug products such as Paclitaxel Injection. For example, with regards to ethanol safety, the Paclitaxel Ebewe PI (maximum total daily intake of 23 g) only contains the text "... Paclitaxel Ebewe does contain alcohol. Patients should exercise caution" under the sub-section entitled "Effects on ability to drive and use machines".

²⁸ Rowe RC, Sheskey PJ, Cook WG, et al. Propylene glycol. In: Rowe RC, Sheskey PJ, Cook WG, editors. Handbook of Pharmaceutical Excipients. 7th ed. London: Pharmaceutical Press; 2012: p. 407-408.

²⁹ Zar T, Graeber C, Perazella MA. Recognition, treatment, and prevention of propylene glycol toxicity. Semin Dial. 2007 May-Jun;20(3):217-9

³⁰ <<http://www.pbs.gov.au/medicine/item/5581R-5582T-5583W-5584X-5585Y-7281F-7282G-7283H-7284I-7285K>> (Accessed on 6 September 2012).

³¹ <http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003412.pdf>

Similarly, the Paclitaxel Pfizer PI only states "Paclitaxel contains dehydrated alcohol 396 mg/mL; consideration should be given to possible central nervous system and other effects of alcohol". These general statements indicate that the side effects from a total daily intake of up to 23 g ethanol do not cause any significant safety concerns to the end-user and therefore no warning statements regarding ethanol content in Docetaxel-PF (maximum total daily intake of 6.4 g) is necessary.

The PI for Phenytoin Injection (maximum total daily intake of 8.7 g propylene glycol) contains one precautionary statement on propylene glycol-related alcohol-like symptoms. The PI recommends the end-user not to exceed an administration rate of 50 mg active ingredient per minute (equivalent to 0.42 g propylene glycol per minute). This statement is not relevant to Docetaxel-PF, where a maximum dose of 7.5 g propylene glycol is intended to be administered over an hour (equivalent to 0.13 g propylene glycol per minute).

In summary, Pfizer acknowledges that the proposed wording in the Docetaxel-PF PI in relation to ethanol/propylene content is excessive, and not appropriate given the ethanol and propylene glycol doses, and the intended use of Docetaxel-PF in the hospital setting. Pfizer proposes to align the PI for Docetaxel-PF with the Taxotere PI, as well as the PI for Docetaxel Sandoz.

Conclusion

Based on the *in vitro* and *in vivo* studies, the behaviour of docetaxel active ingredient in Docetaxel-PF will be similar to Taxotere when administered intravenously as a one hour infusion. The modestly higher levels of ethanol and the use of propylene glycol in Docetaxel-PF are not expected to produce clinically meaningful differences in the safety profile compared to Taxotere. The PI for Docetaxel-PF similarly does not warrant extensive warning statements and has been amended in alignment with the Taxotere PI. The safety of the Docetaxel-PF formulation is also confirmed by the availability of high-ethanol and high-propylene glycol containing parenteral products such as Paclitaxel Injection and Phenytoin Injection, as well as the availability of high-ethanol containing docetaxel injection drug products such as Docetaxel Sandoz on the Australian Register of Therapeutic Goods (ARTG).

Pfizer is committed to working with the TGA to ensure that the most appropriate and relevant wording is used in the Product Information to communicate potential safety risks to the end-user.

Advisory committee considerations

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

The ACPM, taking into account the submitted evidence of quality, safety and efficacy agreed with the Delegate that these products have an overall negative benefit-risk profile for the proposed indication.

In making this recommendation the ACPM considered that:

- The evidence does not support the claim that these products are bioequivalent to the reference product, Taxotere, especially in the higher levels of ethanol and presence of propylene glycol in the proposed formulation.
- There are inadequate data on the physicochemical comparison of micelles formed by the proposed products and the innovator product. In addition, the fate of the micelles *in vivo* has not been determined.

- There remain safety concerns of potential neurological impairment that can be directly attributed to the alcohol and propylene glycol content and with the undefined interaction with the active ingredient.
- Overall, there has been an inadequate consideration of the impact of the formulation differences, the toxicity profile and the impact on a range of body systems, including potential neurological impairment and the undefined interaction with the active ingredient.

Outcome

The application was withdrawn by the sponsor (Pfizer Australia Pty Ltd) on 18 December 2012, before a decision was made.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia

Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605

<http://www.tga.gov.au>

Reference/Publication #