Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Cabazitaxel

Proprietary Product Name: Jevtana

Sponsor: Sanofi-Aventis Australia Pty Ltd

February 2012

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 <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.

Contents

I. Introduction to product submission

Submission details

Type of submission:	New Chemical Entity
Decision:	Approved
Date of decision:	5 December 2011
Active ingredient:	Cabazitaxel (as acetone solvate)
Product names:	Jevtana, Cabazitaxel Winthrop, Cabazitaxel Sanofi
Sponsor's name and address:	Sanofi-Aventis Australia Pty Ltd
Dose form:	Concentrated Injection
Strength:	60 mg/1.5 mL
Container:	1.5 mL vial with a 4.5 mL diluent vial
Pack size:	One pack contains the concentrate and diluent vial
Approved therapeutic use:	In combination with prednisone or prednisolone for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel containing regimen
Route of administration:	Intravenous
Dosage:	25 mg/m2 1h infusion every 3 weeks with oral prednisone or prednisolone 10 mg daily throughout treatment
ARTG number:	*Awaiting ARTG inclusion*

Product background

Cabazitaxel is a semisynthetic compound derivative from 10-deacetylbaccatin III, which is extracted from European yew needles. This new taxane, which promotes the tubulin assembly *in vitro* and stabilises microtubules against cold induced depolymerisation as efficiently as docetaxel, was selected for development based on a better anti-proliferative activity on resistant cell lines than docetaxel. Using cell lines with acquired resistance to doxorubicin, vincristine, vinblastine, paclitaxel and docetaxel, the resistance factors ranged from 1.8 to 10 and 4.8 to 59, for cabazitaxel and for docetaxel, respectively. Cabazitaxel exhibited a broad spectrum of *in vivo* antitumour activity, not only in docetaxel sensitive tumour models, but also in tumour models in which docetaxel was poorly or not active. In addition, this compound was found to penetrate the blood brain barrier and marked antitumor activity was obtained in nude mice bearing intracranial glioblastomas.

Prostate cancer is a major worldwide health problem. The initial treatment for metastatic adenocarcinoma of the prostate consists of androgen ablation, either surgically with bilateral orchiectomy or medically with luteinizing hormone releasing hormone (LH-RH) receptor agonists. Responses are observed in up to 85% of patients. At this stage, further hormonal manipulations such as treatment with antiandrogens, and subsequent

antiandrogen withdrawal can be associated with responses of short duration but without improvement in survival duration. Treatment options for patients with hormone refractory disease remain limited and include palliation of symptoms (especially pain) and/or systemic cytotoxic chemotherapy. Once a patient progresses to metastatic hormone refractory prostate cancer (mHRPC) the standard first line chemotherapy is docetaxel. This is the only chemotherapy currently registered in Australia which has been shown to prolong survival. After treatment with docetaxel and prednisolone patients may be relatively fit and well but there is no second line chemotherapy currently available which effectively prolongs survival in mHRPC.

This AusPAR describes the evaluation of a submission by Sanofi-Aventis Pty Ltd (the sponsor) for the registration of cabazitaxel, in combination with prednisone or prednisolone, for the treatment of patients with mHRPC previously treated with a docetaxel containing regimen. The proposed indication was:

In combination with prednisone or prednisolone, treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel containing regimen.

Regulatory status

The drug has been approved for similar indications in the Canada (16 June 2011), EU (17 March 2011), Switzerland (6 April 2011) and the USA (17 June 2010). The indication in Canada is:

Jevtana (cabazitaxel) in combination with prednisone or prednisolone is indicated for the treatment of patients with castration resistant (hormone refractory) metastatic prostate cancer previously treated with a docetaxel containing regimen.

The indication in the EU is:

Jevtana in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel containing regimen.

The indication in Switzerland is:

The targeted indication is in combination with prednisone or prednisolone for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel containing regimen.

The indication in the US is:

Jevtana is a microtubule inhibitor indicated in combination with prednisone for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen.

Product information

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

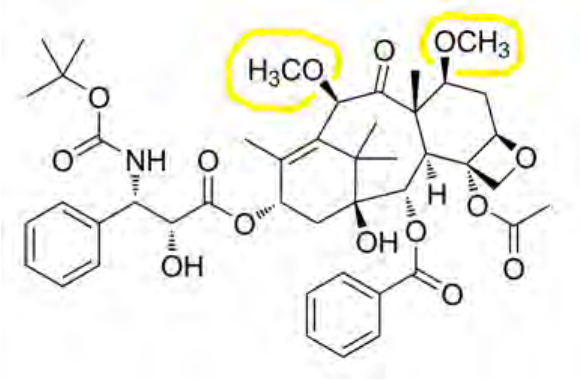
II. Quality findings

Drug substance (active ingredient)

Cabazitaxel is a complex semisynthetic molecule:

Cabazitaxel has been proposed as an Australian approved name (AAN). Cabazitaxel has multiple stereogenic centres and the drug substance is a single enantiomer as shown. The structure has been established, including the relative stereochemistry, by single crystal X-Ray diffraction. The compound is very lipophilic and practically insoluble in water (about 8 µg/mL, that is, 125 mL to dissolve 1 mg). Polymorphism has been investigated and many solvates can be formed, but the drug is dissolved in the finished product.

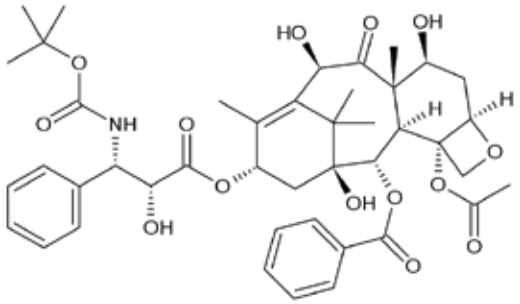
Cabazitaxel is closely related to paclitaxel and especially docetaxel (it is a dimethylated analog):



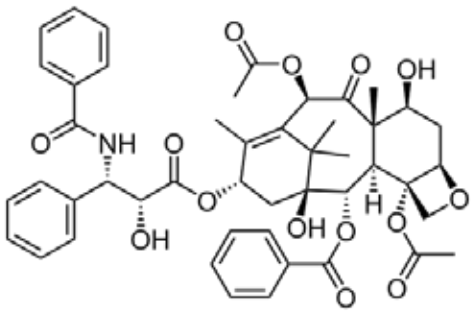
cabazitaxel

$C_{45}H_{57}NO_{14}$ MW 835.93 (cabazitaxel)

$C_{45}H_{57}NO_{14},C_3H_6O$ MW 894.01 (cabazitaxel acetone solvate)



docetaxel



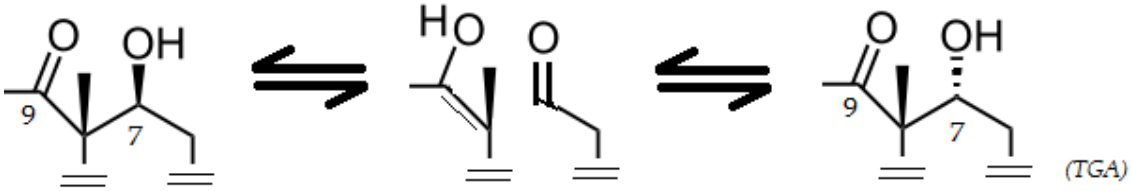
paclitaxel

Cabazitaxel is made from 10-deacetylbaccatin III ("10-DAB", isolated from Taxus species) by selective dimethylation, selective acylation of a secondary alcohol with a protected side chain and deprotection.

The drug substance is purified as the acetone solvate by crystallisation, although the melting point range reported is wide (140-175ºC, DSC) and not routinely controlled.

The drug substance specification was reviewed. Impurities are toxicologically qualified.[1]

The British Pharmacopoeia (BP) monograph for the related docetaxel controls: 10-dehydroxy-10-oxodocetaxel (oxidation product);7-epi-docetaxel (epimerisation) and 10-dehydroxy-**10-oxo**-7-epi-docetaxel (epimerisation and oxidation); similarly the monograph for paclitaxel controls 7-epi-paclitaxel. C7 epimerisation is possible for docetaxel and paclitaxel via a retro-aldol reaction:



(TGA)

This is blocked for cabazitaxel by methylation of the hydroxyl groups. Similarly C10-oxo formation is likely to be inhibited by methylation

Acetone solvate

The drug substance is cabazitaxel acetone solvate. The choice of a solvate as a drug substance is relatively unusual. The rationale for the choice of this solvate compares the acetone solvate and the most thermodynamically stable nonsolvate/anhydrous form.

The drug substance is dissolved during finished product manufacture. Note that the acetone is removed during finished product manufacture. The use of the solvate was considered acceptable.

Drug product

The cabazitaxel injection concentrate (60 mg/1.5 mL) is a viscous, non-aqueous solution in polysorbate 80 (prepared via evaporation of ethanol). The drug concentrate is supplied in a vial together with a diluent vial containing 4.5 mL of aqueous ethanol (13% w/w).

Addition of the diluent gives a 'premix solution' (10 mg/mL) which is administered after dilution into either 0.9% sodium chloride or 5% glucose injections by intravenous infusion over 1 hour. The product information (PI) recommends use of an in-line filter.

Both the premix and the infusion solution are supersaturated. In the premix the solubility is 3.44 mg/mL but the cabazitaxel concentration is 10 mg/mL. In the infusion solution the cabazitaxel solubility is 0.06 mg/mL at 25°C {0.08 mg/mL at 5°C}; the infusion concentration is 0.26 mg/mL.

The 'premix solution' is not isotonic, but, after dilution in either 0.9% sodium chloride solution for injection or 5% glucose solution for injection, the osmolality is in the range 285-293 mOsmol/kg.

Formulation

The formulation shown in the report as "cabazitaxel (as acetone solvate): 60 mg per vial" is ambiguous. The finished product is formulated with "cabazitaxel acetone solvate 60 mg" but with the footnote "expressed as solvent-free and anhydrous drug substance". Thus the nominal vial content is 60 mg cabazitaxel. Both the drug and diluent vials are made with overfills to allow withdrawal of the nominal volumes.

[1] Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

Cabazitaxel solubility in ethanol is 16 mg/mL and in polysorbate 80 63 mg/mL. In the concentrate formulation, the solubility is 86 mg/mL at 15ºC and 34 mg/mL at 30ºC (that is, with an unusual temperature dependence).

The concentrate is prepared by evaporating an anhydrous ethanolic solution of cabazitaxel and polysorbate 80 (pH adjusted with citric acid). The use of nitrogen is probably prudent given that peroxides can be generated in polysorbate 80, although peroxide degradation studies reported show that cabazitaxel is not sensitive to oxidation.[2,3]

The polysorbate used has a vegetable origin. It is treated as non-compendial by the sponsor because it does not meet the acid value test (as it is treated with citric acid).

Specifications

The most direct precedent is the United States Pharmacopoeia monograph for *Paclitaxel Injection*.

The release and expiry assay limits are almost identical. The only specified degradant in the finished product is the hydrolysis product RPR202670.

Stability

There is precipitation in the concentrate in vials stored at 5ºC with formation occurring in all three batches after 6 months. This was attributed to polysorbate 80, not cabazitaxel, but "Do not refrigerate" was recommended.

The stability of the prepared infusion solution was also investigated, including the extraction of DEHP. Polyurethane infusion sets gave significant assay declines (presumably due to drug adsorption). Crystallisation was seen under some storage conditions outside the recommended label conditions. The PI recommends against PVC infusion containers (bags or bottles) and polyurethane infusion sets (tubing, filter, pumps): it may be desirable to include positive recommendations.

Other aspects

Container safety, sterility and endotoxin aspects were all evaluated to the satisfaction of the TGA.

Biopharmaceutics

It has been reported that non-ionic surfactants such as polysorbate 80 influence the disposition of solubilised drugs that are administered intravenously. It has also been reported that there is reduced cellular uptake of the drug from the micelles which act as the principal carrier of circulating drug, which alters drug accumulation in erythrocytes.[4]

No bioavailability or pharmacokinetic data were reviewed by the quality reviewer as is normal practice for intravenous solutions.

[2] Ha E, Wang W, Wang YJ. J Pharm Sci 2002; 91: 2252-2264.
[3] Wasylaschuk WR, Harmon PA, Wagner G et al. J Pharm Sci 2007; 96: 106-116.
[4] Ten Tije AJ, VerweijJ, Loos WJ, Sparreboom A. Pharmacological effects of formulation vehicles: Implications for cancer chemotherapy. Clin Pharmacokin 2003; 42: 665-685.

Advisory committee considerations

The application was reviewed at the 139th and 140th meetings of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM). Provided outstanding issues were addressed, there were no objections to registration. Issues to be resolved at the time related to finished product specifications, sterility and Good Manufacturing Practice.

Quality summary and conclusions

Outstanding issues were resolved and there was no objection to registration.

III. Nonclinical findings

Introduction

The overall quality of the submission was good. Cabazitaxel was well characterised, with relevant aspects of the drug being investigated. With occasional exceptions (predominantly in the primary pharmacology section), studies were well conducted and reported. Where relevant, studies were Good laboratory Practice (GLP) compliant and were preceded by dose range finding studies in order to select appropriate dose levels.

Pharmacology

Primary pharmacodynamics

Mechanism of action

Like docetaxel and paclitaxel, cabazitaxel was shown to promote the assembly of tubulin (purified from porcine brain) into microtubules and to inhibit microtubule disassembly (cold induced depolymerisation). This leads to a decrease in free tubulin (not directly demonstrated in the submitted study) and disrupts the microtubular network which is vital to cell mitotic and interphase functions. For both promotion of tubulin assembly and inhibition of disassembly, cabazitaxel and docetaxel had identical activity, while paclitaxel was slightly less active.

Taxanes are also believed to stimulate apoptosis (Kovar et al., 2009 and Sorger et al., 1997) but this was not investigated for cabazitaxel.[5,6]

Antitumour activity in vitro

Cabazitaxel showed good *in vitro* cytotoxic activity against a variety of tumour cell lines after continuous exposure for several days . Although the proposed indication is prostate cancer, a prostatic cancer cell line was not investigated. Cabazitaxel showed activity against both murine tumour cell lines (P388 and L1210 leukaemia) and human tumour cell lines (HL60 leukaemia, KB epidermoid carcinoma, Calc18 and MCF7 mammary adenocarcinomas, CaCo-2 colon carcinoma, A549 lung adenocarcinoma and LOX IMV1 melanoma). Median inhibitory concentration (IC_{50}) values were in the range 2.6–34 ng/mL, this is well below the maximum plasma concentration (C_{max}) of 226 ng/mL at the maximum recommended human dose (MRHD). Depending on the extent of

[5] Kovar J, Ehrlichova M, Smejkalova B, Zanardi I, Ojima I, Gut I. Comparison of Cell Death-inducing Effect of Novel Taxane SB-T-1216 and Paclitaxel in Breast Cancer Cells. Anticancer Res 2009; 29: 2951-2960.
[6] Sorger PK, Dobles M, Tournebize R, Hyman AA. Coupling cell division and cell death to microtubule dynamics. Curr Opin Cell Biol 1997; 9: 807-814.

vascularisation, the tumour C_{max} may well be lower than plasma C_{max}. This appeared to be the case for the murine mammary adenocarcinoma 16/C where the tumour C_{max} was 74% lower than the plasma C_{max}. When comparisons were made with docetaxel in docetaxel-sensitive cell lines (variants of murine P338 leukaemia and human HL60 leukaemia, KB epidermoid carcinoma, Calc18 mammary adenocarcinoma and CaCo-2 colon carcinoma), cabazitaxel showed similar or slightly greater (1.2–4.9 fold) cytotoxic activity than docetaxel.

The cytotoxic activities of the 7- and 10-O-demethyl metabolites of cabazitaxel (RPR112698 and RPR123142, respectively [precursors of docetaxel]) against the murine leukaemia (P388) cell line were compared with that of cabazitaxel. Although the data were of poor quality, both metabolites were active. RPR123142 has similar activity to cabazitaxel, while RPR112698 had slightly lower activity than cabazitaxel. As these two compounds constitute only a small fraction of the circulating drug related material (≤4% combined in human plasma), they are unlikely to contribute significantly to the pharmacological activity.

Antitumour activity in vivo

Cabazitaxel toxicity and efficacy were investigated for different dosing schedules to reveal the optimal clinical schedule. The toxicity results in the pharmacology studies and results in the repeat dose toxicity studies (see below) support the proposed intermittent clinical dosing schedule.

Cabazitaxel showed varying *in vivo* activity against murine tumours grafted in syngenic mice but prostate tumours were not tested. Against solid tumours, it showed high activity against mammary adenocarcinomas 16/C and 17/A and advanced colon adenocarcinoma C38 and pancreatic ductal adenocarcinoma P03, moderate to good activity against melanoma B16, colon adenocarcinoma C51 and Lewis lung carcinoma but had little activity against pancreatic ductal adenocarcinoma P02. It also showed good activity against P388 leukaemia. Cabazitaxel showed broadly similar activity to docetaxel when both were tested against the same docetaxel sensitive murine tumours.

Intravenous (IV) cabazitaxel showed good activity against all 14 human xenografts in nude mice, although activity varied from moderate to high. Tested xenografts included a prostate carcinoma (DU 145), as well as mammary and colon adenocarcinomas, mammary, colon, lung, pancreatic, head and neck, and kidney carcinomas, glioblastomas and a gastric tumour. Most of the tested xenografts were treated at an advanced stage of disease and, with a few exceptions, treatment resulted in complete tumour regression in a proportion of the animals at doses that were non toxic. Long term tumour free survivors were observed for 6 tumour types (colon carcinoma HCT 116, pancreatic carcinoma MIA PaCa-2, head and neck carcinoma SR475, prostate carcinoma DU 145, and glioblastomas U251 and SF-295). Particularly good activity was observed against prostate carcinoma DU 145, with complete regression in 6/6 mice at the 7.4 and 12 mg/kg/dose, with 3/6 and 5/6 tumour free survivors (on Day 75) at these respective doses. The dose of 7.4 mg/kg corresponds to 22 mg/m^2 (using a mg/kg to mg/m^2 conversion factor of 3) which is similar to the proposed human dose of 25 mg/m^2, although frequency of dosing was higher in the mice studies compared to that proposed in humans.

Cabazitaxel showed broadly similar activity to docetaxel when - tested against the same docetaxel sensitive human tumour xenografts. Cabazitaxel showed good activity against some xenografts against which docetaxel was poorly active (GXF-209 gastric tumour and UISO BCA-1 mammary carcinoma). Cabazitaxel crosses the blood brain barrier and it showed better activity than docetaxel against intracranially implanted human glioblastomas, U251 and SF-295.

Activity against drug resistant cell lines

The mechanisms leading to resistance to taxanes have not been fully elucidated but overexpression of P-glycoprotein (P-gp) appears to be one mechanism (Zunino et al., 1999).[7] Cabazitaxel was tested *in vitro* for activity against 20 drug resistant tumour cell lines (murine and human cell lines resistant to a number of standard cytotoxic drugs), including cell lines which overexpressed P-gp. Generally, in the resistant cell lines, cabazitaxel did not show any marked reduction in activity compared to activity against the parent cell line (that is, resistance to various cytotoxic drugs did not confer cross resistance to cabazitaxel).

In general, resistance factors (IC_{50} resistant cell line/IC_{50} parent cell line) for cabazitaxel ranged from 0.5 to 10. In only 6 of the cell lines was the relative resistance factor >3, with the maximum resistance factor being about 10 for two resistant tumour cell lines. In a comparative study (cabazitaxel vs docetaxel) in 7 cell lines with acquired resistance to various cytotoxic drugs (doxorubicin, vincristine, vinblastine, docetaxel and paclitaxel) and which overexpressed P-gp, cabazitaxel had lower resistance factors (1.8–10) than docetaxel (4.8–59), probably reflecting a lower recognition of cabazitaxel than docetaxel by P-gp. MDR-1 (P-gp gene) expression levels correlated with docetaxel and cabazitaxel resistance, confirming a role for this transporter in resistance.

Overall, the *in vitro* studies support the use of cabazitaxel in cancer patients previously treated with a docetaxel containing regimen.

A limited number of resistant tumour cell lines were investigated *in vivo* (murine docetaxel resistant B16 melanoma and vincristine resistant P388 leukaemia, and human docetaxel resistant Calc18 mammary adenocarcinoma and UISO BCA-1 mammary carcinoma). Despite the highly promising results for activity of cabazitaxel against resistant cell lines *in vitro*, when tested *in vivo* using the IV route, the activity of cabazitaxel was variable (no activity against the resistant murine leukaemia cell line or the human mammary adenocarcinoma cell line; variable activity against the resistant murine melanoma line, and relatively good activity against the resistant human mammary carcinoma cell line).

Secondary pharmacodynamics

Cabazitaxel, tested at concentrations up to 10 μM (37 times the C_{max} at the MRHD) had little (<22% inhibition) or no affinity for the 25 receptor binding sites tested, which covered a broad range of physiological functions.

Safety pharmacology

A battery of core safety pharmacology studies and some supplementary studies were submitted. These studies investigated the effects on the central and autonomic nervous systems, the cardiovascular and respiratory systems, and the renal and gastrointestinal systems. All were GLP compliant, adequately conducted and generally included appropriate positive controls.

Tissue distribution studies in mice and rats, indicated cabazitaxel and/or its metabolites crossed the blood brain barrier, with significant exposures in the brain, particularly after short IV infusions. In specialised safety pharmacology studies, central nervous system (CNS) function was unaffected in rats treated with doses up to 5 mg/kg IV (short IV infusion) (estimated exposure based on C_{max} ~10 times the clinical C_{max}).[8] No central

[7] Zunino F, Cassinelli G, Polizzi D, Perego P. Molecular mechanisms of resistance to taxanes and therapeutic implications. Drug Resist Update 1999; 6: 351-357.
[8] Based on a C_{max} of 2174 ng/mL estimated from data in Study RPR/RD/CRVA 98-028.

neurotoxicity was seen in rats or dogs in toxicity studies. However, both clinical signs and microscopic signs of central neurotoxicity were evident in mice in submitted toxicity studies. Clinical signs included incoordination, limited/lost use of limbs, piloerection and laboured breathing. Histopathological findings in the CNS of mice included neuronal necrosis and/or vacuolation in the brain and axonal swelling and degeneration in the cervical spinal cord (see *General toxicity*). The No Observable Effect Level (NOEL) for central neurotoxicity in mice was considered to be 10 mg/kg IV (~1 minute [min] infusion) (estimated exposure ratio based on C_{max} [ER_{Cmax}] 37[9]).

Respiratory function was unaffected in rats and anaesthetised dogs at doses up to 5 mg/kg (30 mg/m^2, short IV infusion; ER_{Cmax} ~10) and 0.45 mg/kg (9 mg/m^2, 60 min infusion; ER_{Cmax} 0.3[10]), respectively. In studies to investigate the potential for delayed ventricular repolarisation (QT prolongation), cabazitaxel, at concentrations up to 30 µM (>100 times the expected clinical C_{max}), had minimal inhibitory effects on hERG K+ channels, while at concentrations up to 10 µM, there were no significant effects on action potential parameters in isolated sheep Purkinje fibres. Therefore, QT prolongation is not predicted from *in vitro* data. There were no consistent effects on QT/QTc interval in the cardiovascular safety study in dogs or in the 13 cycle dog study (ER_{Cmax} 0.3). However, these findings were confounded by vehicle effects attributed to polysorbate 80 which is a non-specific histamine releaser in dogs (Masini et al., 1985) and, due to the low doses of cabazitaxel achievable in these studies, limited information or conclusions can be drawn from the negative findings.[11]

Supplementary safety pharmacology studies included investigation of effects on the renal system (urine parameters and electrolyte excretion in saline loaded rats) and the gastrointestinal system (*in vivo* transit time and *in vitro* response to ileal spasmogens), with the *in vivo* studies at doses up to 5 mg/kg IV in rats and *in vitro* concentrations up to 10 µM. In all these studies, cabazitaxel showed no (or minimal) effects, except for a significant reduction in urinary potassium excretion in the study of renal function. No specific findings on the renal system were observed in rats or in dogs in other toxicity studies. Histological changes to the intestines following a single IV dose of 5 or 10 mg/kg to rats did not translate into a functional change in terms of gastrointestinal transit after 5 mg/kg.

Overall, the safety pharmacology studies indicate that cabazitaxel had a similar profile to other taxanes on the cardiovascular, respiratory, renal and gastrointestinal systems. The microscopic findings seen in the CNS of treated rats is not a common feature of the taxane class.

Pharmacokinetics

Absorption

Clearance was high in all species investigated. Volume of distribution at steady state appeared to be large (greater than body water) in all these species (although estimates in mice and dogs varied considerably), consistent with wide tissue distribution of cabazitaxel/metabolites to tissues. In humans, terminal half-life (123 hours [h]) was longer than in the laboratory animal species (0.35-26 h), although estimates in mice and dogs were variable.

[9] Based on a C_{max} of 8400 µg eq/mL (radioactivity) from Study DMPK/FR.2295.
[10] Estimated from data in Study DMPK/FR 2242 where a C_{max} of 81 ng/mL was observed for a 0.5 mg/kg IV dose (72–91 min infusion).
[11] Masini E, Planchenault J, Pezziardi F, Gautier P, Gagnol JP. Histamine releasing properties of polysorbate 80 in vitro and in vivo: correlation with its hypotensive action in the dog. Agents and Actions 1985; 16: 470-477.

There was no clear evidence of a sex difference in the absorption of cabazitaxel in either rats or dogs (only females were investigated in mice), nor in the distribution kinetics in rats. There was little evidence of accumulation following any of the repeated dosing schedules investigated in mice, rats or dogs. Exposure to cabazitaxel increased in an approximately dose proportional manner in mice but generally in a supra dose proportional manner in rats and dogs, possibly due to saturation of metabolic pathways. The proposed Product Information (PI) notes that there was no major deviation to dose proportionality in patients with advanced solid tumours over the relatively narrow dose range of 10 to 30 mg/m^2.

The cabazitaxel metabolites, docetaxel and RPR123142 were only detectable at high doses (10 mg/kg IV, but not 1 mg/kg IV) in mice and rats. Docetaxel was not detectable in dogs but only low doses were achievable in this species. These findings are consistent with cabazitaxel being the main circulating drug related compound.

Distribution

In vitro protein binding was high in all species. At concentrations up to 10 µg/mL, protein binding was >98% in mice, 96–97% in dogs, 95–97% in rats, 85–93% in rabbits and 89-92% in humans , as determined by equilibrium dialysis using [14C]cabazitaxel and, with the exception of mice, there was little evidence of saturation. Some concentration dependent changes in protein binding were seen with mouse plasma, although protein binding remained high at concentrations seen in toxicity studies. Quantitatively lower values were obtained by ultrafiltration using [3H]cabazitaxel but similar species differences were observed. Cabazitaxel was shown to be highly bound to human serum albumin (82.0%) and lipoproteins (high density lipoprotein [HDL] [87.9%]> low density lipoprotein [LDL] [69.8%]> very low density lipoprotein [VLDL] (55.7%)).

Following IV administration of [14C]cabazitaxel, radioactivity was widely distributed to tissues in mice and rats (although the number of tissues examined in mice was relatively limited), as might be expected for a lipophilic compound. The majority of tissues were more highly labelled than blood at all time points examined with the exception of the brain, eye, testis, spinal cord and sciatic nerve which were poorly labelled and elimination from some of these tissues was slower than from blood. Highly perfused tissues and glandular tissues were generally the most highly labelled. Generally, distribution was rapid, although some tissues did not reach peak labelling at the first time point examined. The high labelling of small and large intestinal contents presumably reflects biliary excretion. There was no evidence from pigmented rats of an affinity of drug/metabolites for melanin. There were also no sex differences in distribution in rats. Elimination was largely complete by 168 h (data from pigmented rats).

After administration of 40 mg/kg [14C]cabazitaxel to mice bearing mammary adenocarcinoma 16/C, cabazitaxel was rapidly distributed to the tumour. The area under the plasma concentration time curve from time zero to time t (AUC_{0-t}) for radioactivity in the tumour was higher than in plasma. Although similar findings might be expected for other tumour types, the extent to which the data for mammary adenocarcinoma 16/C are representative of other tumour types is unclear.

Distribution to the brain was examined in particular detail (in mice, rats and dogs; all single dose studies) in order to provide a basis for understanding the central neurotoxic effects of cabazitaxel that were observed in mice but not in rats or dogs. In all these species, radioactivity was rapidly distributed to brain, and although high concentrations of radioactivity were not found in brain, radioactivity was more slowly eliminated from brain than from blood or other organs, and brain:blood AUC ratios ranged from 1–10 in mice, 1–3 in rats and 0.25 in dogs (only one dose tested) and was dependent on infusion rate. In mice, exposure to radioactivity in brain, and brain:blood radioactivity ratios, after a 1 h

infusion were lower than after a 45 second infusion of [14C]cabazitaxel in two studies. Brain:blood and brain:plasma ratios increased with increasing dose. Brain:blood or brain:plasma AUC radioactivity ratios were similar in mice and rats and were slightly lower in dogs but this would have been influenced by dose selection. There were no marked differences in brain metabolic profile in mice, rats and dogs, with the parent drug being the major compound detected in all three species at both time points investigated. In all three species, the distribution of radioactivity within the brain, as revealed by autoradioluminography, was heterogeneous, with highest concentrations in the ventricular system (that is, the lateral and third and fourth ventricles). Ventricle:brain ratios of radioactivity were 6–27 in mice, 12–40 in rats and 103 in dogs. This area of the brain was also where the most marked toxic effects were observed histologically.

A notable finding in the distribution studies in mice, rats and dogs was an increase in blood:plasma radioactivity ratios over time post dose. This might reflect a greater affinity for blood cells of cabazitaxel metabolites compared to parent drug.

Metabolism

Following IV administration, cabazitaxel was extensively metabolised in the liver, with little unchanged drug being excreted in any species. In faeces (the major excretion route), unchanged drug was not detected in rats, dogs and humans with only small amounts (2% of total faecal radioactivity) being detected in mice. In all species, unchanged drug also represented only a small proportion of total urinary radioactivity (<4% in mice, rats, dogs and humans). Overall, ~30 metabolites of cabazitaxel were detected in the various species, with many remaining unidentified. Given the extensive role of hepatic metabolism in the clearance of cabazitaxel, patients with hepatic impairment may be at greater risk of some of the toxicities seen with cabazitaxel and a warning statement in the PI regarding this patient group may be appropriate.

Both *in vivo* and *in vitro* data suggested qualitatively similar biotransformation pathways in humans, mice, rats and dogs.

The main metabolic pathways observed both *in vitro* and *in vivo* were two O-demethylations leading to 7-O-demethyl-cabazitaxel (RPR112698) and 10-O-demethyl-cabazitaxel (RPR123142), and a t-butyl hydroxylation on the lateral chain, followed by cyclisation leading to oxazolidine or oxazolidinone type compounds.

A minor pathway was cleavage of cabazitaxel, leading to RPR130523 (lateral side chain) and the taxane ring.

Many combinations of these metabolic pathways were observed, most notably, di-demethylation to form docetaxel (7,10-O-demethyl-cabazitaxel, RP 56976). These four metabolic pathways were found in all species (mice, rats, dogs and humans). *In vitro* experiments revealed a major role of human cytochrome P450 (CYP)3A4 and CYP3A5, and to a lesser extent, CYP2C8, in the metabolism of cabazitaxel.

Despite the extensive metabolism of cabazitaxel, the parent drug was the main circulating compound in all species investigated, representing 70% of plasma radioactivity under the plasma concentration time curve from time zero to 5 or 11 hours ($AUC_{0\text{-}5/11h}$) in humans, 65% and 82% of the AUC from 0 to 24 hours ($AUC_{0\text{-}24h}$) in mice and rats, respectively, and 80% of the AUC from 0 to 48 hours ($AUC_{0\text{-}48h}$) in dogs.

Relatively few of the metabolites formed from cabazitaxel were detected in plasma. The major circulating metabolite in humans was RPR123142 but it only represented 3.6% of plasma radioactivity $AUC_{0\text{-}5/11h}$. The major circulating metabolite in mice was also RPR123142, representing 16.5% of $AUC_{0\text{-}24h}$. In dogs, although RPR123142 was not the major circulating metabolite, it represented 4.4% of plasma radioactivity $AUC_{0\text{-}48h}$, a higher

percent than in humans. RPR123142 was detected in the plasma of male rats but was not a major circulating metabolite in this species.

Excretion

The pattern of excretion following IV administration was similar in humans and the laboratory animal species (mice, rats and dogs), with faeces being the major route of excretion and less than 5% of the administered dose being excreted in urine over the measured intervals in all species. In bile duct cannulated rats, it was demonstrated that the majority of faecal excretion was via bile. The extent of enterohepatic recycling was not investigated, although the finding of secondary peaks in plasma cabazitaxel concentrations in some studies in dogs suggests that this may have occurred, at least in this species.

In conclusion, mice, rats and dogs are acceptable models for the study of cabazitaxel, with cabazitaxel pharmacokinetic characteristics (absorption, metabolism and excretion) in these species being similar to those in humans.

Pharmacokinetic drug interactions

No *in vivo* drug interaction studies were conducted and there were no specific nonclinical investigations of cabazitaxel interactions with prednisone/prednisolone.

In vitro, no clinically relevant inhibition of CYP1A2, 2B6, 2C9, 2C19, 2D6 or 2E1 enzyme activities was seen with cabazitaxel concentrations up to 200 μM. The only notable inhibition was on CYP3A (midazolam substrate; inhibitory rate constant [K_i] 2 μM, about 7× C_{max}). The K_i for cabazitaxel inhibition of paclitaxel metabolism (mediated by CYP2C8) was 3.3 μM (about 12× the clinical C_{max}). In human hepatocytes, there was no consistent evidence of the induction of CYP1A2, 2C9 or 3A4 (gene expression and marker enzyme activity), with cabazitaxel concentrations tested up to 10 μM. With the possible exception of CYP3A, cabazitaxel at the maximum recommended human dose (MRHD) is unlikely to cause any clinically relevant inhibition or induction of CYP450 enzymes.

As cabazitaxel is mainly metabolised by CYP3A, its metabolism might be expected to be influenced by coadministered drugs that inhibit or induce CYP3A or are also primarily metabolised by CYP3A. This is noted in the PI. Inhibition of cabazitaxel metabolism by various drugs was investigated in human liver microsomes. The data suggested that there was unlikely to be inhibition by dexchlorpheniramine, granisetron, morphine, ondansetron, ranitidine, omeprazole, acetaminophen or warfarin.

Cabazitaxel was found to be a highly permeable compound, as might be expected from its lipophilicity. It was shown to be a P-gp substrate at circulating concentrations *in vivo*. Cabazitaxel was found to be a P-gp inhibitor, but IC_{50} values (10–17 μM) were well above the clinical C_{max} (37 fold) and therefore inhibition of P-gp is unlikely to occur with the proposed clinical dose. Cabazitaxel was not a substrate for hMRP1, hMRP2 or hBCRP efflux transporters and no clinically relevant inhibition of the hMRP1, hMRP2 or hBCRP transporters was seen.

Toxicology

Single dose toxicity

Single dose toxicity studies using only the intravenous route were conducted in mice, rats and dogs. Appropriate observation periods were included. The maximum non-lethal doses were 25 mg/kg (75 mg/m^2) in mice, 2.5 mg/kg (15 mg/m^2) in rats and 0.5 mg/kg (10 mg/m^2) in dogs. There was very little margin between non-lethal and lethal doses, suggesting a high order of toxicity in these species. In the rat and dog studies, deaths

occurred at doses similar to the clinical dose (based on body surface area). The target organs for toxicity were the CNS (in mice), male reproductive organs (rats and dogs), bone marrow (rats and dogs), liver (rats and dogs) and the gastrointestinal tract (dogs only). Haematological changes associated with bone marrow toxicity (lymphopenia, neutropenia and anaemia) developed from Day 3 and showed a trend to recovery from Day 14.

Repeat dose toxicity

All toxicity studies were conducted with administration by the IV route which is the proposed clinical route of administration. The duration of administration of the dose varied between a short infusion (generally about 1 min) to a longer infusion (generally about 1 h). Repeat dose toxicity studies were conducted in mice, rats and dogs.

As noted above, these species are acceptable models. Studies were generally adequate in terms of duration, dosing frequency, animal numbers, the timing of investigations and other aspects of study design. The doses chosen, limited by toxicity, were generally acceptable, . Exposures at the highest adequately tested doses were >10 in mice and 2 in rats but were subclinical in dogs. Different dosing schedules were tested including daily administration (mice, rats and dogs), weekly administration (mice and dogs) and administration once every 3 weeks (mice, rats and dogs). The latter, as this is proposed clinical schedule, was chosen and cabazitaxel administered by 1 h infusion in these studies. Additionally, in rats, a study with daily administration for 4 weeks provided information for the selection of doses for the reproductive toxicity studies. The vehicle used in most of these studies was prepared from a stock solution of cabazitaxel in polysorbate 80 by dilution with 13% ethanol and then 5% glucose and was comparable to that proposed for registration. As expected, in all species, lethality, as well as other toxic effects, was influenced by dose, dosing frequency and dosing interval. Relative exposure of cabazitaxel in repeat dose toxicity studies is shown in Table 1.

Table 1: Relative exposure of cabazitaxel in repeat dose toxicity studies

Species (Strain)	Duration/frequency	Dose (mg/kg/IV dose)	AUC0–24h (ng·h/mL)	AUC over 3 weeks (ng·h/mL)	Exposure ratio based on AUC[a]
Mouse (CD-1)	5 cycles (1h infusion/ 3 weeks)	5	5593	5593	6
		10	14146	14146	15
		15	13147	13147	14
Rat (SD)	5 days (1 min daily)	0.25	11.2[b]	56	0.06
		0.5	20.6 [b]	103	0.1
		1	76.9 [b]	385	0.4
	10 cycles (1 h infusion/ 3 weeks)	1	144	144	0.2
		5	942	942	1.0
		10	1910	1910	2

Species (Strain)	Duration/frequency	Dose (mg/kg/IV dose)	AUC0–24h (ng·h/mL)	AUC over 3 weeks (ng·h/mL)	Exposure ratio based on AUC[a]
		20	9445	9445	10[d]
Dog (Beagle)	5 days (1h infusion daily)	0.1	6.7[c]	34	0.04
	13 cycles (1h infusion/ 3 weeks)	0.1	9	9	0.01
		0.25	49	49	0.05
		0.5	157	157	0.2
Human	2 cycles (1h/3 weeks)	[25 mg/m^2]	953	953	–

a calculated as animal:human AUC over 3 weeks; data are for the sexes combined, and averages across sampling days;
b AUC_{0-6h}
c AUC_{0-2h}
d only one dose achievable at this level due to severe toxicity, dose was lowered to 10 mg/kg

Toxicological effects typical of the taxane class

Most of the findings of toxicity were typical for this class of drugs and included peripheral neurotoxicity (axonal degeneration of the sciatic nerve; mice at ≥5 mg/kg/3 weeks and rats at ≥1 mg/kg/3 weeks), bone marrow hypocellularity with secondary haematological changes (anaemia, lymphopenia, neutropenia and thrombocytopenia; rats at ≥1 mg/kg/3 weeks and dogs at 0.5 mg/kg/3 weeks), lymphoid atrophy and/or lymphocytolysis in the thymus, spleen and/or lymph nodes (rats at ≥1 mg/kg/3 weeks and dogs at 0.325 mg/kg/week), epithelial cell necrosis and/or cell degeneration/regeneration of the gastrointestinal tract (≥1 mg/kg/3 weeks in rats and ≥0.25 mg/kg/3 weeks in dogs) and atrophy, cell necrosis and/or regeneration in male reproductive organs (rats at ≥1 mg/kg/3 weeks and dogs at ≥0.225 mg/kg/week). The loss of mucosal integrity in the gastrointestinal tract was associated with diarrhoea in dogs. Following multiple cycle dosing to rats, drug related changes were seen on the skin (alopecia correlated microscopically with cell degeneration), which is not unusual for this type of drug. With the exception of peripheral neurotoxicity, all of these findings showed a trend to reversion following an 8 week treatment free period.

Toxicological findings distinct from other taxanes

Additional findings not typically observed with taxanes were hepatotoxicity, central neurotoxicity, ocular findings and effects on bone growth plates. Hepatic lesions were observed in all species and generally with higher incidence and greater severity with more frequent dosing. Chronic inflammation was observed in mice treated with 5 mg/kg/day cabazitaxel for 5 days. Hepatocellular necrosis was seen in rats treated with 0.3 mg/kg/day for 4 weeks with Kupffer cell pigmentation and degeneration/regeneration of bile ducts seen in this species treated with 10 mg/kg/3 weeks for 10 cycles. Hepatocellular necrosis/atrophy, bile ductule hyperplasia and/or intrahepatic cholestasis were seen in

dogs treated with 0.325 mg/kg/week for 4 weeks or ≥0.2 mg/kg/day for 5 days. In dogs, these changes were accompanied by increases in alanine aminotransferase (ALT), alkaline phosphatase (ALP) and cholesterol levels. Only transient, inconsistent hepatic changes were seen in all species with a 3 week dosing regimen.

Central neurotoxicity was characterised by neuronal necrosis and/or vacuolation in the brain (cerebellum region close to the lateral and fourth ventricles) and axonal degeneration of the spinal cord. These findings were seen in mice after single or repeated doses (≥15 mg/kg; approximately 14 times the clinical AUC). CNS lesions were restricted to the spinal cord (axonal degeneration) in rats treated with ≥5 mg/kg/3 weeks; however, a dose related increase in incidence was not always apparent.

Lens fibre swelling/degeneration seen in almost all animals and single cell necrosis in the cornea seen in some animals treated with 10 mg/kg/3 weeks. After an 8 week treatment free period, 9 of the 10 rats that had received 10 mg/kg/3 weeks cabazitaxel had lens fibre swelling and/or degeneration, suggesting this abnormality was not reversible. No eye abnormalities were noted in dogs treated for 13 cycles. However, systemic exposures were low in the dog study and the duration of treatment in mice could potentially be too short for these eye abnormalities to manifest. Therefore, limited conclusions can be drawn from the negative findings in these two species. The clinical relevance of the eye changes is uncertain. As they occurred at exposures similar to or marginally greater than that expected clinically, appropriate monitoring may be required during clinical use.

Atrophic and dysplastic changes were seen in the incisor teeth of rats treated with ≥1 mg/kg/3 weeks for 10 cycles. No gross changes were seen in the molars of rats or in the teeth of dogs. The changes observed in rats are associated with growing teeth (rat incisors grow continuously) and are not clinically relevant for an adult population. Irregularity of growth plates was seen in the femur of rats treated with ≥5 mg/kg/3 weeks. There was no evidence of reversibility of the teeth or growth plate findings after an 8 week treatment free period. Taken together, the findings suggest an effect of cabazitaxel on growth and development. This is not of particular concern for the intended patient population.

Many of the toxic effects of cabazitaxel (most notably, haematopoietic toxicity and toxicity to lymphoid organs, the gastrointestinal tract, male reproductive system, skin and peripheral nervous system) were similar to those induced by other taxanes such as paclitaxel and docetaxel, and are consistent with the pharmacological activity of this group of drugs (Rowinsky et al., 1990; Bissery et al., 1995; Cavaletti et al., 1997).[12,13,14] The liver and biliary system are exposed to drug/metabolites since it is the major organ of metabolism and excretion. The lenticular changes are of unknown clinical relevance, while effects on bone growth plates and growing teeth are not clinically relevant for the intended patient population. Many of these effects occurred at or below clinical exposures, indicating low or no safety margins. The central neurotoxicity observed in mice occurred at sufficiently high exposures that it is unlikely to be of concern at the proposed clinical dose. No toxicity studies were conducted with a cabazitaxel/prednisone combination.

Genotoxicity

An acceptable package of genotoxicity studies was submitted, including two bacterial reverse mutation studies, a chromosomal aberration study in peripheral blood

[12] Rowinsky EK, Cazenave LA, Donehower RC. Taxol: A novel investigational antimicrotubule agent. JNCI 1990; 82: 1247-1258.
[13] Bissery M-C, Nohynek G, Sanderlink G-J, Lavelle F. Docetaxel (Taxotere®): a review of preclinical and clinical experience. Part I: preclinical experience. Anti Cancer Drugs 1997; 6: 339-368.
[14] Cavaletti G, Cavaletti E, Montaguti P, Oggioni N, De Negri O, Tredici G. Effect on the peripheral nervous system of the short-term intravenous administration of paclitaxel in the rat. NeuroToxic 1997; 18: 137-146.

lymphocytes and an *in vivo* rat micronucleus study. Metabolic activation in the *in vitro* studies was achieved with rat liver S9 mix which metabolic studies revealed to be adequate for metabolising cabazitaxel. Positive controls gave the expected findings in all studies. The bacterial reverse mutation tests, which gave negative results, were adequately conducted, with appropriate strains and cabazitaxel was tested up to precipitating concentrations. The chromosomal aberration study involving two separate assays gave negative results for structural aberrations but cabazitaxel increased the number of polyploidy cells. Increases in mitotic index were observed, as might be expected given the pharmacological activity of the drug but concentrations tested were adequate. In the rat micronucleus test, all tested doses elicited significant increases in the incidence of micronucleated polychromatic erythrocytes, as might be expected from the pharmacological activity of the drug. Therefore, as with paclitaxel and docetaxel (Bissery et al., 1995), cabazitaxel is clastogenic.[13]

Carcinogenicity

Based on its positive findings in genotoxicity tests, and on its mode of action, cabazitaxel may be a carcinogen. No carcinogenicity studies were submitted but this is considered acceptable as the proposed indication is for the treatment of advanced cancer .[15]

Reproductive toxicity

Reproductive toxicity studies examined both male and female fertility (in rats) and embryofetal development (rats and rabbits). Although the proposed indication is for males only, the submitted studies allow for easy extensions of indication in the future. All the reproductive toxicity studies used daily IV dosing which is appropriate, but doses used, based on body surface area, were generally below that expected clinically (Table 2).

Table 2: Reproductive toxicity studies

Study	Dose frequency	mg/kg/dose	mg/kg/3 weeks	mg/m^2/3 weeks	Relative dose based on BSA[a]
Fertility study (Rats)	daily	0.05	1.1	6.6	0.26
		0.1	2.1	13	0.5
		0.2	4.2	25	1
Embryofetal studies (Rats)	daily	0.04	0.84	5.0	0.2
		0.08	1.7	10	0.4
		0.16	3.4	20	0.8
		0.25	5.3	32	1.3
Embryofetal	daily	0.01	0.21	2.5	0.1

[15] EMEA, ICH Topic S9, Nonclinical Evaluation for Anticancer Pharmaceuticals, November 2009. Note for Guidance on Nonclinical Evaluation for Anticancer Pharmaceuticals (EMEA/CHMP/ICH/646107/2008).

Study	Dose frequency	mg/kg/dose	mg/kg/3 weeks	mg/m²/3 weeks	Relative dose based on BSA[a]
studies (Rabbits)		0.02	0.42	5.0	0.2
		0.03	0.63	7.6	0.3
		0.04	0.84	10	0.4
		0.08	1.7	20	0.8
Human	every 3 weeks	–	–	25	–

a: BSA = body surface area

The fertility studies used an appropriate number of animals and dosing periods. There was no effect of cabazitaxel on mating performance or fertility in either males or females at the doses tested, up to 0.2 mg/kg/day in both sexes, with the high dose eliciting toxicity (reduced food consumption and body weight gain) in the treated animals of both sexes. However, due to the low relative doses used in these studies, limited conclusions can be drawn from the negative findings. In repeat dose toxicity studies, seminiferous tubular atrophy in the testes, degeneration/regeneration of the seminal vesicles and oligospermia were observed in male rats treated with ≥5 mg/kg/3 weeks IV cabazitaxel (approximately equivalent to the clinical exposure based on AUC). Histopathological changes were also seen in the female reproductive organs at these doses, suggesting an effect on both male and female fertility cannot be dismissed. Both docetaxel and paclitaxel have been reported to have adverse effects on fertility (both male and female), and therefore, the same may be expected with cabazitaxel.

Cabazitaxel and/or its metabolites crossed the placenta in rats with drug related material detected in the fetal liver. Embryofetal development studies in rats and rabbits were adequately conducted, with appropriate dosing regimens and investigations, sufficient animals and dose levels based on the results of dose range finding studies. In rats, pre-implantation loss was not affected by cabazitaxel treatment but post-implantation loss was increased at ≥0.16 mg/kg/day, associated with increases in the number of dead fetuses, with a resulting reduced number of live fetuses/litter. There was no evidence of an effect of treatment on external or visceral fetal findings but fetal weights were reduced and there were delays in skeletal ossification of some bones and small, dose related increases in incidences of skeletal variations (misaligned sternebra and supernumerary ribs) at ≥0.08 mg/kg/day. No historical control data for incidences of skeletal variations were provided for the laboratory undertaking the study, but fetal and litter incidences of both supernumerary ribs and misaligned sternebra were within historical control ranges. Embryofetal toxicity was observed at a dose below that eliciting maternal toxicity, suggesting a direct effect of cabazitaxel in the adverse effects. Similar findings (increased number of resorptions, decreased fetal weight and delayed ossification) have been reported for docetaxel.

In rabbits, there were no effects on embryofetal development (pre-implantation loss, post-implantation loss, live fetuses/litter, fetal weights, or external or visceral fetal findings) in either the main study or the dose range finding study (at up to lethal doses in the latter). There was a small increase in incidence of absent or small interparietal bone in the skull at the high dose (HD) in the main study (14.1% of fetuses affected vs 4.2% for the control

group) but this was said to lie within the historical control range for this finding in this laboratory (maximum 16.5%; data not presented).

Cabazitaxel and/or its metabolites were excreted in milk with drug related material detected in the stomach and intestinal contents of breastfed pups. It was estimated that 0.23% to 1.5% of the dose was excreted in milk over 24 h. No postnatal development studies were submitted, which is considered acceptable given the intended indication.

Local tolerance

Appropriate local tolerance studies were conducted for a drug to be administered intravenously (compatibility with human serum, plasma and whole blood and parenteral tolerance in rabbit ears [IV, paravenous and intra-arterial routes]). The vehicle used in these studies was prepared from a stock solution of cabazitaxel in polysorbate 80 by dilution with 13% ethanol and then 5% glucose and was comparable to that proposed for registration. In the haemocompatibility study, cabazitaxel was tested at concentrations up to 1 mg/mL which is higher (4×) than the concentration in the final diluted preparation proposed for clinical use (0.1–0.26 mg/mL). There was no evidence of incompatibility with any of these matrices, but slight haemolysis was observed at 0.5 and 1 mg/mL for cabazitaxel and/or the corresponding vehicle control, presumably due to the presence of polysorbate 80.

Cabazitaxel was tested at 1 and 2 mg/mL in the parenteral local tolerance study. There was no evidence of a local irritant effect of cabazitaxel or vehicle in this study, except for some dermal inflammation after paravenous administration. The toxicity studies did not reveal any notable irritation at the injection site.

Impurities

In the proposed drug substance specifications for cabazitaxel, 5 impurities are specified above the qualification threshold outlined in the TGA-adopted EU guideline (that is, 0.15%) (Table 3).[16] To support toxicological qualification, the sponsor submitted an *in vitro* bacterial mutagenicity study and toxicity studies with cabazitaxel batches containing appreciable levels of these impurities.

Table 3: Details of impurities tested

Impurity	Limit in drug substance	Maximum clinical dose[a] (mg/m²/3 weeks)
RPR226213	0.20%	50
RPR225590	0.20%	50
RPR224036 + RPR224038	0.20%	50
RPR225992	0.40%	100
RPR204899	0.20%	50

a: based on a 25 mg/m²/3 week dose

[16] EMEA, ICH Topic Q 3 A (R), 21 February 2002. Note for Guidance on Impurities Testing: Impurities in New Drug Substances (Revision of CPMP/ICH/142/95), CPMP/ICH/2737/99.

Although there was no evidence of mutagenicity in the submitted Ames test, the concentrations of impurities in this assay were too low to adequately ascertain the genotoxic potential of individual impurities (Kenyon et al., 2007).[17] This is not considered a deficiency, as cabazitaxel itself is clastogenic, so extensive genotoxicity testing of these impurities would generally not be required. Toxicity studies in mice and rats using batches of cabazitaxel with appreciable levels of these impurities, revealed no novel toxicities that could be attributed to the impurities. The levels of RPR226213, RPR225590, RPR224036/RPR224038, RPR225992 and RPR204899 in these studies were ≥2 times the maximum expected dose in patients (based on body surface area).

Therefore, the proposed limits for RPR226213, RPR225590, RPR224036/RPR224038, RPR225992 and RPR204899 can be considered toxicologically qualified.

Methyl iodide, a reagent used in the synthesis of cabazitaxel, has been shown to be mutagenic in an Ames test (McCann et al., 1975).[18] Methyl iodide was apparently not detected in batches of cabazitaxel. The limit of detection (LOD) was 150 ppm. With a clinical dose of cabazitaxel (25 mg/m^2/3 weeks), the maximum level of methyl iodide, based on its LOD, would be 3.8 µg/m^2/3 weeks or 0.3 µg/day, based on a body surface area of 1.7 m^2. As this is below the threshold of toxicological concern (1.5 µg/day), levels of methyl iodide <150 ppm in the drug substance are considered acceptable.

Nonclinical summary and conclusions

Like other taxanes, the mechanism of action of cabazitaxel is to disrupt the microtubular network which is vital to cell mitotic functions. Cabazitaxel showed good *in vitro* cytotoxic activity against a range of murine and human tumour cell lines. IC_{50} values (2.6–34 ng/mL) were below plasma C_{max} values expected at the maximum recommended human dose (MRHD). Against drug resistant cell lines, cabazitaxel had lower resistance factors than docetaxel. *In vivo*, cabazitaxel showed variable activity against murine tumours but good activity against advanced human tumour xenografts, including prostate carcinoma DU 145. Cabazitaxel was active against docetaxel sensitive tumours. *In vivo* activity against drug resistant tumours was variable.

No clinically relevant inhibition of 25 receptor binding sites was observed. Cabazitaxel showed few effects in safety pharmacology studies in rats and anaesthetised dogs. Studies included supplementary, as well as core studies, and maximum possible doses were tested. At concentrations up to 30 µM (significantly higher than the clinical C_{max}), cabazitaxel had no significant effects on hERG current (hERG channel expressed in CHO cells) or on action potential parameters in isolated sheep Purkinje fibres.

Cabazitaxel pharmacokinetics following IV administration were characterised by rapid clearance and a large volume of distribution in all species (mice, rats, dogs and humans), although half life was longer in humans than in the laboratory animal species. Cabazitaxel and/or its metabolites were widely distributed in rats, with high concentrations in highly perfused tissues, the gastrointestinal tract (consistent with biliary excretion) and glandular tissues/organs. Radioactivity was more slowly eliminated from the brain than from blood or other organs. Distribution of radioactivity within the brain was heterogeneous, with highest concentrations in the ventricular system. There was no evidence in pigmented rats of an affinity of drug/metabolites for melanin. *In vitro* protein binding was high (>85%) in all species. Cabazitaxel/metabolites crossed the placenta in pregnant rats and small amounts were excreted into milk in lactating rats.

[17] Kenyon MO, Cheung JR, Dobo KL, Ku WW. An evaluation of the sensitivity of the Ames assay to discern low-level mutagenic impurities. Regul Toxicol Pharmacol 2007; 48: 75-86.
[18] McCann J, Choi E, Yamasaki E, Ames B. Detection of carcinogens as mutagens in the salmonella/microsome test: assay of 300 chemicals. Proc Natl Acad Sci USA 1975; 72: 5135-5139.

The major metabolic pathways for cabazitaxel were O-demethylations and a t-butyl hydroxylation on the lateral chain, followed by cyclisation leading to oxazolidine or oxazolidinone type compounds. These pathways were found in all species (mice, rats, dogs and humans). In all tested species, although cabazitaxel was extensively metabolised with little excreted as parent drug, cabazitaxel was the main circulating compound. Metabolism of cabazitaxel was shown to be largely catalysed by CYP3A4 and CYP3A5 and to a lesser extent by CYP2C8. Excretion was largely biliary (<5% in urine in mice, rats, dogs and humans).

No *in vivo* drug interaction studies were conducted but *in vitro* studies suggested that, with the possible exception of CYP3A, cabazitaxel at the MRHD is unlikely to cause any clinically relevant inhibition or induction of CYP450 enzymes.

An acceptable package of toxicity studies was submitted. The highest non lethal doses in the pivotal studies were similar to those in the single dose studies. Toxicokinetic data were limited in mice but at the highest non lethal dose, exposure ratios (ER; based on AUC) would be expected to be >10, whereas in rats and dogs, they were generally <1. In all species, death was preceded by body weight loss (associated with reduced food consumption) and general debilitation with mortalities in the rat and dog studies occurring at doses similar to the clinical dose on a body surface area basis.

Nervous system (peripheral and central) toxicity was extensively studied in mice. It was characterised by dose related degenerative changes consisting of axonal/neuronal necrosis, fragmentation and dilatation/swelling, and vacuolation and formation of ellipsoids. At 20 weeks after a single dose in mice changes observed in the CNS had largely resolved but peripheral nervous systemic changes had only partially resolved. The NOEL for CNS toxicity was 10 mg/kg (ER based on AUC =15), while a NOEL was not determined for peripheral nerve fibre degeneration (ER at the lowest observable effect level was about 6).

In rats and dogs, the main target organs were those with rapid cell turnover: bone marrow with secondary haematological changes, lymphoid tissues, gastrointestinal tract, the male reproductive tract and the skin (including alopecia). These are also target organs for other taxanes. Additional toxicity findings that are potentially clinically relevant were in the liver (mainly hepatocellular necrosis and/or vacuolation) and ocular tissues (lens fibre swelling/degeneration). Most of the effects were seen at or below the clinical exposure, suggesting no or low safety margins. Abnormalities seen in growing teeth and growth plates in bones are unlikely to be of clinical concern for the intended patient population. With the exception of lenticular changes and teeth/growth plate deformities, all changes recovered or showed a trend to recovery after an 8 week treatment free period.

Genotoxicity studies included bacterial mutagenicity and *in vitro* clastogenicity studies and an *in vivo* rat micronucleus study. Cabazitaxel was not mutagenic in bacterial cells but an increase in the number of polyploidy cells was seen in the *in vitro* clastogenicity study and an increase in micronucleated cells was seen in the *in vivo* study. The positive findings are expected from the pharmacological activity of the drug. Carcinogenicity studies were not submitted.

Male and female fertility studies in rats and embryofetal development studies in rats and rabbits used daily IV dosing which achieved dose ratios well below 1. At these low doses, there was no effect of cabazitaxel on mating performance or fertility in either sex, although the reproductive system (particularly in males) is a target organ for cabazitaxel toxicity. There were no effects on embryofetal development in rabbits at up to lethal doses. In rats, increased rates of post-implantation fetal loss, reduced fetal weights and ossification delays in some bones were observed. Similar findings have been observed with other taxanes. Pre-postnatal studies were not submitted.

Cabazitaxel showed little or no effects in local tolerance studies (compatibility with blood and plasma, and IV, intra-arterial and paravenous local irritation on rabbit ears; concentrations higher than in the formulation for registration) or at the injection site in the toxicity studies.

The proposed specifications of a number of impurities in the cabazitaxel drug substance were adequately qualified by submitted data.

In summary, cabazitaxel was well characterised in nonclinical studies. It showed good *in vivo* activity against a range of tumour cell lines, including a human prostate tumour cell line treated at an advanced stage, thus supporting the proposed indication. However, relatively high toxicity was observed in nonclinical studies, with bone marrow and lymphoid tissue changes with secondary haematological effects (lymphopenia, neutropenia, anaemia and thrombocytopenia), gastrointestinal toxicity, alopecia, peripheral neurotoxicity and effects on the male reproductive tract. All of these have been observed with other taxanes. Additional toxicities unique to cabazitaxel, and of unknown clinical relevance, were hepatotoxicity and lenticular changes. Drug related deaths occurred in rats and dogs at or below the proposed therapeutic dose, based on body surface area, while toxicities were seen at exposures below or within the range anticipated clinically.

Thus, a safety margin has not been established for the intended clinical use of cabazitaxel. Therefore, registration of cabazitaxel at the proposed clinical dose was not supported by the nonclinical data.

IV. Clinical findings

Introduction

The submission contained the following clinical information:

Studies TED 6188, TED 6189, TED 6190, ARD 6191 and TCD 6945 are dose finding studies, and including Study BEX 6702 and Study MEH 0033, provided pharmacokinetic data.

Study POH 0124: population pharmacokinetic analyses.

Study POH 0258 provided pharmacokinetic/pharmacodynamic data.

Study EFC 6193: pivotal efficacy/safety study.

Pharmacokinetics

Introduction

Table 4 shows the studies relating to each pharmacokinetic (PK) topic.

Table 4: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID
PK in patients	General PK - Single dose	EFC 6193 ARD 6191
	Multi-dose	TED 6188

PK topic	Subtopic	Study ID
		TED 6189 TED 6190 BEX 6702 MEH 0033
	Combination with capecitabine	TCD 6945
Population PK analyses	Healthy subjects	n/a
	Target population	POHO 124
	Other	

In the PK studies, cabazitaxel was administered as a one hour intravenous (IV) infusion once every 3 weeks in studies TED 6188 (21 patients), TED 6190 (25 patients), BEX 6702 (4 patients) TCD 6945 (34 patients), ARD 6191 (71 patients) and EFC 6193 (67 patients). In study TED 6189 (31 patients), cabazitaxel was administered weekly for 4 weeks of every 5 week cycle as a one hour IV infusion. In all the studies, PK sampling was performed on Days 1 and 22 of each cycle, over 2 consecutive cycles and possibly a third. The calculation of PK parameters was achieved using non-compartmental analysis, by individual modelling or by population PK analysis. The population PK study (POH 0124), used data from studies TED 6188, TED 6189, TED 6190, ARD 6191 and EFC 6193. Population PK corrected the impact of the different sampling durations after infusion, which ranged from 48 hours (h) to 240 h and demonstrated longer terminal half-life, larger volume of distribution at steady state and lower clearance values than those obtained in individual studies.

Cabazitaxel was converted into 3 demethylated metabolites: RPR123142, RPR112698 and docetaxel. The main metabolite, RPR 123142, corresponded to 3.6% of radioactivity AUC and 5.1% of parent AUC. All the other circulating metabolites represented an average less than 2.3% radioactivity AUC (BEX 6702, MEH 0033).

Pharmacokinetics in the target population

Absorption

Sites and mechanisms of absorption

The mean population PK predicted maximum concentration after an IV infusion of cabazitaxel 25 mg/m^2 over 1 h in 67 patients with hormone refractory prostate cancer (EFC 6193) was similar to the range of values obtained when cabazitaxel was administered as monotherapy in studies TED 6190, TED 6189 and BEX 6702 at the same dose level.

Bioavailability

Absolute bioavailability

In study TED 6189, 9 of 11 patients were treated with cabazitaxel 8.4 mg/m^2 orally on Day 1. This was followed by an IV infusion of cabazitaxel 8.4 mg/m^2 on Day 8. The bioavailability was low at 5.76% (coefficient of variation [CV]: 98%). In study TED 6190, 8 of 11 patients were treated with cabazitaxel 20 mg/m^2 orally on Day 1 and cabazitaxel 20 mg/m^2 as a one hour IV infusion on Day 21. The bioavailability was again low at 7.37%

(CV: 103%). The low bioavailability is most likely due to high first pass effect, which was expected for cabazitaxel, which has a high plasma clearance mediated by the liver.

Distribution

Volume of distribution

In study BEX 6702, after a 1 h infusion of 25 mg/m^2 of [^{14}C]-cabazitaxel, the mean value of the radioactive blood to plasma ratio at mid and end of infusion, where unchanged drug was the main component circulating in plasma, was 1.1. This indicates that cabazitaxel is equally distributed between blood cells and plasma. The mean volume of distribution at steady state in the final population PK model for a non-breast cancer patient with a body surface area (BSA) of 1.84 m^2 was 4870 L.

Plasma protein binding

Cabazitaxel was strongly bound to plasma.

Erythrocyte distribution

No specific affinity for red cells was observed but the increase of radioactivity blood to plasma ratio suggests an affinity of some metabolites for erythrocytes.

Metabolism

In vitro experiments have shown that cabazitaxel is converted to 3 hydroxylated compounds, RPR 112698, RPR 123142 and RP56976 (docetaxel), and then from successive oxidation processes to RPR 104952 and RPR 111026. Study BEX 6702 showed that > 80% of the radiolabeled cabazitaxel was excreted in faeces as metabolites and only 2.3% of the dose in urine as cabazitaxel, indicating that cabazitaxel is extensively metabolised and excreted.

In plasma, cabazitaxel accounted for 70% on average of the total radioactivity. All the metabolites quantified in plasma accounted for < 4% of radioactivity AUC. The main metabolite, RPR 123142 accounted for 3.6% of the radioactivity AUC and 5.1% of the parent drug AUC. The pharmacologically active metabolites, RPR 123142 and RPR 112698, would therefore appear to be clinically irrelevant.

Excretion

Routes and mechanisms of excretion

In study BEX 6702, following the administration of 25 mg/m^2 of [^{14}C]-cabazitaxel, the radioactivity was mainly excreted in faeces (76% of the administered dose) as metabolites. Urinary excretion accounted for 3.7% of the dose with 2.3% excreted as unchanged drug (study MEH0033). The mean recovery was 79.7% of the dose within 2 weeks.

The elimination profile of cabazitaxel has been shown to be triphasic, with rapid initial and intermediate phases (half-life [$t_{1/2}$]: 4.4 minutes [min] and 1.6 h respectively) followed by a long terminal phase with a half-life of 95.1 h (Study POH 0124).

Renal clearance

Following a 1 h infusion of cabazitaxel, the clearance was a population value of 48.5 L/h (for a patient with median BSA of 1.84 m^2). This was comparable with the clearance estimated in patients with advanced solid tumours. However, it was more than twofold higher than that estimated in patients with metastatic breast cancer in Study ARD 6191.

Pharmacokinetics in other special populations

Pharmacokinetics in subjects with impaired hepatic function

Cabazitaxel is mainly metabolized by the liver. However, the limited number of patients with abnormal liver function prevents any conclusion being reached.

Pharmacokinetics in subjects with impaired renal function

Cabazitaxel is minimally excreted via the kidneys. In the population PK analysis, of the 170 patients, 14 patients had moderate renal impairment (creatinine clearance [CLcr] ≥30 to ≤50 mL/min) and 59 had mild renal impairment (CLcr ≥50 to ≤80 mL/min). Mild to moderate renal impairment appears not to have significant effects on the PK of cabazitaxel.

Pharmacokinetics according to age

The population PK analysis did not identify age as a significant factor in cabazitaxel PK.

Pharmacokinetics related to genetic factors (sex, ethnicity, genetic polymorphism)

Plasma clearance in studies of patients with advanced solid tumours was the same in both males and females. In Study TCD 6945, the plasma clearance of cabazitaxel when used in combination with capecitabine for the treatment of patients with metastatic breast cancer was similar to that when cabazitaxel was used as monotherapy in patients with advanced solid tumours. In Study ARD 6191 of cabazitaxel monotherapy in patients with metastatic breast cancer, the clearance was much lower. The evaluator noted that it is possible that tumour type rather than gender was the possible cause for the difference. The sponsor indicated that the lower plasma CL value observed in study ARD6191 is most likely attributed to a study effect rather than a tumour type effect or gender effect.

Pharmacokinetic interactions

Pharmacokinetic interactions demonstrated in human studies

In Study TCD 6945, cabazitaxel was used in combination with capecitabine in the treatment of patients with metastatic breast cancer. Capecitabine is converted to 5-fluorouracil (5-FU) in tumours. The PK parameters for capecitabine at dose levels I and III were (AUC: 6060 - 8870 ng.h/mL) and 5-FU (AUC: 334 - 495 ng.h/mL) and were similar to that reported in the literature at the same dose. Cabazitaxel therefore does not appear to alter the PK of capecitabine and 5-FU. Similarly capecitabine appears not to alter the PK of cabazitaxel.

Evaluator's overall conclusions on pharmacokinetics

Cabazitaxel exposure showed dose proportionality over the 10 - 30 mg/m^2 range infused every 3 weeks. There was no difference in exposure between Cycle 1 and Cycle 2. The pharmacokinetics of cabazitaxel showed a high clearance, a large volume of distribution at steady state and a long terminal half-life. It was rapidly metabolised in the liver and mainly excreted in faeces. Urinary excretion was low. The plasma clearance of cabazitaxel was positively correlated with BSA. There were no other intrinsic factors that impacted on the pharmacokinetics of cabazitaxel.

Pharmacodynamics

Studies providing pharmacodynamic data

POH 0258: Pharmacokinetic/pharmacodynamic analysis of cabazitaxel

The studies providing pharmacokinetic/pharmacodynamic (PK/PD) data for the analysis of cabazitaxel in patients with solid tumours were studies TED 6188, TED 6190, ARD 6191 in patients with metastatic breast cancer and EFC 6193 in hormone refractory prostate cancer patients. In all these studies the patients were treated with cabazitaxel as a 1 h IV infusion every 3 weeks at doses ranging from 10-30 mg/m^2.

The main objective of this analysis was to investigate PK parameters of cabazitaxel as prognostic factors for clinical outcome. The analysis was conducted using individual variables of clearance, exposure ($C_{max,}$ AUC), patients' baseline characteristics, pathophysiologic status (demographics, disease spread, renal or hepatic status) and extent of prior treatment.

The efficacy endpoint selected was overall survival (OS). Only data from study EFC 6193 was considered because this was the target indication in this submission. The safety endpoints selected were: neutropenia, febrile neutropenia, nausea/vomiting, mucositis/stomatitis/peripheral neurotoxicity, renal toxicity (Grade ≥3 at first cycle) and all other toxicities leading to dose reduction.

The relationship between safety parameters at Cycle 1 (binary variable: any event occurring or not) and the diagnostic PK parameters (AUC, C_{max} or clearance) were analysed using a logistics regression model. The relationship between OS and cumulative AUC and the diagnostic PK parameters until the last cycle of treatment was analysed using a proportional hazards model.

Grade ≥3 neutropenia was experience in 74 (51%) of the 145 patients. No significant relationship was found between any PK parameter of cabazitaxel. Age was the only significant prognostic parameter of neutropenia Grade ≥3 ($p < 0.05$).

None of the PK parameters were statistically significant prognosticators of efficacy. Hepatic impairment appeared to be a significant prognosticator. However, the small number of patients with hepatic impairment in this analysis prevents any conclusions from being reached.

Evaluator's overall conclusions on pharmacodynamics

This PK/PD analysis showed that there was no significant relationship between any PK estimate and neutropenia Grade ≥3. Age was the only significant factor of neutropenia. In the subset of 67 patients with hormone resistant prostate cancer (study EFC 6193), none of the PK parameters had a significant association with overall survival (OS).

Efficacy

Dosage selection for the pivotal study

In the Phase I dose finding studies TED 6188 and TED 6190, cabazitaxel was administered once every 3 weeks as an IV infusion. The maximum tolerated dose (MTD) in study TED 6190 was reached at 25 mg/m^2 in which 3 of 7 patients experienced febrile neutropenia. The recommended dose was therefore 20 mg/m^2. In study TED 6188, the 25 mg/m^2 dose was considered viable because the 3 episodes of neutropenia occurred in the one patient without clinical consequences. In the Phase II study ARD 6191, in 21 of 71 patients, the dose escalation from 20 to 25 mg/m^2 after the first cycle was well tolerated. The 21

patients, however, were selected on the basis that they tolerated cabazitaxel well in the first cycle.

The 25 mg/m^2 dose was chosen for the pivotal study (EFC 6193) to provide optimal dose intensity and potentially increase clinical benefit.

Pivotal efficacy study

The pivotal efficacy study was study EFC 6193 which was a randomized, open label, multicentre study of cabazitaxel at 25 mg/m^2 in combination with prednisone every 3 weeks, compared with mitoxantrone in combination with prednisone for the treatment of hormone refractory metastatic prostate cancer previously treated with a docetaxel (Taxotere) containing regimen.

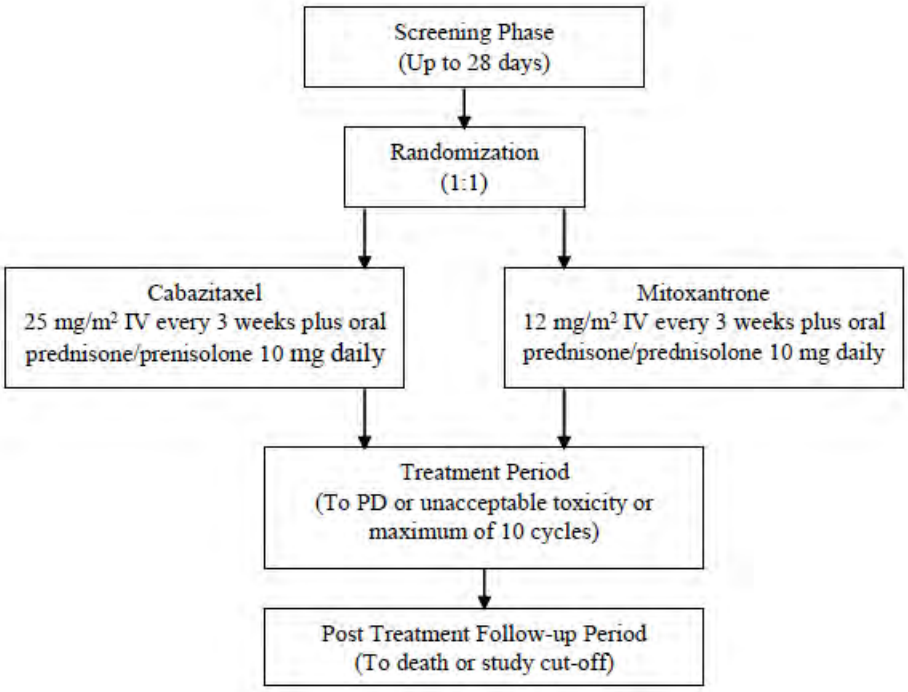
Study design, objectives, locations and dates

This randomised open label study was conducted in 26 countries (Argentina, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, Finland, France, Germany, Hungary, India, Italy, Korea, Mexico, Netherlands, Russia, Singapore, Slovakia, South Africa, Spain, Sweden, Taiwan, Turkey, UK and USA).

The first patient was enrolled on 2 January 2007. The last patient completed the study (data cut-off date) on 25 September 2009. Patients were randomized (1:1) after screening (Figure 1). The screening process included medical history, physical examination, ECOG performance status, prior treatments, blood counts, serum biochemistries, serum testosterone, left ventricular ejection fraction (LVEF), electrocardiogram (ECG), prostate specific antigen (PSA) level, bone scan, radiological tumour measurements, pain assessment (present pain intensity [PPI] score) and analgesic use.[19] These assessments were repeated at the beginning and end of each cycle. Laboratory tests, including LVEF, bone scan and radiological tumour measurements were repeated at every even numbered cycle and finally performed at the end of treatment or at study withdrawal.

[19] ECOG Performance Status. The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:
0 - Fully active, able to carry on all pre-disease performance without restriction
1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5 – Dead

Figure 1: Flow chart



Each patient was to be treated until disease progression, death, unacceptable toxicity, or for a maximum of 10 cycles (30 weeks). The maximum duration of the study, including treatment and long term follow up was intended to be about 134 weeks.

Patients who discontinued study treatment prior to documented disease progression and had not started another chemotherapy regimen were followed up for disease progression (with CT/MRI), PSA and pain progression, every 6 weeks for the first 6 months and then 3 monthly until disease progression or commencement of other chemotherapy. Once a patient had progressed or started another anticancer therapy, the follow up visits were every 3 months for a maximum of 2 years (104 weeks).

Objectives

The primary objective was to determine whether cabazitaxel in combination with prednisone improves overall survival (OS) when compared to mitoxantrone in combination with prednisone.

Secondary objectives were:

To compare efficacy between the two treatment groups.

Progression free survival (PFS): defined as the first occurrence of any of the following events: tumour progression per Response Evaluation Criteria in Solid Tumours (RECIST) criteria, PSA progression, pain progression, or death due to any cause.[20]

Overall response rate (ORR).

PSA progression.

PSA response.

Pain progression.

Pain response.

[20] RECIST: The Response Evaluation Criteria in Solid Tumors (RECIST) is a voluntary, international standard using unified, easily applicable criteria for measuring tumor response using X-ray, CT and MRI.

To assess the overall safety of cabazitaxel in combination with prednisone.

To assess the pharmacokinetics of cabazitaxel and its metabolite, RPR 123142, in this patient population and the effect of prednisone on the pharmacokinetics of cabazitaxel.

Inclusion and exclusion criteria

Patients over the age of 18 years with a life expectancy > 2 months and an ECOG performance status of 0-2, with a histologically or cytologically proven diagnosis of adenocarcinoma of the prostate that was refractory to hormone treatment and to previous treatment with a docetaxel containing regimen were included in the study. The exclusion criteria included congestive heart failure or myocardial infarction within the last 6 months, previous treatment with mitoxantrone, previous treatment with a cumulative dose of docetaxel of < 225 mg/m^2, active Grade ≥ 2 peripheral neuritis or stomatitis and inadequate organ function.

Study treatments

The patients were centrally randomized 1:1 and stratified for measurability of disease per RECIST criteria and ECOG PS to the following treatments in 3 weekly cycles:

> Treatment groups A: Mitoxantrone 12 mg/m^2 IV over 15-30 min every 3 weeks and prednisone 10 mg orally daily.
>
> Treatment group B: Cabazitaxel 25 mg/m^2 IV over 1 h every 3 weeks and prednisone 10 mg orally daily.

Treatment was initiated only when patients had an absolute neutrophil count (ANC) ≥1.5 x 10^9/L, platelet count ≥7.5 x 10^9/L and non-haematological toxicities recovered to baseline levels. Prophylactic use of granulocyte colony stimulating factor (G-CSF) was permitted, except for Cycle 1, to reduce the risk or manage neutropenia complications. Patients in group A had premedication with an H_2 antagonist at the discretion of the investigator. Patients in group B were pre-medicated with an antihistamine, steroid and an H_2 antagonist.

The 25 mg/m^2 dose was chosen for cabazitaxel, based on the results of Phase I studies (TED 6188 and TED 6190) and a Phase II study (ARD 6191). Dose reduction to cabazitaxel 20 mg/m^2 or mitoxantrone 10 mg/m^2 was permitted when necessary. Only one dose reduction was allowed for each patient. Supportive treatment including blood transfusions, antibiotics, antiemetics and analgesics when appropriate were permitted.

Efficacy variables and outcomes

The primary efficacy outcome was overall survival (OS), defined as the time interval from the date of randomization to the date of death due to any cause. In the absence of confirmation of death, the survival time was censored at the last date patient was known to be alive or at the cut-off date, whichever came first.

Other efficacy outcomes included:

> Progression free survival (PFS): defined as the time between randomization and date of progression or death (due to any cause) where a progression was either a PSA progression, a tumour progression, or a pain progression.
>
> Tumour assessment: CT or MRI of the whole body (chest, abdomen and pelvis) was done at baseline, at even numbered treatment cycles, whenever disease progression was suspected and at end of treatment/withdrawal. Bone scan was done at baseline and only if progression was suspected. Response was evaluated by RECIST. No data was provided about response evaluation.
>
> PSA response: In patients with a baseline PSA ≥20 ng/mL, a decline of ≥50%, confirmed by a second PSA 3 weeks later.

PSA progression: In nonresponders, progression was defined as a ≥25% increase over the nadir, confirmed a week later. In PSA responders, progression was defined as a ≥50% increase over the nadir, confirmed a week later.

Pain response: using the PPI scale and the analgesic score (AS - derived from analgesic consumption) was defined as a ≥2-point reduction from baseline median PPI with no concomitant increase in analgesic score or a reduction of at least 50% in analgesic use from baseline mean AS with no concomitant increase in pain.

Pain progression was defined as an increase of ≥1 point in the median PPI from its nadir on 2 consecutive visits 3 weeks apart or a requirement for local palliative radiotherapy.

Statistical methods

Previously untreated patients with metastatic prostate cancer had an OS of 12 to 14 months when treated with mitoxantrone. On the assumption that the median OS was 8 months for mitoxantrone treated patients who had progressed following previous docetaxel treatment, it was decided that a total of at least 511 deaths in the two treatment groups were needed to detect a 25% reduction in hazard rate in the cabazitaxel group relative to the comparator, with a power of 90% at a 2-sided 5% alpha level. To achieve the target number of deaths, approximately 720 patients (360 per arm) were required for randomization within 24 months. The 511 deaths had to be reached after 30 months from first patient enrolment.

The patients were randomized 1:1. This was an open label study.

The "intent to treat" (ITT) population included all the randomized patients and was the primary population for the analyses. The "per protocol" (PP) population and the safety population included all the patients who had received at least one dose of the study drug.

OS, PFS, tumour progression, PSA progression and pain progression were compared between the two treatment groups by the log rank test procedure, stratified by the stratification factors. The estimates of the hazard ratio and its 95% confidence interval (CI) were obtained using a Cox proportional hazard model stratified by the stratification factors.

The protocol was amended (Amendment 5) on 21 July 2008 to include a second interim efficacy analysis to be performed when 307 deaths had occurred, to assess OS (a first interim efficacy analysis was planned on 225 PFS events). This was based on the fact that the event rate for the primary efficacy endpoint (OS) in the two arms combined was lower than had been estimated at the start. At the second interim analysis in June 2009, since 365 deaths had occurred instead of the planned 307 deaths, the Independent Data Monitoring Committee (IDMC) recommended that the trial should continue to the final analysis.

Participant flow

A total of 755 patients were centrally randomized, with 377 patients in arm A (mitoxantrone [MTX] + prednisone [pred]) and 378 patients in arm B (cabazitaxel [CBZ] + pred). The median number of cycles was 4 in arm A and 6 in arm B. In all 13.5% of patients in arm A and 29.4% in arm B completed all 10 treatment cycles. The most common reason for treatment discontinuation was disease progression, 70.8% of patients in arm A and 47.6% in arm B. The second most common reason for treatment discontinuation was completed study treatment (without progression), 12.2% of patients in arm A and 27.8% in arm B. Six patients in arm A and 7 patients in arm B were randomized but not treated. Of the 7 patients who discontinued treatment for 'other reasons' in arm A, 4 had protocol violations, 2 had clinical progression and 1 was discontinued by the investigator. Of the 10 patients who discontinued treatment for 'other reasons' in arm B, 2 refused treatment, 2 had protocol violations, 2 had adverse events (abnormal liver function tests (LFTs), fever

with increased white blood cell (WBC) count, 1 had disease progression that was not confirmed by standard means.

Baseline data

The demographic characteristics were well balanced between the two arms. Almost half the patients in the two arms had non-measurable disease. As per protocol over 99% of the patients had had prior hormone therapy and over 80% (MTX+pred: 87.3%; CBZ+pred: 87.8%) had received docetaxel as their first chemotherapy. The majority of patients in each group were randomized within 6 months of docetaxel treatment. Overall, 75.6% of patients in arm A and 72.2% of patients in arm B had relapsed within 3 months of completing that docetaxel treatment. The majority of patients had 1 or 2 metastatic sites.

At baseline, anaemia was the most common haematological abnormality. Because of the high incidence of bone metastases in this population, abnormal levels of alkaline phosphatase (ALP) were common.

Concomitant medications included corticosteroids, antihistamines and H_2 antagonists.

Results for the primary efficacy outcome

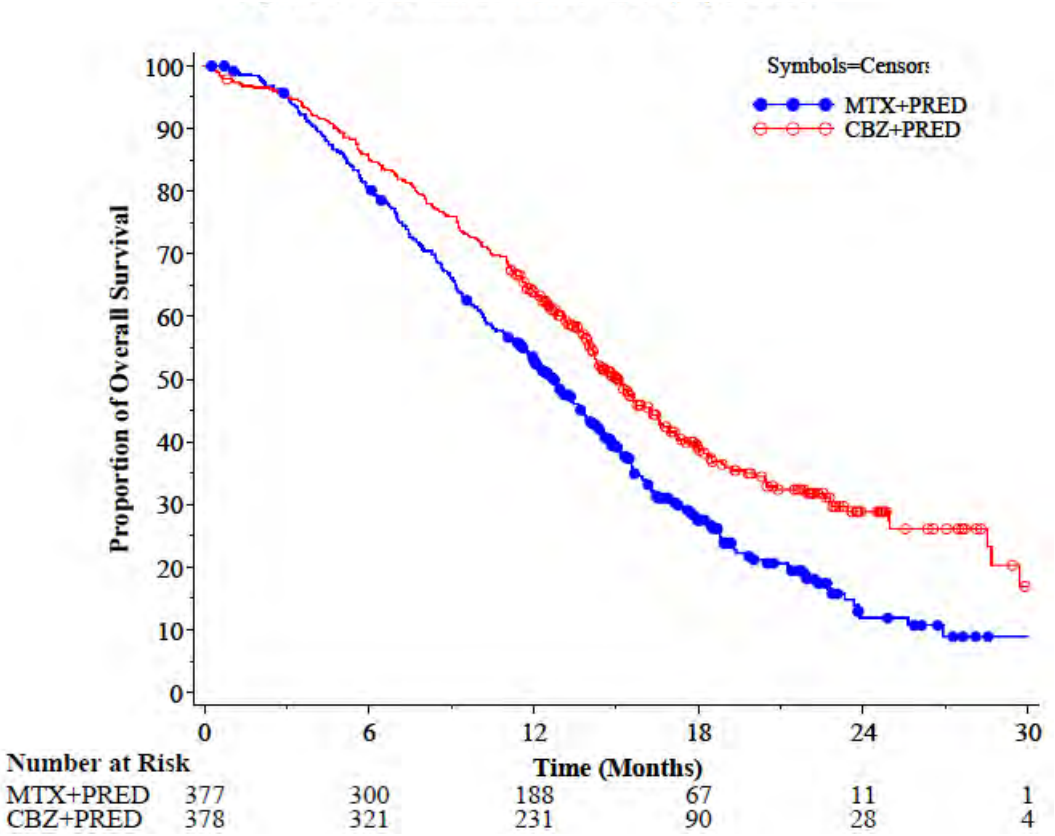
The median survival was 12.7 months in arm A and 15.1 months in arm B. The difference was statistically significant (Table 5, Figure 2). The hazard ratio (HR) was 0.70 (95% CI: 0.59 - 0.83) in favour of cabazitaxel.

Table 5: Descriptive analysis of overall survival - ITT population

	MTX+PRED (N=377)	CBZ+PRED (N=378)
Number of patients with deaths (%)	279 (74.0%)	234 (61.9%)
Number of patients censored (%)	98 (26.0%)	144 (38.1%)
Median survival in months (95% CI)	12.7 (11.6 - 13.7)	15.1 (14.1 - 16.3)
Probability of alive at 6 months*	0.80 (0.76-0.84)	0.85 (0.81-0.88)
Probability of alive at 12 months*	0.53 (0.48-0.58)	0.64 (0.59-0.68)
Probability of alive at 18 months*	0.28 (0.23-0.33)	0.39 (0.33-0.44)

*Refer to Kaplan-Meier curve for the interpretation of the probability of overall survival

Figure 2: Overall survival (OS) – ITT population



In the subgroup analysis for OS, the general trend appeared to favour the cabazitaxel arm (Figures 3 and 4).

Figure 3: Hazard ratio of OS for baseline data – CBZ+PRED vs MXT+PRED – ITT population

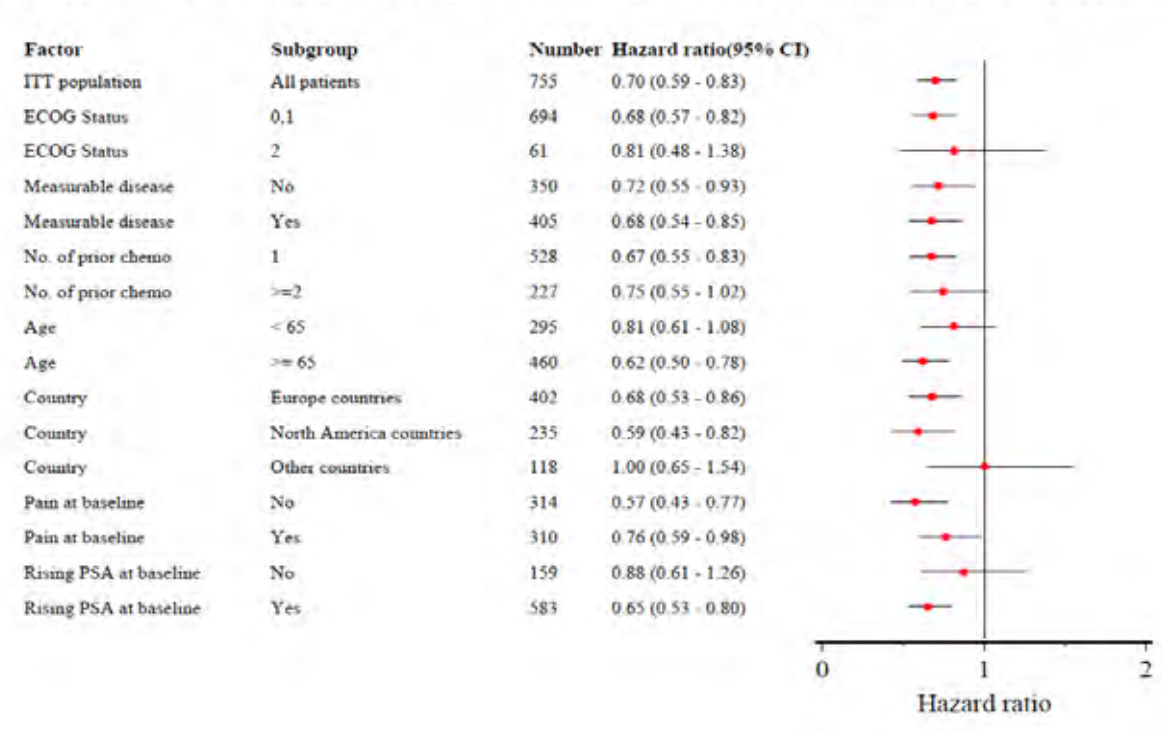
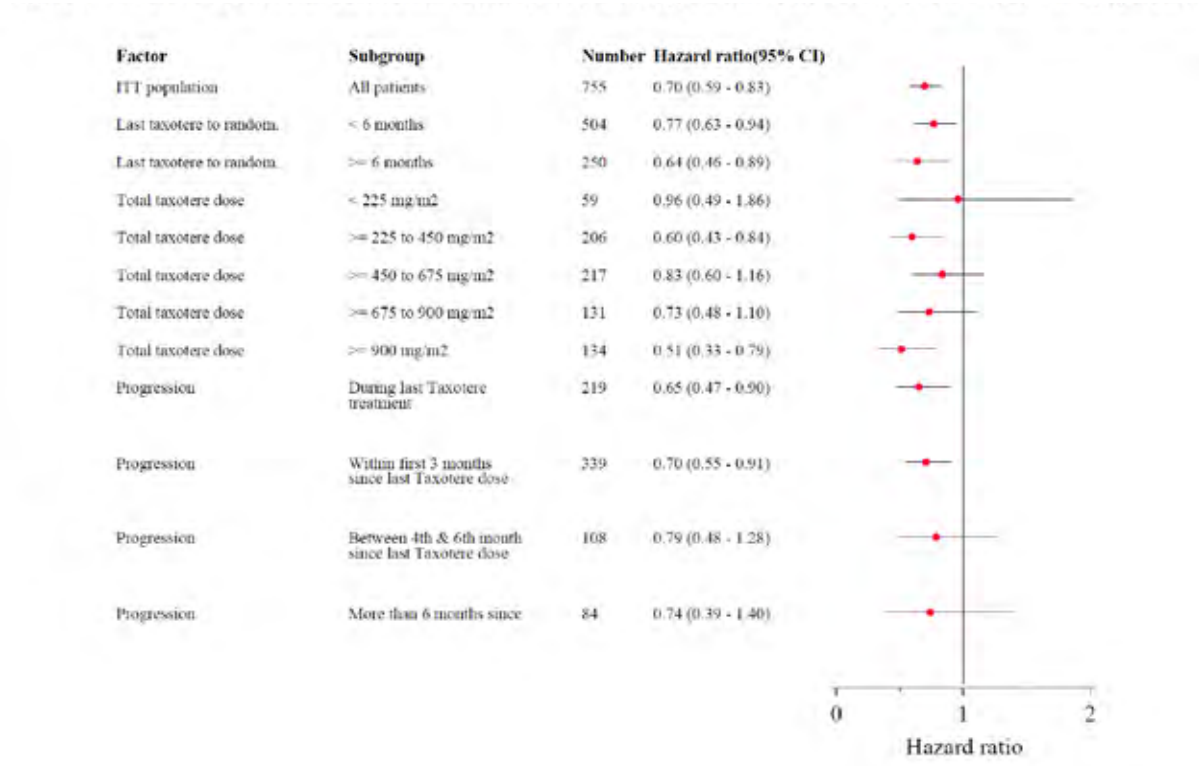


Figure 4: Hazard ratio of OS for docetaxel dose and progression – CBZ+PRED vs MXT+PRED – ITT population



The subgroups to show a HR of 1 were 'patients with a prior docetaxel dose of < 225 mg/m²' and 'other countries'. The number of 'patients with a prior docetaxel dose of < 225 mg/m²' was small (59) and may be the reason for the HR of 1. The 'other countries' were made up of 9 countries with 28 study sites. Some had statistically significant HRs and others not.

ECOG performance status at baseline, measurability of disease at baseline, time from last dose of docetaxel to randomization, time of progression after last docetaxel treatment and pain score at baseline were significant prognostic factors (Table 6).

Table 6: Univariate analysis of prognostic factors and their interaction on OS - ITT population

Prognostic factor	Hazard ratio of treatment	Hazard ratio of prognostic factor	P-value of interaction
ECOG performance status 2 (yes vs no)	0.76 (0.57 - 1.00)	3.17 (2.40 - 4.19)	0.4761
Measurable disease (yes vs no)	0.70 (0.58 - 0.83)	1.26 (1.06 - 1.50)	0.5713
Number of prior chemotherapies >=2 (yes vs no)	0.71 (0.58 - 0.85)	0.93 (0.77 - 1.12)	0.5851
Age >=65 (yes vs no)	0.71 (0.59 - 0.85)	1.04 (0.87 - 1.24)	0.1102
Last taxotere to randomization <6 months (yes vs no)	0.70 (0.57 - 0.85)	1.79 (1.48 - 2.18)	0.3556
Last taxotere to progression <6 months (yes vs no)	0.67 (0.48 - 0.95)	2.31 (1.64 - 3.26)	0.9251
Total taxotere dose >=225 mg/m² (yes vs no)	0.84 (0.59 - 1.19)	1.18 (0.83 - 1.67)	0.2360
Pain (yes vs no)*	0.66 (0.54 - 0.80)	1.95 (1.60 - 2.37)	0.1305
Rising PSA (yes vs no)**	0.75 (0.61 - 0.92)	0.74 (0.61 - 0.92)	0.1794

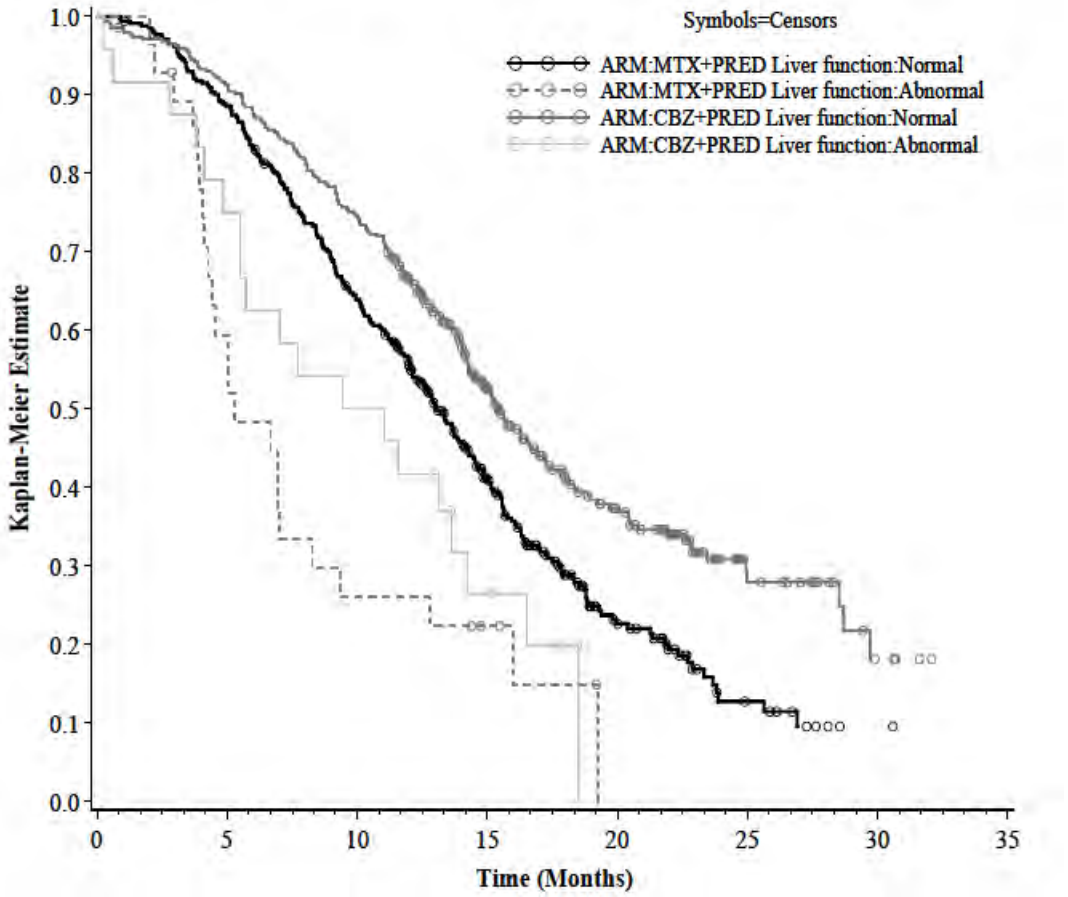
* Pain: No is PPI<2 and AS<10 at baseline, Yes is otherwise

** Rising PSA: Yes is two consecutive PSA increase at baseline, No is otherwise

The impact of liver function on OS was examined. The Cox proportional hazard model showed a statistically significant benefit in OS for cabazitaxel treatment but the interaction of treatment and liver function test on OS was not statistically significant

(p=0.9909). This would suggest that cabazitaxel treatment benefit over mitoxantrone treatment was not influenced by the patients liver function (Figure 5).

Figure 5: Kaplan-Meier curves of OS (months) by treatment group and baseline liver function – ITT population

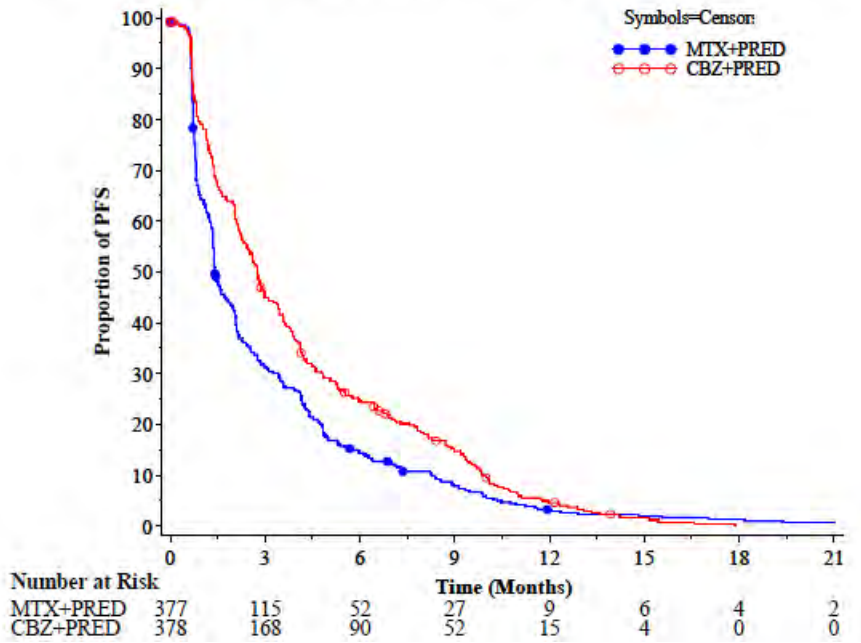


Results for other efficacy outcomes

Progression free survival (PFS)

PFS was defined per protocol as a composite endpoint evaluated from the day of randomisation to the date of tumour progression, PSA progression, pain progression, or death due to any cause, whichever occurred first. The sponsor claims that 20% of the patients in each arm reported pain progression as the criterion for PFS. The median PFS was 1.4 months in arm A and 2.8 months in arm B. The difference was statistically significant in favour of the cabazitaxel arm. The HR was 0.74 (95% CI: 0.64-0.86) corresponding to a 26% reduction in risk of death in the cabazitaxel arm (Figure 6). Two sensitivity analyses were performed to assess the impact of 9 patients in arm A and 6 patients in arm B who were not assessed or had delayed assessment of PFS. The results of these analyses confirmed a HR 0.74 for both analyses.

Figure 6: Kaplan-Meier curves for PFS – ITT population



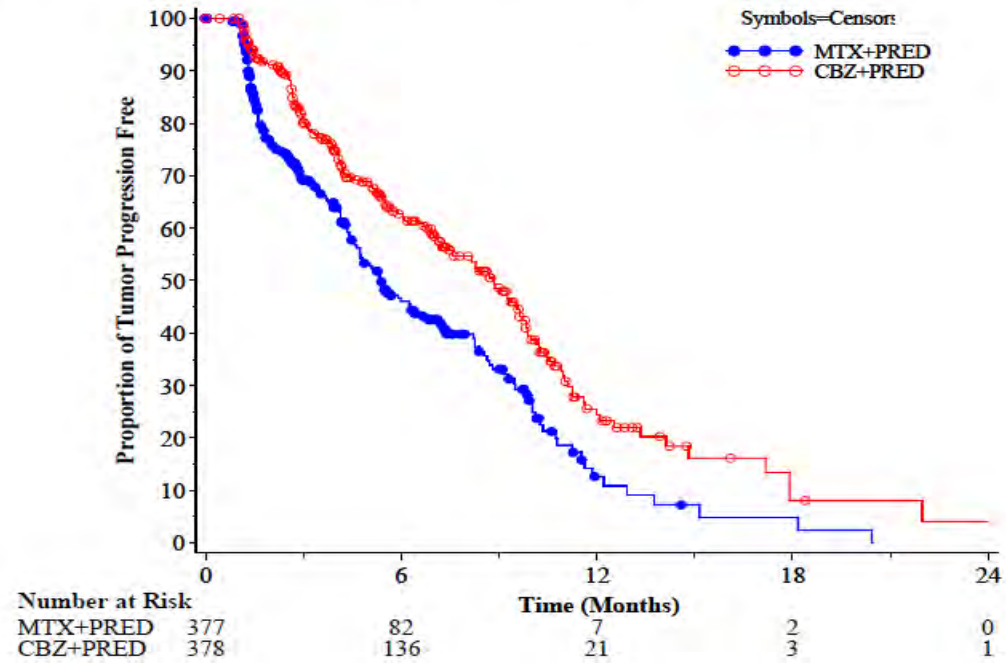
Overall tumour response rate (objective response)

This was evaluated only in patients with measurable disease (arm A: 204 patients [54.1%], arm B: 201patients [53.2%]). The ORR was 4.4% in arm A and 14.4% in arm B (p=0.0005).

Time to tumour progression

The median time to tumour progression, calculated in all the randomized patients, was 5.4 months in arm A and 8.8 months in arm B (p<0.0001). The HR was 0.61 (95% CI: 0.49-0.76) in favour of cabazitaxel, corresponding to a 39% reduction in risk of progression (Figure 7). About equal numbers (24 in arm A and 21 in arm B) had skipped/delayed assessments. Two sensitivity analyses of tumour progression were performed. The outcomes of these were very similar to the primary analysis (HR 0.62 and 0.60).

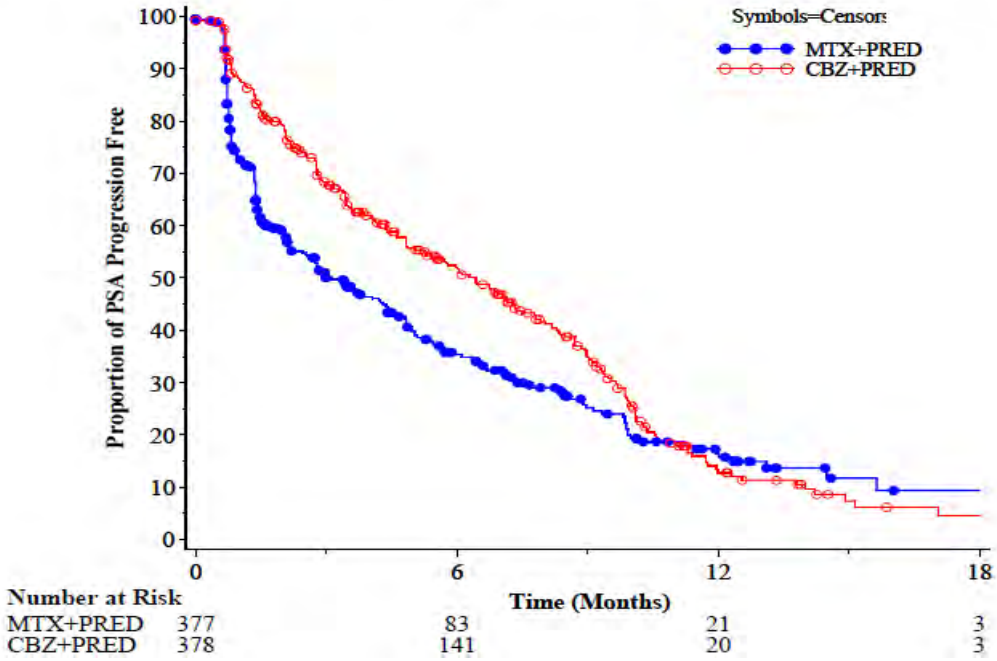
Figure 7: Kaplan-Meier curves of time to tumour progression – ITT population



PSA progression

PSA progression was statistically significantly longer in the cabazitaxel arm (6.4 months) than in the mitoxantrone arm (3.1 months, P=0.0010). The HR was 0.75 (95% CI: 0.63-0.90), corresponding to a 25% reduction in the risk of PSA progression (Figure 8). Similar numbers of patients (13 and 12 respectively in arms A and B) had skipped/delayed visits for PSA. Two sensitivity analyses were conducted and showed that the results were similar to the primary analysis (HR: 0.75 and 0.76).

Figure 8: Kaplan-Meier curves of PSA progression – ITT population



PSA response

PSA was evaluated only in patients who had a baseline PSA > 20 ng/ml (325 patients in arm A and 329 patients in arm B). The PSA response rate was 17.8% in arm A and 39.2% in arm B (p=0.0002).

Pain progression

The median time to pain progression was 11.1 months in the cabazitaxel arm but was not reached in the mitoxantrone arm. There was no statistically significant difference between the treatment arms (HR: 0.91 and 95% CI: 0.69-1.19).

Pain response

Pain response was evaluated in patients with a median PPI ≥2 on the McGill-Melzak score and/or a mean analgesic score ≥10 points at baseline (168 patients in arm A, 174 patients in arm B). There was no statistically significant difference between the two arms of the study.

Tumour related symptoms

Most of the patients had ECOG scores that remained stable (unchanged from baseline score). Similarly, in most patients in the two study arms, the PPI score remained stable.

Evaluator's conclusions on clinical efficacy

This was a randomized, open label, multicentre study to determine whether improvement in overall survival (OS) would be greater with cabazitaxel in combination with prednisone than with mitoxantrone in combination with prednisone in patients with hormone

refractory metastatic prostate cancer previously treated with a docetaxel containing regimen. The randomization and stratification were carried out centrally. Stratification allowed for analysis of OS in the subgroups, which included age, country, pain at baseline, PSA status, time from last docetaxel to randomization, docetaxel dose and time of progression from last docetaxel. The patient demographics and baseline characteristics were well balanced in the two arms of the study. The study population was a good representation of the target patient population with almost all (99%) the patients having received hormone therapy and chemotherapy. About 60% had received radiotherapy. All patients had previous docetaxel treatment with about 75% of patients progressing while on docetaxel or within 3 months after of this docetaxel therapy, thus being possible as being classified as taxane resistant. Twenty five percent of the patients progressing 3 months or more after end of previous docetaxel based therapy. Therefore, it appears that not all the patients were docetaxel resistant and some may have benefited from docetaxel rechallenge (although improvement of OS with docetaxel re-challenge in second line mHRPC has not yet been demonstrated in a controlled study).

The OS in patients treated with cabazitaxel plus prednisone was statistically significantly longer than in patients treated with mitoxantrone plus prednisone. The hazard ratio (HR) corresponded to a 30% reduction in the risk of death in the cabazitaxel arm of the study compared with the mitoxantrone arm. The subgroup analysis of OS showed a trend favouring the cabazitaxel arm. The effect of liver function on OS showed that the interaction of treatment and liver function on OS was not significant. This would suggest that the treatment benefit of cabazitaxel was independent of liver function abnormality at baseline.

The secondary endpoints also showed benefit in favour of cabazitaxel. The median progression free survival (PFS) was 2.8 months in the cabazitaxel arm and 1.4 months in the mitoxantrone arm. Response rates for PSA and tumour assessments were significantly better in the cabazitaxel arm. Similarly, the time to PSA and tumour progression were significantly longer in the cabazitaxel arm. Tumour response rate and tumour progression results, however, are representative of only half the patient population who had measurable disease. Measurement of the tumour is also open to inter-observer bias and variability.-Pain response and time to pain progression, determined by the need for analgesia, were not statistically different between the two arms of the study.

Safety

Studies providing evaluable safety data

The following studies provided evaluable safety data:

Pivotal efficacy studies

In the pivotal efficacy study (EFC 6193), the following safety data were collected:

General adverse events (AEs) and serious adverse events (SAEs) were assessed and graded according to the NCI CTCAE and summarized using MedDRA terminology, at the beginning and at the end of each cycle.[21] Adverse events were collected from the time of the first dose until 30 days after the last cycle of treatment. AEs and SAEs considered to be treatment related were followed until resolution.

Laboratory tests, including haematology (red blood cells [RBCs], haemoglobin [Hb], platelets, WBC) biochemistry (sodium, potassium, blood urea nitrogen, creatinine, glucose,

[21] **Common Terminology Criteria** (CTC) is a standardised classification of side effects used in assessing drugs for cancer therapy, in particular. Specific conditions and symptoms may have values or descriptive comment for each level, but the general guideline is 1 – Mild, 2 – Moderate, 3 – Severe, 4 - Life threatening, 5 - Death.

chloride, bicarbonate, AST, ALT, alkaline phosphatase, total bilirubin), serum testosterone and PSA were performed at every even numbered cycle and finally performed at the end of treatment or at study withdrawal.

Other assessments included physical examination, ECOG PS, ECG, and LVEF.

Clinical pharmacology studies

There were:

Phase I dose finding studies TED 6188, TED 6190 and TED 6189

Phase I study BEX 6702

Phase I/II study ARD 6191

Phase I/II combination therapy study TCD 6945.

Patient exposure

In all 371 patients in Study EFC 6193 and 132 patients in the Phase I/II studies had been treated with cabazitaxel once every 3 weeks. An additional 55 patients in studies TED 6189 and ARD 6191 had cabazitaxel on a weekly schedule at lower doses, so that, in all, 558 patients had been treated with cabazitaxel (Table 7).

Table 7: Analysis populations - by study and treatment group (Phase III study EFC 6193 and Phase I/Phase II studies)

	EFC6193		TED6188, TED6190, ARD6191, BEX6702		TED6189, ARD6191	All
Study treatment status	MTX+PRED	CBZ+PRED	<25 mg/m^2 CBZ	≥25 mg/m^2 CBZ	Weekly CBZ	CBZ treated
Randomized/enrolled population	377	378	110	22	55	565
Safety population [a]	371	371	89	43	55	558

Note: The safety population patients are tabulated according to treatment actually received

[a] Twenty-one (21) patients in ARD6191, who were in the 20 mg/m^2 CBZ group at Cycle 1 and started with 25 mg/m^2 at Cycle 2, are assigned to the pooled ≥25 mg/m^2 group.
CBZ: cabazitaxel, MTX: mitoxantrone, PRED: prednisone/prednisolone

In study EFC 6193, a 25 mg/m^2 dose was chosen. In the two Phase I studies (TED 6188 and TED 6190) and the Phase II study of patients with metastatic breast cancer (ARD 6191), the dose ranged from 20 to 25 mg/m^2 every 3 weeks.

The median duration of treatment ranged from 6.4 weeks to 18.6 weeks. In the pivotal study, the patients in the cabazitaxel arm received more cycles of study treatment (median 6 cycles) compared with the mitoxantrone arm (median 4 cycles). Dose reductions of > 20% were required in 9.8% of cycles in the cabazitaxel arm compared to 5.1% of cycles in the mitoxantrone arm. The median relative dose intensity (RDI) was 96.12% for the cabazitaxel arm and 97.25% for the mitoxantrone arm, suggesting that both arms were equally able to receive their respective intended doses. In the Phase I/II studies the median RDI for cabazitaxel <25 mg/m^2 was 99.45% and for cabazitaxel >25 mg/m^2 was 95%. In the combination treatment study (TCD 6945), the median RDIs were 95.5% and 87.4% for cabazitaxel and capecitabine, respectively.

Adverse events

Treatment related adverse events (adverse drug reactions)

Pivotal study

In study EFC 6193, 95.7% of patients in the cabazitaxel arm and 88.4% of patients in the mitoxantrone arm reported a treatment emergent adverse effect (TEAE). Grade > 3 TEAEs

were reported in 57.4% of the cabazitaxel arm and 39.4% of the mitoxantrone arm. Serious TEAEs were reported in 39.1% of the cabazitaxel arm and 20.8% of the mitoxantrone arm (Table 8).

Table 8: Brief summary of adverse events - safety population

	MTX+PRED (N=371)	CBZ+PRED (N=371)
Patients with any TEAE	328 (88.4%)	355 (95.7%)
Patients with grade>=3 TEAE	146 (39.4%)	213 (57.4%)
Patients with any serious TEAE	77 (20.8%)	145 (39.1%)
Patients with any TEAE leading to permanent treatment discontinuation	31 (8.4%)	68 (18.3%)
Patients with any TEAE leading to death	17 (4.6%)	19 (5.1%)
AEs other than disease progression	7 (1.9%)*	18 (4.9%)
Disease Progression reported as an AE	9 (2.4%)	1 (0.3%)
Disease Progression, Hepatic Failure	1 (0.3%)	0

MTX+PRED: Mitoxantrone + Prednisone/Prednisolone
CBZ+PRED: Cabazitaxel + Prednisone/Prednisolone
*Five patients died due to disease progression coded as adverse events and 1 patient died because of a motor vehicle accident.

The most common adverse events in both arms of the study were haematological adverse events, which included neutropenia and febrile neutropenia. They were more prominent in the cabazitaxel arm. Gastrointestinal adverse events included diarrhoea, nausea and vomiting, and general disorders which included fatigue and asthenia were also reported more commonly in the cabazitaxel arm. Peripheral neuropathy was reported more frequently in the cabazitaxel arm of the study (Table 9).

Table 9: Number (%) of patients with TEAEs in >=5% of patients (all grades or Grade >=3) in any treatment group (sorted by decreasing frequency by events Grade >=3 in the cabazitaxel group) - cabazitaxel safety population.

	MTX+PRED (N=371)		CBZ+PRED (N=371)	
Preferred term	All grade	Grade >= 3	All grade	Grade >= 3
Any AE	328 (88.4%)	146 (39.4%)	355 (95.7%)	213 (57.4%)
Neutropenia	40 (10.8%)	26 (7.0%)	81 (21.8%)	79 (21.3%)
Febrile Neutropenia	5 (1.3%)	5 (1.3%)	28 (7.5%)	28 (7.5%)
Diarrhoea	39 (10.5%)	1 (0.3%)	173 (46.6%)	23 (6.2%)
Fatigue	102 (27.5%)	11 (3.0%)	136 (36.7%)	18 (4.9%)
Asthenia	46 (12.4%)	9 (2.4%)	76 (20.5%)	17 (4.6%)
Back Pain	45 (12.1%)	11 (3.0%)	60 (16.2%)	14 (3.8%)
Leukopenia	11 (3.0%)	5 (1.3%)	20 (5.4%)	14 (3.8%)
Anaemia	20 (5.4%)	5 (1.3%)	40 (10.8%)	13 (3.5%)
Thrombocytopenia	10 (2.7%)	1 (0.3%)	20 (5.4%)	9 (2.4%)
Nausea	85 (22.9%)	1 (0.3%)	127 (34.2%)	7 (1.9%)
Vomiting	38 (10.2%)	0	84 (22.6%)	7 (1.9%)
Haematuria	14 (3.8%)	2 (0.5%)	62 (16.7%)	7 (1.9%)
Abdominal Pain	13 (3.5%)	0	43 (11.6%)	7 (1.9%)
Pain In Extremity	27 (7.3%)	4 (1.1%)	30 (8.1%)	6 (1.6%)
Dyspnoea	17 (4.6%)	3 (0.8%)	44 (11.9%)	5 (1.3%)
Constipation	57 (15.4%)	2 (0.5%)	76 (20.5%)	4 (1.1%)
Pyrexia	23 (6.2%)	1 (0.3%)	45 (12.1%)	4 (1.1%)
Arthralgia	31 (8.4%)	4 (1.1%)	39 (10.5%)	4 (1.1%)
Urinary Tract Infection	11 (3.0%)	3 (0.8%)	27 (7.3%)	4 (1.1%)
Pain	18 (4.9%)	7 (1.9%)	20 (5.4%)	4 (1.1%)
Anorexia	39 (10.5%)	3 (0.8%)	59 (15.9%)	3 (0.8%)
Bone Pain	19 (5.1%)	9 (2.4%)	19 (5.1%)	3 (0.8%)
Oedema Peripheral	34 (9.2%)	1 (0.3%)	34 (9.2%)	2 (0.5%)
Neuropathy Peripheral	4 (1.1%)	1 (0.3%)	30 (8.1%)	2 (0.5%)
Hypotension	9 (2.4%)	1 (0.3%)	20 (5.4%)	2 (0.5%)
Musculoskeletal Pain	20 (5.4%)	3 (0.8%)	18 (4.9%)	2 (0.5%)
Mucosal Inflammation	10 (2.7%)	1 (0.3%)	22 (5.9%)	1 (0.3%)
Peripheral Sensory Neuropathy	5 (1.3%)	0	20 (5.4%)	1 (0.3%)
Dysgeusia	15 (4.0%)	0	41 (11.1%)	0
Cough	22 (5.9%)	0	40 (10.8%)	0
Alopecia	18 (4.9%)	0	37 (10.0%)	0
Weight Decreased	28 (7.5%)	1 (0.3%)	32 (8.6%)	0
Dizziness	21 (5.7%)	2 (0.5%)	30 (8.1%)	0
Headache	19 (5.1%)	0	28 (7.5%)	0
Muscle Spasms	10 (2.7%)	0	27 (7.3%)	0
Dyspepsia	6 (1.6%)	0	25 (6.7%)	0
Dysuria	5 (1.3%)	0	25 (6.7%)	0
Abdominal Pain Upper	5 (1.3%)	0	20 (5.4%)	0

Only rows with frequency of at least 5% in at least one column are shown
MTX+PRED: Mitoxantrone + Prednisone/Prednisolone
CBZ+PRED: Cabazitaxel + Prednisone/Prednisolone

Other studies

In the Phase I/II studies, the incidence of TEAEs was similar to that in the pivotal study (Table 10). The incidence of neutropenia in these studies was lower (2.2%, 9.3% and 9.1% in the ≤ 25 mg/m^2, ≥ 25 mg/m^2 and weekly cabazitaxel). The pattern for the other TEAEs was similar to that in the pivotal study (Table 11). The pattern of distribution of Grade ≥3 TEAEs in these studies was similar to that in the pivotal study, with diarrhoea, fatigue, asthenia, neutropenia and febrile neutropenia being the most frequent.

Table 10: Overview of safety - by study and treatment group (Phase III study EFC 6193 and Phase I/Phase II studies

	EFC6193		TED6188, TED6190, ARD6191, BEX6702		TED6189, ARD6191
Study treatment	MTX+PRED	CBZ+PRED	<25 mg/m^2 CBZ	≥25 mg/m^2 CBZ	Weekly CBZ
Class	(N=371)	(N=371)	(N=89)	(N=43)	(N=55)
Patients with any TEAE	328 (88.4%)	355 (95.7%)	85 (95.5%)	42 (97.7%)	55 (100%)
Patients with any Grade ≥3 TEAE	146 (39.4%)	213 (57.4%)	44 (49.4%)	24 (55.8%)	34 (61.8%)
Patients with any SAE	77 (20.8%)	145 (39.1%)	28 (31.5%)	16 (37.2%)	25 (45.5%)
Patients with TEAEs that led to treatment discontinuation	31 (8.4%)	68 (18.3%)	3 (3.4%)	4 (9.3%)	9 (16.4%)
Patients with death within 30 days from last infusion[a]	9 (2.4%)	18 (4.9%)	4 (4.5%)	2 (4.7%)	6 (10.9%)

[a] Deaths within 30 days from all causes including disease progression are listed as TEAEs Extracted from Table 23: PGM=PRODOPS/XRP6258/OVERALL/SCS_SCE_09/REPORT/PGM/TEAE_dth.sas OUT=REPORT/OUTPUT/TEAE_dth_i.rtf (11DEC2009 - 12:05)

CBZ: cabazitaxel, MTX: mitoxantrone, N: population size, PRED: prednisone/prednisolone, SAE: serious adverse event; TEAE: treatment-emergent adverse event

Table 11: TEAEs (all grades) regardless of relationship to study by preferred drug term (all Grades >=5% incidence in any treatment group) - by study and treatment group (Phase III study EFC 6193 and Phase I/Phase II studies)

	EFC6193		TED6188, TED6190, ARD6191, BEX6702		TED6189, ARD6191
Preferred term	MTX+PRED (N=371)	CBZ+PRED (N=371)	<25 mg/m² CBZ (N=89)	≥25 mg/m² CBZ (N=43)	Weekly CBZ (N=55)
Any event	328 (88.4%)	355 (95.7%)	85 (95.5%)	42 (97.7%)	55 (100%)
Diarrhoea	39 (10.5%)	173 (46.6%)	39 (43.8%)	26 (60.5%)	24 (43.6%)
Fatigue	102 (27.5%)	136 (36.7%)	50 (56.2%)	30 (69.8%)	12 (21.8%)
Nausea	85 (22.9%)	127 (34.2%)	42 (47.2%)	23 (53.5%)	27 (49.1%)
Vomiting	38 (10.2%)	84 (22.6%)	26 (29.2%)	12 (27.9%)	22 (40.0%)
Neutropenia	40 (10.8%)	81 (21.8%)	2 (2.2%)	4 (9.3%)	5 (9.1%)
Asthenia	46 (12.4%)	76 (20.5%)	7 (7.9%)	1 (2.3%)	29 (52.7%)
Constipation	57 (15.4%)	76 (20.5%)	21 (23.6%)	6 (14.0%)	11 (20.0%)
Haematuria	14 (3.8%)	62 (16.7%)	6 (6.7%)	1 (2.3%)	3 (5.5%)
Back pain	45 (12.1%)	60 (16.2%)	6 (6.7%)	5 (11.6%)	5 (9.1%)
Anorexia	39 (10.5%)	59 (15.9%)	22 (24.7%)	17 (39.5%)	15 (27.3%)
Pyrexia	23 (6.2%)	45 (12.1%)	15 (16.9%)	9 (20.9%)	10 (18.2%)
Dyspnoea	17 (4.6%)	44 (11.9%)	15 (16.9%)	9 (20.9%)	10 (18.2%)
Abdominal pain	13 (3.5%)	43 (11.6%)	12 (13.5%)	10 (23.3%)	6 (10.9%)
Dysgeusia	15 (4.0%)	41 (11.1%)	7 (7.9%)	4 (9.3%)	5 (9.1%)
Anaemia	20 (5.4%)	40 (10.8%)	1 (1.1%)	1 (2.3%)	1 (1.8%)
Cough	22 (5.9%)	40 (10.8%)	10 (11.2%)	8 (18.6%)	7 (12.7%)
Arthralgia	31 (8.4%)	39 (10.5%)	7 (7.9%)	5 (11.6%)	7 (12.7%)
Alopecia	18 (4.9%)	37 (10.0%)	13 (14.6%)	13 (30.2%)	7 (12.7%)
Oedema peripheral	34 (9.2%)	34 (9.2%)	7 (7.9%)	4 (9.3%)	7 (12.7%)
Weight decreased	28 (7.5%)	32 (8.6%)	17 (19.1%)	9 (20.9%)	15 (27.3%)
Dizziness	21 (5.7%)	30 (8.1%)	9 (10.1%)	2 (4.7%)	3 (5.5%)
Neuropathy peripheral	4 (1.1%)	30 (8.1%)	0	0	0
Pain in extremity	27 (7.3%)	30 (8.1%)	1 (1.1%)	4 (9.3%)	5 (9.1%)
Febrile neutropenia	5 (1.3%)	28 (7.5%)	2 (2.2%)	1 (2.3%)	1 (1.8%)
Headache	19 (5.1%)	28 (7.5%)	15 (16.9%)	8 (18.6%)	12 (21.8%)
Muscle spasms	10 (2.7%)	27 (7.3%)	0	0	3 (5.5%)
Urinary tract infection	11 (3.0%)	27 (7.3%)	8 (9.0%)	1 (2.3%)	2 (3.6%)
Dyspepsia	6 (1.6%)	25 (6.7%)	7 (7.9%)	3 (7.0%)	5 (9.1%)
Dysuria	5 (1.3%)	25 (6.7%)	7 (7.9%)	3 (7.0%)	2 (3.6%)
Mucosal inflammation	10 (2.7%)	22 (5.9%)	6 (6.7%)	0	1 (1.8%)
Abdominal pain upper	5 (1.3%)	20 (5.4%)	3 (3.4%)	5 (11.6%)	9 (16.4%)
Hypotension	9 (2.4%)	20 (5.4%)	2 (2.2%)	1 (2.3%)	2 (3.6%)
Leukopenia	11 (3.0%)	20 (5.4%)	0	0	0
Pain	18 (4.9%)	20 (5.4%)	0	0	2 (3.6%)
Peripheral sensory neuropathy	5 (1.3%)	20 (5.4%)	21 (23.6%)	13 (30.2%)	18 (32.7%)
Thrombocytopenia	10 (2.7%)	20 (5.4%)	0	1 (2.3%)	0
Bone pain	19 (5.1%)	19 (5.1%)	11 (12.4%)	5 (11.6%)	2 (3.6%)
Dehydration	10 (2.7%)	18 (4.9%)	5 (5.6%)	1 (2.3%)	1 (1.8%)
Insomnia	18 (4.9%)	18 (4.9%)	3 (3.4%)	3 (7.0%)	5 (9.1%)
Musculoskeletal pain	20 (5.4%)	18 (4.9%)	1 (1.1%)	2 (4.7%)	0
Myalgia	10 (2.7%)	14 (3.8%)	12 (13.5%)	9 (20.9%)	10 (18.2%)
Anxiety	4 (1.1%)	11 (3.0%)	7 (7.9%)	5 (11.6%)	3 (5.5%)
Musculoskeletal chest pain	10 (2.7%)	11 (3.0%)	2 (2.2%)	3 (7.0%)	0
Cystitis	5 (1.3%)	10 (2.7%)	2 (2.2%)	1 (2.3%)	3 (5.5%)
Chest pain	6 (1.6%)	9 (2.4%)	3 (3.4%)	3 (7.0%)	1 (1.8%)
Flatulence	4 (1.1%)	8 (2.2%)	2 (2.2%)	0	3 (5.5%)
Depression	8 (2.2%)	7 (1.9%)	8 (9.0%)	5 (11.6%)	3 (5.5%)
Nail disorder	11 (3.0%)	7 (1.9%)	3 (3.4%)	0	4 (7.3%)

	EFC6193		TED6188, TED6190, ARD6191, BEX6702		TED6189, ARD6191
Preferred term	MTX+PRED (N=371)	CBZ+PRED (N=371)	<25 mg/m² CBZ (N=89)	≥25 mg/m² CBZ (N=43)	Weekly CBZ (N=55)
Oedema	2 (0.5%)	7 (1.9%)	2 (2.2%)	2 (4.7%)	6 (10.9%)
Stomatitis	10 (2.7%)	7 (1.9%)	10 (11.2%)	7 (16.3%)	6 (10.9%)
Chills	3 (0.8%)	6 (1.6%)	5 (5.6%)	3 (7.0%)	0
Decreased appetite	7 (1.9%)	6 (1.6%)	5 (5.6%)	2 (4.7%)	1 (1.8%)
Rhinitis	6 (1.6%)	6 (1.6%)	0	1 (2.3%)	3 (5.5%)
Tachycardia	0	6 (1.6%)	8 (9.0%)	2 (4.7%)	1 (1.8%)
Contusion	3 (0.8%)	5 (1.3%)	6 (6.7%)	1 (2.3%)	0
Hypersensitivity	0	5 (1.3%)	6 (6.7%)	3 (7.0%)	1 (1.8%)
Vertigo	1 (0.3%)	5 (1.3%)	2 (2.2%)	0	6 (10.9%)
Epistaxis	2 (0.5%)	3 (0.8%)	3 (3.4%)	2 (4.7%)	6 (10.9%)
Pleural effusion	3 (0.8%)	3 (0.8%)	1 (1.1%)	3 (7.0%)	1 (1.8%)
Presyncope	2 (0.5%)	3 (0.8%)	0	0	3 (5.5%)
Weight increased	2 (0.5%)	3 (0.8%)	5 (5.6%)	4 (9.3%)	0
Ileus	0	2 (0.5%)	0	1 (2.3%)	4 (7.3%)
Performance status decreased	0	1 (0.3%)	0	1 (2.3%)	3 (5.5%)
Peripheral motor neuropathy	5 (1.3%)	1 (0.3%)	6 (6.7%)	0	0
Erythema multiforme	0	0	1 (1.1%)	4 (9.3%)	0
Fluid retention	0	0	7 (7.9%)	2 (4.7%)	0
Not coded	0	0	12 (13.5%)	3 (7.0%)	6 (10.9%)
Rash maculo-papular	0	0	1 (1.1%)	3 (7.0%)	5 (9.1%)
Tumour pain	0	0	13 (14.6%)	4 (9.3%)	22 (40.0%)

CBZ: cabazitaxel, MTX: mitoxantrone, PRED: prednisone/prednisolone; TEAE: treatment-emergent adverse event

In the combination study (TCD 6945), the incidence of Grade 3-4 TEAEs was 69.7%. Serious adverse events were reported in 51.5% of the patients. The distribution of TEAEs was similar to that in the pivotal study. The incidence of neutropenia was 21.2% and similar to that reported in the pivotal study.

Deaths and other serious adverse events

Pivotal study

By the cut-off date (25 September 2009), 227 patients (61.2%) in the cabazitaxel arm and 275 patients (74.1%) in the mitoxantrone arm had died. Progressive disease was the cause of death in 53.1% of deaths in the cabazitaxel arm and 68.2% of deaths in the mitoxantrone arm. In the cabazitaxel arm, 18 (4.9%) died from TEAE within 30 days of last infusion, compared with 7 (1.9%) in the mitoxantrone arm (Table 12). Deaths from TEAEs in the cabazitaxel arm included infection and cardiac disease (Table 13).

Table 12: Patients who died by study period (on treatment, post treatment) and cause of death - safety population

	EFC6193	
	MTX+PRED (N=371)	CBZ+PRED (N=371)
Any death during on treatment or post treatment phase	275 (74.1%)	227 (61.2%)
Progression	253 (68.2%)	197 (53.1%)
TEAE [a]	7 (1.9%)	18 (4.9%)
Other	15 (4.0%)	12 (3.2%)
Death during treatment phase [b]	9 (2.4%)	18 (4.9%)
Progression	4 (1.1%)	0
TEAE	5 (1.3%)	18 (4.9%)
Other	0	0
Death during post treatment phase [c]	266 (71.7%)	209 (56.3%)
Progression	249 (67.1%)	197 (53.1%)
TEAE	2 (0.5%)	0
Other	15 (4.0%)	12 (3.2%)

Note: If the same patient experienced several adverse events with the same term, the patient is counted once for that term

Table 13: Summary of TEAEs leading to death - number (%) of patients - safety population

Disease progression/AE Preferred term	MTX+PRED (N=371)	CBZ+PRED (N=371)
Any TEAE	17 (4.6%)	19 (5.1%)
Patients died due to disease progression (reported on AE page)	10 (2.7%)	1 (0.3%)
Disease Progression	9 (2.4%)	1 (0.3%)
Disease Progression, Hepatic Failure	1 (0.3%)	0
Patients died due to AEs other than disease progression	7 (1.9%)	18 (4.9%)
Cardiac Arrest	0	2 (0.5%)
Cardiac Failure	0	1 (0.3%)
Sudden Death	0	1 (0.3%)
Ventricular Fibrillation	0	1 (0.3%)
Neutropenic Sepsis	0	2 (0.5%)
Fungal Sepsis	0	1 (0.3%)
Sepsis	0	1 (0.3%)
Pneumococcal Sepsis	1 (0.3%)	0
Abdominal Pain, Enterocolitis, Febrile Neutropenia, Renal Failure, Septic Shock	0	1 (0.3%)
Anaemia, Neutropenia, Thrombocytopenia	0	1 (0.3%)
Renal Failure	0	2 (0.5%)
Renal Failure Acute, Respiratory Failure	0	1 (0.3%)
Electrolyte Imbalance	0	1 (0.3%)
Haematuria	1 (0.3%)	0
Dyspnoea	1 (0.3%)	1 (0.3%)
Aspiration, Vomiting	0	1 (0.3%)
Pleural Effusion	1 (0.3%)	0
Cerebral Haemorrhage	0	1 (0.3%)
Multiple Fractures	1 (0.3%)	0
Metastases To Meninges	1 (0.3%)	0
Prostate Cancer Metastatic	1 (0.3%)	0

MTX+PRED: Mitoxantrone + Prednisone/Prednisolone
CBZ+PRED: Cabazitaxel + Prednisone/Prednisolone
AEs other than disease progression were grouped into the following categories: cardiac, neutropenia and clinical consequences, dehydration and hydroelectrolyte imbalance, dehydration leading to renal failure, disease progression, motor vehicle accident, and other.

Serious adverse events were reported in 145 patients (39%; Grade ≥3: 35.6%) in the cabazitaxel arm and in 77 patients (21%; Grade ≥3: 18%) in the mitoxantrone arm. The most common Grade ≥3 SAEs in the cabazitaxel arm were febrile neutropenia, neutropenia, diarrhoea and pneumonia. In the mitoxantrone arm, the most common SAEs were disease progression and pulmonary embolism (Table 14).

Table 14: Number (%) of patients experiencing a serious adverse event at a percentage >=1% in any treatment group - by preferred term (worst grade by patient) - safety population

	MTX+PRED (N=371)		CBZ+PRED (N=371)	
Preferred term	All grade	Grade >= 3	All grade	Grade >= 3
Any AE	77 (20.8%)	67 (18.1%)	145 (39.1%)	132 (35.6%)
Febrile Neutropenia	4 (1.1%)	4 (1.1%)	25 (6.7%)	25 (6.7%)
Neutropenia	3 (0.8%)	1 (0.3%)	18 (4.9%)	18 (4.9%)
Haematuria	3 (0.8%)	2 (0.5%)	10 (2.7%)	6 (1.6%)
Diarrhoea	0	0	9 (2.4%)	7 (1.9%)
Pneumonia	2 (0.5%)	2 (0.5%)	6 (1.6%)	5 (1.3%)
Renal Failure	0	0	6 (1.6%)	5 (1.3%)
Abdominal Pain	0	0	6 (1.6%)	4 (1.1%)
Vomiting	2 (0.5%)	0	6 (1.6%)	3 (0.8%)
Pyrexia	1 (0.3%)	0	6 (1.6%)	2 (0.5%)
Pulmonary Embolism	6 (1.6%)	5 (1.3%)	5 (1.3%)	5 (1.3%)
Renal Failure Acute	0	0	5 (1.3%)	4 (1.1%)
Spinal Cord Compression	3 (0.8%)	3 (0.8%)	4 (1.1%)	4 (1.1%)
Dehydration	1 (0.3%)	0	4 (1.1%)	4 (1.1%)
Sepsis	0	0	4 (1.1%)	4 (1.1%)
Septic Shock	0	0	4 (1.1%)	4 (1.1%)
Ureteric Obstruction	0	0	4 (1.1%)	4 (1.1%)
Hydronephrosis	1 (0.3%)	1 (0.3%)	4 (1.1%)	3 (0.8%)
Urinary Tract Infection	3 (0.8%)	3 (0.8%)	4 (1.1%)	1 (0.3%)
Back Pain	4 (1.1%)	4 (1.1%)	3 (0.8%)	2 (0.5%)
Disease Progression	11 (3.0%)	11 (3.0%)	1 (0.3%)	1 (0.3%)

Only rows with frequency of at least 1% in at least one column are shown
MTX+PRED: Mitoxantrone + Prednisone/Prednisolone
CBZ+PRED: Cabazitaxel + Prednisone/Prednisolone

Other studies

The incidence of patient deaths in the Phase I/Phase II studies was similar to that in the pivotal study. Most of the deaths were due to disease progression. There were 4 deaths due to TEAEs within 30 days of the last dose and 1 from an unknown cause. In the combination study TCD 6945, 4 deaths occurred during the study due to disease progression.

Serious adverse events were reported in 28 (31.5%), and 16 (37.2%) patients in the ≤ 25 mg/m^2 and ≥ 25 mg/m^2 groups respectively and in 25 (45.5%) patients in the weekly group. Febrile neutropenia and diarrhoea were the most common causes of death. In the combination study, SAEs were reported in 17 patients. There was no pattern to the SAEs.

Discontinuation due to adverse events

Pivotal study

In all 68 patients (18.3%) in the cabazitaxel arm and 31 patients (8.4%) in the mitoxantrone arm withdrew from the study due to AEs. The most common causes of discontinuation in the cabazitaxel arm were neutropenia, febrile neutropenia, haematuria, diarrhoea, fatigue, renal failure and sepsis. One patient discontinued from the study because of Grade 3 peripheral sensory neuropathy. In the mitoxantrone arm, the most common causes were asthenia, back pain, pulmonary embolism, cardiotoxicity including a decreased ejection fraction. There was one discontinuation due to Grade 3 peripheral sensory neuropathy.

Other studies

There were 16 discontinuations in the Phase I/Phase II studies. The reasons for discontinuation were similar to those in the pivotal study. In the combination study, there were 9 discontinuations due to TEAEs. These included haematological and renal causes and neutropenia.

Laboratory tests

Clinical chemistry

Pivotal and other studies

The proportion of patients with clinical chemistry abnormalities Grade ≥3 was similar in the two arms of the study.

The incidence of clinical chemistry abnormalities in patients in the Phase I/Phase II studies was higher than in the pivotal study but they were mostly Grade 1/2. In the combination study, the incidence of clinical chemistry abnormalities was high, but the abnormalities were mainly Grades 1/2.

Liver function

Pivotal and other studies

The incidence of abnormal LFTs was generally similar between the two arms of the pivotal study. The incidence of abnormal LFTs was higher in patients in the Phase I/ Phase II studies but most of the increase was in Grades ≤2 abnormalities.

Renal and urinary disorders

Pivotal and other studies

Renal and urinary disorders were more frequent in the cabazitaxel arm than in the mitoxantrone arm (30.7% vs 11.3%). Renal failure and impairment was reported in 4% of patients in the cabazitaxel arm and 0.8% of those in the mitoxantrone arm and severe renal failure and impairment was reported in 3.2% of patients in the cabazitaxel arm and 0.3% in the mitoxantrone arm.

Of the 15 patients in the cabazitaxel arm with acute renal failure, 8 patients recovered and 7 failed to recover.

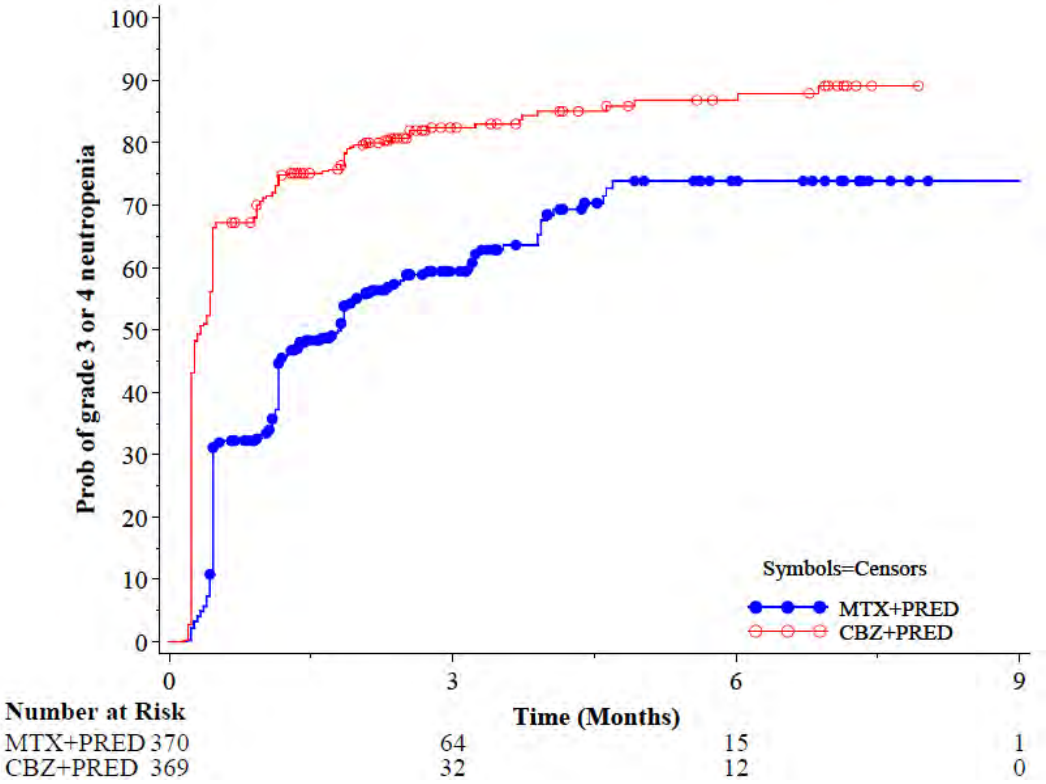
Serum creatinine increases in the Phase I/ Phase II studies in patients with normal values at baseline were similar to that in the pivotal study.

Haematology

Pivotal and other studies

Myelosuppression, resulting in neutropenia and anaemia, was more frequently reported in the cabazitaxel arm than in the mitoxantrone arm. Grade ≥3 neutropenia was reported in 81.7% of patients in the cabazitaxel arm and 58% of those in the mitoxantrone arm. The first occurrence of neutropenia in the cabazitaxel arm was within the first 2 weeks in 70 to 80 % of patients (Figure 9).

Figure 9: Time to first neutropenia (Grade >=3) - safety population



The incidence of Grade ≥3 abnormalities in the Phase I/Phase II studies and in the combination study was similar to that in the pivotal study.

Other safety issues

Safety in special populations

The TEAEs in patients < 65 years were compared with patients > 65 years. In the cabazitaxel arm, the adverse reactions reported at rates >5% higher in the > 65 year population compared to the < 65 year population included fatigue, asthenia, neutropenia, pyrexia, dizziness, urinary tract infections and dehydration.

Evaluator's overall conclusions on clinical safety

The cabazitaxel arm received more cycles of intended study treatment (median 6 cycles) than the mitoxantrone arm (median 4 cycles). Both arms were equally able to receive their respective treatments as reflected by similar and high median RDIs. The incidence of TEAEs was higher in the cabazitaxel arm (95.7%) than in the mitoxantrone arm (88.4%). Of the TEAEs, there were more Grade ≥3 abnormalities in the cabazitaxel arm (57.4%) than in the mitoxantrone arm (39.4%). Similarly, the incidence of SAEs was higher in the cabazitaxel arm (39.1%) than in the mitoxantrone arm (20.8%). TEAEs including disease progression that was reported as an adverse event resulted in 18.3% in the cabazitaxel arm and 8.4% in the mitoxantrone arm discontinuing from the study.

The most frequent Grade ≥3 toxicity based on laboratory values was neutropenia which was reported in 81.7% of patients in the cabazitaxel arm versus 58% in the mitoxantrone arm. The incidence of Grade ≥3 neutropenia adverse events in the TROPIC trial was 21.3% in cabazitaxel arm versus 7.0% in mitoxantrone arm. This difference was reflected in the rates of febrile neutropenia (cabazitaxel: 7.5%; mitoxantrone: 1.3%). As expected, the incidence of Grade ≥3 infections in the cabazitaxel arm (10.2%) was higher than in the

mitoxantrone arm (5.1%). Based on laboratory data, more patients in the cabazitaxel arm developed neutropenia faster than in the mitoxantrone arm. This result was however confounded by possible myelosuppression already present following previous extensive chemotherapy and/or radiotherapy.

Gastrointestinal disorders were more common in the cabazitaxel arm. Grade ≥3 diarrhoea (6.2% vs 0.3%) and nausea and vomiting (3% vs 0.3%) were more common in the cabazitaxel arm. The incidences of stomatitis and mucositis, however, were similar.

Grade ≥3 renal and urinary disorders were more common in the cabazitaxel arm. The incidence of severe renal failure or impairment was 3.2% in the cabazitaxel arm versus 0.3% in the mitoxantrone arm. The aetiology was multifactorial and consisted of pre-renal and obstructive causes. Of the 15 patients in the cabazitaxel arm who developed acute renal failure, 8 recovered.

Cardiac disorders were more common in the cabazitaxel arm compared to the mitoxantrone arm. Cardiac arrhythmias were more common in the cabazitaxel arm. Grade ≥3 cardiac arrhythmias were reported in 6 patients (1.6%) in the cabazitaxel arm and in 1 patient (0.3%) in the mitoxantrone arm.

There were 18 deaths due to adverse events, other than disease progression, reported in the cabazitaxel arm and 7 deaths in the mitoxantrone arm, which occurred within 30 days of last study treatment dose. Of the 18 deaths in the cabazitaxel arm, 7 were due to neutropenia and its consequences, 5 were due to cardiac events, 3 were due to renal disorders, 1 was due to dehydration and electrolyte imbalances and 2 were due to other causes. In the mitoxantrone arm, 5 deaths were due to disease progression which had been coded as adverse events, 1 was due to neutropenia and its consequences and 1 was due to a motor vehicle accident.

In conclusion, the profile of adverse events was in keeping with that of other taxane drugs.

Clinical summary and conclusions

Benefit risk assessment and recommendations

Assessment of benefits

The benefits of cabazitaxel in the proposed usage are:

Patients treated with cabazitaxel had a statistically significantly longer median survival than patients treated with mitoxantrone. The hazard ratio in favour of cabazitaxel corresponded to a 30% reduction in the risk of death.

Progression free survival was statistically significantly longer in the cabazitaxel arm compared with the mitoxantrone arm.

Assessment of risks

The risks of cabazitaxel in the proposed usage are:

1. Haematological toxicity with special reference to neutropenia, the most frequent haematological toxicity, and its consequences of febrile neutropenia and infection.
2. Gastrointestinal toxicity which includes nausea, vomiting and diarrhoea. The consequent dehydration increases the risk of renal failure.
3. Renal failure is an identifiable risk.
4. Peripheral neurotoxicity.
5. Cardiac arrhythmia

6. Lens toxicity was observed in nonclinical studies in rats.

Assessment of benefit-risk balance

The benefit risk balance of cabazitaxel given the proposed usage is favourable.

V. Pharmacovigilance findings

Risk Management Plan

Safety Specification

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR). The summary of the Ongoing Safety Concerns as specified by the sponsor is shown at Table 15.

Table 15: Ongoing safety concerns for cabazitaxel

Important identified risks	Deaths related to drug toxicity
	Neutropenia and associated clinical events (febrile neutropenia, neutropenic infection, neutropenic sepsis, sepsis, septic shock)
	Gastro-intestinal disorders (vomiting and diarrhoea) and associated complications (dehydration and electrolytes imbalance)
	Renal failure
Important potential risks	Cardiac arrhythmia (ventricular arrhythmia and cardiac arrest)
	Lens toxicity (observed in a nonclinical study in rats)
	Use in non-evaluated indications
Important missing information	Drug-drug interaction (concomitant administration with substrates or with inhibitors of CYP3A)
	Use in patients with hepatic impairment

The nonclinical evaluator noted that most relevant nonclinical findings have been identified and adequately described in the safety specification in the Risk Management Plan (RMP). The only exception is the description of ocular findings. It states that lenticular changes were "partially reversible after the 2 month recovery period". According to the submitted toxicity studies, there was no indication of reversibility of ocular findings. Furthermore, ocular findings were observed at clinically relevant exposures. The ocular findings are of unknown clinical relevance, but to remain cautious, they should be considered potentially relevant to human use. Appropriate modification of this section of the safety specification was recommended.

The OPR reviewer noted the summary of the Ongoing Safety Concerns was acceptable.

Pharmacovigilance plan

The sponsor proposed routine pharmacovigilance activities to monitor all the specified ongoing safety concerns.[22]

In addition the sponsor proposed to further monitor the important potential risks 'Cardiac arrhythmia (ventricular arrhythmia and cardiac arrest)' and 'Lens toxicity (observed in a nonclinical study in rats)' by collecting and assessing clinical AE data from ongoing life cycle management (LCM) trials.

Furthermore for the important potential risk: 'Cardiac arrhythmia (ventricular arrhythmia and cardiac arrest)', a prospective multicentre, multinational (USA, Europe), open label study (TES10884) has been initiated to assess the potential effect on QTcF (QTc using the Fridericia correction) interval of cabazitaxel in cancer patients. Patients enrolled must have a solid malignancy (confirmed by a cytology or pathologic report) for which standard curative treatment does not exist and a treatment with a novel taxane agent is considered.

For the important missing information: 'Use in patients with hepatic impairment', a Phase I study (POP6792) designed as an open label, dose escalation, multicentre study of cabazitaxel in cancer patients with varying degrees of hepatic impairment (patients being enrolled in 4 cohorts based on hepatic function) has been initiated to determine the maximum tolerated dose of cabazitaxel and to assess safety and pharmacokinetics of cabazitaxel administered to advanced solid tumour patients with varying degrees of hepatic impairment.

For the important missing information: 'Drug-drug interaction (concomitant administration with substrates or with inhibitors of CYP3A)', recruitment has started for a Phase I/II study (TCD10870) to assess *in vivo* the potential of CYP3A inhibitors to inhibit the CYP3A mediated metabolism of cabazitaxel using aprepitant, a moderate CYP3A inhibitor. Cabazitaxel is mainly metabolised by CYP3A *in vitro* (80% to 90%). Therefore, it is important to assess in patients the potential of CYP3A inhibitors to inhibit the CYP3A mediated metabolism of cabazitaxel.

Furthermore for the above important missing information, recruitment has started for a Phase I study (POP6792, in cohort with patients with normal hepatic function) to determine *in vivo* CYP inhibition potential of cabazitaxel on CYP3A by using oral midazolam. It is important to assess *in vivo* the potential of cabazitaxel to inhibit CYP3A, as about half of marketed drugs are metabolised by this CYP, and numerous anticancer agents that could be used in combination with cabazitaxel are substrates of this CYP.

In principle the OPR reviewer had no objection to the sponsor implementing additional pharmacovigilance activities to further monitor the specified ongoing safety concerns.

The specified ongoing and initiated studies were not considered to be part of the planned clinical studies in the pharmacovigilance plan, therefore the related study protocols have not been reviewed. Nevertheless an update on the progress/results/analysis of these studies as outlined in the RMP will be expected in future Periodic Safety Update Reports (PSURs).

[22] Routine pharmacovigilance practices involve the following activities:
All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
Reporting to regulatory authorities;
Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
Submission of PSURs;
Meeting other local regulatory agency requirements.

Risk minimisation activities

The sponsor stated that the proposed PI for cabazitaxel describes the safety profile and recommendations for the safe use of this drug in patients with metastatic hormone refractory prostate cancer. As stated in the PI (Dosage and Administration Section), the use of cabazitaxel should be confined to units specialised in the administration of cytotoxics, and should only be administered under the supervision of a physician qualified in the use of anticancer chemotherapy, therefore familiar with the management of antineoplastic associated toxicities, including those for taxanes. In addition, cabazitaxel should only be manipulated by personnel trained in the handling of cytotoxic agents.

Safety issues identified that require physicians vigilance are addressed in the proposed PI for cabazitaxel, and are likely to be effectively managed through recourse to specific therapies or, when required, a reduction or temporary delay in dosing. The sponsor stated that none of the important identified risks are unexpected based on the mechanism of action of cabazitaxel, nor would they be considered unusual or be unfamiliar for oncologists to be able to recognise or manage accordingly. In addition, patients with such a diagnosis have frequent interactions with healthcare professionals (HCPs) due to the treatment schedule, which will allow the HCP to become apprised of, assess and manage adverse drug reactions.

As a result, the sponsor considers that no additional risk minimisation activities beyond appropriate labelling statements are deemed necessary for the defined important risks, that is, routine risk minimisation.[23]

The OPR reviewer noted that the sponsor's justification for such conclusion was reasonable.

Routine risk minimisation activities will include warnings or notification of undesirable effects in the Australian PI for all the specified ongoing safety concerns, except for the important potential risk: 'Cardiac arrhythmia (ventricular arrhythmia and cardiac arrest)' as the sponsor claims it has not been confirmed in patients.

The OPR reviewer noted that the sponsor's proposed risk minimisation activities would appear to be reasonable, except for the sponsor's conclusion that no information is deemed necessary in the PI for the important potential risk: 'Cardiac arrhythmia (ventricular arrhythmia and cardiac arrest)'. Consequently it was recommended that the sponsor reconsider this particular course of action.

It was recommended to the Delegate that the draft PI be revised to include information relating to 'Cardiac Disorders - Arrhythmia' aligned with the currently approved US monograph.

Pharmacovigilance summary and conclusions

The nonclinical section of the Safety Specification of the RMP should be amended according to the recommendation of the nonclinical evaluator.

In principle there is no objection to the sponsor implementing additional pharmacovigilance activities to further monitor the specified ongoing safety concerns.

The specified ongoing and initiated studies are not considered to be part of the planned clinical studies in the pharmacovigilance plan, therefore the related study protocols have not been reviewed. Nevertheless an update on the progress/results/analysis of these studies as outlined in the RMP will be expected in future PSURs.

[23] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

The sponsor's proposed risk minimisation activities were reasonable, except for the sponsor's conclusion that no information is deemed necessary in the PI for the important potential risk: 'Cardiac arrhythmia (ventricular arrhythmia and cardiac arrest)'.

In regard to the proposed routine risk minimisation activities, it was recommended to the Delegate that the draft product information document be revised.

VI. Overall conclusion and risk/benefit assessment

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

Quality

Cabazitaxel is a complex, semisynthetic molecule practically insoluble in water. It is formulated with the non-ionic surfactant polysorbate 80. When diluted with water, polysorbate assembles as micelles and cabazitaxel dissolves in the micelles. With this formulation, compatible infusion containers and sets are required.

The application was reviewed at the 139th and 140th meetings of the PSC. Provided outstanding issues were addressed, there were no objections to registration. Issues to be resolved at this time included finished product specifications, sterility and Good Manufacturing Practice. Outstanding issues were resolved and there was no objection to registration.

Nonclinical

Relatively high toxicity was seen in the nonclinical studies, in particular, haematological and gastrointestinal effects, alopecia, peripheral neurotoxicity and effects on the male reproductive tract, which are common to the taxanes, and central neurotoxicity, hepatotoxicity and lenticular changes unique to cabazitaxel. The unique effects included neuron necrosis and vacuolation in the brain, axonal swelling and degeneration in the cervical spinal cord in mice, bile duct hyperplasia, arteriolar/periarteriolar necrosis and hepatocellular necrosis in dogs and subcapsular lens fibre swelling in rats.

Embryofetal toxicity was seen in rats at exposures well below those in patients at the recommended dose. Excretion of cabazitaxel occurs in the milk of rats. The evaluator recommended contraindicating the drug in pregnancy and lactation.

There were no carcinogenicity studies. Genotoxic findings were similar to other taxanes.

The evaluator did not support registration of cabazitaxel because a safety margin had not been established for the intended clinical use.

Clinical

Pharmacology

Based on population pharmacokinetic analysis in 170 subjects with advanced solid tumours including prostate cancer, cabazitaxel has a large volume of distribution (Vss 4,870 L) and is extensively metabolised and slowly eliminated. Active metabolites represent about 5% of drug exposure. The plasma elimination half-life is approximately 95 h.

Metabolism is mainly by CYP3A4 (80-90%). Interaction data are limited. Cabazitaxel may inhibit drugs that are CYP3A4 substrates and drugs that are CYP3A inducers or inhibitors may affect cabazitaxel concentrations.

Cabazitaxel exposure is likely to be increased in patients with hepatic impairment. Data are limited. Contraindication was proposed in these patients.

The maximum tolerated dose of cabazitaxel was 25 mg/m^2 when administered as a 1 h intravenous infusion every 3 weeks in patients with advanced solid tumours. Neutropenia was the dose limiting toxicity.

Efficacy

One efficacy trial was submitted, a randomised, open label trial in patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel containing regimen (EFC6193). Cabazitaxel was compared with mitoxantrone. Cabazitaxel 25 mg/m^2 was infused IV over 1 h and mitoxantrone 12 mg/m^2 infused IV over 15-30 min. Both treatment groups also received prednisone 10 mg orally daily. The median age of subjects was 68 years (range 46-92). ECOG performance status was 0-2. Whilst there are no established second line therapies, the sponsor stated that the comparator mitoxantrone used second line was consistent with Australian practice.

Threshold neutrophil and platelet counts and recovery of non-haematological toxicities were required prior to initiation and continuation of therapy. Treatment was continued until disease progression. Cabazitaxel subjects received a median 6 cycles (range 1-10) and mitoxantrone subjects a median 4 cycles (range 1-10). The primary endpoint was overall survival which was significantly longer with cabazitaxel than mitoxantrone (Table 16). Secondary endpoints also favoured cabazitaxel.

Table 16: Efficacy in hormone refractory metastatic prostate cancer (Tropic EFC6193 trial) – ITT population

	Cabazitaxel +prednisone *n=378*	Mitoxantrone +prednisone *n=377*	Hazard Ratio[4] [95% CI] or p-value of diff[5]
Survival median *mths*	15.1	12.7	0.70 [0.59, 0.83]
Progression[1] Free Survival median *mths*	2.8	1.4	0.74 [0.64, 0.86]
PSA Progression median *mths*	6.4	3.1	0.75 [0.63, 0.90]
Overall Tumour Response[2]	14.4% *n=201*	4.4% *n=204*	p=0.0005
PSA Response[3]	39.2% *n=329*	17.8% *n=325*	p=0.0002

[1] Tumour progression (RECIST criteria), PSA progression (≥ 25% increase for non-responders and ≥ 50% increase for responders, confirmed a week later), pain progression (≥ 1 point increase in median Present Pain Intensity on 2 consecutive 3 week apart visits or requirement for local palliative radiotherapy) or death.

[2] Investigator assessed in subjects with measurable disease from CT, MRI and bone scans using RECIST criteria and confirmed at least 4 weeks later.
[3] PSA reduction ≥ 50%, confirmed 3 weeks later, in subjects with PSA > 20 ng/mL at baseline.
[4] Cox model. [5] χ^2 test.

Although the trial population was a good representation of the target population, some subjects may have been docetaxel sensitive and benefited from docetaxel retreatment. All subjects had received prior docetaxel and two thirds of these had received ≥ 450 mg/m^2 (the recommended dose over 6 cycles).

Safety

Safety data for cabazitaxel was available in 558 patients, the majority (371) from the efficacy trial EFC6193. In the majority, the dose was 25 mg/m^2 and the median duration of treatment 18 weeks, range 3-36 weeks.

In the efficacy trial, the incidences of severe and serious adverse events and adverse events leading to treatment discontinuation were significantly greater with cabazitaxel (57% severe, 39% serious and 18% discontinuation) than mitoxantrone (39% severe, 21% serious and 8% discontinuation). The incidence of severe neutropenia (based on laboratory tests) was 82% with cabazitaxel and 58% with mitoxantrone. Other adverse events significantly more frequent with cabazitaxel than mitoxantrone were fatigue (37% vs 28%), asthenia (21% vs 12%), nausea (34% vs 23%), vomiting (23% vs 10%), diarrhoea (47% vs 11%), haematuria (17% vs 4%) and peripheral neuropathy (8% vs 1%). Renal and urinary disorders were also more frequent with cabazitaxel than mitoxantrone (31% vs 11%).

There was a higher incidence of deaths due to adverse events with cabazitaxel than mitoxantrone in the efficacy trial (4.9% vs 1.9%). The adverse event deaths with cabazitaxel were mostly cardiac or infective.

The pattern of adverse events in the other trials was similar to the efficacy trial. Differences in incidence across trials are unlikely to be significant because of lower numbers of subjects than the efficacy trial.

In the efficacy trial, cabazitaxel patients received premedication with an antihistamine, corticosteroid and H_2 antagonist to reduce the incidence and severity of adverse reactions. Premedication was discretionary in mitoxantrone patients. Prophylactic G-CSF, except for Cycle 1, was permitted in both treatment groups to manage neutropenia.

Clinical evaluation

The evaluator supported registration.

Risk management plan

Issues in the RMP evaluation were satisfactorily addressed by the sponsor in their responses. Implementation of the Australian RMP version 2.0 submitted was recommended as a condition of registration.

Based on the nonclinical and clinical data, the Safety Specification was adequate. There are ongoing studies to clarify the safety of cabazitaxel including studies of drug interactions, impact on QTc interval, impact on renal function and use in patients with hepatic impairment.

Risk-benefit analysis

Delegate considerations

Cabazitaxel significantly increased overall survival by a median 2.4 months in second line treatment of hormone refractory metastatic prostate cancer compared with mitoxantrone, another second line drug. There is no standard second line treatment. The standard first line drug, docetaxel, demonstrated a similar gain in survival over mitoxantrone in a first line population. There was support from secondary endpoints.

Cabazitaxel had considerably greater toxicity than mitoxantrone. However, the toxicity appeared comparable to that of other taxanes, although there was no direct comparison. Neutropenia and infection were very common with some deaths due to infection. Monitoring of the blood count weekly during the first cycle of treatment and before each subsequent cycle is recommended with dose adjustment as necessary. The incidences of some adverse effects appeared to be greater with cabazitaxel than docetaxel based on cross trial comparison, in particular, vomiting, diarrhoea, cardiac arrhythmias and renal failure. There were cardiac related deaths. The nonclinical evaluator noted unique neurological, hepatic and lens effects with cabazitaxel.

Premedication with an antihistamine, corticosteroid, H_2 antagonist and an antiemetic was recommended to reduce the incidence and severity of adverse reactions.

There are ongoing postmarket studies to clarify the cardiac and renal toxicity of cabazitaxel, interactions with other drugs and use in patients with hepatic impairment.

The dose of cabazitaxel in the efficacy study was 25 mg/m^2, the maximum tolerated in the pharmacology studies. In view of significant toxicity at this dose in the efficacy trial and as a postmarketing requirement in the USA, an ongoing trial is comparing a lower dose 20 mg/m^2 with 25 mg/m^2.

The proposed indication generally reflects the study population in the efficacy trial since 87% of subjects had received prior docetaxel treatment. It was not clear if some subjects remained docetaxel sensitive before entering the trial. About a third of subjects had received < 450 mg/m^2 of docetaxel. Some of these may have been highly resistant to docetaxel and relapsed early. The EU product information notes that in a subgroup of 59 subjects who received prior docetaxel < 225 mg/m^2 there was no significant difference in survival between cabazitaxel and mitoxantrone; however, this analysis could not be relied upon because of the small number of subjects. *The sponsor was invited to comment in their pre-ACPM Response.*

It seems the majority of subjects were docetaxel resistant, had limited treatment options and significantly benefited from cabazitaxel treatment. Therefore, despite the toxicity, the benefit risk balance is in favour of approval of cabazitaxel as proposed.

The Delegate proposed to approve cabazitaxel for the indication:

In combination with prednisone or prednisolone, treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel containing regimen.

Proposed conditions of registration included implementation of the Australian Risk Management Plan, version 2.0, and subsequent revisions as agreed with the Office of Product Review.

Other conditions may be required depending on the resolution of pharmaceutical chemistry issues.

Response from sponsor

Quality

The sponsor indicated there were now no outstanding quality issues.

Clinical

The sponsor provided a response to a comment raised by the Delegate as follows:

Although the trial population was a good representation of the target population, some subjects may have been docetaxel sensitive and benefited from docetaxel re-treatment, 87% of subject had received prior docetaxel and two-thirds of these had received ≥ 450 mg/m^2 (the recommended dose over 6 cycles).

The sponsor indicated that the percentage of 87% corresponds to the percentage of patients who had received docetaxel as first prior chemotherapy regimen. Indeed, some patients received more than one prior chemotherapy regimen and docetaxel was not always the first one.

All patients randomized in the TROPIC study were pre-treated with docetaxel. The 3 patients (0.8%) in cabazitaxel arm in the category missing received docetaxel but the cumulative dose was not known. Therefore "87% of subjects had received docetaxel" needs to be modified in "all patients had received prior docetaxel". This also needs to be modified in the comment by the Delegate discussed below.

The sponsor provided a response to a comment raised by the Delegate as follows:

The proposed indication reflects the study population in the efficacy trial since 87% of subjects had received prior docetaxel treatment. It was not clear if some subjects had received <450 mg/m^2 of docetaxel. Some of these may have been highly resistant to docetaxel and relapsed early. The EU product information notes that in a subgroup of 59 subjects who received prior docetaxel <225mg/m^2 there was significant difference in survival between cabazitaxel and mitoxantrone; however, this analysis could not be relied upon because of the small number of subjects.

The sponsor had addressed this issue as part of the clinical evaluation response and agreed that it is conceivable that some of these patients that had received low cumulative dose of prior docetaxel may have benefited from docetaxel rechallenge. In the absence of other treatment options prior to availability of positive results from TROPIC, upon progression of disease following docetaxel based therapy, it was not uncommon for patients with metastatic hormone refractory prostate cancer to be rechallenged with docetaxel. However, the studies on docetaxel rechallenge reported in the literature are retrospective studies or small uncontrolled studies with overall response rate or progression free survival (PFS) as endpoints. There is no controlled study that has demonstrated an improvement in overall survival (OS) following docetaxel rechallenge.

Jevtana in combination with prednisone/prednisolone has demonstrated an improvement in OS compared to an active control regimen of mitoxantrone and prednisone/prednisolone for the overall population and for most subsets of patients with prior docetaxel exposure.

RMP

Further to the registration of the product, the sponsor committed to implement the Australian Risk Management Plan version 3.0 and any subsequent revisions as agreed with the Office of Product Review.

Conclusions

The sponsor was in agreement with Delegate's draft decision to approve cabazitaxel for the above indication.

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:

Efficacy

Cabazitaxel significantly increased overall survival by a median 2.4 months in the second line treatment of hormone refractory metastatic prostate cancer compared with the comparator, mitoxantrone. The standard first line drug, docetaxel, had demonstrated a similar gain in survival over mitoxantrone in a first line population.

The secondary endpoints including progression free survival, response rate and PSA response also supported efficacy.

Safety

The ACPM noted that the nonclinical evaluator did not support registration of cabazitaxel because a safety margin had not been established for the intended clinical use.

Cabazitaxel has considerably greater toxicity than mitoxantrone; however, the toxicity appeared comparable to that of other taxanes, although no direct comparison was submitted. Neutropenia and infection were very common with some deaths due to infection.

It was noted that there are ongoing postmarket studies to clarify the cardiac and renal safety profile and use in cancer patients with renal impairment, interactions with other drugs and use in patients with hepatic impairment. The dose of cabazitaxel in the efficacy study was the maximum tolerated in the pharmacology studies. In view of significant toxicity at this dose an ongoing trial is comparing a lower dose of 20 mg/m^2 with 25 mg/m^2.

The ACPM agreed with the Delegate's suggestions of monitoring of the blood count weekly during the first cycle of treatment and before each subsequent cycle with dose adjustment as necessary and premedication with an antihistamine, corticosteroid, H_2 antagonist and antiemetic to reduce the incidence and severity of adverse reactions.

The ACPM was of the view that, as second line options for this patient group are limited and prognosis is generally poor, the proven efficacy with a survival benefit shown is significant so, despite the toxicity, the benefit risk balance is positive.

The ACPM noted that given the considerable toxicities reported, the committee agreed with the Delegate that the Risk Management Plan should be comprehensively implemented.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of safety and efficacy provided for cabazitaxel 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 Jevtana /Cabazitaxel Winthrop/Cabazitaxel Sanofi concentrated injection containing cabazitaxel 60 mg/1.5 mL vial, indicated for:

In combination with prednisone or prednisolone for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel containing regimen.

Among the specific conditions of registration was the implementation in Australia of the cabazitaxel Risk Management Plan (RMP) version 3.2, and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/>.

Therapeutic Goods Administration

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