PROFESSIONAL INFORMATION FOR CAPHET 60 mg/1,5 ml INJ

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CAPHET 60 mg/1,5 ml INJ, Concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 60 mg cabazitaxel in 1,5 ml. After initial dilution with the entire solvent, each ml of solution contains 10 mg cabazitaxel.

Excipient with known effect:

CAPHET 60 mg/1,5 ml INJ is sugar free.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion is a clear yellow to brownish yellow viscous solution and diluent (solvent) is a clear colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CAPHET 60 mg/1,5 ml INJ 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.

Each diluent (solvent) vial contains: Ethanol 96 % (573,3 mg), water for injection.

4.2 Posology and method of administration

Posology

General

The use of **CAPHET 60 mg/1,5 ml INJ** should be confined to units specialised in the administration of cytotoxics and it should be administered under the supervision of a medical practitioner qualified in the use of anticancer chemotherapy.

Premedication:

Premedicate prior to each administration of **CAPHET 60 mg/1,5 ml INJ** with the following intravenous medications to reduce the incidence and severity of a hypersensitivity reaction:

- antihistamine (dexchlorpheniramine 5 mg or diphenhydramine 25 mg or equivalent),
- corticosteroid (dexamethasone 8 mg or equivalent) and with
- H2 antagonist (ranitidine or equivalent) (see **section 4.4**).

Antiemetics prophylaxis is recommended and can be given orally or intravenously as needed.

Dosage:

The recommended dose of **CAPHET 60 mg/1,5 ml INJ** is 25 mg/m^2 administered as a 1-hour intravenous infusion every 3 weeks in combination with oral prednisone (or prednisolone) 10 mg administered daily throughout **CAPHET 60 mg/1,5 ml INJ** treatment.

Dosage adjustments:

Dosage modifications should be made if patients experience the following adverse reactions.

Recommended Dosage Modifications for adverse reaction in patients treated with **CAPHET 60 mg/1,5 ml INJ**

Adverse reactions	Dosage Modification
Prolonged grade ≥ 3 neutropenia (greater than 1 week) despite appropriately medication including G-CSF	Delay treatment until neutrophil count is > 1 500 cells/mm^3, then reduce dosage of **CAPHET 60 mg/1,5 ml INJ** from 25 mg/m^2 to 20 mg/m^2.
Febrile neutropenia	Delay treatment until improvement or resolution, and until neutrophil count is > 1 500 cells/mm^3, then reduce

	dosage of **CAPHET 60 mg/1,5 ml INJ** from 25 mg/m^2 to 20 mg/m^2.
Grade ≥ 3 diarrhoea or persisting diarrhoea despite appropriate medication, fluid and electrolytes replacement	Delay treatment until improvement or resolution, then reduce dosage of **CAPHET 60 mg/1,5 ml INJ** from 25 mg/m^2 to 20 mg/m^2.

Discontinue **CAPHET 60 mg/1,5 ml INJ** treatment if a patient continues to experience any of these reactions at 20 mg/m^2.

Special populations

The elderly ≥ 65 years:

No specific dose adjustment for the use of **CAPHET 60 mg/1,5 ml INJ** in senior adult patients is recommended (see **sections 4.4, 4.8** and **5**)

Patients with hepatic impairment:

CAPHET 60 mg/1,5 ml INJ is extensively metabolised by the liver. No formal studies were conducted in patients with severe hepatic impairment. As a precautionary measure, **CAPHET 60 mg/1,5 ml INJ** should not be given to patients

with hepatic impairment [bilirubin ≥ 1 x Upper Limit of Normal (ULN), or AST/SGOT and/or ALT/SGPT ≥ 1,5 x ULN] (see **sections 4.3, 4.4** and **5**).

Patients with renal impairment:

CAPHET 60 mg/1,5 ml INJ is minimally excreted through the kidney. No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance (CL_{CR}): 50 to 80 ml/min). Data in patients with moderate (CL_{CR}: 30 to 50 ml/min) and severe renal impairment (CL_{CR} < 30 ml/min) is limited; therefore these patients should be treated with caution and monitored carefully during treatment (see **section 5**).

Dose delay or reduction should be considered in the event of adverse effects.

Paediatric population

The safety and the efficacy of **CAPHET 60 mg/1,5 ml INJ** in children have not been established.

Method of administration

Intravenous infusion.

Use an in-line filter of 0,22 micrometre nominal pore size during administration.

4.3 Contraindications

- Known hypersensitivity to cabazitaxel or other medicines formulated with polysorbate 80 or to any of the excipients of **CAPHET 60 mg/1,5 ml INJ** (see section 6.1).
- Neutrophil counts ≤ 1 500/mm^3.
- Hepatic impairment (bilirubin ≥ 1 x ULN, or AST/SGOT and/or ALT/SGPT ≥ 1,5 x ULN).
- Concomitant vaccination with yellow fever vaccine

4.4 Special warnings and precautions for use

Neutropenia

Neutropenia is the most common adverse reaction of **CAPHET 60 mg/1,5 ml INJ** (see **section 4.8**). The use of G-CSF has been shown to limit the incidence and severity of neutropenia and its complications. Monitoring of complete blood count is essential on a weekly basis during cycle 1 and before each treatment cycle thereafter so that the dose can be adjusted, if needed (see **section 4.2**).

Reduce dose in case of febrile neutropenia, or prolonged neutropenia despite appropriate treatment (see **section 4.2**).

Retreat only when neutrophils recover to a level > 1 500/mm^3 (see **section 4.3**).

Hypersensitivity reactions

All patients should be premedicated prior to the initiation of the infusion of **CAPHET 60 mg/1,5 ml INJ** (see **section 4.2**).

Patients should be observed closely for hypersensitivity reactions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of **CAPHET 60 mg/1,5 ml INJ**, thus facilities and equipment for the treatment of hypotension and bronchospasm should be available. Severe reactions can

occur and may include generalised rash/erythema, hypotension and bronchospasm. Severe hypersensitivity reactions require immediate discontinuation of **CAPHET 60 mg/1,5 ml INJ** and appropriate therapy. Patients who have a history of severe hypersensitivity reactions should not be rechallenged with **CAPHET 60 mg/1,5 ml INJ** (see **section 4.3**).

Gastrointestinal symptoms

If patients experience diarrhoea following administration of **CAPHET 60 mg/1,5 ml INJ** they may be treated with commonly used anti-diarrhoeal medications. Appropriate measures should be taken to rehydrate the patients. Treatment delay or dosage reduction may be necessary for grade ≥ 3 diarrhoea (see **section 4.2**). If patients experience nausea or vomiting, they may be treated with commonly used anti-emetics.

Renal disorders

Renal disorders, have been reported in association with sepsis, severe dehydration due to diarrhoea, vomiting and obstructive uropathy. Renal failure including cases with fatal outcome has been observed. Appropriate measures should be taken to identify the cause and intensively treat the patients if this occurs.

Bone marrow suppression

Bone marrow suppression manifested as neutropenia, anaemia, thrombocytopenia or pancytopenia may occur.

Peripheral neuropathy

Cases of peripheral neuropathy, peripheral sensory neuropathy (e.g., paraesthesias, dysaesthesias) and peripheral motor neuropathy have been observed in patients receiving cabazitaxel. Patients under treatment with cabazitaxel should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop. Medical practitioners should assess for the presence or worsening of neuropathy before each treatment. Treatment should be delayed until improvement of symptoms. The dose of cabazitaxel should be reduced from 25 mg/m^2 to 20 mg/m^2 for persistent grade ≥ 2 peripheral neuropathy (see **section 4.2**).

Anaemia

Anaemia has been observed in patients receiving cabazitaxel (see **section 4.8**). Haemoglobin and haematocrit should be checked before treatment with cabazitaxel and if patients exhibit signs or symptoms of anaemia or blood loss. Caution is recommended in patients with haemoglobin <10 g/dl and appropriate measures should be taken as clinically indicated.

Respiratory disorders

Interstitial pneumonia/pneumonitis and interstitial lung disease have been reported and may be associated with fatal outcome (see **section 4.8**).

If new or worsening pulmonary symptoms develop, patients should be closely monitored, promptly investigated, and appropriately treated. Interruption of cabazitaxel therapy is recommended until diagnosis is available. Early use of supportive care measures may help improve the condition. The benefit of resuming cabazitaxel treatment must be carefully evaluated.

Risk of cardiac dysrhythmias

Cardiac dysrhythmias have been reported, most commonly tachycardia and atrial fibrillation (see **section 4.8**).

Interactions

Co-administration with strong CYP3A inhibitors should be avoided since they may increase the plasma concentrations of cabazitaxel (see **sections 4.2** and **4.5**). If co-administration with a strong CYP3A inhibitor cannot be avoided, close monitoring for toxicity and a cabazitaxel dose reduction should be considered (see **sections 4.2** and **4.5**).

Co-administration with strong CYP3A inducers should be avoided since they may decrease plasma concentrations of cabazitaxel (see **sections 4.2** and **4.5**).

Elderly patients ≥ 65 years

Senior adult patients (≥ 65 years of age) may be more likely to experience certain adverse reactions including neutropenia (see **section 4.8**).

Patients with liver impairment

Treatment with **CAPHET 60 mg/1,5 ml INJ** is contraindicated (see **sections 4.2** and **4.3**).

Excipients:

The solvent contains 573.3 mg ethanol 96% (15% v/v),

Harmful for those suffering from alcoholism.

To be taken into account in high-risk groups such as patients with liver disease, or epilepsy.

4.5 Interaction with other medicine and other forms of interaction

No formal clinical studies to assess the potential interaction between **CAPHET 60 mg/1,5 ml INJ** and other medicines have been performed.

In vitro studies have shown that **CAPHET 60 mg/1,5 ml INJ** is mainly metabolised through CYP3A (80 % to 90 %) and inhibits CYP3A.

The metabolism of **CAPHET 60 mg/1,5 ml INJ** may be modified by the concomitant administration of compounds which are known to be potent inhibitors (e.g., ketoconazole) or inducers (e.g., rifampicin, carbamazepine, phenobarbital or phenytoin) of CYP3A.

Coadministration of **CAPHET 60 mg/1,5 ml INJ** with medicines that are known to be primarily metabolised through CYP3A may increase the exposure of these medicines.

Therefore, caution should be exercised in patients concurrently taking medicines known to be either primarily metabolised through CYP3A or to be potent inhibitors or inducers of this enzyme (see **section 5.2**).

Prednisone/prednisolone administered at 10 mg daily did not affect the pharmacokinetics of **CAPHET 60 mg/1,5 ml INJ**.

OATP1B1

In vitro, cabazitaxel has also been shown to inhibit the transport proteins of the Organic Anion Transport Polypeptides OATP1B1. The risk of interaction with OATP1B1 substrates (e.g. statins, valsartan, repaglinide) is possible, notably during the infusion duration (1 hour) and up to 20 minutes after the end of the infusion. A time interval of 12 hours is recommended before the infusion and at least 3 hours after the end of infusion before administering the OATP1B1 substrates.

Vaccinations

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic medicines may result in serious or fatal infections. Vaccination with a live attenuated vaccine should be avoided in patients receiving cabazitaxel. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential and female/male contraception

CAPHET 60 mg/1,5 ml INJ is not recommended for use in women of childbearing potential not using contraception.

Due to potential exposure via seminal liquid, men with partners of childbearing potential should use reliable contraception throughout treatment and are recommended to continue this for up to 3 months after the last dose of **CAPHET 60 mg/1,5 ml INJ**.

Pregnancy

There are no data from the use of **CAPHET 60 mg/1,5 ml INJ** in pregnant women. Studies in animals have shown reproductive toxicity and that **CAPHET 60 mg/1,5 ml INJ** crosses the placenta barrier. **CAPHET 60 mg/1,5 ml INJ** is not recommended for use during pregnancy.

Breastfeeding

Available pharmacokinetics data in animals have shown excretion of **CAPHET 60 mg/1,5 ml INJ** and its metabolites in milk. **CAPHET 60 mg/1,5 ml INJ** should not be used during breastfeeding.

Fertility

The effect of **CAPHET 60 mg/1,5 ml INJ** on human fertility is unknown. Animal studies showed that **CAPHET 60 mg/1,5 ml INJ** affected the reproductive system in male rats and dogs.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, based on the safety profile, **CAPHET 60 mg/1,5 ml INJ** may have moderate influence on the ability to drive and use machines as it may cause fatigue and dizziness. Patients should be advised to not drive or use machines if they experience these adverse reactions during treatment.

4.8 Undesirable effects

a) Summary of the safety profile

The safety of **CAPHET 60 mg/1,5 ml INJ** in combination with prednisone or prednisolone was evaluated in 371 patients with hormone refractory metastatic prostate cancer, in a randomised open label, controlled phase III study. Patients received a median duration of 6 cycles of **CAPHET 60 mg/1,5 ml INJ.**

The most frequent Grade ≥ 3 adverse reactions in the cabazitaxel group were clinical neutropenia, febrile neutropenia, diarrhoea, fatigue, and asthenia.

Discontinuation of treatment due to adverse drug reactions occurred in 68 patients in the **CAPHET 60 mg/1,5 ml INJ** group and 31 patients in the mitoxantrone group. The most frequent adverse reaction leading to treatment discontinuation in the **CAPHET 60 mg/1,5 ml INJ** group was neutropenia.

b) Tabulated list of adverse reactions

CAPHET 60 mg/1,5 ml INJ in combination with prednisone or prednisolone

Infections and infestations

Frequent: Urinary tract infection, Septic shock, Sepsis, Cellulitis, Influenza, Cystitis, Upper respiratory tract infection, Herpes zoster, Candidiasis

Blood and lymphatic system disorders

Frequent: Neutropenia, anaemia, leukopenia, thrombocytopenia, febrile neutropenia

Immune system disorders

Frequent: Hypersensitivity

Metabolism and nutrition disorders

Frequent: Anorexia, dehydration, Hyperglycaemia, Hypokalemia

Psychiatric disorders

Frequent: Anxiety, Confusional state

Nervous system disorders

Frequent: Dysgeusia, neuropathy peripheral, dizziness, headache, peripheral sensory neuropathy, Paraesthesia, Lethargy, Hypoaesthesia, Sciatica.

Eye disorders

Frequent: Conjunctivitis, Lacrimation increased.

Ear and labyrinth disorders

Frequent: Tinnitus, Vertigo.

Cardiac disorders

Frequent: Atrial fibrillation, Tachycardia.

Vascular disorders

Frequent: Hypotension, Deep vein thrombosis, Hypertension, Orthostatic hypotension, Hot flush, Flushing.

Respiratory, thoracic and mediastinal disorders

Frequent: Dyspnoea, cough, Oropharyngeal pain, Pneumonia.

Gastrointestinal disorders

Frequent: Diarrhoea, nausea, vomiting, constipation, abdominal pain, dyspepsia, upper abdominal pain, haemorrhoids, gastro-oesophageal reflux disease, Rectal haemorrhage, Dry mouth, Abdominal distension.

Skin and subcutaneous tissue disorders

Frequent: Alopecia, Dry skin, Erythema.

Musculoskeletal and connective tissue disorders

Frequent: Back pain, arthralgia, muscle spasms, Pain in extremity, Myalgia, Musculoskeletal chest pain, Flank pain.

Renal and urinary disorders

Frequent: Haematuria, dysuria, urinary incontinence, acute renal failure, Renal failure, Renal colic, Pollakiuria, Hydronephrosis, Urinary retention, Urinary incontinence, Ureteric obstruction.

Reproductive system and breast disorders

Frequent: Pelvic pain.

General disorders and administration site conditions

Frequent: Fatigue, asthenia, pyrexia, peripheral oedema, mucosal inflammation, Pain, Chest pain, Oedema, Chills, Malaise.

Investigations

Frequent: Weight decreased, Aspartate aminotransferase increased, Transaminases

Increased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za or to the Holder of certificate of registration through the mail: pvg.cdma@heterogroups.com

4.9 Overdose

The anticipated complications of overdose would be exacerbation of adverse reactions as bone marrow suppression and gastrointestinal disorders.

There is no known antidote to **CAPHET 60 mg/1,5 ml INJ**. In case of overdose, the patient should be kept in a specialised unit and closely monitored. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 26 Cytostatic Agents

Pharmacotherapeutic group: Antineoplastic agents, taxanes**, ATC code: L01CD04**.

Cabazitaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells. Cabazitaxel binds to tubulin and promotes the assembly of tubulin into microtubules while simultaneously inhibiting their disassembly. This leads to the stabilisation of microtubules, which results in the inhibition of mitotic and interphase cellular functions.

5.2 Pharmacokinetic properties

Absorption:

After a 1-hour IV administration dose of cabazitaxel at 25 mg/m^2, in patients with metastatic prostate cancer the mean C_{max} was 226 ng/ml (coefficient of variation, CV 107 %) and was reached at the end of the 1-hour infusion (T_{max}). The mean AUC was 991 ng.h/ml (CV: 34 %).

No major deviation to the dose proportionality was observed from 10 to 30 mg/m^2 in patients with advanced solid tumours.

Distribution

The volume of distribution (Vss) was 4 870 l (2 640 l/m^2 for a patient with a median BSA of 1,84 m^2) at steady state.

In vitro, the binding of cabazitaxel to human serum proteins was 89 to 92 % and was not saturable up to 50 000 ng/ml, which covers the maximum concentration observed in clinical studies. Cabazitaxel is mainly bound to human serum albumin (82,1 %) and lipoproteins (87,9 % for HDL, 69,8 % for LDL, and 55,8 % for VLDL). The *in vitro* blood-to-plasma concentration ratios in human blood ranged from 0,90 to 0,99 indicating that cabazitaxel was equally distributed between blood and plasma.

Biotransformation

Cabazitaxel is extensively metabolised in the liver (≥ 95 %), mainly by the CYP3A4 isoenzyme (80 to 90 %). Cabazitaxel is the main circulating compound in human plasma. Seven metabolites were detected in plasma (including 3 active metabolites issued from O-demethylation), with the main one accounting for 5 % of parent exposure. Around 20 metabolites of cabazitaxel are excreted into human urine and faeces.

Based on *in vitro* data, the potential risk of inhibition by cabazitaxel at clinically relevant concentrations is possible for medicines that are mainly substrate of CYP3A. However, there is no potential risk of inhibition of medicines that are substrates of other CYP enzymes (1A2, 2B6, 2C9, 2C8, 2C19, 2E1, and 2D6) as well as no potential risk of induction by cabazitaxel on medicines that are substrates of CYP1A, CYP2C9, and CYP3A.

Elimination

After a 1-hour IV infusion [^{14}C]-cabazitaxel at 25 mg/m^2 in patients, approximately 80 % of the administered dose was eliminated within 2 weeks. Cabazitaxel is mainly excreted in the faeces as numerous metabolites (76 % of the dose); while renal excretion of cabazitaxel and metabolites account for less than 4 % of the dose (2,3 % as unchanged medicine in urine).

Cabazitaxel had a high plasma clearance of 48,5 l/h (26,4 l/h/m^2 for a patient with a median BSA of 1,84 m^2) and a long terminal half-life of 95 hours.

Characteristics in specific groups of patients

The elderly ≥ 65 years:

In the population pharmacokinetic analysis in 70 patients of 65 years and older (57 from 65 to 75 and 13 patients above 75), no age effect on the pharmacokinetics of cabazitaxel was observed.

Hepatic impairment:

No formal studies in patients with hepatic impairment have been conducted.

Renal impairment:

Cabazitaxel is minimally excreted via the kidney (2,3 % of the dose). No formal pharmacokinetic studies were conducted with cabazitaxel in patients with renal impairment. However, the population pharmacokinetic analysis carried out in 170 patients that included 14 patients with moderate renal impairment (creatinine clearance in the range of 30 to 50 ml/min) and 59 patients with mild renal impairment (creatinine clearance in the range of 50 to 80 ml/min) showed that mild to moderate renal impairment did not have meaningful effects on the pharmacokinetics of cabazitaxel.

Paediatric patients:

Safety and effectiveness of cabazitaxel have not been established in children.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Concentrate for solution for infusion:

- Nitrogen
- Polysorbate 80

Diluent (solvent):

- Ethanol

- Nitrogen

Water for injection

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

Do not use PVC infusion containers and polyurethane infusion sets for the preparation and administration of **CAPHET 60 mg/1,5 ml INJ**.

6.3 Shelf life

24 months.

After opening:

Concentrate and solvent vials must be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

After initial dilution:

Chemical and physical in-use stability for the resulting concentrate-solvent mixture has been demonstrated for one hour at ambient temperature. From a microbiological point of view, the concentrate-solvent mixture should be used immediately.

After final dilution:

Chemical and physical stability of the infusion solution has been demonstrated for 8 hours at ambient temperature (including the 1-hour infusion time) and for 48 hours under refrigerated conditions. From a microbiological point of view, the infusion solution should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C unless dilution has taken place in controlled and validated aseptic conditions.

As the infusion solution is supersaturated, it may crystallise over time. In this case, the solution must not be used and should be discarded.

6.4 Special precautions for storage

- Store at or below 25 °C.
- Do not refrigerate.

Keep the vials in the outer carton until required for use.

6.5 Nature and contents of container

Concentrate for solution for infusion: 1,5 ml (deliverable volume) of **CAPHET 60 mg/1,5 ml INJ** concentrate for solution for infusion in a 15 ml type-I, round clear tubular glass vial with 20 mm serum rubber GCB stopper with flurotec coating and 20 mm purple colour flip off aluminium seal.

Diluent (solvent): 4,5 ml (deliverable volume) of solvent in a 15 ml type-I, round clear tubular glass vial with 20 mm serum rubber GCB stopper with flurotec coating and 20 mm white colour flip off aluminium seal.

Pack size: 1 vial of concentrate for solution for infusion and 1 vial of diluent (solvent) together are packed in an outer carton.

6.6 Special precautions for disposal and other handling

Caution should be exercised when handling and preparing **CAPHET 60 mg/1,5 ml INJ** solutions. The use of gloves is recommended.

If **CAPHET 60 mg/1,5 ml INJ**, at any step of its handling, should come into contact with the skin, wash immediately and thoroughly with soap and water. If it should come into contact with mucous membranes, wash immediately and thoroughly with water.

CAPHET 60 mg/1,5 ml INJ should only be prepared and administered by personnel trained in handling cytotoxic agents. Pregnant staff should not handle it.

Any unused product or waste material should be disposed of in accordance with local requirements.

The following 2-step dilution process must be carried out in an aseptic manner for preparing the solution for infusion:

Step 1: Initial dilution of CAPHET 60 mg/1,5 ml INJ 60 mg/1,5 ml concentrate for solution for infusion with the supplied solvent.

- Set aside the **CAPHET 60 mg/1,5 ml INJ** 60 mg/1,5 ml concentrate vial and the supplied solvent. The concentrate solution should be clear if appropriately stored (see **section 6.4**).

- Withdraw the entire content of the supplied solvent using a syringe, by partially inverting the vial, and inject it into the corresponding vial of **CAPHET 60 mg/1,5 ml INJ** 60 mg/1,5 ml concentrate. To limit as much as possible foaming when injecting the solvent, direct the needle onto the inside wall of the vial of concentrate solution and inject slowly.
- Remove the syringe and needle and mix manually and gently by repeated inversions until obtaining clear and homogeneous solution. It could take approximately 45 seconds.
- Let stand this solution for few minutes (approximately 5 minutes) and check then that the solution is homogeneous and clear. It is normal for foam to persist after this time period.

This resulting concentrate-solvent mixture contains 10 mg/ml of cabazitaxel (at least 6 ml deliverable volume). It should be immediately diluted as detailed in step 2.

Step 2: Preparation of the infusion solution.

- Withdraw the required amount of initial diluted **CAPHET 60 mg/1,5 ml INJ** solution (10 mg/ml of cabazitaxel), with a graduated syringe and inject in a sterile PVC-free container of either 5 % glucose solution or 0,9 % sodium chloride solution for infusion. The concentration of the infusion solution should be between 0,10 mg/ml and 0,26 mg/ml.

As an example, a dose of 45 mg **CAPHET 60 mg/1,5 ml INJ** would require 4,5 ml of the concentrate-solvent mixture prepared following step 1. More than one vial of the initial diluted solution may be necessary to administer the prescribed dose.

- Since foam may persist on the wall of the vial of this solution, following its preparation described in step 1, it is preferable to place the needle of the syringe in the middle when extracting.
- Remove the syringe and mix the content of the infusion bag or bottle manually using a rocking motion.
- As with all parenteral products, the resulting infusion solution should be visually inspected prior to use. Solution containing a precipitate should be discarded.

The **CAPHET 60 mg/1,5 ml INJ** infusion solution should be used immediately.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Hetero Drugs South Africa (Pty) Ltd

Waterfall Corporate Campus

Building No. 2, First floor

74 Waterfall Drive

Midrand

2066

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