National Essential Medicine List
Tertiary Medication Review Process
Component: Oncology

MEDICINE MOTIVATION:

1. **Executive Summary**

Date: June 2019
Medicine (INN): Docetaxel
Medicine (ATC): L01CD02
Indication (ICD10 code): Metastatic prostate cancer. C61
Patient population: Patients with Castrate Resistant prostate cancer
Prevalence of condition: 7057 newly diagnosed cases of prostate cancer (incidence), age standardized ratio (ASR) 26.65 cases per 100 000/year (2014)[1](commonest cancer in males in South Africa). In 2009, 2331 deaths from prostate cancer reported, 42% black, 23% unknown, 22% coloured, 11% white, 2% Asian/indian.[2]
Level of Care: Tertiary/Quaternary
Prescriber Level: Oncologist
Current standard of Care: Mitoxantrone plus Prednisone
Efficacy estimates: (preferably NNT): 20 (absolute OS benefit at 3 years = 5%) 3 year survival was 18.6% compared with the Mitoxantrone/Prednisone arm (13.5%).[3]

2. **Name of author(s)/motivator(s):** Tertiary/Quaternary Expert Review Committee
3. **Author affiliation and conflict of interest details***:* No relevant conflicts noted.

4. **Introduction/ Background**

Prostate cancer (PC) is the most common cancer affecting South African men, with 1 in 28 men expected to be diagnosed in their lifetime. The majority of those diagnosed in South Africa present with locally advanced and/or metastatic disease. In addition, up to 30% of patients initially diagnosed with local disease and treated with curative intent progress to this stage. Standard treatment for newly diagnosed locally advanced and metastatic PC (without high volume visceral or skeletal metastases) is androgen deprivation therapy (ADT) as these cancers are almost uniformly hormone sensitive (HSPC) at diagnosis. ADT may be in the form of bilateral orchiectomy or the use of long acting GnRH agonists. Unfortunately, the majority of HSPC patients eventually become refractory to ADT usually associated with clinical disease progression despite castrate levels of testosterone. This leads to the development of "castrate resistant prostate cancer" (CRPC).

The prognosis for these patients is poor as the disease is incurable and will progress in the future. However, many patients have a diminished quality of life due to the presence of skeletal disease and associated pain. Therefore, the docetaxel/prednisone regimen is palliative in nature and the intention for motivating for its inclusion on the Tertiary/Quaternary EML is to hopefully improve quality and quantity of life for these patients. Many of the newer drugs, including abiraterone, enzalutamide and cabazitaxel available have also been shown to achieve this, but are expensive

and not justifiable in the State setting. Based on the available evidence, docetaxel presents an affordable less costly and potentially attainable option for these patients.

5. Purpose/Objective i.e. PICO question:

-P *(patient/population):* Castrate resistant metastatic prostate cancer (CRPC)
-I *(intervention):* Intravenous chemotherapy with docetaxel plus oral prednisone
-C *(comparator):* Mitoxantrone plus prednisone
-O *(outcome):* Median overall survival, palliation response

6. Methods:

a. Data sources: Pubmed, Google Scholar.

b. **Search strategy:** "Docetaxel"[Mesh] AND "Prostatic Neoplasms"[Mesh] AND (Randomized Controlled Trial[ptyp] AND "humans"[MeSH Terms] AND English[lang])

c. **Excluded studies:**

- Studies in patient with hormone sensitive prostate cancer
- Studies with with carbazitaxel, CYP17 inhibitors, 3rd/4th generation ARBs and radiopharmaceuticals including carbazitaxel, abiraterone, enzalutamide and apalutamide; and Radium 223.

d. Evidence synthesis

Title, Author, date	Type of study	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Hormone sensitive prostate cancer							
Tannock et al, 1996[4]	RCT	161	Metastatic castrate resistant prostate cancer	Mitoxantrone (MP) 10-12mg/m2 every 3wks plus Prednisone 10mg daily vs Prednisone 10mg daily.	Palliative response	Palliative response 29% (95% CI 19-40) vs. 12% (95% CI 6-22). Palliation duration: 43 weeks vs. 18 weeks (p<0.0001)	No OS difference
TAX327: Tannock et al, 2004 [5]	RCT	1006	Metastatic castrate resistant prostate cancer	Mitoxantrone (MP) 12mg/m2 every 3wks vs docetaxel (D3P) 75mg/m2 every 3weeks vs docetaxel (D1P) 30mg/m2 weekly. Duration 18 weeks. All patients received prednisone 5mg bid.	OS	Median overall survival: MP 16.5 months vs D3P 18.9 months [HR 0.76; 95% CI 0.62-0.94; p=0.009] MP 16.5 months vs D1P (17.4 months [HR 0.91; 95% CI 0.75-1.11; p=0.36]. Pain response: D3P 35% (95% CI 27 – 43) pain response versus 22% (16 – 29), P = 0.01. Quality of life: D3P 22% (17-27) response versus 13% (9-18), P = 0.009.	• Evidence of improved outcomes with D3P but not D1P. • Limitations: Company sponsored, Bonferroni correction used, double dosing of prednisone in control arm.
TAX327: (Follow up: Dominik R et al, 2007)[3]	RCT	1006	Metastatic castrate resistant prostate cancer	Mitoxantrone (MP) 12mg/m2 every 3wks vs docetaxel (D3P) 75mg/m2 every 3weeks vs docetaxel (D1P) 30mg/m2 weekly. All patients received prednisone 5mg bid.	OS	Median overall survival: D3P 19.2 months (95% CI, 17.5 to 21.3 months) (p=0.004) vs. MP 16,3 months (95% CI, 14.3 to 17.9 months) D1P 17.8 months (95% CI, 16.2 to 19.2 months). 3 year survival in the D3P and D1P arms was 18.6% & 16.6%, compared with the MP arm (13.5%).	Evidence of improved outcomes with D3P and D1P.

e. **Evidence quality:** Level 1: randomized phase 3 clinical trial, 1006 patients in 3 arms. Note: study was sponsored by theOriginator manufacturer. Quality issues as outlined above: use of bonferroni correction, company sponsorship and differing prednisone dosing in control and trial arms.

7. **Alternative agents:** abiraterone, enzalutamide, cabazitaxel, radium 223

8. **Adverse effects:** Myelosuppression, peripheral neuropathy, infusion reaction

9. **Cost of therapy**

Dose: 75 mg/m2 3 weekly for 6-8 weeks

	Rounded dose for 1.73m2 male adult	Cost*	Cost/mg	No. vials needed	Cost per dose (1.73m2)	Cost for 6 cycles	Cost for 8 cycles
Docetaxel	120 mg	R460 (80mg)	R5.75	1	R460.00	**R4,830.00**	**R6,440.00**
		R172.50 (20mg)	R8.63	2	R345.00		
				TOTAL	**R805.00**		

**Contract Price, Master Procurement Catalogue 1 July 2019*

Death data from Prostate Cancer (2009) reported 2331 deaths.

Cost considerations: As this is a palliative intervention, the aim of treatment is not curative. It is thus not possible to provide cost savings in terms of preventing hospital visits and admissions. The observed improvements may prevent complications like spinal cord compression and skeletal events (which would be cost saving), however this may only be a delay in these events and not a prevention. The inherent aim of docetaxel's use is to improve the quality and quantity of life for these patients. Tannock et. al.[5] report statistically significant pre-defined reductions in pain and improvements in the quality of life.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [X] Not confident [ ] Uncertain [ ]	
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [ ] No [X] List the members of the group. List specific exclusion from the group:	Rationale for therapeutic alternatives included: References: Rationale for exclusion from the group: References:
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [X] Major [ ] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	

<table>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?

More intensive | Less intensive | Uncertain
[ ] | [ ] | [X]
Unclear of cost benefit in terms of prevention of hospitalisation, QoL and reduction in pain</td><td>Cost of medicines/ month:
<table><tr><th>Medicine</th><th>Cost (ZAR)</th></tr><tr><td>6 cycles docetaxel</td><td>R6,440.00</td></tr></table>
Additional resources:</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?

Yes | No | Uncertain
[ ] | [ ] | [X]</td><td>Affects predominantly affects black males.</td></tr>
<tr><td>FEASIBILITY</td><td>Is the implementation of this recommendation feasible?
Yes | No | Uncertain
[X] | [ ] | [ ]</td><td></td></tr>
</table>

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☐	☐	**X**

Recommendation

It is recommended that Docetaxel 75mg/m2 intravenously 3 weekly plus Prednisone 10mg daily orally x 6 cycles is be included on the Essential Medicine list for metastatic CRPC.

Rationale:

Level of Evidence:

LoE: I

Review indicator:

Reduction in cost and availability of 3rd generation ARBs eg. enzalutamide and CYP17 inhibitors eg. abiraterone

Evidence of efficacy	Evidence of harm	Price reduction
☐	☐	☐

VEN status:

Vital	Essential	Necessary
☐	X	☐

Monitoring and evaluation considerations

Research priorities

References

[1] National Cancer Registry, 2014. http://www.nicd.ac.za/wp-content/uploads/2017/03/2014-NCR-tables-1.pdf

[2] Babb C, Urban M, Kielkowski D, Kellet P. Prostate Cancer in South Africa: Pathology Based National Cancer Registry data (1986-2006) and mortality rates (1997-2009).

[3]Dominik R. Berthold, Gregory R. Pond, Freidele Soban, Ronald de Wit, Mario Eisenberger, and Ian F. Tannock. Docetaxel Plus Prednisone or Mitoxantrone Plus Prednisone for Advanced Prostate Cancer: Updated Survival in the TAX 327 Study. *Journal of Clinical Oncology* 2007; 26:242-245.

[4]Tannock IF, Osoba D, Stockler MR, Ernst DS, Neville AJ, Moore MJ, Armitage GR, Wilson JJ, Venner PM, Coppin CM, Murphy KC. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone resistant prostate cancer: a Canadian randomized trial with palliative end points. *Journal of Clinical Oncology* 1996; 14 (6):1756–64.

[5] Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, Oudard S, Theodore C, James ND, Turesson I, Rosenthal MA, Eisenberger MA, Investigators TAX327. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *New England Journal of Medicine* 2004;351(15):1502–12.