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 hormone sensitive prostate cancer (HSPC)
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
Prescriber Level: Oncologist
Current standard of Care: Androgen deprivation therapy (ADT)
Efficacy estimates: (preferably NNT):

- Median overall survival (OS): 57.6 months for docetaxel plus ADT versus 47.2 months for ADT alone, hazard ratio 0.72 (95% CI, 0.59 to 0.89; P = .0018); NNT = 16
- Median overall survival in high-volume disease: 51.2 months for docetaxel plus ADT versus 34.4 months with ADT alone, hazard ratio 0.63 (95% CI, 0.50 to 0.79; P < 0.001); NNT = 6.[3]

2. **Name of author(s)/motivator(s):** Tertiary Expert Review Committee. Lead authors: P Ruff and E Maramba.

3. **Author affiliation and conflict of interest details***:* No specific conflicts of interest identified.

4. **Introduction/ Background**

Prostate cancer (PCa) is the commonest cancer in SA males with 1 in 28 men getting PCa in their lifetime and upwards of 20% of these diagnosed cases dying from the disease. PCa is also the second leading cause of cancer mortality after lung cancer. The majority of males in South Africa present with locally advanced and/or metastatic disease. In addition, up to 30% of prostate cancer treated with curative intent progress to this stage.

Standard treatment for locally advanced and metastatic PCa is androgen deprivation therapy (ADT). The vast majority of HSPC eventually stop responding to ADT leading to the development of so called castrate resistant prostate cancer (CRPC) usually with clinical progression of the disease.

High volume disease: defined as the presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis.[3]

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

-P *(patient/population):* Hormone sensitive metastatic prostate cancer

-I *(intervention):* Docetaxel

-C *(comparator):* Androgen deprivation therapy (ADT)

-O *(outcome):* Median overall survival

6. **Methods:**
   a. **Data sources**: Pubmed, Cochrane, Google Scholar
   b. **Search strategy**
   ("docetaxel"[MeSH Terms] OR "docetaxel"[All Fields]) AND ("hormones"[Pharmacological Action] OR "hormones"[MeSH Terms] OR "hormones"[All Fields] OR "hormone"[All Fields]) AND ("hypersensitivity"[MeSH Terms] OR "hypersensitivity"[All Fields] OR "sensitive"[All Fields]) AND ("prostatic neoplasms"[MeSH Terms] OR ("prostatic"[All Fields] AND "neoplasms"[All Fields]) OR "prostatic neoplasms"[All Fields] OR ("prostate"[All Fields] AND "cancer"[All Fields]) OR "prostate cancer"[All Fields])

   Results were filtered for randomized controlled trials and meta-analyses.

   c. **Excluded studies:**
   - GETUG-AFU 15, 2013[4]: Suboptimal study: very small patient numbers; and excessive docetaxel cycles used (9 cycles docetaxel instead of 6).

   d. **Evidence synthesis**

Title, Author, date	Type of study	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Chemo-hormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer (initial CHAARTED group) Sweeney et al, 2015[5]	Phase III	790	Metastatic, hormone-sensitive prostate cancer (HSPC)	ADT plus docetaxel (6 cycles)vs ADT alone	Overall survival (OS) (median follow up 28.9 months)	Median OS 57.6 vs. 44.0 months; HR for death 0.61(95% CI 0.47 to 0.80; P < 0.001)	Subgroup analysis of high-volume disease - median overall survival 49.2 months vs. 32.2 months. HR for death, (0.60; CI 0.45 to 0.81; P<0.001) *This study was not powered for subgroup analyses but for the entire population*

Title, Author, date	Type of study	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial. Kyriakopoulos CE et.al. 2018[3]	Long term follow up of above (Sweeney et al)				Overall survival (OS) (median follow up 53.7 months)	Median OS 57.6 vs 47.2 months HR 0.72(95% CI, 0.59 to 0.89; P =0.0018). High-volume disease (n = 513), the median OS 51.2 versus 34.4 months. HR 0.63 (95% CI, 0.50 to 0.79; P < 0.001). Low-volume disease (n = 277) showed no OS benefit was observed (HR, 1.04; 95% CI, 0.70 to 1.55; P = .86).	The clinical benefit from chemo-hormonal therapy in prolonging OS was confirmed for patients with high-volume disease; however, for patients with low-volume disease, no OS benefit was discerned.
STAMPEDE trial James et.al, 2016[6]	RCT	2962 1184 – ADT alone 592 –docetaxel and ADT 593 – zoledronic acid and ADT 593 – zoledronic acid and docetaxel and ADT	High-risk locally advanced, metastatic or recurrent prostate cancer	Zoledronic acid + ADT vs Docetaxel (6 cycles) + ADT vs Zoledronic + docetaxel +ADT vs ADT alone	OS	Median OS of 71 months (ADT alone) vs 81 months (Docetaxel group +ADT), HR 0.78 (CI 0.66-0.93; p=0.006). *(no analysis of docetaxel groups together)*	Docetaxel plus ADT showed evidence of improved OS. Zoledronic acid showed no evidence of survival improvement and should not be part of standard of care for this population

e. Evidence quality:

- CHAARTED (Sweeney et. al. and Kyriakopoulos et. al.): high quality 2 arm randomized Phase III study with long-term follow-up data.
- STAMPEDE: confused as 4 arms with zoledronate in 2 arms.

f. Alternative agents: ADT alone.

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 [ ]	The adverse effects associated with the use of docetaxel are consistent as seen in other treatment indications. Reported adverse events in trial[5] included: • 6% had neutropaenic fever • 2% had grad 3 or 4 neutropaenia • 2% had treatment related allergic reactions • 4% had grade 3 fatigue • 1% or less had diarrhea, stomatitis, motor neuropathy, sensory neuropathy • 1% had thromboembolic event
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [X] No [ ] List the members of the group. ADT alone 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 [ ]	
RESOURCE	**How large are the resource requirements?**	Cost of medicines/ month: **Medicine** | **Cost (ZAR)** 6 cycles docetaxel | **R6,440.00**

	More intensive: X Less intensive: Uncertain:	**Note:** Docetaxel already on EML for breast and lung cancer as well as CRPC.
EQUITY	**Would there be an impact on health inequity?** Yes: No: X Uncertain:	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes: X No: Uncertain:	

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 be included on the Essential Medicine List to be used together with androgen deprivation therapy for the management of hormone sensitive prostate cancer, high-volume disease.

Level of Evidence:

Phase III, long term follow-up

Review indicator:

Evidence of efficacy: X
Evidence of harm:
Price reduction:

VEN status:

Vital:
Essential: X
Necessary:

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] Kyriakopoulos CE, Chen YH, Carducci MA, Lui G, Jarrard DR, Hahn NM, et.al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: Long-Term survival analysis of the randomized phase III E3805 CHAARTED TRIAL. Journal of Clinical Oncology. 2018, 36 (11): 1080 – 1087.

[4] Gravis G, Fizazi K, Joly F et al. (2013) Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. Lancet Oncology 14: 149–58

[5] Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, et. al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. New England Journal of Medicine. 2015, 373 (8): 737-746.

[6]James NS, Sy3des MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, et. al. Addition of docetaxel, zolendronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistate, platform randomized controlled trial. Lancet, 2016: 387: 1163-1177.