National Essential Medicine List
Tertiary Medication Review Process
Component: Oncology - Fulvestrant

MEDICINE MOTIVATION:

1. **Executive Summary**

Date: March 2021
Medicine (INN): Fulvestrant
Medicine (ATC): L02BA03
Indication (ICD10 code): Advanced Breast Cancer (ABC) Hormone Receptor Positive (HR+) [C50] – third or fourth line therapy
Patient population: post-menopausal women with advanced breast cancer hormones receptor positive, who have failed aromatase inhibitor therapy and/or tamoxifen and/or other chemotherapy.
Prevalence of condition: 10 to 30 maximum per year Probably much less as there will be a natural attrition as patients succumb to the disease (9500 BC in latest cancer registry -70% hormone+, then 50% public/private, 50% late/early). This is an extrapolation based on estimates.
Level of Care: Tertiary
Prescriber Level: Specialist Oncologist
Current standard of Care: Chemotherapy (Currently approved agents for metastatic breast cancer are: cisplatin plus gemcitabine, gemcitabine alone, vinorelbine IV)
Efficacy estimates: (preferably NNT):
There is no direct evidence for use of fulvestrant in the third/fourth line setting versus chemotherapy for the management of advanced, hormone receptor positive breast cancer.
Motivator/reviewer name(s): Prof L Dreosti

2. **Name of author(s)/motivator(s):** Prof L Dreosti

3. **Author affiliation and conflict of interest details:** Prof Dreosti: Conference sponsorship and honoraria (Eli Lily); Congress sponsorship (AbbVie), and Clinical Trials (Various Pharma), Congress sponsorship and honorarium for Ad Board (Janssen). Assessed as potentially significant, all decisions made by committee as a collective and not the lead reviewer.

4. **Introduction/ Background**

Metastatic breast cancer/Advanced Breast Cancer is not curable with a median overall survival of 36 months. Yet some patients with hormone receptor positive disease and bone only disease may live for many years. Such patients often receive several lines of therapy particularly endocrine therapy. The choice for first line of therapy for post-menopausal women is often tamoxifen or an aromatase inhibitor unless there is evidence of impending visceral crisis, in which case the choice is chemotherapy.[1] (ESMO ABC Guidelines) The choice of second line therapy is dependent upon the treatment received in first line. Fulvestrant was introduced as a second line or third line therapy.

Fulvestrant is an oestrogen receptor antagonist that down regulates the oestrogen receptor and does not have the partial agonistic properties of tamoxifen. Fulvestrant results in rapid degradation of both the oestrogen receptor and the progesterone receptor

5. Purpose/Objective i.e. PICO question

-P *(patient/population):* post-menopausal women with advanced breast cancer hormone receptor positive
-I *(intervention):* Fulvestrant (intramuscularly monthly)
-C *(comparator):* Chemotherapy
-O *(outcome):* Progression Free Survival, quality of life

6. Methods:

a. Data sources: Pubmed, Google Scholar

b. Search strategy

(fulvestrant[MeSH Terms]) AND (breast cancer[MeSH Terms])

- Pubmed lists 1637 publications of which 133 were clinical trials. World cat lists 752 results of which 454 were peer reviewed.
- The following were excluded: single centre experiences, reviews, combination therapies of fulvestrant, patient database registries.
- Final result: 8 randomised controlled trials for First line Therapy, 4 randomised controlled trials for Second line therapy.
- No evidence was found for use of fulvestrant in advanced breast cancer in the third/fourth line setting after tamoxifen and/or and aromatase inhibitor versus chemotherapy.

c. Excluded studies:

All 250mg dosing excluded, besides CONFIRM STUDY (which compared 500mg to 250mg)

d. Evidence synthesis

SECOND LINE THERAPY - Dose finding study

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes	Comments
CONFIRM STUDY, Leo et.al, 2010.[2]	Phase III multicenter, double blind parallel-group	362 fulvestrant 500mg 374 fulvestrant 250mg	Post-menopausal women following progression on prior hormonal therapy	Fulvestrant 500mg Vs Fulvestrant 250mg	Progression-free survival (PFS)	PFS was significantly longer for Fulvestrant 500mg than 250mg, HR = 0.8, 95% CI 0.68 to 0.94, p =0.006 (20% reduction in risk of progression.	• Higher dose was well tolerated
Final CONFIRM, Leo et. al. 2014[3]	As above	As above	As Above	As Above	Final survival analysis (median overall survival)	Median overall survival was 26.4 months for fulvestrant 500mg and 22.3 months for 250mg (hazard ratio = 0.81, 95% CI = 0.69 to 0.96, nominal p = 0.02	

FIRST LINE THERAPY

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Robertson, et.al. 2009[4]	Phase II open label randomised multicenter parallel group trial	Fulvestrant 102 Anastrozole 103	Patients with advanced hormone receptor-positive breast cancer in postmenopausal women (first-line therapy)	Fulvestrant versus anastrozole	Clinical benefit rate (CBR) (proportion of patients experiencing an objective response or stable disease for > 24 weeks	Clinical benefit rate was 72.5% for fulvestrant vs 67% for anastrozole. ORR was similar between the two arms 36% vs 35%. TTP was longer in the fulvestrant arm (TTP not reached vs 12.5 months)	• There were no significant differences in incidence of adverse events.

THIRD LINE THERAPY

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Chia S et.al.[5]	Randomised, double-blind, placebo controlled,	Fulvestrant = 351 Exemestane = 342	Postmenopausal women with hormone receptor positive advanced breast	Exemestane	Time to progression (TTP)	Median TTP was 3.7 months for both groups (hazard ratio = 0.963, 95% CI, 0.819 to 1.133, p = 0.6531	• Fulvestrant and exemestane shown to be no difference to one another.

	multicenter phase III trial		cancer progressing or recurring after nonsteroidal aromatase inhibitor.			Overall response rate: 7.4% for Fulvestrant versus 6.7% for exemestane, p = 0.736 Clinical benefit rate: 32.2% for Fulvestrant versus 31.5% for exemestane, p = 0.853	• Approximately 60% of patients had received at least 2 prior endocrine therapies.

Quality of life

There is currently no data on comparison of hormonal therapy versus chemotherapy for third or four line care of patients with metastatic breast cancer. The use of Fulvestrant however does provide for a simpler regimen [intramuscular monthly injection, (twice monthly for first month)], as compared to chemotherapy (infusions plus additive medicines like corticosteroids and anti-emetics). Additionally the adverse event profile of Fulvestrant is favorable over chemotherapy *(see section 8. Adverse effects).*

e. **Evidence quality:** No data in the third/fourth-line setting is available. Data included Phase II and III studies. Robertson et.al, was a phase II study, with limitations of having limited power and an open-label setting.

7. **Alternative agents:** No other hormonal alternative. Next option would be EML approved chemotherapy. This is third or fourth-line therapy.

8. **Adverse effects:** These are similar to all the AI's and Tamoxifen currently in use. The main side effects include hot flushes, joint pains, and fatigue in first-line (same risk as aromatase inhibitors). Chemotherapy adverse effects include fatigue, nausea and neutropenia. Neutropenic sepsis can occur, alopecia, and renal failure (particularly with cisplatin). Gemcitabine can result in prolonged bone marrow failure and pneumonitis. Pneumonitis and bone marrow failure can result in death.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident: [ ] Not confident: [ ] Uncertain: [x]	There is no evidence in the third and fourth line setting versus chemotherapy, however in the first line setting Fulvestrant has been shown to be as effective as the aromatase inhibitors.[4]
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms: [x] Harms outweigh benefits: [ ] Benefits = harms or Uncertain: [ ]	Fulvestrant has tolerable side effects. . It has a better side effect profile when compared to chemotherapy
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes: [ ] No: [x] List the members of the group. none List specific exclusion from the group: n/a	No therapeutic alternatives. The alternatives would be chemotherapy or not treating.
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: [ ] Major: [ ] Uncertain: [X] **Is the option acceptable to key stakeholders?** Yes: [X] No: [ ] Uncertain: [ ]	The use of fulvestrant is anticipated to be more acceptable due to the better side effect profile, simpler regimen, and less administration burden.

RESOURCE USE

How large are the resource requirements?

More intensive	Less intensive	Uncertain
		X

Similar costs for same duration of care

Current state offer: R1380 (250mg vials x 2) *(December 2020)*

Cost / year or course (8 months)*:

Regimen	Cost (ZAR)	Source	Notes
Fulvestrant – State Offer	R12 420.00	State offer – Dec 2020	Medicine costs alone
Cisplatin plus gemcitabine	R12 036.11	Contract Price December 2020	Medicine regimen**
Gemcitabine	R9 120.35	Contract Price December 2020	Medicine regimen**
Vinorelbine (IV)	R12 130.59	Contract Price December 2020	Medicine regimen**

*****Refer to appendix 1 below*

*** Fulvestrant is an IM injection, with no additional medications needed. The chemotherapy administration and regimens are more complex with infusion needed and additional agents such as steroids and anti-emetics.*

EQUITY

Would there be an impact on health inequity?

Yes	No	Uncertain
	×	

FEASIBILITY

Is the implementation of this recommendation feasible?

Yes	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
	☐	☐	☐	☒	☐

Recommendation

There is no direct evidence for the use of Fulvestrant in the third and fourth line setting prior to use of chemotherapy. Fulvestrant however has a better side effect profile and at a similar cost, it is recommended as an additional agent for post-menopausal patients with ER and /or PR positive tumors, who have experienced progression of disease on prior therapy with tamoxifen and an aromatase inhibitor (AI).

Reference price: Recommended for inclusion if price is within 10% of chemotherapy alternative regimens.

Rationale:

Fulvestrant provides an additional line of hormonal therapy. The cost implications of this would be similar to a chemotherapy options.

Level of Evidence:

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
X	X	X

VEN status:

Vital	Essential	Necessary
	X	

Monitoring and evaluation considerations

Research priorities

References

[1] Cardoso F, Paluch-Shimon, Senkus E, Curigiliano G, Aapro MS, Andre F, et. al. 5th ESO-ESMO International consensus guidelines for advanced breast cancer. Annals of Oncology. 2020, 31 (12): 1623 – 1649.

[2]Leo AD, Jerusalem G, Petruzelka L, Torres R, Bondarenko IN, Khasanov R, et. al. Results of the CONFIRM Phase III Trial comparing fulvestrant 250mg with fulvestrant 500mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. Clinical Oncology. 2010, 28 (30): 4594-4600.

[3] Leo AD, Jerusalem G, Petruzelka L, Torres R, Bondarenko IN, Khasanov R, et. al. Final overall survival: Fulvestrant 500mg vs 250mg in randomized CONFIRM trial. J Natl Cancer Inst. 2014 Jan;106(1): 2-7.

[4] Robertson JF, Llombart-Cussac A, Rolski J, Feltl D, Dewar J, Macpherson E, et.al. Activity of fulvestrant 500mg versus anastrazole 1mg as first-line treatment for advanced breast cancer: results from the FIRST study. 2009.

[5] Chia S, Gradishar W, Mauriac L, Bines J, Amant F, Federico M. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: Results from EFECT. Clinical Oncology. 2008, 26 (10).

Appendix 1: Cost Comparison and Budget Impact

Summary:

Cost of regimen		
Fulvestrant	R12,420.00	8 months
Gemcitabine plus Cisplatin	R12,036.11	8 month course
Gemcitiabine Alone	R9,120.35	8 month course
Vinorelbine IV	R12,130.59	8 month course
Budget impact for 30 patients		
Fulvestrant (State price)	R372,600.00	
Cisplatin plus gemcitabine	R361,083.30	
Gemcitabine alone	R273,610.50	
Vinorelbine (IV)	R363,917.70	

Cost comparison

Note: Fulvestrant is an IM injection, with no additional medications needed. The chemotherapy administration and regimens are more complex with infusion needed and additional agents such as steroids and anti-emetics.

	Agent	**Regimen**	**Strength/vial**	**Price**	**Source**	**Cost per 8 months**	**Total regimen cost**
	Fulvestrant	500mg monthly (initially second dose at 14 days)	250mg x 2 (500)	R1,380.00	STATE PRICE*	R12,420.00	**R12,420.00**
	Fulvestrant	500mg monthly (initially second dose at 14 days)	250mg x 2 (500)	R11,334.87	Single exit price (AstraZeneca)	R102,013.79	**R102,013.79**
	Fulvestrant	500mg monthly (initially second dose at 14 days)	250mg x 2 (500)	R7,934.40	Single exit price (Teva)	R71,409.60	**R71,409.60**
		Regimen	**Strength/vial**	**Price**	**Source**	**Cost per course**	**Total regimen cost**
Cisplatin plus gemcitabine regimen	**Cisplatin plus gemcitabine**	Cisplatin 60-75mg/m^{2}day 1 every 21 days (8 cycles)	50mg	R120.06	on contract	R10,425.44	**R12,036.11**
		Gemcitabine 1g/m2 plus days 1 and 8 every 21 days (8 cycles)	1g	R235.75	on contract		
	Dexamethasone	16mg	4mg	R6.31	on contract	R403.84	

	Ondansetron	8mg	8mg	R0.74	on contract	R23.71	
	Sodium Chloride 1L	1 litre for infusion, 1 litre post infusion	1 litre	R10.69	on contract	R342.08	
	Infusion set	per dose		R9.58	HM contract	R153.28	
	Needle	per dose		R1.12	HM contract	R35.84	
	Syringe	Mixing		R0.97	HM contract	R15.52	
	Full blood count	1 per cycle		R52.23	NHLS	R417.84	
	Creatinine	1 per cycle		R27.32	NHLS	R218.56	
Gemcitabine alone regimen	**Gemcitabine**	Gemcitabine 1g/m2 plus days 1 and 8 every 21 days (8 cycles)	1g	R235.75	on contract	R7,544.00	**R9,120.35**
	Dexamethasone	16mg	4mg	R6.31	on contract	R403.84	
	Ondansetron	8mg	8mg	R0.74	on contract	R23.71	
	Sodium Chloride 200ml	200ml per infusion		R6.78	on contract	R108.48	
	Infusion set	per dose		R9.58	HM contract	R153.28	
	Needle	per dose		R1.12	HM contract	R35.84	
	Syringe	Mixing		R0.97	HM contract	R15.52	
	Full blood count	1 per cycle		R52.23	NHLS	R835.68	
Vinorelbine IV regimen	**Vinorelbine IV**	25-30mg/m2 plus hydrocortisone 100mg days 1 and 8 every 21 days	50mg	R544.78	on contract	R8,716.48	**R12,130.59**
	Hydrocortisone	100mg	100mg/2ml	R 11.96	on contract	R2,197.44	
	Ondansetron	8mg	8mg	R0.74	on contract	R23.71	
	Ranitidine	50mg	50mg/ml	R2.76	on contract	R44.16	
	Sodium Chloride 200ml	200ml per infusion		R6.78	on contract	R108.48	
	Infusion set	per dose		R9.58	HM contract	R153.28	
	Needle	per dose		R1.12	HM contract	R35.84	
	Syringe	Mixing		R0.97	HM contract	R15.52	
	Full blood count	1 per cycle		R52.23	NHLS	R835.68	

Budget impact

Budget impact for 30 patients	
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