National Essential Medicine List
Tertiary/Hospital Medication Review Process
Component: Oncology

MEDICINE MOTIVATION:

1. **Executive Summary**

Date: July 2019
Medicine (INN): Cisplatin and Paclitaxel
Medicine (ATC): *L01CD01 paclitaxel*
Indication (ICD10 code): Metastatic cervical carcinoma C53.0 – C53.-9
Patient population: Potentially 100 patients per year countrywide (*survey of treating sites – March 2019*).
Incidence of condition: 5735 newly diagnosed cases, age standardized ratio (ASR) 20.73 cases per 100 000/year (2014)[1]
Level of Care: Tertiary and Quaternary
Prescriber Level: Specialist Oncologist
Standard of Care: Cisplatin alone
Efficacy estimates: (preferably NNT):
Objective response rate of cisplatin-paclitaxel was 36% (15% complete response, 21% partial response) versus 19% (6% complete response, 13% partial response) for cisplatin alone (P = 0.002). This is was no difference in overall survival. [2]

Objective response rate of cisplatin-paclitaxel was 29.1%, compared to 25.9% cisplatin-vincristine [odds ratio 1.17 95% CI 0.54to 2.58)], 22.3% cisplatin-gemcitabine [odds ratio 1.43 (95% CI 0.65 to 3.19)], 23.4% cisplatin-topotecan [odds ratio 1.34 (0.61 to 2.98)]. Median overall survival for cisplatin-paclitaxel was 12.87 months (95% CI 10.02 to 16.76), compared to cisplatin-vincristine 9.99 months (95% CI 8.25 to 12.25), cisplatin-gemcitabine 10.28 months (95% CI 7.62 to 11.60), and cisplatin-topotecan 10.25 months (95% CI 8.61 to 11.66). [3]

2. **Name of author(s)/motivator(s)** Tertiary and Quaternary Committee

3. **Author affiliation and conflict of interest details:** No applicable conflicts of interest noted

4. **Introduction/ Background**

Cervical carcinoma is a common malignancy amongst women in South Africa with over 7000 new cases per year, more than half will die of this disease.

If diagnosed with local disease patients either undergo a hysterectomy in very early disease or receive upfront chemo-radiation with weekly Cisplatin chemotherapy 40mg/m^2 x 5-6.

Patient who relapse, have persistent disease or are diagnosed with metastatic disease at first staging are managed with palliative chemotherapy to improve distressing symptoms and quality of life.

Effective treatment in the metastatic setting is limited and the current standard is Cisplatin 50mg/m^2 three weekly for 6 cycles. Cisplatin side-effects include haematological toxicity; l renal dysfunction; emesis; peripheral neuropathy. These adverse effects are uncommon with low dose Cisplatin (<75mg/m^2).

Studies comparing this to platinum-based doublets have shown that combination with paclitaxel has a higher response rate than cisplatin alone. In the case of poor renal function Carboplatin may be substituted if renal function tests show a glomerular filtration rate of 30ml-60ml/min.

Paclitaxel is available in generic form at low cost. The regimen can be delivered on an outpatient basis. The most common adverse effects include infusion reaction; alopecia; haematological toxicity; febrile neutropaenia; peripheral neuropathy.
The addition of a targeted agent, bevacuzimab has changed the standard of care in high income countries with many centres having adopted this regimen.
This is not reviewed in this motivation due to the prohibitive cost of the medicine. But it is noted that all recent published reviews focus on the incorporation of targeted agents and not on the comparison of Cisplatin to combination therapy.

5. **Purpose/Objective i.e. PICO question** [comparison to current standard of care for a specific indication]:

-P (patient/population): persistent, recurrent, metastatic cervical carcinoma.
-I (intervention): chemotherapy – (Cisplatin 50mg/m^2 OR Carboplatin AUC 5) + paclitaxel 135mg/m^2 over 24 hours OR Paclitaxel 175mg/m^2 over 3 hours.
-C (comparator): Cisplatin 50mg/m2 alone OR cisplatin with alternate agent (gemcitabine/vincristine/topotecan).
-O (outcome): Response rate, median overall survival, adverse effects.

6. **Methods:**
   a. **Data sources** Pubmed, Cochrane Database, Google Scholar

7. **Search strategy**
   a. ((((cervix cancer) AND paclitaxel)) AND metastatic) AND recurrent.
   ((cervix cancer) AND metastatic) AND meta-analysis

   Phase III studies included: GOG 169, GOG 204
   GOG=Gynecologic Oncology Group

   Search for meta-analyses provided 2 results. Cochrane database review was available from 2012 and provided clear data outcomes.

   a. **Excluded studies:**
   All retrospective analyses, Phase II studies excluded as sufficient evidence exists from Phase III data or Phase III studies not answering the PICO questions

Author, date	***Type of study***	***Reason for exclusion***
Cisplatin alone (GOG 26) (Thigpen et al;1981) [4]	Phase II study	Not answering the question: Combination cisplatin/paclitaxel versus cisplatin
Cisplatin dose variation. (GOG 43) (P Bonomi, et al. 1985)[5]	Randomised phase III	
Cisplatin vs Cisplatin/Topotecan (GOG 179) (Long et al., 2005)[6]	Randomised phase III	
Cisplatin/Paclitaxel vs Carboplatin/Paclitaxel (Kitagawa et al., 2015)[7]	Randomised phase III	

Historical development - trials in metastatic cervical cancer

Cisplatin alone (GOG 26) (Thigpen et al;1981)[4]	• 34 patients Phase 2 • Cisplatin 50mg/m2 vs best supportive care – response rate (RR) 38% on Cisplatin.
Cisplatin dose variation. (GOG 43) (P Bonomi, et al. 1985)5	• 500 patients • 50mg/m2 vs 100mg/m2 vs 20mg/m2x 5 – RR 20% vs 31% vs 25%; but no significant difference in progression free survival (PFS) or median overall survival (OS). • 100mg/m2 needs to be delivered as an inpatient, higher risk of toxicity, renal dysfunction.
Cisplatin vs Cisplatin/Paclitaxel (GOG 169) (Moore et al., 2004)[2]	• 264 patients • Overall response rate (ORR) 19% vs 36% (p=0.002); PFS 2.8 vs 4.8 months (<0.001); • Median OS 8.8 vs **9.7 months** • No significant difference in Quality of Life
Cisplatin vs Cisplatin/Topotecan (GOG 179) (Long et al., 2005)[6]	• Not included in this analysis –Topotecan toxicity
Cisplatin/Paclitaxel (C/P) vs Cisplatin/Vinorelbine (C/V)vs Cisplatin/Gemcitabine C/G) vs Cisplatin/Topotecan (C/T) (GOG 204) (Monk et al., 2009)[3]	• >100 patients per arm, PS 0-1, • Median OS **C/P 12.87mths (10.02-16.76)** ▪ C/V 9.99mths ▪ C/G 10.28 months ▪ C/T 10.25 months NSD • HR C/P vs C/V 1.15(CI 0.79-1.67); C/P vs C/G 1.32 (0.91-1.92); C/P vs C/T 1.26(0.86-1.82) • Improved overall survival the longer relapse free period from primary therapy • Quality of life reported: no observed difference between all arms of the study
Cisplatin/Paclitaxel vs Carboplatin/Paclitaxel (Kitagawa et al., 2015)[7]	• Japanese study JCOG0505 • 250 patients • Non-inferiority • Carboplatin/ Paclitaxel vs Cisplatin/paclitaxel: overall survival (OS) HR 0.994 (0.79-1.25) p=0.032 • Median OS 17.5 vs **18.3months**

b. Evidence synthesis

Auth, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes			
						Overall response rate (ORR)	**Overall survival (OS)** *months*	**Progression free survival (PFS)**	**Adverse effects**
GOG 169; Moore 2004[2]	Phase III randomised trial	264	Advanced, recurrent or persistent cervical cancer	Cisplatin vs Cisplatin/ Paclitaxel	Overall response rates (ORR)	19% vs 36% (p=0.002)	Median OS 8.8 vs 9.7 months	2.8 vs 4.8 months (p<0.001)	Grade 3 and 4 anaemia and neutropaenia more common in cisplatin/paclitaxel arm. Neutropaenia grade 3: 20.9% vs 2.3%. Neutropaenia grade 4: 45.7% vs 0.8%. Anaemia grade 3: 22.5% vs 9.2%. Anaemia grade 4: 5.4% vs 3.8%.
GOG 204; Monk 2009[3]	Phase III randomized trial	513	Mets cervix Ca	Cisplatin/ Paclitaxel vs Cisplatin/ Gemcitabine vs Cisplatin/ Vinorelbine vs Cisplatin/ Topotecan	Overall survival	Overall response rate of cisplatin-paclitaxel was 29.1%, compared to 25.9% cisplatin-vincristine [odds ratio 1.17 95% CI 0.54to 2.58)], 22.3% cisplatin-gemcitabine [odds ratio 1.43 (95% CI 0.65 to 3.19)], 23.4% cisplatin-topotecan [odds ratio 1.34 (0.61 to 2.98)].	Median overall survival for cisplatin-paclitaxel was 12.87 months (95% CI 10.02 to 16.76), compared to cisplatin-vincristine 9.99 months (95% CI 8.25 to 12.25), cisplatin-gemcitabine 10.28 months (95% CI 7.62 to 11.60), and cisplatin-topotecan 10.25 months (95% CI 8.61 to 11.66).	5.82 months (95% CI, 4.53 to 7.59 months) for cisplatin-paclitaxel; vs 3.98 months (95% CI, 3.19 to 5.16 months) for cisplatin-vincristine; vs 4.70 months (95% CI, 3.58 to 5.59 months) for cisplatin-gemcitabine; vs 4.57 months (95% CI, 3.71 to 5.75 months) for cisplatin-topotecan. When compared to cisplatin-paclitaxel, hazard ratios for PFS were 1.36 (95% CI, 0.97 to 1.90) for cisplatin-vincristine, 1.39 (95% CI, 0.99 to 1.96) for cisplatin-gemcitabine, and 1.27 (95% CI, 0.90 to 1.78) for cisplatin-topotecan	All groups had similar leucopaenia, neutropaenia, thrombocytopaenia, anaemia, and infection/fever. Grade 2 alopecia significantly higher in cisplatin-paclitaxel arm (54%), P = 0.0001).

OTHER STUDIES/SYSTEMATIC REVIEWS

Moore et.al. Review of prognostic groups[8]:(Moore et al., 2010)

Patients who received a cisplatin-containing combination in the GOG protocols (428 patients) were evaluated for baseline clinical characteristics.

Lowest response if:

- Time from primary CRT to relapse <12months,
- African-American,
- Pelvic disease (in previous field of RT),
- Performance status >0,
- Previous Cisplatin,
    - Increased failure with increased number of factors.

Cochrane review: (Scatchard, et al, 2012)[9]

- Twenty six randomised trials included.
- Many studies inadequate reporting overall survival and progression free survival.
- Primary end point: response rate – percentage of patients with evidence of reduction in tumour size.
- Meta-analysis of five RCTs (Alberts 1987; Cadron 2005; Long 2005; Moore 2004; Omura 1997), assessing 1114 participants, found that the proportion of women who responded to treatment was significantly lower in the group who received chemotherapy as a single agent than in the group who received combination chemotherapy (RR 0.60; 95% CI 0.44 to 0.81).
- Overall survival with cisplatin alone was between 6.5 to 9 months with progression free survival of approximately three months. The addition of a taxane led to overall survival of 12.9 to 15.4 months with progression free survival of between 5.8 to 7.9 months. *(no confidence intervals).*
- Risks: Combination increases haematological toxicity; no decrease in QoL between Cisplatin alone and Cisplatin/Paclitaxel from limited available data.

Evidence quality:

Level 1 evidence – multiple Phase III trials; systematic reviews and meta-analyses

8. **Alternative agents:** Topotecan, Vinorelbine and Gemcitabine - less efficacious, toxicity (topotecan); Bevacizimab - cost.

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 [ ]	Based on Phase III trials – increased response rate and median OS 12-18 months in selected patients
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [x] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	Improved median OS and no reduction in QoL as per Cochrane review
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [x] No [ ] List the members of the group. Topotecan List specific exclusion from the group: Gemcitabine Vinorelbine	Rationale for therapeutic alternatives included: Some efficacy but high cost and increased toxicity References: Rationale for exclusion from the group: Poor efficacy References: Eskander & Tewari, 2014)[10]
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 [ ] No [ ] Uncertain [x]	

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

More intensive [x] Less intensive [ ] Uncertain [ ]</td>
<td>Cost of medicines/ month:
<table><tr><th>Medicine</th><th>Cost (ZAR)</th></tr><tr><td>Paclitaxel (BSA 1.7m2)</td><td>R438 (3 vials) per cycle x 6 = R2628</td></tr><tr><td>Additional supporting drugs</td><td>R50</td></tr></table>
Total = Approximate additional R270 000 annual cost based on 100 patients

Additional resources: Additional time in chemotherapy suite = 3 hours

See attached cost-effective analysis (Geisler, Swathirajan, Wood, & Manahan, 2012)</td>
</tr>
<tr>
<td>EQUITY</td>
<td>Would there be an impact on health inequity?

Yes [x] No [ ] Uncertain [ ]</td>
<td>Cervical cancer community underserved, vulnerable population with little access to multiple lines of therapy.</td>
</tr>
<tr>
<td>FEASIBILITY</td>
<td>Is the implementation of this recommendation feasible?
Yes [x] No [ ] Uncertain [ ]</td>
<td>Outpatient treatment in established chemotherapy centres.</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
	☐	☐	☐	☒	☐

Recommendation

Allow the use of combination chemotherapy with paclitaxel for patients who are:

1. Newly diagnosed with metastatic diasease
2. Patients who are > 12 months from primary chemoradiation prior to relapse/distant disease.
   Note - Patients with GFR <30ml/min are not suitable for any platinum-based chemotherapy

- Performance status <0,
- No previous cisplatin.

Rationale: Compared with Cisplatin alone higher response rate and increased median overall survival. International standard

Level of Evidence: Level 1

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
x		

VEN status:

Vital	Essential	Necessary
	x	

Monitoring and evaluation considerations

Research priorities

National database on incidence of persistent, recurrent, metatastic cervical carcinoma

Response to palliative chemotherapy in local populaton

References:

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

[2] Moore, D. H., Blessing, J. A., McQuellon, R. P., Thaler, H. T., Cella, D., Benda, J., … Rocereto, T. F. (2004). Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: A Gynecologic Oncology Group study. *Journal of Clinical Oncology*, *22*(15), 3113–3119. https://doi.org/10.1200/JCO.2004.04.170

[3] Monk, B. J., Sill, M. W., McMeekin, D. S., Cohn, D. E., Ramondetta, L. M., Boardman, C. H., … Cella, D. (2009). Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: A Gynecologic Oncology Group study. *Journal of Clinical Oncology*, *27*(28), 4649–4655. https://doi.org/10.1200/JCO.2009.21.8909

[4] Thigpen T, Shingleton H, Homesley H, et al.: Cis-platinum in treatment of advanced or recurrent squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Cancer 1981, 48:899–903

[5] Bonomi P, Blessing JA, Stehman FB, DiSaia PJ, Walton L, Major FJ. Randomized trial of three cisplatin dose schedule in squamous-cell carcinoma of cervix: a Gynecologic Oncology Group study. Journal of Clinical Oncology. 1985, 3(8): 1079 – 1085.

[6] Long HJ III, Bundy BN, Grendys EC, *et al.*: Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group Study. *J* Clin Oncol 2005, **23:**4626–4633.

[7] Kitagawa, R., Katsumata, N., Shibata, T., Kamura, T., Kasamatsu, T., Nakanishi, T., … Yoshikawa, H. (2015). Paclitaxel plus carboplatin versus paclitaxel plus cisplatin in metastatic or recurrent cervical cancer: The open-label randomized phase III trial JCOG0505. Journal of Clinical Oncology, 33(19), 2129–2135. https://doi.org/10.1200/JCO.2014.58.4391

[8] Moore, D. H., Tian, C., Monk, B. J., Long, H. J., Omura, G. A., & Bloss, J. D. (2010). Prognostic factors for response to cisplatin-based chemotherapy in advanced cervical carcinoma: A Gynecologic Oncology Group Study. Gynecologic Oncology, 116(1), 44–49. https://doi.org/10.1016/J.YGYNO.2009.09.006

[9] Scatchard, K., Forrest, J. L., Flubacher, M., Cornes, P., & Williams, C. (2012). Chemotherapy for metastatic and recurrent cervical cancer. The Cochrane Database of Systematic Reviews, 10(10), CD006469. https://doi.org/10.1002/14651858.CD006469.pub2

[10] Eskander RN, Tewari KS. Targeting angiogenesis in advanced cervical cancer. Therapeutic Advances in Medical Oncology. 2014, vol 6 (6): 280-292.