Enfortumab Vedotin-ejfv (PADCEV) National Drug Monograph November 2021
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action
- Enfortumab vedotin-ejfv is a Nectin-4 directed antibody-drug conjugate (ADC) comprised of a fully human anti-Nectin-4 IgG1 monoclonal antibody conjugated to a small molecule microtubular disrupting agent, monomethyl auristatin E (MMAE, aka vedotin). Anticancer activity is due to binding to Nectin-4 expressing cells, followed by internalization of the ADC and release of MMAE via proteolytic cleavage. MMAE disrupts the microtubular network in the cell resulting in cell cycle arrest and apoptotic cell death.

Indication(s) Under Review in This Document
A Nectin-4-directed monoclonal antibody and microtubule inhibitor conjugate (ADC) for treatment of patients with locally advanced or metastatic urothelial carcinoma who:
- have previously received a PD-1 or PD-1 inhibitor and platinum-containing chemotherapy, or
- are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy.

Dosage Form(s) Under Review
- For injection: 20mg and 30mg of enfortumab vedotin as a lyophilized powder

Clinical Evidence Summary

Efficacy Considerations
- Efficacy from the phase III trial versus chemotherapy, and two cohorts from the phase II trial are included.
- Efficacy data are summarized in Table 1

Table 1: Efficacy results from clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>ECOG PS</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>EV-301</td>
<td>Global, open label, Phase 3 vs chemotherapy</td>
<td>0-1</td>
<td>Enfortumab vedotin 1.25 mg/kg over 30 mins</td>
<td>Enfortumab vedotin: N=301 Chemo: N=307</td>
</tr>
<tr>
<td>Powles, et al.¹</td>
<td>LA/M urothelial carcinoma</td>
<td></td>
<td></td>
<td>Median OS: 12.88 vs 8.97 months</td>
</tr>
<tr>
<td>Primary EP: OS</td>
<td>Progression or relapse after PD-1 or PD-L1 inhibitor and prior platinum containing chemotherapy</td>
<td>D 1, 8, 15 of each 28 day cycle</td>
<td>HR OS: 0.70 (95%CI 0.56-0.89) 12-month OS: 51.5 vs 39.2%</td>
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<tr>
<td></td>
<td>Exclude: active brain mets, grade ≥2 sensory or motor neuropathy, active keratitis or corneal ulceration</td>
<td>Chemo (inv. Choice) every 21 days</td>
<td>Median PFS: 5.55 vs 3.71 months HR PFS: 0.62 (95%CI 0.51-0.75)</td>
<td></td>
</tr>
</tbody>
</table>

**EV-201 Cohort 1**

Rosenberg, et al.2

<table>
<thead>
<tr>
<th>Primary EP: ORR</th>
<th>Two-cohort, single arm, phase II</th>
<th>Enfortumab vedotin 1.25 mg/kg over 30 mins D 1, 8, 15 of each 28 day cycle</th>
<th>Cohort 1: N=125 ORR by BICR: 44% (95%CI 35.1-53.2%) CR: 12% PR: 32%</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>LA/M urothelial carcinoma</td>
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<tr>
<td></td>
<td>Progression during or after PD-1 or PD-L1 inhibitor and platinum containing chemotherapy</td>
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<tr>
<td></td>
<td>Exclude: active brain mets, grade ≥2 sensory or motor neuropathy, uncontrolled diabetes, active corneal ulcerations or keratitis</td>
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</table>

**EV-201 Cohort 2**

Yu, et al.3

<table>
<thead>
<tr>
<th>Primary EP: ORR</th>
<th>Previous PD-1 or PD-L1 inhibitor therapy and ineligible for cisplatin</th>
<th>Enfortumab vedotin 1.25 mg/kg over 30 mins D 1, 8, 15 of each 28 day cycle</th>
<th>Cohort 2: N=89 ORR by BICR: 52% (95%CI 41-62) CR: 20% PR: 31%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ECOG=2, Clcr ≥30 and &lt;60 mL/min; or grade 2 or worse hearing loss, 2grade 2 neuropathy</td>
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</tbody>
</table>

LA=locally advanced; M=metastatic; h/o=history of; DM=diabetes mellitus; EP=endpoint; OS=overall survival; PFS=progression-free survival; ORR=objective response rate; CR=complete response; PR=partial response

**EV-301**

- Patients: locally advanced (unresectable) or metastatic urothelial carcinoma.
  - Median age: 68
  - Male: 79%
  - History of diabetes or hyperglycemia: 19%

Updated version may be found at PBM INTERnet or PBM INTRANet
Progression or relapse during or after PD-1 or PD-L1 inhibitor therapy and previous platinum-based chemotherapy; progression within 12 months of completion following platinum-based neoadjuvant or adjuvant

- **Intervention**
  - Enfortumab vedotin 1.25 mg/kg IV Days 1, 8, & 15 every 28 days vs

- **Comparator**
  - Investigator’s Choice of chemotherapy:
    - Docetaxel
    - Paclitaxel
    - Vinflunine

- **Outcomes (other)**
  - Overall Response Rate: 40.6% vs 17.9%
  - Complete Response: 4.9% vs 2.7%
  - Med Duration of Response: 7.39 vs 8.11 months
  - Point estimates favored enfortumab vedotin in all large subgroups

- **Limitations**
  - Subgroup analysis for overall survival in females did not favor enfortumab vedotin, however the number of female patients was small and the confidence interval was wide and crossed 1.00.
  - Nectin-4 expression measured but not required for study entry due to expression in a majority of advanced urothelial carcinomas in prior studies.

**EV-201 Cohort 1**

- **Patients:** locally advanced (unresectable) or metastatic urothelial carcinoma
  - Median age: 69
  - Male: 70%
  - Med number of prior therapies: 3
  - Response to prior PD-1 or PD-L1 therapy: 20%
  - Med Nectin-4 H-score: 290 (N=120 samples)(0=no expression, 300=maximum expression)

- **Intervention**
  - Enfortumab vedotin 1.25 mg/kg IV Days 1, 8, & 15 every 28 days

- **Outcomes (other)**
  - Responses across most subgroups including liver metastases, three or more lines of prior therapy
  - Med time to response: 1.84 months
  - Med duration of response: 7.6 months (0.95-11.3+)
  - Med Progression-free Survival: 5.8 months
  - Med Overall Survival: 11.7 months

- **Limitations**
  - Single-arm
  - Phase 2
• **EV-201 Cohort 2**
  • Patients: locally advanced (unresectable) or metastatic urothelial carcinoma
    o Could have received platinum in the neoadjuvant or adjuvant setting but not eligible in the locally advanced or metastatic setting
    o 75% did not respond to prior PD-1 or PD-L1 therapy
    o Median age: 75
    o Male:
  • Intervention
    o Enfortumab vedotin 1.25 mg/kg IV Days 1, 8, & 15 every 28 days
  • Outcomes (other)
    o Responses in patients with liver metastases and upper tract disease
    o Median Duration of Response: 10.9 months
    o Median PFS: 5.8 months
    o 12 months PFS: 33%
    o Median OS: 14.7 months
  • Limitations
    o Single-arm

**Safety Considerations**

**Safety Results from Clinical Trials:**
  • Safety results from the phase III trial and both cohorts of the phase II trial.
Table 2: Safety results from clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>EV-301</td>
<td>Any AE: 93.9 vs 91.8%</td>
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<tr>
<td></td>
<td>TRAE Grade 3-4: 51.4 vs 49.8%</td>
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<tr>
<td></td>
<td>Serious adverse events: 2.4 vs 2.8%</td>
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<tr>
<td></td>
<td>AEs leading to discontinuation: 13.5% (most common: peripheral neuropathy and rash)</td>
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<tr>
<td></td>
<td>AEs leading to dose interruption/modification: 83%</td>
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<tr>
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<td>Deaths due to AE: 0.1% vs 0.1%</td>
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<tr>
<td>EV-201 (1)</td>
<td>Any AE: 100%</td>
</tr>
<tr>
<td></td>
<td>TRAE Grade 3-4: 54%</td>
</tr>
<tr>
<td></td>
<td>Serious adverse events: 19%</td>
</tr>
<tr>
<td></td>
<td>AEs leading to discontinuation: 12%</td>
</tr>
<tr>
<td></td>
<td>AEs leading to dose interruption/modification: 32%</td>
</tr>
<tr>
<td></td>
<td>Deaths due to AE: 0%</td>
</tr>
<tr>
<td>EV-201 (2)</td>
<td>Any AE: 100%</td>
</tr>
<tr>
<td></td>
<td>TRAE Grade 3-4: 55%</td>
</tr>
<tr>
<td></td>
<td>Serious adverse events: 17%</td>
</tr>
<tr>
<td></td>
<td>AEs leading to discontinuation: 16%</td>
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<tr>
<td></td>
<td>AEs leading to dose interruption/modification: 46%</td>
</tr>
<tr>
<td></td>
<td>Deaths due to AE: 3%</td>
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</tbody>
</table>

- **Boxed warnings:**
  - Can cause severe and fatal cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
  - Immediately withhold the drug and consider referral to specialized care for suspected SJS or TEN or severe skin reactions
  - Permanently discontinue therapy in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions

- **Contraindications:** None

- **Other warnings / precautions:**
  - Skin reactions: 55% in clinical trials (23% maculopapular; 33% pruritus). Grade 3-4 in 13% including maculopapular rash, rash erythematous, rash or drug eruption, symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), dermatitis bullous, dermatitis exfoliative, and palmar-plantar erythrodysesthesia. Skin reactions lead to discontinuation in 2.6%.
  - Hyperglycemia: 14%; Grade 3-4 in 7%; 5% required initiation of insulin. Patients excluded from trial with baseline A1C ≥8%. Hold drug if blood glucose >250 mg/dL.
  - Pneumonitis: 3.1%; Grade 3-4 in 0.7%; some cases severe and life-threatening
  - Peripheral neuropathy: 52% (more sensory than motor); Grade 3-4 in 4%; occurred in patients with and without pre-existing neuropathy
Ocular disorders: 40% (majority corneal: keratitis, blurred vision, increased lacrimation, conjunctivitis, limbal stem cell deficiency, keratopathy). Consider prophylactic artificial tears for dry eyes. Consider ophthalmic topical steroids is indicated. Consider dose interruption or dose reduction for symptomatic ophthalmic disorders.

Infusion-site extravasation: 1.6%; Grade 3-4 0.3% skin and soft tissue reactions. Ensure adequate venous access prior to administration. Stop infusion if extravasation occurs.

Embryo-fetal toxicity: based on mechanism of action

Adverse reactions

Common: rash, fatigue, peripheral neuropathy, alopecia, decreased appetite, diarrhea, nausea, pruritis, dysgeusia, anemia, weight decrease, dry skin; increased: aspartate aminotransferase, glucose, creatinine, alanine aminotransferase, lipase; decreased: lymphocytes, hemoglobin, sodium, phosphate, albumin, neutrophils, urate, platelets.

Serious Adverse events / Deaths / Discontinuation:
  - Serious: in 46% including urinary tract infections, cellulitis, febrile neutropenia, diarrhea, sepsis, acute kidney injury, dyspnea, rash
  - Fatal: 3.2% including acute respiratory failure, aspiration pneumonia, cardiac disorder, sepsis, pneumonitis
  - Discontinuation: in 16%; most common due to peripheral neuropathy in 6%

Drug-drug interactions:
  - Dual P-gp and CYP3A4 inhibitors: may increase unconjugated MMAE (vedotin) exposure, increasing risk of toxicities.

Other Considerations

- Geriatric use: no differences in safety or efficacy observed between this population and a younger population
- Hepatic impairment: avoid use in moderate or severe hepatic impairment; limited use in 3 patients with moderate impairment and no data in severe impairment.
- Renal impairment: no dose adjustments for mild (CrCL >60-90 mL/min), moderate (CrCL 30-60 mL/min), or severe (CrCL <30 mL/min) renal impairment
- Infertility: based on animal models, may impair male fertility (decrease in testes weight, depletion of spermatocytes, abnormal spermatids)

Risk-Benefit Assessment

- Outcome in clinically significant area: Overall Survival
- Effect Size: HR 0.70 (95%CI 0.56-0.89)
- Potential Harms: Grade 3-4 adverse events >20%
- Net Clinical Benefit: Moderate (High Benefit with High Risk of Harm)
Other Therapeutic Options
Alternative treatments for locally advanced or metastatic urothelial carcinoma that is previously treated with PD-1 or PD-L1 inhibitor and platinum-containing chemotherapy are listed in table 3 below.
Table 3  Treatment Alternatives

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulary status</th>
<th>Clinical Guidance</th>
<th>Other Considerations</th>
</tr>
</thead>
</table>
| **Enfortumab-vedotin** (PADCEV) | TBD              | • LA/Met urothelial carcinoma previously treated with PD-1 or PD-L1 inhibitor plus platinum-based chemotherapy  
• Cisplatin ineligible patients who previously received 1 or more prior lines of therapy | • OS advantage over taxanes in Phase III trial  
• Store in refrigerator  
• Dose: 1.25 mg/kg (max 125 mg) iv over 30 minutes D1, 8, 15 of a 28 day cycle |
| **Pembrolizumab**           | F-PA             | • LA/M urothelial carcinoma with progression during or following platinum-containing chemotherapy | Phase III data vs chemotherapy  
OS HR 0.73 (95%CI 0.59-0.91)  
No prior PD-1, PD-L1, Anti-CTLA-4  
Non-selective for FGFR alterations  
• Limited due to potential use of avelumab for maintenance therapy  
• FGFR mutation not expected to respond well to PD-1/PD-L1 inhibition |
| **Gemcitabine and cisplatin or carboplatin** | F               | • LA/M urothelial carcinoma                                                       | • Post checkpoint inhibitor if not used previously  
• Similar outcome (cisplatin) to standard MVAC with fewer toxic deaths; dose dense  
MVAC with growth factor improves efficacy and less toxic than standard MVAC |
| **Erdafitinib** (BALVERSA)  | NF w/CFU         | • FGFR3 or FGFR2 mutation positive LA/M urothelial carcinoma after at least 1 prior platinum-containing regimen | Phase II data  
FGFR3 mutation or FGFR2/3 fusion  
Accelerated approval  
ORR 34%  
Med DoR=5.6 months |
| **Docetaxel**               | F-PA             | No FDA Indication                                                                  | Phase II  
ORR 13.3% Partial Response |
| **Paclitaxel**              | F-PA             | No FDA Indication                                                                  | Randomized Phase 2 (vs nab-paclitaxel)  
ORR 25% (95%CI 16-35) |
Projected Place in Therapy

- Urothelial carcinoma is the most common cancer of the urinary tract and the 3\textsuperscript{rd} or 4\textsuperscript{th} most common cancer in the VA. Most cases are organ-confined and managed surgically. However, 10-15\% develop locally advanced (unresectable) or metastatic disease.
- Platinum-based chemotherapy still remains the first line standard of care for eligible patients. Maintenance therapy with avelumab is also recommended. For patients not eligible for either cisplatin or carboplatin, pembrolizumab is recommended for first-line therapy.
- Second-line therapies can depend on what therapy was received in the first-line setting. For patients who received platinum-based chemotherapy in the first-line setting, second line settings include a variety of PD-1 and PD-L1 inhibitors, single-agent taxanes, or erdafitinib for FGFR mutated tumors. Pembrolizumab is the only drug until now with approval in the second-line setting based on phase III data and improvement in overall survival. However, now that avelumab may be used for maintenance therapy in the first-line setting, the use of another checkpoint inhibitor (pembrolizumab) in the second-line setting is less likely. Patients who received pembrolizumab alone in the first-line setting may be eligible for platinum-based chemotherapy in the second-line setting. The remaining second-line choices are based on phase II data and produce very modest effects on tumor size.
- Enfortumab vedotin originally received accelerated approval based on response and response duration based on EV-201 cohorts. The EV-301 phase III was a confirmatory trial that led to full approval.
- Enfortumab vedotin, an antibody drug conjugate, improved Overall Survival in a phase III trial in patients previously treated with platinum-containing chemotherapy and PD-1 or PD-L1 inhibitor therapy compared to single-agent taxanes, making it the second therapy (pembrolizumab was the first) to receive regular approval in the second-line setting for previously treated urothelial carcinoma.
- Tolerance to enfortumab vedotin therapy may be difficult. A vast majority of patient required dose interruptions or modification. Discontinuation rates due to treatment-related adverse events was in the range of 12-16\%.
- There is some concern over post-marketing adverse events leading to a Warning about the development of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis. Post-marketing reporting by the FDA Pharmacovigilance Division\textsuperscript{4} and case reports from M.D. Anderson Cancer Center\textsuperscript{5} highlight the potential for severe dermal reactions and potential development of SJS/TEN. Whether this is due to on-target effects of inhibition of Nectin-4, weakly to moderately expressed in skin, the binding of Nectin-4 in the skin and delivery of the MMAE (vedotin) payload, or MMAE itself is unknown. Other ADC using MMAE as a payload report increased incidences of dermal reactions.
- NCCN Guidelines list enfortumab vedotin as:
  - Alternative second-line therapy post platinum (likely to also be preferred with the next update)
  - A preferred therapy second-line for cisplatin ineligible patients who received pembrolizumab in the first-line setting (also gemcitabine/carboplatin)
  - Preferred subsequent-line therapy (3\textsuperscript{rd} line)
• In VA, enfortumab vedotin should be an additional potential therapy available for use following previous therapy (platinum-based and immune checkpoint inhibitors or other therapies if platinum ineligible) but considering the modest survival benefit and significant toxicities and barriers/exclusions for use, other agents may be used if this agent cannot be prescribed safely. Patients whose tumor has an FGFR mutation should receive erdafitinib prior to enfortumab vedotin.
References

4. Nguyen MN, Reyes M, Jones SC. Postmarketing cases of enfortumab vedotin-associated skin reactions reported as Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis. JAMA Derm 2021; published online.

Appendix A. Acquisition Prices and Cost Considerations

Refer to VA pricing resources for updated information