Sulbactam/durlobactam (XACDURO)
DRAFT Drug Monograph
November 2023

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

- XACDURO is a co-packaged product containing two drugs – sulbactam (SUL) is a beta-lactam (BL) antibiotic and beta-lactamase inhibitor (BLI) and durlobactam (DUR) is a beta-lactamase inhibitor.
- Sulbactam has activity in vitro against *Acinetobacter baumannii calcoaceticus* complex by inhibition of penicillin-binding proteins PBP1 and PBP3, but resistance to sulbactam can occur due to the production of beta-lactamases.
- Durlobactam is a BLI with a broad spectrum of activity against Ambler Class A, Class C and importantly against Class D beta-lactamases (e.g., OXA carbapenemases) which are a common cause of resistance against carbapenems and traditional BLIs in *Acinetobacter spp.* It restores activity against many strains of multi-drug-resistant *Acinetobacter.*
- Several surveys found MIC_{90} ranging from 2-4 mg/L, including in carbapenem-resistant isolates. The provisional CLSI breakpoint for susceptibility is 4 mg/L.

Indication(s) Under Review in This Document

- SUL/DUR was approved by the FDA on 5/23/23, indicated in patients 18 years of age and older for the treatment of hospital acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP), caused by susceptible isolates of *Acinetobacter baumannii-calcoaceticu*s complex.

Dosage Form(s) Under Review

- SUL/DUR is a co-packaged product containing a 1-gram vial of sulbactam and two 0.5-gram vials of durlobactam. Both are lyophilized powder and must be reconstituted with sterile water for injection and added to 100 mL of 0.9% sodium chloride for infusion.
- The recommended dose is 1g SUL and 1g DUR given every 6 hours as a 3-hour intravenous infusion.
    - Dose adjustments are recommended for patients with CrCl > 129 mL/min or less than 45 mL/min (see special populations)

Clinical Evidence Summary

Efficacy Considerations

- Approval of SUL/DUR was based on one randomized, assessor blinded, active-controlled (colistin) Phase 3 trial (ATTACK) in patients with hospital-acquired bacterial pneumonia (HABP) and ventilator-acquired bacterial pneumonia (VABP) caused by carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* (CRABC). Because there are limited treatment options for CRABC, the FDA considered this an unmet medical need, and set a prespecified 20% noninferiority margin for the primary endpoint of 28-day all-cause mortality.
- Supportive safety, pharmacokinetic and in vitro data came from pre-clinical data and a phase 1 human trial, and a phase 2 trial of cUTI (safety only)
- Efficacy data are summarized in Table 1

Table 1: Efficacy results from clinical trials SUL/DUR

Study	Design	Demographics	Results / Comments
ATTACK **Phase 3 trial**	Randomized, assessor-blinded, active-controlled trial. 2nd arm allowed open-label SUL/DUR for colistin-resistance or ineligibility for RCT. **Treatment:** SUL/DUR 1g/1g IV q6h (n=91) over 3 hours Colistin 2.5 mg/kg IV q12h (n=86) - After loading dose 2.5-5 mg/kg *Both groups also received imipenem 1g IV q6h as background therapy* Duration: 7 - 14 days **Inclusion:** Adults with HABP/VABP or bacteremia caused by *A. baumannii calcoaceticus* - Monomicrobial and polymicrobial infections allowed* APACHE II: 10-30 or SOFA < 12 No more than 48 hours potentially effective therapy or was failing treatment. **Primary endpoint**: 28-day all-cause mortality in CRABC m-MITT population: patients who received medication with confirmed CRABC infection who did not withdraw consent by day 28. 20% non-inferiority (NI) margin allowed by FDA. **Secondary endpoints:** 14-day all-cause mortality Clinical cure at test of cure (TOC) visit Favorable microbiologic assessment (eradication or presumed eradication) at TOC visit	125 patients were included in the m-MITT population (63 SUL/DUR and 62 colistin) **Baseline demographics** (SUL/DUR vs. colistin, respectively) Mean age: 62 vs. 66 years. Male sex: 72% vs. 77% Race - White: 56% vs. 42% - Asian: 36% vs. 53% Mean Apache II: 16 vs. 17 SOFA: 3 vs. 4 Mechanical ventilation at baseline: 73% vs. 78% Monomicrobial: 58% vs. 70% There were more subjects > 75 years, Asian subjects and HABP in the colistin arm of treatment. **96% overall had pneumonia.** - **VABP: 59% vs. 47%** - **HABP: 38% vs. 48%** **Bacteremia: 3% vs. 2%** Median treatment duration: 8 vs. 7 days	**28-day all-cause mortality:** • **SUL/DUR: 19%** • **Colistin: 32%** • **Difference 13%** ○ **(95% CI -30%, 3.5%)** **SUL/DUR was non-inferior to colistin for 28-day mortality.** **Secondary Outcomes:** 14-day mortality • SUL/DUR: 6% • Colistin 19% • Difference: 13% ○ 95% CI -28%, 2% **Clinical cure at TOC** • SUL/DUR: 62% • Colistin: 40% • Difference 22% ○ 95% CI 3%, 40% **Favorable micro response**** • SUL/DUR: 68% • Colistin 42% ○ 95% CI 8%, 45%

*polymicrobial infections with the following pathogens for pneumonia was not allowed: *S.pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella pneumonphila, respiratory syncytial virus, influenza, parainfluenza, Middle East respiratory syndrome coronavirus, mycobacteria, aspergillus, mucormycosis*

**Difference was primarily in presumed eradication at TOC based on a favorable clinical response

Efficacy Summary:

SUL/DUR was non-inferior to colistin for treatment of carbapenem-resistant *A. baumannii* pneumonia. Given the paucity of agents for treatment of this multidrug-resistant pathogen and significant toxicity associated with colistin/polymyxin, a single phase 3 randomized, assessor blind trial with a 20% noninferiority margin was accepted by the FDA as sufficient evidence for this approval, although they also met a stricter 10% noninferiority margin.

Safety Considerations

Safety Results from Clinical Trials:

- The overall safety database for SUL/DUR includes 172 subjects from the Phase 3 and a phase 2 UTI trial who received the recommended dosing regimen.
  - In the Phase 3 trial (ATTACK), 91 patients received SUL/DUR compared with 86 for colistin which comprises the majority of the safety data.

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- No unexpected safety signals beyond what is seen with other beta-lactam/beta-lactamase inhibitors in the overall safety database.

Table 2: Safety results from clinical trials

Study	Results (SUL/DUR vs. colistin, %)	Comments
ATTACK, Phase 3 trials	Treatment emergent adverse events: 88% vs. 94% - **Drug related TEAEs: 13% vs. 30%** Serious adverse events: 40% vs. 49% Discontinuation due to adverse events: 11% vs. 16% Adverse reaction: 88% vs. 94% - The only adverse reactions more common with SUL/DUR were diarrhea (17% vs. 11%), hypokalemia (12% vs. 11%) and thrombocytopenia (6% vs. 4%) - **Acute kidney injury: 6% vs. 36% with colistin** o **≥ 50% decrease in CrCl: 2% vs. 25%** Adverse events of special interest: - Seizures occurred in 1 SUL/DUR (0.8%) vs. 6 colistin (7%) patients. - Hypersensitivity reactions 17% vs. 12% o 1 case of anaphylaxis with SUL/DUR - *C.difficile* infection: 1 case with SUL/DUR (1%) vs. 3 with colistin (4%)	Overall safety with SUL/DUR similar to what is seen with beta-lactam antibiotics – 1 case of anaphylaxis and another of hives occurred with SUL/DUR in ATTACK Acute kidney injury and seizures were more common with colistin, expected based on the known side effect profile

Boxed warnings: none

Contraindications: known hypersensitivity to the components of SUL/DUR

Other warnings / precautions:

- **Hypersensitivity reactions**
- ***C.difficile* associated diarrhea**

Resistance to SUL/DUR

- Not active against *Acinetobacter baumannii* that produce Ambler class B metallo-beta-lactamases or have PBP3 target site alteration. Varying combinations of other beta-lactamases (especially Class D OXA) may result in MIC > 4 mg/L. One in vitro review noted 9/246 CRAB isolates had MIC > 4 mg/L (3.7%). Another survey noted 39/1722 *Acinetobacter baumannii* had MIC > 4 mg/L (2.3%)
  - CLSI Breakpoint is 4/4 mg/L.
- During screening for the phase 3 trial: 6 isolates out of the 155 included in the m-MITT had baseline resistance to SUL/DUR (3.9%)
- One subject in the phase 3 trial had a persistent isolate of where the MIC increased from 4 to 8 mg/L at the TOC visit.

Pharmacokinetics:

- Cmax (ug/mL): SUL 32, DUR 29
- AUC (h*ug/mL): SUL 515, DUR 471
- Binding to plasma proteins: SUL 38%, DUR 10%
- V_{ss} : SUL 25 L, DUR 30L

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- Half-life: SUL 2.15 hrs., DUR 2.52 hrs.
    - % excreted unchanged in urine: SUL 75-85%, DUR 78%
    - Clearance of SUL and DUR is greater in those with CrCl ≥ 130 mL/min and is recommended to be dosed every 4 hours in these patients.
- Effectively removed by hemodialysis with 40% of a SUL dose and 33% of DUR dose excreted in dialysate.

Special populations:

Renal dysfunction

- Dose adjustments are needed for estimated CrCl < 45 mL/min or > 130 mL/min.
    - Usual dose is 1g/1g IV every 6 hours over 3 hours.
    - If CrCl is > 130 mL/min decrease dosing interval to every 4 hours
    - For CrCl 30 – 44 mL/min: increase the dosing interval to every 8 hours.
    - For CrCl 15-29 mL/min: increase the dosing interval to every 12 hours.
    - For CrCl < 15 mL/min: Give every 12 hours for 3 doses, then give every 24 hours.

Pregnancy/Lactation

- There are no available data on use of SUL/DUR in pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes.
- DUR administered to pregnant mice and rats during organogenesis showed no drug-induced fetal malformations but an increased incidence of skeletal variations was observed at 2 and 4 times the maximum recommended human dose.
- There are no data on presence of DUR in human or animal milk. SUL is present in low concentrations.

Other Therapeutic Options

Alternative treatments for pneumonia due to carbapenem-resistant *A. baumannii* are listed below.

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Drug	Formulary status	Clinical Guidance	Other Considerations
SUL/DUR (XACDURO)	TBD	Indicated for HABP/VABP due to susceptible strains of *A. baumannii.* Generally well-tolerated and often susceptible in MDR strains	Susceptibility testing should be used to guide treatment, especially in strains resistant to sulbactam alone. Very small safety database at this point Hypersensitivity reactions were common, although all patients were also given imipenem/cilastatin – needed for other microorganisms.
Ampicillin/ sulbactam	F	Sulbactam has antibacterial activity against *Acinetobacter spp.* By binding to PBP1a/1b and PBP3 First-line therapy in IDSA Guidance documents in combination with another agent even when non-susceptibility documented. Meta-analyses suggest amp/sulbactam regimens most effective at reducing mortality	High doses used (6-9 grams sulbactam) which requires total daily doses of 18-27g of amp/sulbactam. Provides unnecessary exposure to ampicillin, limited in patients with severe penicillin allergy. Many strains are not susceptible (although still recommended)
Colistin / polymyxin B	F	Often used as a drug last resort or in combination with another primary agent for CRAB Colistin more studied but IDSA guidance suggest polymyxin due to better PK	Significant nephrotoxicity and neurotoxicity Reliably active in vitro against CRAB Not recommended as primary therapy or monotherapy
Cefiderocol	PA-F	Up to 95% of CRAB isolates susceptible. IDSA guidance recommend limiting Cefiderocol to infections refractory to other agents or when tolerance or resistance preclude use	Human trials showed poor outcomes for CRAB infections with mortality 49% compared to 18% for other therapy (largely polymyxin regimens), especially in pneumonia and bacteremia. Another follow up trial found lower mortality but higher recurrence than colistin-based regimens
Minocycline	F	Not recommended as monotherapy for CRAB but can be considered with another active agent if susceptible. Mino preferred over tigecycline if using a tetracycline	While high doses appear more effective in vitro, no clinical safety data to support use. Only active against 60-80% of CRAB
Tigecycline	F	Not recommended as monotherapy for CRAB but can be considered with another active agent if susceptible	Minocycline cannot be used to predict susceptibility to tige and no breakpoints available. Meta-analyses suggest tigecycline associated with higher mortality vs. alternative regimens for pneumonia. Poorly tolerated – GI, nausea/vomiting common and often treatment limiting

Projected Place in Therapy

- Carbapenem-resistant *Acinetobacter baumannii* (CRAB) infections are increasing at a rate outpacing other multi-drug resistant gram-negative infections, particularly during the COVID-19 pandemic. Management of these infections is difficult as they typically are resistant to most other antibiotics except for polymyxins.

- Appanneal et al. described trends in *A. baumannii* in VHA from 2010 to 2018, including the frequency of carbapenem-resistance, multi-drug resistance and extensive drug-resistance. They found 19,376 cultures over the time period, with decreasing incidence over time. Inpatient and CLC isolates were more likely to be carbapenem-resistant (inpatient 28%, CLC 36% vs. 6% of outpatient isolates in 2018 of total of 1684 isolates that year).
    - Respiratory isolates were the most common source of CRAB.
    - From that article, approximately 268 CRAB isolates were identified in 2018.
    - The same group found CRAB in hospitalized patients was associated with significantly greater mortality than non-CRAB infections (25% vs. 8.5%), as well as a greater likelihood of length of stay > 10 days or reinfection within 30 days of discharge.

- The IDSA has produced guidance on the treatment of antimicrobial-resistant gram-negative infections, including CRAB, although the place of SUL/DUR has not yet been included. Their recommended approach is combination therapy using high-dose ampicillin/sulbactam + at least one other agent (polymyxin/colistin, minocycline, tigecycline or Cefiderocol) given there is limited clinical data for any single agent.

- Sulbactam/durlobactam was non-inferior to colistin in patients with *A. baumannii* pneumonia in terms of mortality and had higher rates of clinical cure and favorable microbiologic outcomes. Importantly, it is unclear how outcomes with SUL/DUR compare to the recommended first-line options (high-dose SUL in combination with another active agent). In addition, susceptibility testing may not be readily available in some facilities.

- Where SUL/DUR is likely to be most beneficial is in patients with pneumonia with CRAB when
    - The isolate is not susceptible to sulbactam AND where another no other active agent can be used in combination, due to resistance or tolerability concerns OR
    - In patients failing ampicillin/sulbactam based combination therapy
    - In either case, susceptibility testing should be obtained, as somewhere between 3-6% of isolates appear to be nonsusceptible based on global surveys and screening for the ATTACK trial.

- Infectious Diseases experts should be involved in the decision to prescribe SUL/DUR to avoid overuse and development of resistance.

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