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CEFTAZIDIME-AVIBACTAM FOR THE TREATMENT OF CARBAPENEM-RESISTANT PATHOGENS ASSOCIATED WITH HEALTHCARE-ASSOSIATED INFECTIONS: A BUDGET IMPACT ANALYSIS IN ARGENTINA

Jorge Elgart[1], Carolina Pein[2], Natalia Albaytero[3], Mariana Glancszpigel[3], Wajeeha Ansari[4], Carolina Carballo[2], Mercedes Mac Mullen[2]
[1] Unidad de Economía de la Salud, CENEXA (UNLP-CONICET), La Plata, Argentina; [2] Pfizer, Buenos Aires, Argentina; [3] 3Eff, Buenos Aires, Argentina; [4] Pfizer Inc., New York, NY USA

Introduction

- CAZ-AVI, a fixed-combination drug containing ceftazidime and avibactam, has been approved in Argentina for complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI), hospital-acquired pneumonia (HAP) including ventilator-associated pneumonia (VAP) and aerobic Gram-negative infections with limited treatment options.
- CAZ-AVI was developed to treat a broad range of Gram-negative bacterial infections, which are becoming resistant to existing antibiotics and pose an increasing threat to public health.
- Seven randomized, multicentre, double blind, phase III clinical trials had demonstrated CAZ-AVI efficacy and the no inferiority with the best available therapy1,2,3

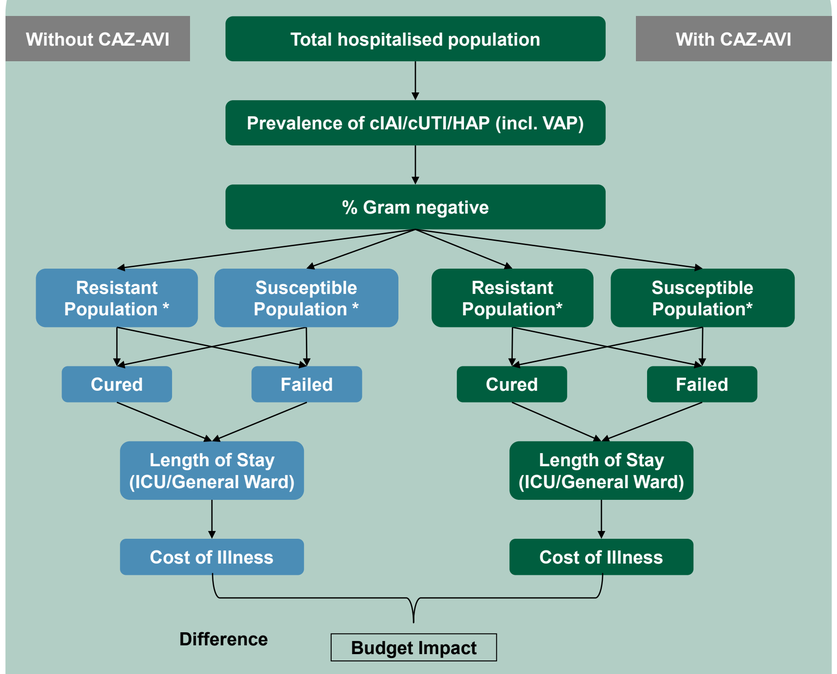
Objective

- Our objective was to estimate the budgetary impact of adding Ceftazidime-Avibactam (CAZ-AVI) as a therapy option for Multidrug resistant Gram-negative bacteria (MDRGN) infections specially Klebsiella pneumoniae carbapenemase (KPC) and Oxacillin-hydrolyzing (OXA) carbapenemase in Argentina.

Methods

- A global economic model was adapted to estimate the budget impact of adding CAZ-AVI to a hospital formulary in the Argentinean population over three years. The model structure is displayed in Figure 1.
- Costs were calculated based on the number of eligible patients, treatment duration, length of hospital stay, adverse event (AE) rates, market share of various treatments and costs (i.e., drug acquisition, hospitalisation and AE management costs).
- The model performed side-by-side comparisons between "without CAZ-AVI" and "with CAZ-AVI" scenarios, and calculated the budget impact by multiplying the proportion of patients with cUTI, cIAI and HAP/VAP treated with each of the respective treatment options by drug acquisition, hospitalisation and AE costs associated with the treatment used in a given year.

Figure 1. Model Structure



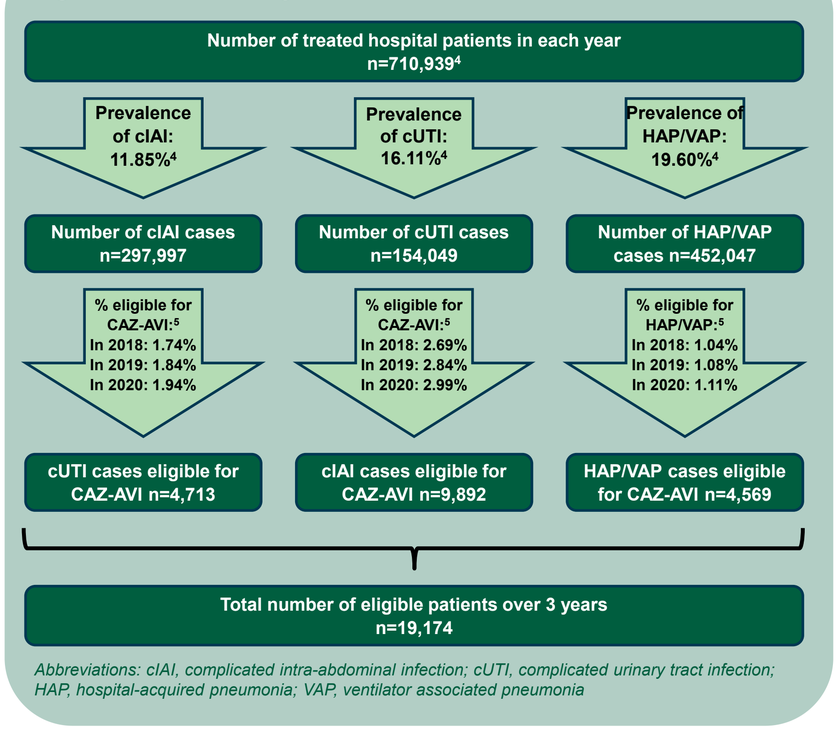
Abbreviations: CAZ-AVI, ceftazidime-avibactam; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; ICU, intensive care unit; VAP, ventilator associated pneumonia
** Resistant Population = patients infected by pathogen(s) resistant to the treatment received, Susceptible Population = patients infected by pathogen(s) susceptible to the treatment received*

Model Inputs

Patient Population

- The Number of eligible patients was estimated based on epidemiological data from Argentina (Figure 2).
- For a total hospitalised population due to infection of 710.939 [4] 4,713 cIAI, 9,892 cUTI, 2,225 HAP/VAP, and altogether 16,830 patients were estimated to be eligible for CAZ-AVI over three years.
- Drug resistance data were obtained from National Institute of Microbiology Dr. Malbrán and validated by local experts.

Figure 2. Number of Eligible Patient Over 3 Years



Abbreviations: cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; VAP, ventilator associated pneumonia

Market Shares

- Treatments considered in the analysis were those utilised in Argentina for the treatment of cIAI, cUTI and HAP/VAP caused by Gram-negative pathogens multiresistant KPC and OXA.
- The current market share mix (without CAZ-AVI) was calculated based on data from the National Institute of Microbiology Dr. Malbrán and validated by local experts.
- The indication-specific uptakes of CAZ-AVI in the revised market (with CAZ-AVI) were based on the forecasting data of Pfizer.

Efficacy Inputs

- Probability of clinical cure by each treatment used in the model data were obtained from RECAPTURE,[1] RECLAIM[2] and REPROVE[3] trials, and published clinical trials for other treatment options.

Table 1. Clinical cure rates

Treatment	cIAI	cUTI	HAP/VAP
CAZ-AVI	98.00%	98.00%	77.43%
Colistin + Tigecycline	77.34%	80.56%	70.90%
Colistin + carbapenem (HD)	92.55%	93.64%	78.15%
Fosfomycin (HD) + colistin	54.20%	100.00%	54.20%
Colistin + amikacin	61.00%	88.00%	61.00%
Amikacin+ carbapenem (HD)	54.00%	88.00%	54.00%

Abbreviations: cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; ICU, intensive care unit; VAP, ventilator associated pneumonia
Population: cUTI and cIAI: modified ITT population, HAP/VAP: CE analysis set; HD, High dose

Treatment Costs and Durations

- Drug costs were obtained from list prices of AlfaBeta, the official public database of public access.[7]
- Treatment durations were extracted from the National Administration of Drugs, Foods and Medical Devices (ANMAT) product labels.

Hospitalisation Inputs

- Hospital length of stay inputs, composing the number of days in an intensive care unit (ICU) and in the general ward, for patients with clinical cure and failure were derived from RECAPTURE,[1] RECLAIM[2] and REPROVE[3] trials (Table 2).
- Hospital per-diem costs were based on tariffs from de the Social Security System of Argentina.

Table 2. Inputs on Mean Hospital Length of Stay by Clinical Cure/Failure

	cUTI*		cIAI**		HAP/VAP	
	Failure/Non Responders	Cure/ Responders	Failure/Non Responders	Cure/ Responders	Failure/Non Responders	Cure/ Responders
ICU (days)	0.10	0.05	2.76	3.15	10.70	7.20
General ward (days)	14.10	10.35	21.37	8.56	8.40	9.20
Total hospital (days)	14.20	10.40	24.13	11.71	19.10	16.40

**Calculated from cUTI payers analysis as a weighted average of the mean values of time to hospital discharge from the two treatment arms.*
***Calculated from cIAI payers analysis as a weighted average of the mean values of time to hospital discharge from the two treatment arms.*
Abbreviations: cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; ICU, intensive care unit; VAP, ventilator associated pneumonia
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Results

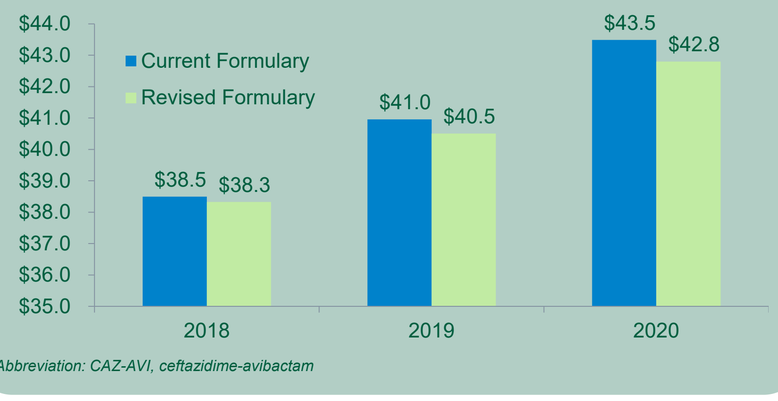
Overall Population Results

- The estimated net budget impact for the introduction of CAZ-AVI was -$171,513; - $452,487 and -$690,710 in each year respectively.
- The cumulative net budget impact was -$1,314,710, representing an impact of -1.07% compared to a scenario without CAZ-AVI, and mainly driven by the reduction in hospital bed days and hospitalization costs.
- The total treatment cost increased $3.5 million, compared to a saving in hospital bed days of $4.8 million.

Table 3. Budget Impact of the Overall Population Over 3 Years

Costs	Current Formulary	Revised Formulary	Difference	% Change in Budget
Total hospital days	312,774	294,409	-18,365	-5,87%
Total hospital days per patient	16.31	15.35	-0.96	-5.87%
Treatment costs	$37,342,391	$40,866,848	$3,524,457	9.44%
Hospitalisation costs	$85,597,826	$80,758,152	-$4,839,674	-5.65%
Total Costs	$122,940,217	$121,625,000	-$1,315,217	-1.07%
Total Cost per Patient	$6,412	$6,343	-$69	-1.07%

Figure 3. Budget Impact per Patient Over 3 Years (Million USD)



Abbreviation: CAZ-AVI, ceftazidime-avibactam

Results by Indication (Table 3)

- The total cost per treated patient, prior to CAZ-AVI introduction, was estimated to be $6,412 [$7,210 (cIAI), $5,265 (cUTI), $8,072 (HAP/VAP)] and $6,343 [$6,918 (cIAI), $5,199 (cUTI), $8,229 (HAP/VAP)] after the introduction of CAZ-AVI.
- Introducing CAZ-AVI to the market decreased the average time spent in hospital by 12.61% per patient in cIAI, 2.75% in cUTI, and by 2.46% per patient in HAP/VAP.

Table 3. Budget Impact by Indication Over 3 Years

Costs	Current Formulary	Revised Formulary	Difference	% Change in Budget
cUTI				
Total hospital days	130,661	126,975	-3,686	-2.82%
Total hospital days per patient	13.21	12.84	-0.37	-2.82%
Total Costs	$52,100,000	$51,400,000	-$651,849	-1.25%
Total Costs per Patient	$5,265	$5,199	-$66	-1.25%
cIAI				
Total hospital days	97,421	84,860	-12,560	-12.89%
Total hospital days per patient	20.67	18.01	-2.67	-12.89%
Total Costs	$34,000,000	$32,600,000	-$1,378,443	-4.06%
Total Costs per Patient	$7,210	$6,918	-$292	-4.06%
HAP/VAP				
Total hospital days	84,693	82,574	-2,118	-2.50%
Total hospital days per patient	18.54	18.07	-0.46	-2.50%
Total Costs	$8,800,000	$10,500,000	$1,684,772	19.09%
Total Costs per Patient	$8,072	$8,229	$157	1.94%

Abbreviations: cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; VAP, ventilator associated pneumonia

Discussion

- The introduction of CAZ-AVI could be expected to produce savings on the total healthcare budget, mainly driven by budget saving in cUTI and cIAI.
- The introduction of CAZ-AVI was expected to result in a reduction in hospital bed days and a reduction in overall hospitalisation costs as more patients receive appropriate empirical antibiotic treatment.
- The drug acquisition cost of CAZ-AVI was estimated to be 34% of the total costs, while hospitalisation costs represented 66% of the costs.
- The increase in antibiotic costs was offset by the reduction in hospitalisation costs associated with CAZ-AVI.

Limitations

- Efficacy and safety data for each treatment were obtained directly from the published sources. Due to data limitations, indirect comparison was not performed.
- As the inputs for CAZ-AVI and the comparator in the clinical trials of RECAPTURE, RECLAIM and REPROVE were derived from these trials, it is assumed that the CAZ-AVI trials appropriately captures the real-world evidence with CAZ-AVI in the treatment of cIAI, cUTI and HAP/VAP in Italy.
- The AEs were not included in the model. In previous studies, AE costs represented less than 2% of the total treatments cost, and also the difference between scenarios showed to be marginal. We ran a sensitivity analysis and the inclusion of AE costs did not modify he interpretation of the results.

Conclusions

- Our results suggest that the inclusion of CAZ-AVI as a therapeutic option in hospitalized patients with cUTI, cIAI, HAP/VAP could generate budgetary savings compared to current treatment options.*Clinical Implications*

Clinical implications

Given the unmet clinical need due to growth in resistance, and the lower budget impact estimated with the introduction of CAZ-AVI, CAZ-AVI should be included in the hospital formulary in Argentina to provide an additional treatment option for multi-resstant patients with cIAI, cUTI and HAP/VAP.

References

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5. The number of multi-resistant patients KPC and OXA within the Gram-negative patients were provided by Pfizer with data from the National Institute of Microbiology Dr. Malbrán, to be to adapt the model to the IIAc, ITUc, NAH / NAV gram-negative population.I
6. AlfaBeta November 2018, at: http://www.alfabeta.net/precio/.

Contact: mercedes.macmullen@Pfizer.com