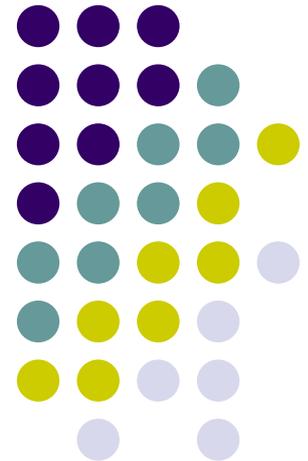


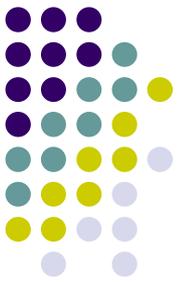
Doripenem Safety Review

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Medical Officer

Division of Anti-Infective and Ophthalmology
Products





Overview of Safety Experience

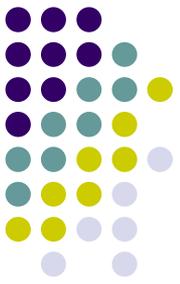
- Doripenem Phase 1, 2, and 3 cUTI and cIAI clinical studies and spontaneous post-marketing reports
- Phase 3 clinical trials for NP, including VAP
- Limitations of doripenem clinical trials safety experience
- Safety of doripenem in relation to other carbapenems

Doripenem Phase 1, 2, and 3 cUTI and cIAI Studies



- **Phase 1**
 - Negative QT/QTc Study
 - Studies in renal impairment and the elderly
 - Terminated aerosolized doripenem study (acute pulmonary inflammatory reaction)
- **Phase 2 (cUTI) and Phase 3 (cUTIs and cIAIs)**
 - Adverse drug reactions: Nausea, diarrhea, headache, phlebitis, rash
 - TEAE frequency imbalances: Renal adverse events
 - Indication-specific TEAEs: Asymptomatic bacteriuria (cUTIs) and Anemia (cIAIs)
 - No convulsions/seizures were reported in doripenem-treated patients

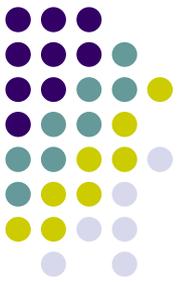
Spontaneous Post-Marketing Safety Experience



- **Spontaneous Post-marketing Safety Reports**
 - Stevens Johnson syndrome, toxic epidermal necrolysis, seizure, interstitial pneumonia
 - Insufficient evidence of causality

Doripenem Clinical Trials

Safety Experience for NP and VAP



- Pneumonia-related serious adverse events and deaths
- Seizures
- Imbalances in treatment-emergent adverse events (TEAEs) and laboratory abnormalities
- Limitations of the safety database

Doripenem Clinical Trials

Safety Experience for NP and VAP



	DORI-09		DORI-10	
	Doripenem N=223 n (%)	Pip/Tazo N=221 n (%)	Doripenem N=262 n (%)	Imipenem N=263 n (%)
≥1 Treatment-emergent adverse events (TEAE)	171 (76.7)	172 (77.8)	249 (95)	238 (90.5)
Drug-related TEAE (Investigator designated)	36 (16.1)	39 (17.6)	45 (17.2)	46 (17.5)
Serious TEAE	67 (30)	58 (26.2)	70 (26.7)	72 (27.4)
Deaths as a TEAE	43 (19.3)	39 (17.6)	35 (13.4)	32 (12.2)
All-cause Mortality	45 (20.2)*	39 (17.6)	35 (13.4)	33 (12.5)**

*Two patients died after having received ≤1 day of study drug.

**One patient died after having received <2 days of study drug.

Doripenem Clinical Trials

Safety Experience for NP and VAP



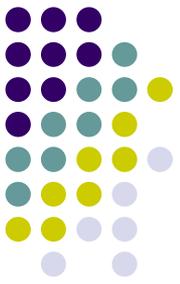
●Pneumonia-related SAEs and Deaths

Protocol	Study Drug N=ITT	Pneumonia- related SAE n (%)	Pneumonia- related Death n (%)	Recovered n (%)	Not Recovered n (%)
DORI-09	Dori N=223	12 (5.4)	9 (4.0)	2 (0.9)	1 (0.4)
	Pip/Taz N=221	3 (1.4)	1 (0.5)	2 (0.9)	0 (0)
DORI-10	Dori N=262	2 (0.8)	1 (0.4)	1 (0.4)	0 (0)
	Imi N=263	5 (1.9)	2 (0.8)	3 (1.1)	0 (0)

ITT=intent-to-treat population; SAE=serious adverse event

Doripenem Clinical Trials

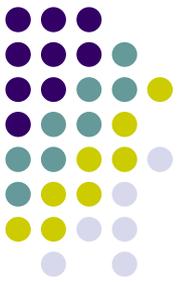
Safety Experience for NP and VAP



- **Seizures:**
 - 6 doripenem, 6 pip/taz, and 10 imipenem-treated patients experienced seizures
 - Of the 6 doripenem-treated patients:
 - History of predisposing CNS disorders or epilepsy
 - 3/6 seized post-EOT; 1/6 had negative rechallenge
- **Imbalances in frequency of TEAEs and laboratory abnormalities**
 - No marked imbalances: hepatic and hematologic laboratory test abnormalities, Hy's Rule, renal events
 - DORI-10: Serum CPK >3 x ULN from normal baseline
 - 12 doripenem and 3 imipenem-treated patients
 - 6/12 doripenem-treated patients had negative rechallenge; remaining 6 had concurrent predisposing factors

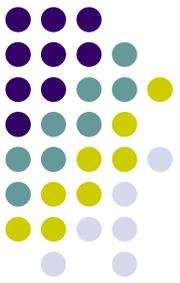
Limitations of the Clinical Trials

Safety Data for NP and VAP



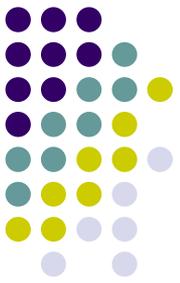
- **Missing safety laboratory data (DORI-09)**
 - Eastern Europe (Belarus, Georgia, Russia, Ukraine)
 - 43% were missing ≥ 1 screening result and 26% were missing ≥ 1 TOC result
- **Oral switch option (DORI-09)**
 - Contributed to heterogeneity in study drug exposure
 - Confounded attribution of AEs to i.v. vs oral switch drug
- **Doripenem 500 mg q8h 1 hr vs 4 hr infusions**
 - Across study differences in patient populations made direct comparisons difficult :
 - Age, APACHE score, co-morbid diseases, concurrent medication use
 - Difference in size of safety population:
 - 4 hour: n=262 (from DORI-10)
 - 1 hour: n=1,076 (pooled from DORI-09 plus phase 3 cUTI and cIAI studies)

Limitations of the Clinical Trials Safety Data for NP and VAP



- **Difficulties in interpretation of clinical and laboratory adverse events**
 - Confounding from concurrent medical illnesses, concurrent medications, abnormal baseline organ function, age
 - Lack of routine hepatitis studies, CPK isoenzyme tests, medical imaging studies of liver and kidneys
 - Limited laboratory data collection (e.g., direct Coombs)

Safety of doripenem in relation to other carbapenems



- **Similar adverse reactions profile:**
 - Nausea, diarrhea, phlebitis/injection site reactions, rash, transient hepatic enzyme elevations
- **Seizure potential:**
 - Imipenem – highest incidence
 - Doripenem – minimal to none (?)
- **Potential drug-drug interaction: valproic acid**
 - Reported with other carbapenems (meropenem, ertapenem)
 - To be evaluated in a doripenem Phase 1 study