

Anti-Infective Advisory Committee

November 20, 2008

Food and Drug Administration

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Questions to the AIDAC

Iclaprim for Injection

NDA 22-269

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Product Overview – Iclaprim for Injection

- Dihydrofolate Reductase (DHFR) Inhibitor
- Concentrated Solution (IV Only)
- NDA 22-269 Submitted March 2008
- Indication: Complicated Skin and Skin Structure Infections (cSSSI)

cSSSI Studies

- IND Submitted February 2005
- Two Studies: ASSIST-1 and ASSIST-2
- Iclaprim Base 0.8 mg/kg Every 12 Hours
- Comparator: Linezolid 600 mg Every 12 Hours
- cSSSI Types (Cellulitis, Major Abscess, Infected Ulcers, Wound Infections, Infected Burns)
- NI Margin – 12.5% for Both Trials

Efficacy Analyses

Primary Outcome Analyses

	Iclaprim Cure/N (%)	Linezolid Cure/N (%)	% Diff. (95% CI)
ASSIST-1			
ITT	204/249 (81.9)	220/248 (88.7)	-6.8% (-13.0, -0.5)
PP	192/206 (93.2)	211/213 (99.1)	-5.9% (-10.2, -2.2)
ASSIST-2			
ITT	201/251 (80.1)	198/243 (81.5)	-1.4 (-8.3, 5.6)
PP	185/209 (88.5)	187/195 (95.9)	-7.4 (-12.8, -2.1)

Secondary Outcomes-Infection Type

ITT Population	Iclaprim Cure/N (%)	Linezolid Cure/N (%)
ASSIST-1		
Cellulitis	96/121 (79.3)	104/117 (88.9)
Abscess	40/53 (75.5)	47/53 (88.7)
Wound Infection	20/29 (69)	36/43 (83.7)
ASSIST-2		
Cellulitis	52/71 (73.2)	55/69 (79.7)
Abscess	60/76 (79)	55/71 (77.5)
Wound Infection	94/112 (83.9)	92/111 (82.9)

Secondary Outcomes - Pathogens

MITT Population	Iclaprim Cure/N (%)	Linezolid Cure/N (%)
ASSIST-1		
<i>S. aureus</i> (All)	115/138 (83.3)	131/144 (91)
MRSA	36/45 (80)	34/36 (94.4)
MSSA	79/93 (85)	97/108 (89.8)
ASSIST-2		
<i>S. aureus</i> (All)	117/149 (78.5)	130/160 (81.3)
MRSA	56/74 (75.7)	62/80 (77.5)
MSSA	61/73 (83.6)	67/78 (85.9)

Secondary Outcomes - Pathogens

MITT Population	Iclaprim Cure/N (%)	Linezolid Cure/N (%)
ASSIST-1		
<i>S. pyogenes</i>	24/30 (80)	30/34 (88.2)
<i>E. faecalis</i>	11/14 (78.6)	11/13 (84.6)
<i>S. agalactiae</i>	1/3 (33.3)	4/7 (57.1)
ASSIST-2		
<i>S. pyogenes</i>	21/28 (75)	19/22 (86.4)
<i>E. faecalis</i>	13/15 (86.7)	14/15 (93.3)
<i>S. agalactiae</i>	3/5 (60)	4/4 (100)

Safety Analyses

Summary of Adverse Events

(Combined Phase 3 Studies)

	Iclaprim (n = 500)	Linezolid (n = 491)
Any treatment emergent AE (TEAE)	249 (49.8%)	257 (52.3%)
Any severe TEAE	34 (6.8%)	34 (6.9%)
Any serious AE	20 (4.0%)	16 (3.3%)
Any TEAE resulting in study drug withdrawal	12 (2.4%)	12 (2.4%)
Deaths	6 (1.2%)	2 (0.4%)

Deaths

(Phase 2 and 3 studies)

- 7 deaths occurred in the pooled ITT safety population of 526.
- 3 were possibly related to iclaprim:
 - All 3 patients were found deceased or unconscious in their hospital beds and had multiple preexisting or comorbid conditions.
 - Associated TEAEs: anemia (in 2 patients), hypoproteinemia, acute renal failure
- 4 deaths occurred before the completion of therapy.

Serious Adverse Events

(Combined Phase 3: ASSIST-1 and ASSIST-2)

MedDRA System Organ Class	Iclaprim (n = 500)	Linezolid (n = 491)
Cardiac	3 (0.6%)	1 (0.2%)
Infections and Infestations	11 (2.2%)	8 (1.6%)
Renal and Urinary	2 (0.4%)	1 (0.2%)
Total SAEs	20 (4.0%)	16 (3.3%)

Serious Adverse Events

(Combined Phase 3: ASSIST-1 and ASSIST-2)

- Most of the secondary infectious complications such as pneumonia, septic arthritis, osteomyelitis or the development of an abscess appear to have been related to underlying conditions or prolonged hospitalizations.
- With the exception of pneumonia (3 patients treated with iclaprim), no specific SAE preferred term was reported in a patient more than once per treatment group.

Study Treatment Withdrawal

(Combined Phase 3: ASSIST-1 and ASSIST-2)

	Iclaprim n=500	Linezolid n=491
Completed study therapy	451	441
Treated but withdrawn prematurely	46	39
Adverse event	4	5
Consent withdrawn	10	8
Infection-related reasons	3	6
Treatment emergent cardiovascular abnormality	2	2
Treatment failure	5	1
Death	3	0

Treatment Emergent Adverse Events

(Combined Phase 3: ASSIST-1 and ASSIST-2)

- Most common among the iclaprim group:
↑AST/ALT (7.2% iclaprim, 6.9% linezolid)
- Increased frequency in iclaprim group compared to linezolid:
Pyrexia (5.2% iclaprim, 2.2% linezolid)
 - Of the patients who had pyrexia reported as a TEAE: 13/26 in the iclaprim group were likely related to infection, compared to 4/11 treated with linezolid.

Other Adverse Events (>3%)

(Combined Phase 3: ASSIST-1 and ASSIST-2)

	Iclaprim	Linezolid
Nausea, vomiting or dyspepsia	8.6%	10.8%
Headache	6.4%	6.1%
Diarrhea or frequent bowel movements	5.8%	4.7%
Constipation	5.4%	4.1%
Pruritis	4%	3.7%
Abdominal pain, distension, tenderness or discomfort	3.4%	2%
Dizziness	3.2%	2%
Insomnia	3.2%	3.7%
Rash	2.8%	3.5%

Renal Adverse Events

Two patients with serious renal AE possibly related to the use of iclaprim:

- Patient 306-34: 70 year-old male who developed septic arthritis 4 days after EOT. Acute renal failure 12 days after EOT, found dead.
- Patient 133-01: 38 year-old male who received 2 days of therapy. Did not respond to treatment, received multiple other antibiotics/NSAID for headache. Creatinine increased to 4.4 mg/dL on Day 4. Renal biopsy: acute tubular necrosis. Recovered.

Cardiac Adverse Events

- Thorough QT Study
 - Concurrent with phase 3 studies
 - Clear dose-response relationship established
 - Concentration-dependent (Infusion Rate)
 - At 0.8 mg/kg, $\Delta\Delta QT_{cF}=12.4$ msec
 - 90% CI (8.6, 16.3)
 - At 1.6 mg/kg $\Delta\Delta QT_{cF}=21.6$ msec
 - 90% CI (17.4, 25.8)

Cardiac Adverse Events

- In comparison to linezolid, treatment with iclaprim demonstrated a higher mean ΔQT_c .
- Incidence of QT_c prolongation exceeding 30 ms occurred at twice the rate seen with linezolid.

Summary of ΔQT_c (Friderica)		Iclaprim	Linezolid
Day 1	Mean ΔQT_{cF}	8.9	2.6
	95% CI	7.90, 9.98	1.51, 3.61
	n > 30ms	16 (3.2%)	4 (0.8%)
	n > 60ms	1 (0.2%)	1 (0.2%)
Day 4 \pm 1	Mean ΔQT_{cF}	10.6	6.1
	95% CI	9.05, 12.18	4.55, 7.68
	n > 30ms	58 (12.1%)	24 (5.0%)
	n > 60ms	3 (0.6%)	2 (0.4%)

Cardiac Adverse Events

- Effects on $\Delta QTcF$ were similar in men and women.
- Patients taking drugs known to prolong QT accounted for 2 of the 3 patients in the iclaprim group who exceeded $\Delta QTcF$ thresholds on Day 4 ± 1 with measurements >60 ms.
- In the combined Phase 3 studies, there were no reported severe AEs, such as torsade de pointes or ventricular arrhythmias related to QTc prolongation, associated with the use of iclaprim for up to 14 days.
- No significant differences were noted in the incidence of abnormal vital signs between the two treatment groups.

Cardiac Adverse Events

Two patients in each treatment group were withdrawn due to QTc prolongation. In the iclaprim group:

- Patient 802-02 was an 81 year-old female with a history of hypertension and peripheral arterial disease. She received only one study dose, and her post-dose mean QTcF increased to 413 ms from a baseline of 405 ms.
- Patient 619-23 received four days of iclaprim, and on the third and fourth day of treatment she had elevations from baseline >60 ms. At the time of the study, she was 56 years of age and had a history of MI, cirrhosis and was on an escalating dose of methadone.

Cardiac Adverse Events

Two deaths may have had a cardiac etiology:

- Patient 306-033, who was “found unconscious”, had two preceding QTcF measurements that were prolonged in post-dose measurements (Δ QTcF on Day 1: +33.7 ms, Day 4: +16 ms)
- Patient 306-034, who was also “found unconscious”, had prolonged QTcF measurements compared to baseline (Δ QTcF on Day 1: +7.3 ms, Day 4: +44 ms)

Hepatic Adverse Events

- Patient 455-007 experienced a serious hepatic AE possibly related to the use of iclaprim.
 - 23 year-old white male, received 10 days of therapy with iclaprim and no other concomitant medications.
 - LFTs were normal from baseline through EOT.
 - At TOC (13 days after his last dose of iclaprim), AST: 314, ALT: 1007, bili: 18.0, alk phos: 122.
 - Abdominal U/S and viral panel was negative.
 - Laboratory values at LFU returned to normal range and he ultimately recovered.

Hepatic Adverse Events

- There were more patients treated with iclaprim who experienced an elevation of ALT $>3xULN$ at TOC (3.9% vs. 2.9%) and LFU (5.3% vs. 1.8%), and slightly more who were found to have elevations in AST $>3xULN$ at LFU (3.3% vs. 2.3%).
- There were no study drug discontinuations due to elevation in aminotransferases, bilirubin or alk phos.
- There were no cases that met criteria for Hy's Law.
- None of the deaths were associated with abnormal liver function tests or indications of hepatotoxicity.

Hematologic Adverse Events

- Anemia was reported as a TEAE in 3.6% patients treated with iclaprim, comparable to linezolid (4.1%).
- There were no reported hematologic AEs associated with premature treatment discontinuation.
- Anemia was an AE associated with the deaths of two patients (306-027 and 306-033) treated with iclaprim; however, patients had multiple co-morbid conditions.
- No meaningful differences were seen between the two groups' hematologic parameters, either outside the normal range or by change in mean values from baseline at each study visit.

Issues for Discussion

- Do the data presented demonstrate the safety and effectiveness of iclaprim for the treatment of cSSSI?
 - If your answer is yes, are there any specific issues that should be addressed in labeling?
 - If your answer is no, what additional data/studies are needed?

Issues for Discussion

- Should there be any limitations on the use of iclaprim? In your response, discuss the following:
 - The comparative outcomes for iclaprim and linezolid from the phase 3 trials
 - The specific clinical situations where iclaprim should be used
 - The basis for any specific restrictions

Acknowledgements

■ Iclaprim Review Team

Charles Bonapace

Peter Coderre

J. Christopher Davi

Mark Gamalo

Scott Komo

Benjamin Lorenz

George Lunn

Rapti Madurawe

Frederic Marsik

Amy Nostrandt

Tatiana Oussova

Sarah Robertson

Wendelyn Schmidt

Thamban Valappil

and Many Others....

Questions for the Committee

Q. 1: Do the data presented demonstrate the safety and effectiveness of iclaprim for the treatment of cSSSI? Please vote Yes/No

- If your answer is yes, are there any specific issues that should be addressed in labeling?
- If your answer is no, what additional data/studies are needed?

Questions for the Committee

Q. 2: Should there be any limitations on the use of iclaprim? Please vote Yes/No. In your response, discuss the following:

- The comparative outcomes for iclaprim and linezolid from the phase 3 trials
- The specific clinical situations where iclaprim should be used
- The basis for any specific restrictions