Safety Review

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Considering Side Effects

- All drugs have side effects
- Drugs are approved when side effects compare favorably to:
  - Efficacy
  - Other drugs labeled for the same indication

Gemifloxacin
Extensive Clinical Trial Program

2002 NDA

- Original Clinical Program (n=6,775)
  - 7-day ABS clinical trials (009,010)
  - 5-day ABS clinical trials (186,206)

2005 sNDA (n=1,344)

  - 5-day CAP (634-001)
  - 5-day open-label ABS (333)
  - Open-label CAP (287)

N=8,119

Ongoing (scheduled interim reports)

  - Phase IV FORCE Study (n=1,821)
  - Prescribing Use Study (n=4,910)
  - U.S. post-marketing experience (n~760,000)

Gemifloxacin
Low Rate of Adverse Events (AEs)

	Overall Gemifloxacin N=8,119		All Comparators N=5,248	
	n	%	n	%
Diarrhea	402	5.0	325	6.2
Headache	345	4.2	273	5.2
Nausea	303	3.7	237	4.5
Rash	283	3.5	59	1.1
Abdominal pain	177	2.2	116	2.2
Dizziness	140	1.7	134	2.6

Gemifloxacin
Low Rate of Adverse Events (AEs)

	Overall Gemifloxacin N=8,119		Gemifloxacin 5-day ABS N=1,122	
	n	%	n	%
Diarrhea	402	5.0	**45**	**4.0**
Headache	345	4.2	**30**	**2.7**
Nausea	303	3.7	**41**	**3.7**
Rash	283	3.5	**29**	**2.6**
Abdominal pain	177	2.2	**8**	**0.7**
Dizziness	140	1.7	**17**	**1.5**

Gemifloxacin

Few Serious AEs / Few Withdrawals Due to AEs

	Overall Gemifloxacin N=8,119		All Comparators N=5,248	
	n	%	n	%
Serious adverse events (SAE)	292	3.6	228	4.3
SAE of rash	7	0.1	1	<0.1
Withdrawals due to AE	290	3.6	226	4.3
Withdrawals due to treatment-related AE	165	2.0	109	2.1
Deaths	40	0.5	30	0.6

Gemifloxacin

Few Serious AEs / Few Withdrawals Due to AEs

	Overall Gemifloxacin N=8,119		Gemifloxacin 5-day ABS N=1,122	
	n	%	n	%
Serious adverse events (SAE)	292	3.6	**43**	**3.8**
SAE of rash	7	0.1	**1**	**0.1**
Withdrawals due to AE	290	3.6	**7**	**0.6**
Withdrawals due to treatment-related AE	165	2.0	**5**	**0.4**
Deaths	40	0.5	**0**	**0.0**

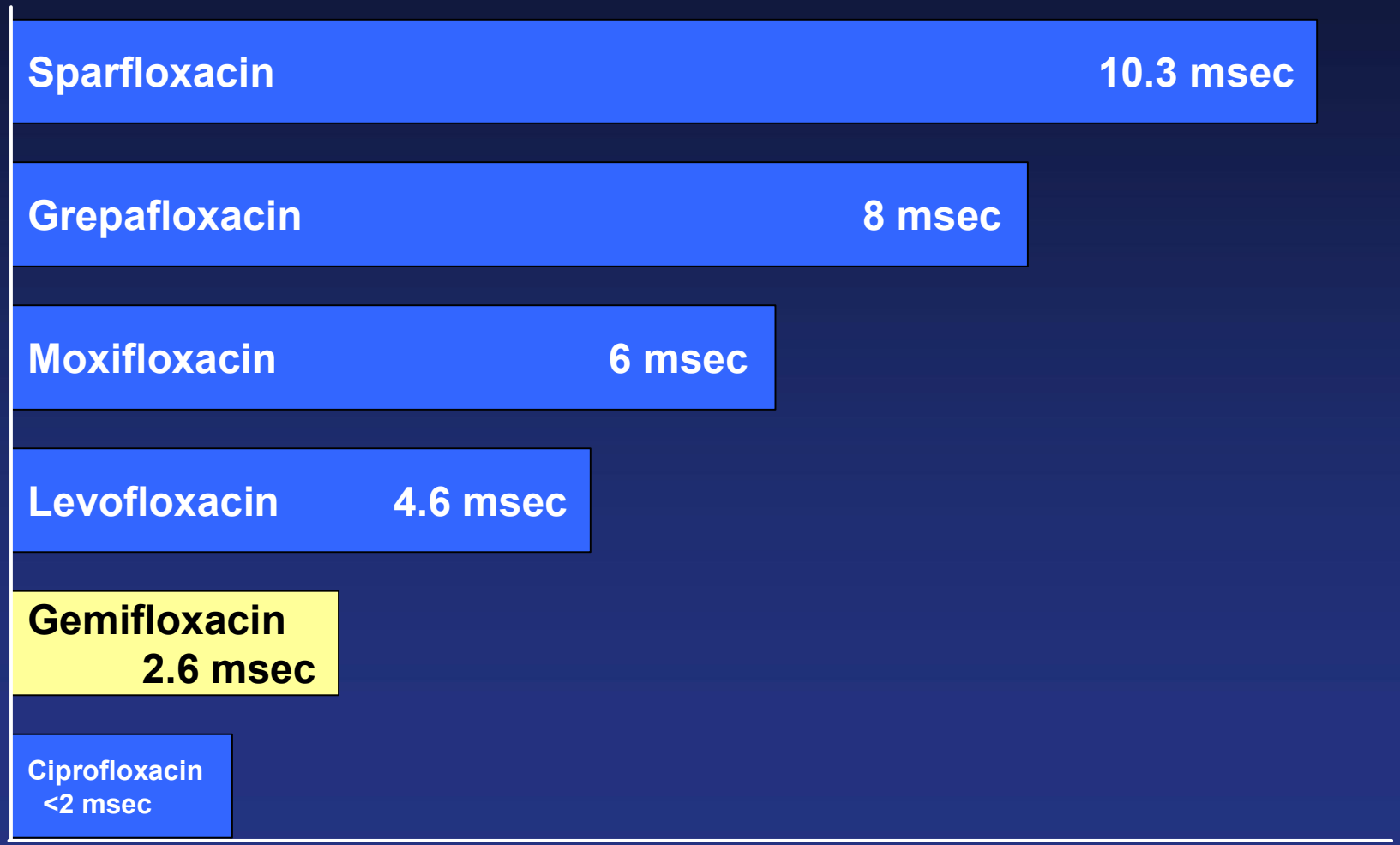
Quinolone Class Effects

Gemifloxacin
Minimal Class Effects

- No cytochrome P450 interaction
- Antacid and sucralfate interactions only
- Low phototoxicity
- No significant dysregulation of glucose homeostasis

Quinolones: Effect on QTc

Gemifloxacin Has Minimal Effect on QTc



Source: Package inserts or publication documenting a more significant prolongation

Hepatic Safety

ALT Values End-of-Therapy
No Signal of Hepatic Safety Issues

Range	Overall Gemifloxacin N=8,000		All Comparators N=5,175	
	n	%	n	%
<ULN	5,706	94.6	3,566	95.8
ULN to <2xULN	278	4.6	129	3.5
2 to <4xULN	39	0.6	27	0.7
4 to <6xULN	6	0.1	2	0.1
6 to <8xULN	0	0	0	0
≥8xULN	0	0	0	0

Patients with pre-treatment normal ALT values

Phase IV Post-Marketing Commitment Study "FORCE"

Factive Outpatient Respiratory Community Experience

FORCE Trial to Evaluate Safety

- Open-label, randomized, active-control
- Evaluate safety in “real-world” setting
  - CAP (gemifloxacin vs. clarithromycin XL)
  - AECB (gemifloxacin vs. amoxicillin/clavulanate)
- Gemifloxacin / active controls
  - 5,000 gemifloxacin / 2,500 active controls

FORCE

Gemifloxacin Low Rate of Adverse Events

	Overall Gemifloxacin N=1,821		All Comparators N=900	
	n	%	n	%
Patients ≥1 AE	**301**	**16.5**	**192**	**21.3**
Diarrhea	35	1.9	61	6.8
Nausea	34	1.9	33	3.7
Rash	33	1.8	5	0.6
Headache	24	1.3	19	2.1

FORCE: Few SAEs, Few Withdrawals Due to AEs

	Overall Gemifloxacin N=1,821		All Comparators N=900	
	n	%	n	%
SAE	35	1.9	21	2.3
SAE of rash	0	0	0	0
Withdrawals due to AE	39	2.1	39	4.3
Deaths	0	0	1	0.1

FORCE: No QTc Effect with Gemifloxacin

	Gemifloxacin N=184	Clarithromycin XL N=96
Mean QTcB Change	-0.1 msec	+1.9 msec
Mean QTcF Change	+4.9 msec	+3.9 msec

Post-Marketing Experience

Domestic Utilization, Crude (not adjudicated) Categorically Serious Report Counts with a Cutaneous Adverse Event, and Reporting Rates for Selected Antimicrobial Products

	Moxifloxacin	Gatifloxacin	Cefditoren	Gemifloxacin	Telitromycin
Approval Date	12/10/99	12/17/99	8/29/01	4/4/03	4/1/04
Estimated dispensed Rx for selected drugs (in 1000s)	5,386	8,237	360	363	5,340
Total reports	226	141	5	38	109
Reporting rate – per million Rx	42	17	14	105	20

Post-Marketing Experience
AE Rates at Comparable Sales Volume

	Gemifloxacin	Moxifloxacin	Gatifloxacin	Cefditoren
Drug Launch	Sept '04	Dec '99	Dec '99	Sept '01
Time period	19 mo	10 mo	6 mo	40 mo
RX's	356,000	376,000	404,000	361,000
AE Rate/1X10^6	2,230	2,085	126	1,141
Cutaneous SAE Rate/1X10^6	101	88	7	77
Overall SAE Rate/1X10^6	208	316	57	296
Death Rate/1X10^6	17	27	5	28

Comparisons of Gemifloxacin's Safety Profile to Other Antibiotics Labeled for ABS

Similarities in Adverse Event Rates from Different NDAs of Antibiotics for ABS

	Gemifloxacin 5-day N=1,122 n / %	Telithromycin 5-day N=675(1) n / %	Levofloxacin 10-day N=626 n / %	Moxifloxacin 10-day N=508 n / %	Gatifloxacin 10-day N=775 n / %
AEs	353 31.5%	141 33.7%	243 38.8%	207 40.7%	422** 54.5%
SAEs	8 0.7%	5 0.7%	3 0.5%	6 1.2%	6 0.8%
Withdrawals due to AEs	7 0.6%	28 4.1%	17 2.7%	18 3.5%	33 4.3%

Source: Levofloxacin SBA; Moxifloxacin SBA; Gatifloxacin SBA; Telithromycin SBA; Gemifloxacin ABS ISS
*FDA medical review of one ABS study (Study 3005) did not provide a total incidence of AEs (only classified by organ class)
**Numbers are for drug-related AEs only
(1) N for Telitrhomycin AEs was 418 patients

Summary
Safety Data is Consistent Across Studies

- Overall clinical trial database (N=8,119)
  - Low rate of AEs, SAEs, discontinuations
  - Low rate of quinolone class effects
  - No significant hepatic or QTc findings
- 5-day ABS clinical safety database (N=1,122)
  Phase IV study (N=1,821)
  - Similar to overall clinical database
- Post-marketing experience (N~760,000)
  - Safety profile similar to clinical trials