Clinical Safety of Moxifloxacin (MFX): an Analysis of "Valid for Safety" Data from Controlled Phase II to Phase IV Studies Performed between 1996 and 2010

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Abstract (edited)

Objectives:
Moxifloxacin (MXF) is approved for the treatment of respiratory tract, skin, pelvic and intra-abdominal infections. Its safety profile is considered favourable in most reviews but has been challenged with respect to rare but potentially fatal adverse reactions. Our objective was to compare the safety profile of MXF with that of comparators using the clinical trial database.

Methods:
Source of data: Double-blind and open-label, actively controlled, Phase II-IV trials (valid for safety patients: *n* = 14,981 [MXF] *vs* 15,023 [comparators; standards of care and/or agreed upon with authorities]) completed between 1996 and 2010 for both approved and other indications, using the recommended MXF dosage (400 mg), administration route (oral, IV-only, or IV/oral), and precautions of use, and including patients at risk (≥ 65 y, diabetes, renal and hepatic impairment, cardiac disorders, BMI <18 kg/m2). Patients with known contraindications were excluded from enrolment by design but any patient having entered a study, even if inappropriately, was included in the analysis.

Analysis: Crude incidences and relative risk estimates (Mantel-Haenszel analysis) of patients with any adverse events (AEs), drug-related adverse events (ADRs), serious adverse events (SAEs), drug-related serious adverse events (SADRs), treatment discontinuation due to AEs and ADRs, fatal outcomes related to AEs and ADRs. Analyses were exploratory in nature and included systematic comparisons between groups and treatments.

Results:
Overall incidence rates of adverse events were similar in MXF and comparator groups, except for AEs and SAEs in IV-only double-blind studies, AEs, ADRs, SADRs in PO, SADRs in IV/PO, and premature discontinuation due to AEs in IV-only open-label studies, which were slightly more frequent in MXF-treated patients (mainly gastrointestinal disorders and "changes observed during investigations" such as asymptomatic QT prolongation). No medically-relevant differences in rates of AEs were seen between MXF and comparators in patients at risk. Incidence rates of hepatic disorders, tendon disorders, surrogates of QT prolongation, serious cutaneous reactions and *Clostridium difficile*-associated diarrhoea were similar with MXF and comparators.

Conclusions:
No higher safety risk for MXF compared to standard therapies was seen in patients receiving the registered MXF dosage and for whom contraindications and precautions of use (as in the product label) were taken into account.

Introduction and Objectives

Moxifloxacin (MXF) is approved for oral and intravenous administration in 123 and 108 countries, respectively, as a once-daily 400 mg antibiotic for the treatment of respiratory tract infections (community-acquired pneumonia [CAP], acute exacerbations of chronic bronchitis [AECB], acute bacterial sinusitis [ABS]) and, depending on the country, pelvic inflammatory disease [PID], complicated and uncomplicated skin and skin structure infections [c/uSSSI] and complicated intra-abdominal infections [cIAI].

An estimated 140 million prescriptions have been issued for MXF worldwide, and the drug is included as an effective alternative in guidelines and/or recommendations for each of these indications.

The safety profile of MXF has, however, been questioned leading to the issue in European countries of '*Dear Healthcare Provider*' letters [1] warning about rare but serious side effects (hepatotoxicity and skin reactions), and a corresponding Statement from the European Medicines Agency [2] accompanied by a label change throughout the European Union.

To gain more insight about the relative risks of MXF-therapy compared to other recommended antibiotics, we decided to perform an in-depth analysis of the manufacturer's clinical trial database for all safety-related events as reported by the investigators for all valid-for-safety patients included in actively controlled studies.

Methods

Studies
- all double-blind and open-label, actively controlled clinical trials performed as part of the Phase II–IV programme (initiated and completed between 1996 and 2010);
- routes of administrations: PO (400 mg tablets), IV (400 mg/250 mL) or IV/PO (sequential);
- diagnosis: PO: streptococcal pharyngitis (1), ABS (10), AECB (17), CAP (12), uSSSIs (4), uPID (3), UTI (4); IV/PO: CAP (7), cSSSIs (3), cIAIs (2), nosocomial pneumonia (2), and lung abscess or aspiration pneumonia (1); IV only: CAP (2), cIAIs (2), AECB (1).

Patients
- geographic origin: Europe, Americas, Middle East, Africa and Asia/Pacific region;
- randomised within an actively controlled clinical trial, with ≥ 1dose and ≥1 observation after initial drug intake;
- including groups with pre-existing risk factors or pathological conditions: elderly (≥65 years); diabetes mellitus; renal insufficiency; hepatic impairment; cardiac disorders; low body mass index (BMI <18 kg/m²);
- excluding patients with contraindications (as known at time of enrolment and/or per product labelling) from entering a study (no patient excluded if having actually entered the study).

Analyses:
- all treatment-emergent events (day 1 through end of follow-up [day 10–27]) with subclassification as adverse events (AEs), adverse drug reactions (ADRs), serious adverse events (SAEs), serious adverse drug reactions (SADRs), premature discontinuations due to AEs, premature discontinuations due to ADRs, AEs with fatal outcome, and ADRs with fatal outcome;
- coding according to the Medical Dictionary for Regulatory Activities (MedDRA; http://www.meddramsso.com/ [version 13.0]). Selected events specifically related to fluoroquinolones were defined by using Standard MedDRA Queries (SMQs) and customized Bayer MedDRA Queries (BMQ);
- causality assessment made by the study investigators;
- descriptive statistical methods with incidence rates calculated as crude rates. Relative risk estimates (with 95% CI) calculated by Mantel–Haenszel analysis [3] stratified by study and with a constant continuity correction term of 0.1 in case of zero value.

Results

1. Population (by route of administration, indication and risk factors)

Parameter	Treatment route					
	PO (n=21298)		IV/PO (n=6846)		IV (n=1860)	
	MXF (n=10613)	COMP (n=10685)	MXF (n=3 431)	COMP (n=3 415)	MXF (n=937)	COMP (n=923)
Age (y) ± SD	48.2 ± 18.0	48.0 ± 17.9	56.8 ± 19.1	56.1 ± 19.2	46.9 ± 17.1	47.1 ± 17.5
BMI (kg/m²) ± SD	26.0 ± 5.9	25.9 ± 5.8	26.9 ± 6.6	26.7 ± 6.4	24.0 ± 4.4	23.9 ± 4.3
Indication (n)						
ABS	2 331	2 641	0	0	0	0
AECB	4 029	3 820	0	0	96	100
CAP	1 790	1 822	1 511	1 539	253	252
uPID	946	919	0	0	0	0
uSSSI	587	582	0	0	0	0
cSSSI	0	0	1130	1077	0	0
cIAI	0	0	618	622	588	571
Other	930	901	172	177	0	0
Risk factor (n)						
Age ≥65 years	2 451	2 403	1 373	1 334	170	191
Diabetic	777	717	926	917	80	72
Renal impairment	1 283	1 229	888	863	203	218
Hepatic impairment	146	163	183	196	46	46
Cardiac disorders	1 476	1 404	1 167	1 136	106	104
BMI <18 kg/m²	318	365	116	115	45	53

2. Main adverse effects (by study design)

A. Double-blind studies

Event	Treatment route					
	PO (n=17465)		IV/PO (n=3745)		IV (n=1159)	
	MXF (n=8822)	COMP (n=8643)	MXF (n=1889)	COMP (n=1856)	MXF (n=588)	COMP (n=571)
AE	3782	3711	1202	1138	**305**	**253**
ADR	2211	2026	455	439	85	83
SAE	318	316	315	282	**74**	**54**
SADR	47	48	53	46	9	7
Prem. disc. due to AE	366	337	144	131	16	9
Prem. disc. due to ADR	261	251	74	63	4	4
AE with fatal outcome	28	36	66	54	21	13
ADR with fatal outcome [a]	3	4	3	3	0	1

[a] **PO:** MXF: pneumonia (2), *Clostridium difficile* colitis and gastrointestinal haemorrhage (1); COMP: acute renal failure, septicaemia and respiratory arrest, viral pneumonia, confusional state;
IV/PO: MXF: acute renal failure and coagulopathy, multi-organ failure, ventricular tachycardia (in the context of an acute myocardial infarction with respiratory failure); COMP: cardio-respiratory arrest (2), acute myocardial infarction and acute respiratory failure;
IV: COMP: multi-organ failure.

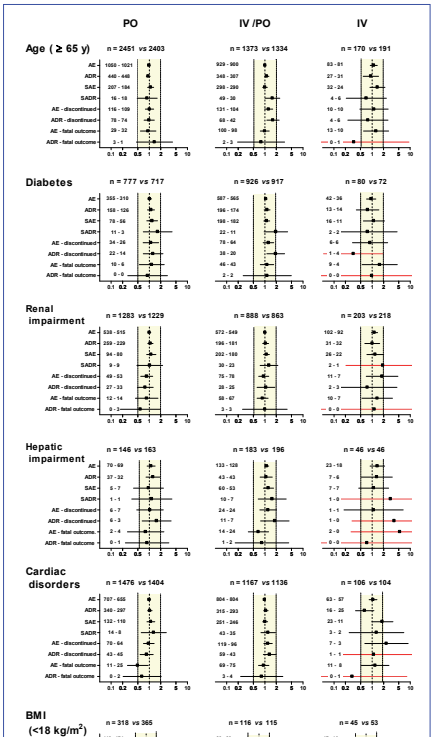
B. Open-label studies

	PO (n=3833)		IV/PO (n=3101)		IV (n=701)	
	MXF (n=1791)	COMP (n=2042)	MXF (n=1542)	COMP (n=1559)	MXF (n=349)	COMP (n=352)
AE	**764**	**766**	891	899	86	84
ADR	**330**	**325**	348	315	49	50
SAE	104	96	280	245	0	1
SADR	**12**	**5**	**42**	**19**	0	0
Premat. disc. due to AE	70	67	137	109	**21**	**11**
Premat. disc. due to ADR	51	49	66	54	17	9
AE with fatal outcome	10	15	64	80	0	0
ADR with fatal outcome [a]	0	0	1	2	0	0

[a] **IV/PO**: MXF: prothrombin time prolonged; COMP: hepatitis (in the context of right ventricular failure, septic shock and acute renal failure) and HIV infection.

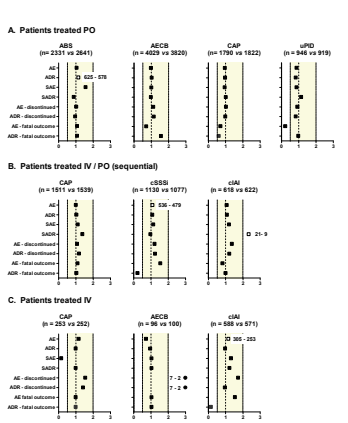
Boxes highlighted in orange denote differences in disfavour of MXF that are ≥2.5% for events with an incidence ≥2.5% in both groups or ≥2-fold for events with incidence <2.5% in one or both groups and for which the number of patients experiencing an event was ≥10 in either group.
Prem. disc.: premature discontinuation

3. Relative risk estimates (for patients at risk)



Relative risk estimate (moxifloxacin / comparator)
horizontal bars: 95 % CI (red if extending beyond 0.1 and/or 10).

4. Relative risk estimates (by indication)



Relative risk estimate (moxifloxacin / comparator)
Circles: values >3 (with number of patients). Open symbols: lower limit of the 95% CI interval >1 (higher risk for MXF; with number of patients)

5. Other key findings

Differences in numbers of ADR (MXF *vs* COMP)
if occurring in ≥0.5% of patients and (i) with differences ≥2.5% for incidences ≥2.5% or ≥2-fold for incidence <2.5%, and (ii) occurring in ≥10 in either group

- in disfavour of MXF:
  Double-blind: nausea (IV: 12 *vs* 3);
  Open-label: ECG QT prolonged (IV/PO: 19 *vs* 3); dizziness (PO: 30 *vs* 4; IV/PO: 10 *vs* 2); dysgeusia (PO: 13 *vs* 2); somnolence (PO: 10 *vs* 2); rash (PO: 16 *vs* 8);
- in disfavour of COMP:
  Double-blind: vomiting (IV/PO: 13 *vs* 26); GGT increased (PO: 11 *vs* 30); dysgeusia (PO: 66 *vs* 171);
  Open-label: diarrhoea (PO: 54 *vs* 141).

Differences in numbers of SADR by organ class (MXF *vs* COMP; all studies)
if ≥2-fold difference and in ≥ 10 patients

- in disfavour of MXF:
  gastrointestinal disorders (IV/PO: 15 *vs* 7); investigations (IV/PO: 23 vs7);
- in disfavour of COMP:
  cardiac disorders (IV/PO: 5 *vs* 11).

Incidence of selected treatment-emergent AE (MXF *vs* COMP; all studies)
by SMQ/BMQ and most preferred terms; if ≥ 0.5%, ≥2-fold difference and ≥10 patients

in disfavour of MXF:
- hepatic function abnormal (PO: 18 *vs* 9, but SADR similar or equivalent);
- depression (IV/PO: 19 vs 6);
- adverse event considered relevant as clinical outcome of QT_c prolongation (IV: 10 *vs* 2; mostly driven by cardiac arrest [8 vs 2, but only 1 case considered as due to the investigation drug]);

neutral (no differences with respect to the criteria defined above)
- severe cutaneous adverse reactions: 49 *vs* 52 (all routes; mostly non-serious; 1 case of Stevens Johnson syndrome);
- adverse events considered as relevant clinical outcome of QTc prolongation (PO: 25 *vs* 23; IV/PO: 37 *vs* 36; IV: see above);
- tendinopathies (PO: 11 *vs* 10; IV/PO: 3 *vs* 2; IV: 0 *vs* 0);
- *Clostridium difficile*-associated diarrhoea (PO: 2 *vs* 5; IV/PO: 19 *vs* 14; IV: 1 *vs* 1)
- anaphylactic reactions (PO: 3 *vs* 3; IV/PO: 9 *vs* 5; IV: 0 *vs* 0)

Discussion and Conclusions

Comprehensive safety data originating from Industry-sponsored controlled studies are usually communicated to regulatory authorities only (Registration applications, Periodic Safety Update Reports, Risk Management Plans) and remain, therefore, largely unknown to clinicians. The benefit of using pooled randomised active-controlled clinical trial data, however, is that risks associated with the study drug can be directly compared with those of clinically valid comparators. Because patients are randomised, groups should be equally balanced with respect to known as well as unknown factors associated with the outcome variables, making comparisons between treatment groups as fair as possible.

Based on the presented data, MXF shows essentially a similar safety profile than comparator therapies (stratification of comparator(s) by antibiotic class [not shown here] did not reveal meaningful additional differences). In cases where MXF caused more untoward effects than COMP, the actual numbers of affected patients were close to those seen with COMP and/or differences were small if considering the denominators (number of patients treated). In several situations, COMP caused more untoward effects than MXF especially for ADR in the double-blind studies.

ADR incidence across treatment groups was low, even though patients with risk factors were included in the studies, which is consistent with trials conducted during a Phase II–IV development programme. Moreover, selected events commonly associated with fluoroquinolones were not seen in excess in moxifloxacin-treated patients.

We conclude that moxifloxacin safety in these trials was comparable to that of standard therapies for patients receiving the currently registered dosage and for whom contraindications and precautions of use (as in the product label or as known at enrolment time) were taken into account.

References

1. Bayer Schering Pharma - Bayer plc. 2008. Direct Healthcare Professional Communication regarding moxifloxacin (Avelox®) and serious hepatic and bullous skin reactions. Medicines and Healthcare products Regulatory Agency, London, U.K. (http://www.mhra.gov.uk) (similar letters in other EU countries)
2. Moxifloxacin. 2007. European Medicines Agency, London, U.K. (http://www.ema.europa.eu)
3. Greenland & Robins JM. Biometrics 1985; 41: 55-68.

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