PACKAGE INSERT - ERELAN

1. NAME OF THE MEDICINAL PRODUCT

Erelan 400mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 400mg moxifloxacin (as hydrochloride).

Excipient(s) with known effect: lactose monohydrate. Each film-coated tablet contains 68 mg lactose monohydrate.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
Red, oval-shaped, biconvex film coated tablets embossed "MC" with dimensions of nucleus 17.6mmx8mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Erelan 400 mg film-coated tablets are indicated for the treatment of adults (≥ 18 years of age) with the following bacterial infections caused by susceptible strains:

- Acute sinusitis
- Acute exacerbation of chronic bronchitis
- Community acquired pneumonia
- Mild to moderately severe inflammatory pelvic diseases (i.e. Infections of the upper female genital tract, including salpingitis and endometritis), without an associated tubo-ovarian or pelvic abscess.
  Erelan 400mg film-coated tablets are not recommended for monotherapy of mild to moderately severe inflammatory pelvic diseases. Preferably, they should be administered in combination with another suited antibiotic (such as cephalosporin), due to the increasing resistance of *Neisseria gonorrhoeae* to moxifloxacin; that is, unless moxifloxacin-resistant Neisseria gonorrhoeae can be ruled out.
- Complicated skin and skin structure infections
- Complicated intra-abdominal infections including polymicrobial infections such as abscesses

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Erelan should be only used:

- When *Pseudomonas fluorescens* is considered AND the patient is allergic to antipseudomonal penicillins/cephalosporin; or
- For resistant organism with other alternative antibiotics available (see section "*Pharmacodybamic properties*" for susceptibility data).

Erelan should not be used >24 hours post operation.

4.2 Posology and method of administration

Posology
Adults
The recommended dose for Erelan is 400mg once daily (1 film-coated tablet) for the above mentioned indications and should not be exceeded.

Method of administration
The film-coated tablet should be swallowed whole with sufficient liquid and may be taken independent of meals.

Missed dose
If a dose is missed, it should be taken anytime but not later than 8 hours prior to the next scheduled dose. If less than 8 hours remain before the next dose, the missed dose should not be taken and treatment should be continued as prescribed with the next scheduled dose. Double doses should not be taken to compensate for a missed dose.

Geriatric patients
No adjustment of dosage is required in the elderly

Pediatric patients
The efficacy of Erelan in children and adolescents has not been established. No recommendation on posology can be made.
The safety of Erelan in children below the age of 6 years has not been established.

Ethnic differences
No adjustment of dosage is required in ethnic groups.

Patients with hepatic impairment
No dosage adjustment is required in patients with impaired liver function (see also "*Special warnings and precautions for use*" in patients with liver cirrhosis).

Patient with renal impairment
No dose adjustment is required in patients with renal impairment (including creatinine clearance ≤ 30 mL/min/1.73m^2) and in patients on chronic dialysis i.e. hemodialysis and continuous ambulatory peritoneal dialysis.

Duration of administration
The duration of treatment should be determined by the severity of the indication or clinical response. The following general recommendations for the treatment of upper and lower respiratory tract infections are made:
Bronchitis: acute exacerbation of chronic bronchitis, 5 days
Pneumonia: community acquired pneumonia, 10 days
Sinusitis: acute sinusitis, 7 days
Mild to moderately severe inflammatory pelvic diseases: 14 days
Complicated skin and skin structure infections total treatment duration for sequential therapy (intravenous followed by oral therapy): 7 – 21 days
Complicated intraabdominal infections total treatment duration for sequential therapy (intravenous followed by oral therapy): 5 – 14 days

4.3 Contraindications

Known hypersensitivity to moxifloxacin or other quinolones or any of the excipients. Pregnancy and lactation.

4.4 Special warnings and precautions for use

The use of moxifloxacin should be avoided in patients who have experienced serious adverse reactions in the past when using fluoroquinolone containing products (see section "*Undesirable effects*"). Treatment of these patients with moxifloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment.

Hypersensitivity
In some instances, the hypersensitivity and allergic reactions already occurred after the first administration, and the doctor should be informed immediately.
Anaphylactic reactions in very rare instances can progress to a life-threatening shock, in some instances after the first administration. In these cases, the treatment with Erelan has to be discontinued, medical treatment (e.g. treatment for shock) is required.
Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with Erelan (see section "*Undesirable Effects*"). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Cardiac disorders
Erelan has been shown to prolong the QT interval of the electrocardiogram in some patients. As women tend to have a longer baseline QTc interval compared with men, they may be more sensitive to QTc-prolonging medications. Elderly patients may also be more susceptible to drug-associated effects on the QT interval.
As the magnitude of QT prolongation may increase with increasing concentrations of the drug, the recommended dose and the infusion rate (400 mg within 60 minutes) should not be exceeded. However, in patients suffering from pneumonia no correlation between plasma concentrations of moxifloxacin and QTc prolongation was observed. QT prolongation may lead to an increased risk for ventricular arrhythmias including torsades de pointes. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with Erelan treatment in clinical studies with more than 9000 patients, however certain predisposing conditions may increase the risk for ventricular arrhythmias.

Therefore, treatment with Erelan should be avoided due to the lack of clinical experience with the drug in these patient populations:
- In patients with known prolongation of QT interval
- In patients with uncorrected hypokalemia
- In patients receiving class IA (e.g. quinidine, procainamide) or class III (e.g. amiodarone, sotalol) antiarrhythmic agents

Erelan should be used with caution as an additive effect of Erelan on the QT interval cannot be excluded for the following conditions:
- In patients treated concomitantly with drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics and tricyclic antidepressants
- In patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia, acute myocardial ischemia
- In patients with liver cirrhosis as pre-existing QT prolongation in these patients cannot be excluded
- In women and elderly patients who, both, may be more susceptible to QTc- prolonging drugs

Hepatobiliary system
Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with moxifloxacin (see section "*Undesirable Effects*"). Patients should be advised to contact their doctor immediately prior to continuing treatment if symptoms related to liver failure occur.

Seizures
Seizures may occur with quinolone therapy. It should be used with caution in patients with known or suspected Central Nervous System (CNS) disorders which may predispose to seizures or lower the seizure threshold.

Gastrointestinal system
Antibiotic associated colitis has been reported with the use of broad-spectrum antibiotics including Erelan; therefore it is important to consider this diagnosis in patients who develop serious diarrhoea in association with the use of Erelan. In this clinical situation adequate therapeutic measures should be initiated immediately. Drugs inhibiting peristalsis are contraindicated in patients who develop serious diarrhoea.

Myasthenia gravis
Erelan should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated. Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in person with myasthenia gravis. Post marketing serious adverse events, including deaths and requirement for ventilator support have been associated with fluoroquinolones use in persons with myasthenia gravis. Avoid fluoroquinolones in patients with known history of myasthenia gravis.

Prolonged, disabling and potentially irreversible serious adverse drug reactions
Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse reactions affecting different, sometimes multiple body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving fluoroquinolones irrespective of their age and pre-existing risk factors. Erelan should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.

Tendinitis and tendon rupture
Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients (above 60 years of age), patients with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.
At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with moxifloxacin should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

Aortic aneurysm and dissection
Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population. Therefore fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).
In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Complicated pelvic inflammatory disease
For patients with complicated pelvic inflammatory disease (e.g. associated with a tubo-ovarian or pelvic abscess), for whom an intravenous treatment is considered necessary, treatment with Erelan 400 mg film-coated tablets is not recommended.

MRSA infections
Moxifloxacin is not recommended for the treatment of MRSA infections. In case of a suspected or confirmed infection due to MRSA, treatment with an appropriate antibacterial agent should be started (see “Pharmacodynamic properties”)

Interaction with tests

Moxifloxacin in vitro activity may interfere with the Mycobacterium spp. culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking Erelan.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with Erelan should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent development of potentially irreversible condition (see "Undesirable effects").

Psychiatric reactions

Psychiatric reactions may occur even after the first administration of fluoroquinolones, including moxifloxacin. In very rare cases depression or psychotic reactions have progressed to suicidal thoughts and self-injurious behaviour such as suicide attempts (see "Undesirable effects"). In the event that the patient develops these reactions, moxifloxacin should be discontinued and appropriate measures instituted. Caution is recommended if moxifloxacin is to be used in psychotic patients or in patients with history of psychiatric disease.

Genital tract infections

Because of the widespread and rising prevalence of fluoroquinolone-resistant *Neisseria gonorrhoeae* infections, monotherapy with moxifloxacin should be avoided in patients with pelvic inflammatory disease, unless fluoroquinolone-resistant *N. gonorrhoeae* can be excluded. If fluoroquinolone-resistant *N. gonorrhoeae* cannot be excluded, the addition of an appropriate antibiotic which is regularly active against *N. gonorrhoeae* (e.g., a cephalosporin) to empirical moxifloxacin therapy, should be considered.

Dysglycemia

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycemia and hyperglycemia have been reported with moxifloxacin. In moxifloxacin-treated patients, dysglycemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g. sulfonylurea) or with insulin. In diabetic patients, careful monitoring of blood glucose is recommended (see "Undesirable effects").

Information about excipients

This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

For the following substances, absence of a clinically relevant interaction with Erelan was proven: atenolol, ranitidine, calcium supplements, theophylline, oral contraceptives, glibenclamide, itraconazole, digoxin, morphine, probenecid. No dose adjustment is necessary for these drugs.

Antacids, minerals and multi-vitamins

Concomitant ingestion of Erelan together with antacids, minerals and multi-vitamins may result in impaired absorption of moxifloxacin after oral administration due to formation of chelate complexes with the multi-valent cations contained in these preparations. This may lead to plasma concentrations considerably lower than desired. Hence, antacids, anti-retroviral drugs (e.g. didanosine), and other preparations containing magnesium or aluminum, sucralfate and agents containing iron or zinc should be administered at least 4 hours before or 2 hours after ingestion of an oral moxifloxacin dose.

Warfarin
No interaction during concomitant treatment with warfarin on pharmacokinetics, prothrombin time and other coagulation parameters has been observed.

Changes in INR (International Normalized Ratio): Cases of increased anticoagulant activity have been reported in patients receiving anticoagulants concurrently with antibiotics, including Erelan. The infectious disease (and its accompanying inflammatory process), age and general status of the patient are risk factors. Although an interaction between Erelan and warfarin was not demonstrated in clinical trials, INR monitoring should be performed and, if necessary, the oral anticoagulant dosage should be adjusted as appropriate.

Digoxin
The pharmacokinetics of digoxin are not significantly influenced by moxifloxacin and vice versa. After repeated dosing in healthy volunteers Erelan increased C_{max} of digoxin by approximately 30 % at steady state without affecting AUC or trough levels.

Charcoal
Concomitant dosing of charcoal and 400 mg oral Erelan reduced the systemic availability of the drug by more than 80 % by preventing absorption *in vivo*. The application of activated charcoal in the early absorption phase prevents further increase of systemic exposure in cases of overdose.
After intravenous drug administration carbo medicinalis only slightly reduces systemic exposure (approx. 20%).

Food and dairy products
Absorption of moxifloxacin was not altered by food intake (including dairy products).
Erelan can be taken independent from food intake.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of moxifloxacin in human pregnancy has not been evaluated. Reversible joint injuries are described in children receiving some fluoroquinolones, however this effect has not been reported as occurring on exposed foetuses. Animal studies have shown reproductive toxicity. The potential risk for humans is unknown.
Consequently, the use of Erelan during pregnancy is contraindicated.

Lactation
As with other fluoroquinolones, Erelan has been shown to cause lesions in the cartilage of the weight bearing joints of immature animals. Preclinical evidence indicates that small amounts of moxifloxacin may be secreted in human milk. There is no data available in lactating or nursing women. Therefore, the use of Erelan in nursing mothers is contraindicated.

4.7 Effects on ability to drive and use machines

Fluoroquinolones including moxifloxacin may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions and vision disorders (see section "*Undesirable Effects*").

4.8 Undesirable effects

Tabulated list of adverse reactions
Adverse drug reactions (ADRs) based on all clinical trials with moxifloxacin 400mg (oral and sequential [IV/oral]/intravenous only administration) sorted by CIOMS III categories of frequency (overall n=17,951, including n=4,583 from sequential/intravenous therapy studies, status: May 2010) are listed below:

ADRs listed under "common" were observed with a frequency below 3% with the exception of nausea and diarrhoea.
ADRs derived from post marketing reports (status: May 2010) are printed in *bold italic*.
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Frequencies are defined as: common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

System Organ Class (MedDRA)	**Common**	**Uncommon**	**Rare**	**Very Rare**
Infections and infestations	Mycotic superinfections			
Blood and lymphatic system disorders		Anaemia Leucopenia(s) Neutropenia Thrombocytopenia Thrombocythemia Prothrombin time prolonged/INR increased	Thromboplastin level abnormal	Prothrombin level increased/INR decreased Prothrombin level/INR abnormal
Immune system disorders		Allergic reaction Pruritus Rash Urticaria Blood eosinophilia	Anaphylactic / anaphylactoid reaction Allergic edema / angioedema (incl. laryngeal edema, potentially life threatening)	Anaphylactic / anaphylactoid shock (potentially life threatening)
Metabolism and nutrition disorders		Hyperlipidemia	Hyperglycemia Hyperuricemia	Hypoglycemia
Psychiatric disorders#		Anxiety reactions Psychomotor hyperactivity / agitation	Emotional lability Depression (*in very rare cases potentially culminating in self-injurious behaviour, such as suicidal ideation / thoughts or suicide attempts*) Hallucinations	Depersonalization Psychotic reactions (*potentially culminating in self-injurious behaviour, such as suicical ideation / thoughts or suicide attempts*)
Nervous system disorders#	Headache Dizziness	Par-and Dysesthesia Taste disorders (inclu. ageusia in very rare cases) Confusion and disorientation Sleep disorders Tremor Vertigo Somnolence	Hypoesthesia Smell disorders (incl. anosmia) Abnormal dreams Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo; *in very rare cases leading to fall with injuries, esp. in elderly)* Seizures of various clinical	Hyperesthesia

			manifestations (incl. grand mal convulsions) Disturbed attention Speech disorders Amnesia Peripheral neuropathy and polyneuropathy	
Eye disorders#		Visual disturbances (especially in the course of CNS reactions)		Transient loss of vision (especially in the course of CNS reactions)
Ear and labyrinth disorders#			Tinnitus Hearing impairment including deafness (usually reversible)	
Cardiovascular system disorders	QT prolongation in patients with hypokalaemia	QT prolongation Palpitations Tachycardia Vasodilatation	Ventricular tachyarrhythmias Syncope Hypertension Hypotension	Unspecified arrhythmias *Torsade de Pointes* ** *Cardiac arrest* ** ** *(especially in patients with severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischemia)*
Respiratory, thoracic and mediastinal disorders		Dyspnea (including asthmatic conditions)		
Gastrointestinal disorders	Nausea Vomiting Gastrointestinal and abdominal pains Diarrhea	Decreased appetite and food intake Constipation Dyspepsia Flatulence Gastroenteritis (excl. erosive gastroenteritis) Increased amylase	Dysphagia Stomatitis Antibiotic associated colitis (in very rare cases associated with life threatening complications)	
Hepato-biliary disorders	Increase in transaminases	Hepatic impairment (incl. LDH increase) Increased bilirubin Increased gammaglutamyltransferase Increase in blood alkaline	Jaundice Hepatitis (predominantly cholestatic)	*Fulminant hepatitis potentially leading to life-threatening liver failure(incl. fatal cases)*

		phosphatase		
Skin and subcutanoues tissue disorders				*Bullous skin reactions like Stevens-Johnson-Syndrome or Toxic Epidermal Necrolysis (potentially life threatening)*
Musculoskeletal, connective tissue and bone disorders#		Arthralgia Myalgia	Tendonitis Increased muscle tone and cramping Muscular weakness	*Tendon rupture* Arthritis *Gait disturbance (caused by muscular, tendon or joint symptoms)* *Exacerbation of symptoms of myasthenia gravis*
Renal and urinary disorders		*Dehydration (caused by diarrhea or reduced fluid intake)*	Renal impairment Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders)	
General disorders and administration site conditions#	Injection and infusion site reactions	Feeling unwell Unspecific pain Sweating Infusion site (thrombo-) phlebitis		

#Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of fluoroquinolones in some cases irrespective of pre-existing risk factors (see "Warning and Precautions").

In isolated instances, some serious adverse drug reactions may be long-lasting (> 30 days) and disabling: such as tendinitis, tendon rupture, musculoskeletal disorders, and other reactions affecting the nervous system including psychiatric disorders and disturbances of senses.

The following undesirable effects have a higher frequency in the subgroup of IV/oral sequentially treated patients:

Common:	Increased gamma-glutamyl-transferase
Uncommon:	Ventricular tachyarrhythmias, Hypotension, Edema, Antibiotic associated colitis (in very rare cases associated with life threatening complications), Seizures of various clinical manifestations (incl. grand mal convulsions), Hallucinations, Renal impairment and Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders

Post Market Experience
Exacerbation of symptoms of myasthenia gravis

Additional information on special populations
Pediatric patients
Adverse reactions in children (>3 months - <18 years) were derived from a clinical study in pediatric patients with complicated intra-abdominal infection. For the safety analysis, data from a total of 301 pediatric patients treated with moxifloxacin were available, thereof 15 patients below the age of 6 years and 286 patients at the age of 6 - <18 years.

Cartilage damage of weight-bearing joints in juvenile animals is a known class effect of fluoroquinolones. Therefore, musculoskeletal events were carefully monitored and followed up over 1 year after the study treatment. The musculoskeletal adverse events observed in the study were mostly rated as mild in intensity, and were equally distributed among the moxifloxacin and the comparator groups. There were no events indicating chondropathy.

Moxifloxacin has been shown to prolong the QT interval of the electrocardiogram in some patients (see Special warnings and precautions for use). The ECG analyses in pediatric patients revealed that QT prolongation is common. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with moxifloxacin treatment in the pediatric study. For specific warnings and precautions for use referring to QT prolongation, see Special warnings and precautions for use.

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults. Sub-set analyses by age groups did not reveal any age-related exceptions. However, the low number of children below the age of 6 years limits the analysis of adverse reactions in younger children.

4.9 Overdose

Only limited data on overdose are available. Single doses of up to 1200 mg and multiple doses of 600 mg moxifloxacin over 10 days were administered to healthy subjects without any significant undesirable effects. In the event of overdosage, it is recommended that appropriate supportive care including ECG measurements should be instituted as dictated by the patient's clinical status.

The use of charcoal early after oral administration may be useful to prevent excessive increase of systemic exposure to moxifloxacin in cases of overdosage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Quinolone antibacterials; Fluoroquinolones
ATC code: J01MA14.

Mechanism of action
Moxifloxacin is a 8-methoxy-fluoroquinolone antibiotic with a broad spectrum of activity and bactericidal action. Moxifloxacin has in vitro activity against a wide range of gram-positive and gram-negative organisms, anaerobes, acid-fast bacteria, and atypicals e.g. *Chlamydia* spp., *Mycoplasma* spp. and *Legionella* spp.
The bactericidal action results from the interference with topoisomerase II and IV. Topoisomerases are essential enzymes which control DNA topology and assist in DNA replication, repair and transcription. Moxifloxacin exhibits concentration dependent bactericidal killing. Minimum bactericidal concentrations are generally similar to minimum inhibitory concentrations.
Moxifloxacin is effective against β-lactam and macrolide resistant bacteria. Studies in animal models of infection have demonstrated high *in vivo* activity.

Resistance
Resistance mechanisms which inactivate penicillins, cephalosporins, aminoglycosides, macrolides and tetracyclines do not interfere with the antibacterial activity of moxifloxacin. There is no cross resistance between moxifloxacin and these agents. Plasmid-mediated resistance has not been observed to date.
It appears that the C8-methoxy moiety contributes to enhanced activity and lower selection of resistant mutants of gram-positive bacteria compared to the C8-H moiety. The presence of the bulky bicycloamine substituent at the C-7 position prevents active efflux, a mechanism of fluoroquinolone resistance.
In vitro studies have demonstrated that resistance to moxifloxacin develops slowly by multiple step mutations. A very low overall frequency of resistance was demonstrated (10^{-7} – 10^{-10}). Serial exposure of organisms to sub-MIC concentrations of moxifloxacin showed only a small increase in MIC values. Cross resistance among fluoroquinolones has been observed. However, some gram-positive and anaerobic organisms resistant to other fluoroquinolones are susceptible to moxifloxacin.

Effect on the intestinal flora in humans
In two volunteer studies, the following changes in the intestinal flora were seen following oral dosing with moxifloxacin. *E. coli*, *Bacillus* spp., *Bacteroides vulgatus*, *Enterococci*, and *Klebsiella* spp. were reduced, as were the anaerobes *Bifidobacterium*, *Eubacterium*, and *Peptostreptococcus*. These changes returned to normal within two weeks. *Clostridium difficile* toxin was not found.

***In vitro* Susceptibility Data**

Susceptible	**Intermediate**	**Resistant**
Gram-positive bacteria		
Gardnerella vaginalis		
*Streptococcus pneumoniae** including multi-drug resistant streptococcus pneumoniae strains [MDRSP] including strains known as PRSP (Penicillin-resistant *S. pneumoniae*), and strains resistant to two or more of the following antibiotics: penicillin (MIC ≥ 2 µg/mL), 2nd generation cephalosporins (e.g., cefuroxime),		

macrolides, tetracyclines, and trimethoprim/sulfamethoxazole		
*Streptococcus pyogenes (group A)**		
Streptococcus milleri group (S. anginosus*, *S. constellatus**, and *S. intermedius*)*		
Streptococcus viridans group *(S. viridans, S. mutans, S. mitis, S. sanguinis, S. salivarius, S. thermophilus, S. constellatus)*		
Streptococcus agalactiae		
Streptococcus dysgalactiae		
Staphylococcus aureus (methicillin susceptible strains) *		*Staphylococcus aureus* (methicillin/ofloxacin resistant strains) [+]
Coagulase negative Staphylococci (*S. cohnii* , S. epidermidis, *S. haemolyticus*, *S. hominis*, *S. saprophyticus*, *S. simulans*) methicillin susceptible strains.		Coagulase negative Staphylococci (S. *cohnii*, *S. epidermidis*, *S. haemolyticus*, *S. hominis, S. saprophyticus, S. simulans*) methicillin resistant strains
	*Enterococcus faecalis** (Vancomycin,Gentamycin, susceptible strains only)	
	*Enterococcus avium**	
	*Enterococcus faecium**	

*/** Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications

[+] Erelan is not recommended for the treatment of methicillin resistant *S. aureus* (MRSA) infections. In case of a suspected or confirmed infection due to MRSA, treatment with an appropriate antibacterial agent should be started.

Susceptible	**Intermediate**	**Resistant**
Gram-negative bacteria		
*Haemophilus influenzae (including ß lactamase negative and positive strains)**		
*Haemophilus parainfluenzae**		
*Moraxella catarrhalis (including ß lactamase negative and positive strains)**		
Bordetella pertussis		
Legionella pneumophila	*Escherichia coli **	
Acinetobacter baumanii	*Klebsiella pneumoniae **	
	Klebsiella oxytoca	
	*Citrobacter freundii**	

	Enterobacter species (*E. aerogenes, E. intermedius, E. sakazaki*)	
	Enterobacter cloacae *	
	Pantoea agglomerans	
		Pseudomonas aeruginosa
	Pseudomonas fluorescens	
	Burkholderia cepacia	
	Stenotrophomonas maltophilia	
	*Proteus mirabilis**	
Proteus vulgaris		
	Morganella morganii	
	*Neisseria gonorrhoea***	
	Providencia species (*P. rettgeri*, *P. stuartii*)	
Yersinia pestis		

*/** Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications

Susceptible	**Intermediate**	**Resistant**
Anaerobes		
	Bacteroides sp (B. fragilis, B. distasoni*, B. thetaiotaomicron*, B. ovatus*, B. uniformis*, B. vulgaris*)*	
Fusobacterium spp		
	Peptostreptococcus spp. *	
Porphyromonas spp		
Prevotella spp		
Propionibacterium spp.	*Clostridium sp* *	

*/ Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications

Susceptible	**Intermediate**	**Resistant**
Atypicals		
*Chlamydia pneumoniae**		
*Chlamydia trachomatis***		
*Mycoplasma pneumoniae**		
Mycoplasma hominis		
Mycoplasma genitalum		
Coxiella burnettii		

*/** Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications

The frequency of acquired resistance may vary geographically and with time for certain species. Local area information on resistance of organisms is desirable, particularly when treating severe infections. The above information is provided as a guide on the probability of an organism being susceptible to moxifloxacin.

Comparison of PK/PD surrogates for intravenous and oral administration of a 400 mg Erelan single dose.

In patients requiring hospitalisation AUC/MIC_{90} parameters greater than 125 and C_{max} / MIC_{90} of 8 – 10 is predictive for clinical cure (Schentag). In outpatients these surrogate parameters are generally smaller, i.e. AUC/MIC_{90} greater than 30-40 (Dudley and Ambrose).

The following table provides the respective PK/PD surrogates for intravenous and oral administration of 400 mg moxifloxacin calculated from single dose data:

Mode of administration	**Intravenous**		**Oral**	
Parameter (median)	AUIC [h]	C_{max}/MIC_{90} [a)]	AUIC [h]	C_{max}/MIC_{90}
MIC_{90} 0.125 mg/L	313	32.5	279	23.6
MIC_{90} 0.25 mg/L	156	16.2	140	11.8
MIC_{90} 0.5 mg/L	78	8.1	70	5.9

[a)]1h infusion

4.10 Pharmacokinetic properties

Absorption and Bioavailability

Following oral administration, moxifloxacin is rapidly and almost completely absorbed. The absolute bioavailability amounts to approximately 91%.

Pharmacokinetics are linear in the range of 50 - 1200 mg single dose and up to 600 mg once daily dosing over 10 days. Steady state is reached within 3 days. Following a 400 mg oral dose peak concentrations of 3.1 mg/l are reached within 0.5 - 4 hours post administration. Peak and trough plasma concentrations at steady-state (400 mg once daily) were 3.2 and 0.6 mg/l, respectively.

Concomitant administration of moxifloxacin together with food slightly prolongs the time to reach peak concentrations by approximately 2 hours and slightly reduced peak concentrations by approximately 16%. Extent of absorption remained unchanged. As AUC/MIC is most predictive for antimicrobial efficacy of fluoroquinolones, this effect is clinically not relevant. Therefore, Erelan can be administered independently from meals.

After a single 400 mg intravenous 1 hour infusion peak concentrations of approximately 4.1 mg/L were reached in the plasma at the end of infusion which corresponds to a mean increase of approx. 26 % relative to the oral application. Exposure to drug in terms of AUC at a value of approximately 39 mg*h/L is only slightly higher compared to the exposure after oral administration (35 mg*h/L) in accordance with the absolute bioavailability of approximately 91%.

Following multiple intravenous dosing (1hour infusion), peak and trough plasma concentrations at steady state (400 mg once daily) were between 4.1 to 5.9 and 0.43 to 0.84 mg/L respectively. At steady-state the exposure to drug within the dosing interval is approximately 30 % higher than after the first dose. In patients mean steady state concentrations of 4.4 mg/L were observed at the end of a 1hour infusion.

Distribution

Moxifloxacin is distributed very rapidly to extra vascular spaces. Exposure to drug in terms of AUC (AUC_{norm}=6 kg*h/L) is high with a volume of distribution at steady state (V_{ss}) of approximately 2 L/kg. In saliva peak concentrations higher than those of plasma may be reached. In *in vitro* and *ex vivo* experiments over a range of 0.02 to 2 mg/L a protein binding of approximately 45 % independent from the concentration of the drug was determined. Moxifloxacin is mainly bound to serum albumin. Due to this low value high free peak concentrations > 10x MIC are observed.

Moxifloxacin reaches high concentrations in tissues like lung (epithelial fluid, alveolar macrophages, biotic tissue), the sinuses (maxillary and ethmoid sinus, nasal polypi) and inflamed lesions (cantharide blister fluid) where total concentrations exceeding those of the plasma concentrations are reached. High free drug concentrations are measured in interstitial body water (saliva, intramuscular, subcutaneous). In addition, high drug concentrations were detected in abdominal tissues and fluids and female genital tract.

Peak concentrations of moxifloxacin found in human tissues following oral administration of a 400 mg single dose (geom. mean):

Tissue	**Concentration (p.o)**	**Site:Plasma ratio (p.o)**
Plasma	3.1 mg/l	-
Saliva	3.6 mg/l	0.75 - 1.3
Blister fluid	1.6[1] mg/l	1.7[1]
Bronchial mucosa	5.4 mg/kg	1.7 - 2.1
Alveolar macrophages	56.7 mg/kg	18.6 - 70.0
Epithelial lining fluid	20.7 mg/l	5 - 7
Maxillary sinus	7.5 mg/kg	2.0
Ethmoid sinus	8.2 mg/kg	2.1
Nasal polyps	9.1 mg/kg	2.6
Interstitial fluid	1.0[2] mg/l	0.8 - 1.4[2,3]

[1]10 h after administration
[2]Unbound concentration
[3]From 3 h up to 36 h post dose

Metabolism
Moxifloxacin undergoes Phase II biotransformation and is excreted via renal and biliary/faecal pathways as unchanged drug as well as in the form of a sulfo-compound (M1) and a glucuronide (M2). M1 and M2 are the only metabolites relevant in humans, both are microbiologically inactive. Neither in *in vitro* nor in clinical Phase I studies metabolic pharmacokinetic interactions with other drugs undergoing Phase I biotransformation involving cytochrome P-450 enzymes were observed.

Independent from the route of administration the metabolites M1 and M2 are found in the plasma at concentrations lower than the parent drug. Preclinical investigations adequately covered both metabolites thus excluding potential implications with respect to safety and tolerability.

Elimination
Moxifloxacin is eliminated from plasma with a mean terminal half-life of approximately 12 hours. The mean apparent total body clearance following a 400 mg dose ranges from 179 to 246 ml/min. Renal clearance amounted to about 24 - 53 ml/min suggesting partial tubular reabsorption of the drug from the kidneys. Concomitant administration of ranitidine and probenecid did not alter renal clearance of the drug (see table below).

Mass balance of the mother compound and Phase II metabolites of moxifloxacin yielded an almost complete recovery of approx. 96-98% independent from the route of administration with no indication of oxidative metabolism. A detailed overview of mass balance according to elimination pathways (renal vs. non-renal, metabolic vs. non-metabolic) and mode of application is given in the table below.

Recovery of a 400 mg single dose (arithmetric mean ± standard deviation (SD))

	Moxifloxacin	**Sulfo-compound (M1)**	**Glucuronide (M2)**	∑

Urine p.o.	19.4 ± 1.2	2.5 ± 0.6	13.6 ± 2.8	35.4 ± 1.8
Faeces p.o.	25.4 ± 3.1	35.5 ± 3.2	-	60.9 ± 5.1
Σ p.o. (n=6)	44.8 ± 3.3	37.9 ± 3.6	13.6 ± 2.8	96.3 ± 4.3
Urine i.v.	21.9 ± 3.6	2.5 ± 0.9	13.8 ± 2.0	38.1 ± 2.1
Faeces i.v.	25.9 ± 4.3	34.4 ± 5.6	-	60.2 ± 9.2
Σ i.v. (n=5)	47.8 ± 7.2	36.8 ± 5.9	13.8 ± 2.0	98.4 ± 10.5

Geriatric patients
Pharmacokinetics of moxifloxacin are not affected by age.

Gender
There was a 33% difference in the pharmacokinetics (AUC, C_{max}) of moxifloxacin between male and female subjects. Drug absorption was unaffected by gender. These differences in the AUC and C_{max} were attributable to the differences in body weight rather than gender. They are not considered as clinically relevant.

Ethnic differences
Possible interethnic differences were examined in Caucasian, Japanese, Black and other ethnic groups. No clinically relevant interethnic differences in pharmacokinetics could be detected.

Patients with renal impairment
The pharmacokinetic properties of moxifloxacin are not significantly changed by renal impairment (including creatinine clearance <30mL/min/1.73 m^2) and in patients on chronic dialysis i.e. hemodialysis and continuous ambulatory peritoneal dialysis.

Patients with hepatic impairment
Moxifloxacin plasma concentrations of patients with mild to severe hepatic impairment (Child Pugh A to C) did not reveal clinically relevant differences compared to healthy volunteers or patients with normal hepatic function, respectively (see "Special Warnings and Precautions for use" in patients with liver cirrhosis).

5. PHARMACEUTICAL PARTICULARS

5.1 List of excipients

Tablet core:
Microcrystalline cellulose (PH101)
Lactose monohydrate
Croscarmellose sodium
Magnesium stearate

Film-coat:
Hypromellose 2910
Macrogol 4000
Titanium dioxide (E171)
Iron Oxide Red (E172)

5.2 Incompatibilities

Not applicable.

5.3 Shelf life

36 months

5.4 Special precautions for storage

Store below 30°C in the original package in order to protect from moisture.

5.5 Nature and contents of container

Tablets are packed in Alu /Alu blisters containing 5, 10, 20 and 50.

5.6 Special precautions for disposal and other handling

No special requirements for disposal.

6. MANUFACTURER

Medochemie (Far East) Ltd. (Oral Facility), No. 40, Street 6 Vietnam Singapore Industrial Park II, Binh Duong Industry Service Urban Complex, Hoa Phu ward, Thu Dau Mot city, Vietnam

7. PRODUCT REGISTRATION HOLDER

Komedic Sdn. Bhd., 4 Jalan PJS 11/14, Bandar Sunway 46150 Petaling Jaya, Selangor

8. DATE OF REVISION OF THE TEXT

09/2025

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