**SCHEDULING STATUS:** S4

**PROPRIETARY NAME AND DOSAGE FORM:** **AVELON Tablets**
**AVELON IV Solution for infusion**

## COMPOSITION:

AVELON film coated tablet contains moxifloxacin hydrochloride equivalent to 400 mg moxifloxacin.
A single sterile unit of AVELON IV 250 ml infusion solution contains moxifloxacin hydrochloride equivalent to 400 mg moxifloxacin.

## PHARMACOLOGICAL CLASSIFICATION:

A. 20.1.1 Broad and medium spectrum antibiotic

## PHARMACOLOGICAL ACTION:

Moxifloxacin is a fluoroquinolone antibacterial with a broad spectrum of bactericidal action.
Moxifloxacin has been shown to be active against most of the following microorganisms *in vitro. In-vitro* sensitivity may not always have been confirmed in clinical infection (see INDICATIONS).

### Microbiology

Moxifloxacin has *in vitro* activity against a wide range of Gram-positive and Gram-negative microorganisms. The bactericidal action of moxifloxacin results from inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV required for bacterial DNA replication, transcription, repair, and recombination. 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 mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to moxifloxacin and other quinolones. There is no known cross-resistance between moxifloxacin and other classes of antimicrobials.

Cross-resistance has been observed between moxifloxacin and other fluoroquinolones against Gram-negative bacteria. Gram-positive bacteria resistant to other fluoroquinolones may, however, still be susceptible to moxifloxacin.

Moxifloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND DOSAGE section.

**Aerobic Gram-positive microorganisms**
*Staphylococcus aureus* (methicillin-susceptible strains only)
*Streptococcus pneumoniae* (including penicillin-resistant and multi-drug resistant strains)
*Streptococcus pyogenes*
**Aerobic Gram-negative microorganisms**
*Enterobacter cloacae*
*Escherichia coli*
*Haemophilus influenzae*

*Haemophilus parainfluenzae*
*Klebsiella pneumoniae*
*Moraxella catarrhalis*
**Other microorganisms**
*Chlamydia pneumoniae*
*Mycoplasma pneumoniae*

**Penicillin-resistant** *Streptococcus pneumoniae (PRSP)* are those strains with a penicillin MIC value of ≥ 2 µg/ml.

**Multi-drug resistant** *Streptococcus pneumoniae (MDRSP)* includes isolates known as *PRSP*, and are strains resistant to two or more of the following antibiotic classes: penicillin (MIC of ≥ 2 µg/ml), second generation cephalosporins (e.g. cefuroxime), macrolides, tetracyclines, and trimethoprim/ sulphamethoxazole

The following *in vitro* data are available, **but their clinical significance is unknown.**

Moxifloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 2 µg/ml or less against most (> 90 %) strains of the following microorganisms, however, the safety and effectiveness of moxifloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

**Aerobic Gram-positive microorganisms**
*Staphylococcus epidermidis* (methicillin-susceptible strains only)
*Streptococcus agalactiae*
*Streptococcus viridans group*
**Aerobic Gram-negative microorganisms**
*Citrobacter freundii*
*Klebsiella oxytoca*
*Legionella pneumophila*
*Proteus mirabilis*
**Anaerobic microorganisms**
*Fusobacterium* species
*Peptostreptococcus* species
*Prevotella* species

**Pharmacokinetics:**

AVELON tablets
Following oral administration Moxifloxacin is absorbed rapidly and almost completely. The absolute bioavailability amounts to approx. 90 % after oral administration of a 400 mg dose.
Pharmacokinetics are linear in the range of 50 - 1200 mg single oral 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 h post administration. Peak and trough plasma concentrations at steady state (400 mg once daily) were 3,2 and 0,6 mg/l, respectively.
AVELON IV
After a single 400 mg intravenous 1 hour infusion, peak plasma concentrations of approximately 4,1 mg/l were observed at the end of the infusion corresponding to about 26 % higher concentrations than those after oral administration (3,1 mg/l). The AUC value of approximately 39 mg.h/l after intravenous administration is only slightly higher than that observed after oral administration (35 mg.h/l) in accordance with the absolute bioavailability of approximately 91 %. In patients, mean peak plasma concentrations of 4,4 mg/l were observed at steady-state.
Pharmacokinetics are linear up to 600 mg single intravenous dose and up to 600 mg once daily dosing over 10 days.

Pharmacokinetic studies with the oral tablet and intravenous solution have therefore shown the two dosage forms are bioequivalent with respect to the systemic exposure pharmacokinetic parameter AUC.

AVELON tablets and AVELON IV

Moxifloxacin is distributed to extravascular spaces. Exposure to drug in terms of AUC ($AUC_{norm}$ = 6 kg*h/l) is high; the volume of distribution at steady state amounts to Vss of approx. 2 l/kg. In saliva peak concentrations and similar to those of plasma may be reached. Due to low protein binding (approx. 45 %) high free peak concentrations > 10 x MIC are observed. In *in vitro* and *in vivo* experiments protein binding over a range of 0,02 to 2 mg/l resulted in a protein binding of approximately 45 % independent from the concentration of the drug. Moxifloxacin is mainly bound to serum albumin.

In tissues like lung (epithelial fluid, alveolar macrophages, biotic tissue), the sinuses (maxillary and ethmoid sinus, nasal polypi) and inflamed lesions (cantharide blister fluid) concentrations exceeding those of the plasma are reached.

The following peak concentrations were observed following intravenous and oral administration of a single dose of 400 mg Moxifloxacin:

| **Tissue** | **Concentration (i.v.) mg/L** | **Site: Plasma ratio (i.v.)** |
|---|---|---|
| Plasma | 4,1 | - |
| Saliva | 5,0 | 0,82 -1,37 |
| Blister fluid | 1,75[(1)] | 1,7[(1)] |
| Interstitial fluid | 1,0[(2)] | 0,8 - 2,5[(2,3)] |
| **Tissue** | **Concentration (p.o.) mg/L** | **Site: Plasma ratio (p.o.)** |
| Plasma | 3,1 | - |
| Saliva | 3,6 | 0,75 -1,3 |
| Blister fluid | 1,6[(1)] | 1,7[(1)] |
| Bronchial mucosa | 5,4 | 1,7 - 2,1 |
| Epithelial lining fluid | 20,7 | 5 - 7 |
| Interstitial fluid | 1,0[(2)] | 0,8 -1,4[(2,3)] |

(1) 10 h after administration
(2) unbound concentration
(3) from 3 h up to 36 h post dose

Moxifloxacin undergoes Phase II biotransformation and is excreted via renal and biliary/faecal pathways as unchanged drug as well as in form of a sulfo-compound (M1) and a glucuronide (M2). M1 and M2 are the only metabolites relevant in humans, both are microbiologically inactive. The recovery from urine (approx. 19 % for unchanged drug, approx. 2,5 % for M1, and approx. 14 % for M2) and faeces (approx. 25 % of unchanged drug, approx. 36 % for M1, and no recovery for M2) totalled to approx. 96,98 % of the dose independent from the route of administration.

Moxifloxacin is eliminated from plasma and saliva 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. Approximately 19 % of the dose is excreted unchanged into the urine and approx. 25 % in the faeces. Approx. 2,5 % is recovered as M1 in the urine and 36 % in the faeces, respectively. About 14 % is recovered as M2 in the urine.

**INDICATIONS:**

**AVELON tablets and AVELON IV solution for infusion**

AVELON tablets and AVELON IV solution for infusion are indicated for the treatment of adults (> 18 years of age) with mild to moderately severe infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

- **Acute bacterial sinusitis** caused by *Streptococcus pneumoniae, Haemophilus influenzae,* or *Moraxella catarrhalis.*
- **Acute bacterial exacerbation of chronic bronchitis** caused by *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Staphylococcus aureus* or *Moraxella catarrhalis.*
- **Community acquired pneumonia** of mild to moderate severity caused by *Streptococcus pneumoniae* (Including penicillin-resistant strains and multi-drug resistant strains), *Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae, Klebsiella pneumoniae, Staphylococcus aureus* or *Moraxella catarrhalis.*
- **Uncomplicated skin and soft tissue infections** caused by *S. aureus, S. pyogenes*.
- **Complicated skin and skin structure infections** (including diabetic foot infections) caused by *Staphylococcus aureus, Streptococcus pyogenes, Enterococcus faecalis, Escherichia coli, Streptococcus agalactiae, Klebsiella pneumoniae, Proteus mirabilis, or Enterobacter cloacae.*
- **Uncomplicated pelvic inflammatory disease** (i.e. infections of female upper genital tract, including salpingitis and endometritis)
- **Complicated intra-abdominal infections** including polymicrobial infections such as abscesses

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to AVELON. Therapy with AVELON may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

**Penicillin-resistant** *Streptococcus pneumoniae* (PRSP) are those strains with a penicillin MIC value of ≥ 2 µg/ml.
**Multi-drug resistant** *Streptococcus pneumoniae (MDRSP)* includes isolates known as PRSP, and are strains resistant to two or more of the following antibiotic classes: penicillin (MIC of ≥ 2µg/ml), second generation cephalosporins (e.g. cefuroxime), macrolides, tetracyclines, and trimethoprim/sulphamethoxazole.

**CONTRA-INDICATIONS:**

Known hypersensitivity to any component of the tablets or infusion solution or other quinolones. Due to limited clinical data in patients with severe hepatic insufficiency (Child-Pugh C), the use of AVELON is not recommended in patients with severe hepatic insufficiency. No dosage adjustment is required in patients with mild to moderate hepatic insufficiency (Child-Pugh A and B).

Quinolones are known to distribute well into breast milk of lactating women. The use of AVELON in pregnancy and breastfeeding mothers is contra-indicated. (See PREGNANCY AND LACTATION.)

AVELON is contra-indicated in children under 18 years and in growing adolescents, (except where no other suitable antimicrobial agent can be used). Experimental evidence indicates that, species variable reversible lesions of the cartilage of weight bearing joints has been seen in immature members of certain animal species.

**WARNINGS:**

**THE SAFETY AND EFFECTIVENESS OF AVELON IN PAEDIATRIC PATIENTS, ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. SEE SPECIAL PRECAUTIONS - PAEDIATRIC USE, PREGNANCY AND LACTATION SUBSECTIONS.)**

**AVELON HAS BEEN SHOWN TO PROLONG THE QT INTERVAL OF THE ELECTROCARDIOGRAM IN SOME PATIENTS. THE DRUG SHOULD BE AVOIDED IN PATIENTS WITH KNOWN PROLONGATION OF THE QT INTERVAL, PATIENTS WITH UNCORRECTED HYPOKALEMIA AND PATIENTS RECEIVING CLASS IA (E.G. QUINIDINE, PROCAINAMIDE) OR CLASS III (E.G. AMIODARONE, SOTALOL) ANTIARRHYTHMIC AGENTS, DUE TO THE LACK OF CLINICAL EXPERIENCE WITH THE DRUG IN THESE PATIENT POPULATIONS.**

Pharmacokinetic studies between AVELON and other drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants have not been performed. An additive effect of AVELON and these drugs cannot be excluded; therefore AVELON should be used with caution when given concurrently with these drugs.

The effect of AVELON on patients with congenital prolongation of the QT interval has not been studied; however, it is expected that these individuals may be more susceptible to drug-induced QT prolongation. Because of limited clinical experience, AVELON should be used with caution in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia, acute myocardial ischemia. The magnitude of QT prolongation may increase with increasing concentrations of the drug; therefore the recommended dose should not be exceeded. QT prolongation may lead to an increased risk for ventricular arrhythmias including torsade de pointes. In patients with paired valid ECGs in Phase III clinical trials, the mean ± SD effect of AVELON 400 mg on the QTc interval was 6 ± 26 msec. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with AVELON treatment in over 4000 patients; however, certain predisposing conditions may increase the risk for ventricular arrhythmias.

The oral administration of AVELON caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species.

Convulsions have been reported in patients receiving quinolones. Quinolones may also cause central nervous system (CNS) events including: dizziness, confusion, tremors, hallucinations, depression, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving AVELON, the medicine should be discontinued and appropriate measures instituted. As with all quinolones, AVELON should be used with caution in patients with known or suspected CNS disorders (e.g. severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold. (See SIDE EFFECTS AND SPECIAL PRECAUTIONS).

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial oedema, dyspnoea, urticaria, and itching. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. AVELON should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Oxygen, intravenous steroids, and airway management, including intubation, may be administered as indicated.

Severe and sometimes fatal events, some due to hypersensitivity, and some of uncertain etiology, have been reported in patients receiving therapy with all antibiotics. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following: rash, fever, eosinophilia, jaundice, and hepatic necrosis.

**Pseudomembranous colitis has been reported with the use of AVELON; therefore, it is important to consider this diagnosis in patients who develop serious diarrhoea in association with the use of AVELON. In this situation adequate therapeutic measures should be initiated immediately.**

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Tendon inflammation and rupture may occur with AVELON, particularly in elderly patients and in those treated concurrently with corticoid steroids. At the first sign of pain or inflammation, the patient should discontinue treatment and rest the affected limb(s).

**The following side effects have a higher frequency in the subgroup of IV/oral sequentially treated patients:**
Increased gamma-glutaryl-transferase.
Ventricular tachyarrythmias, hypotension, vasodilatation, pseudomembranous colitis (in very rare cases associated with life threatening complications), seizures of various clinical manifestations (incl. grand mal convulsions), hallucinations, renal impairment (which in some cases is due to dehydration, can lead to renal failure, esp. in elderly with pre-existing renal disorders).

**INTERACTIONS:**

Food and dairy products: Absorption of AVELON was not altered by food intake. Therefore, AVELON may be taken with or without food.

**Ranitidine:** The concomitant administration with ranitidine which alters the gastric pH did not change the absorption characteristics of AVELON significantly.

**Antacids, minerals and multi-vitamins:** Concomitant ingestion of AVELON together with antacids, minerals and multi-vitamins may result in impaired absorption of the drug 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 and other preparations containing magnesium, aluminium and other minerals such as iron should be administered at least 4 hours before or 2 hours after ingestion of an oral AVELON dose.

**Warfarin:** Cases of increased anticoagulant activity have been reported in patients receiving oral anticoagulants concurrently with AVELON. Infectious and inflammatory conditions, advanced age and poor general status of the patient are risk factors. International Normalised Ratio (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 AVELON (and vice versa).

**Itraconazole:** The pharmacokinetics of AVELON are not significantly altered by itraconazole. No dose adjustment is necessary for itraconazole when given with AVELON and vice versa.

**Theophylline:** No influence of AVELON on theophylline pharmacokinetics (and vice versa) at steady state was detected. Hence, no recommendations with respect to theophylline dosing need to be given.

**Antidiabetics:** Concomitant administration of AVELON tablets with glibenclamide may result in a decrease of approximately 21 % in the peak plasma concentrations of glibenclamide.

**Oral contraceptives:** No interaction has occurred following concomitant oral administration of AVELON with oral contraceptives.

**Calcium supplements:** No interaction has occurred following concomitant oral administration of AVELON with calcium supplements.

**Morphine:** Parenteral administration of morphine with AVELON did not reduce the oral bioavailability of AVELON.

**Atenolol:** The pharmacokinetics of atenolol are not significantly altered by AVELON. Following single dose administration in healthy subjects, the AUC was marginally increased (by approximately 4 %) and peak concentrations were decreased by 10 %.

**Drugs metabolized by Cytochrome P450 enzymes:** *In vitro* studies with Cytochrome P450 isoenzymes (CYP) indicate that AVELON does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2, suggesting that AVELON is unlikely to alter the pharmacokinetics of drugs metabolized by these enzymes (e.g. midazolam, cyclosporine, warfarin, theophylline).

**Nonsteroidal anti-inflammatory drugs (NSAIDs):** Although not observed with AVELON in preclinical and clinical trials, the concomitant administration of a nonsteroidal anti-inflammatory drug with a quinolone may increase the risks of CNS stimulation and convulsions. (See WARNINGS.)

**Charcoal:** Concomitant administration of charcoal with a dose of 400 mg oral or intravenous AVELON will reduce systemic availability of the drug by more than 80 % or 20 % respectively.

## PREGNANCY AND LACTATION:

**Pregnancy:**
The safe use of AVELON in pregnancy has not been established. (See CONTRA-INDICATIONS)
**Lactation:**
There is no data available in lactating or breastfeeding women. (See CONTRA-INDICATIONS)

## DOSAGE AND DIRECTIONS FOR USE:

**AVELON tablets and intravenous solution:**
The recommended dose for AVELON is 400 mg once-daily for all indications.

**Duration of treatment**

The duration of treatment should be determined by the severity of the indication or clinical response. In general, antibiotic therapy should be used for 3-4 days after the manifestations of the infection have cleared.

The following general recommendations for the treatment of upper and lower respiratory tract infections are made:

- Acute exacerbation of chronic bronchitis, 5 days
- Community acquired pneumonia, 7 - 14 days *
- Acute sinusitis. 10 days

The recommended duration of treatment in skin and soft tissue infections is as follows:

- Uncomplicated skin and skin structure infections 7 days
- Complicated skin and skin structure infections 7 – 21 days *

The recommended durations for other infections are:

- Uncomplicated pelvic inflammatory disease 14 days
- Complicated intra-abdominal infections total treatment duration for sequential therapy (intravenous followed by oral therapy) 5 – 14 days

The recommended duration of treatment for the indication being treated should not be exceeded.

AVELON 400 mg tablets and intravenous solution have been studied in clinical trials for up to 21 days (in complicated skin and skin structure infection).

* Therapy may be initial intravenous administration, followed by oral tablet administration (sequential therapy), when clinically indicated. Alternatively, AVELON can be administered intravenously for the entire treatment duration.

**Method of administration - adults**
The tablets are swallowed whole with a glass of water. They can be taken independent of food intake.

The infusion solution should be infused intravenously over 60 minutes. It can be administered directly or together with compatible infusion solutions. The following coinfusions were found to form stable mixtures over a period of 24 hours at room temperature with AVELON infusion solution, and can therefore be considered as compatible:
Water for injections
Sodium chloride 0.9 %
Sodium chloride 1 molar
Glucose 5 %
Glucose 10 %
Glucose 40 %
Ringer solution
Lactated ringer solution

The following coinfusions were found to be incompatible with AVELON infusion solution:
Sodium chloride 10 % and 20 % (precipitation can occur at higher ratios)
Sodium bicarbonate 4.2 % and 8.4 % (causes pH shift, and $CO_2$ bubbles can form)

If AVELON infusion solution is to be given with another drug, each drug should be given separately. Only clear solutions are to be used. Do not use if the solution is cloudy.

**Special Populations**

Elderly
No adjustment of dosage is required in the elderly.

Children
The use of AVELON in children and adolescents in the growth phase is contra-indicated.

Hepatic impairment
No dosage adjustment is required in patients with mild or moderate hepatic insufficiency (Child-Pugh A and B). No pharmacokinetic data is available for patients with severely impaired liver function (Child-Pugh C). Due to limited clinical data, AVELON is not recommended in patients with severe hepatic impairment.

Renal impairment
No dose adjustment is required in patients with any degree of renal impairment (including creatinine clearance ≤ 30 ml/min/1,73 m²). There is no pharmacokinetic data available in patients on dialysis treatment, or in patients with advanced renal impairment who are not on a dialysis programme. AVELON should therefore not be used in these patients.

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

Gender
Dosage adjustments based on gender are not necessary.

**SIDE EFFECTS AND SPECIAL PRECAUTIONS:**

Adverse drug reactions (ADRs) based on all clinical studies with AVELON (oral and sequential therapy) sorted by CIOMS III categories of frequency (overall n=12,984, including n=2,535 for sequential therapy studies; status: December 2005) 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: September 2006) are printed in ***bold italic*.**

| **Clinical description** | **Common**<br>**> 1 % to < 10 %** | **Uncommon**<br>**> 0.1 % to < 1 %** | **Rare**<br>**> 0.01 % to < 0.1 %** | **Very Rare**<br>**< 0.01 %** |
|---|---|---|---|---|
| **Infections and infestations** | | | | |
| **Antibiotic induced superinfections** | Mycotic superinfections | | | |
| **Blood and the lymphatic system disorders** | | | | |
| **Changes in blood cell counts** | | Anaemia<br>Leukopenia(s)<br>Neutropenia<br>Thrombocytopenia<br>Thrombocythemia | | |
| **Changes in coagulation** | | Prothrombin time prolonged/INR increased | Thromboplastin level abnormal | Prothrombin level increased/INR decreased<br>Prothrombin level/ |

| Clinical description | Common<br>> 1 % to < 10 % | Uncommon<br>> 0.1 % to < 1 % | Rare<br>> 0.01 % to < 0.1 % | Very Rare<br>< 0.01 % |
|---|---|---|---|---|
| | | | | INR abnormal |
| **Immune system disorders** | | | | |
| **Acute hypersensitivity reactions** | | Allergic reaction<br>Pruritus<br>Rash<br>Urticaria<br>Blood eosinophilia | Anaphylactic/ anaphylactoid reaction<br>Allergic oedema/ angioedema (incl. laryngeal oedema, potentially life threatening) | Anaphylactic/ anaphylactoid shock (potentially life threatening) |
| **Metabolism and nutrition disorders** | | | | |
| **Changes in laboratory parameters** | | Hyperlipidemia | Hyperglycemia<br>Hyperuricemia | |
| **Psychiatric disorders** | | | | |
| **Behavioural disturbances** | | Anxiety reactions<br>Psychomotor hyperactivity/ agitation | Emotional lability<br>Depression (in very rare cases potentially culminating in self-endangering behaviour)<br>Hallucinations | ***Depersonalization***<br>***Psychotic reactions (potentially culminating in self-endangering behaviour)*** |
| **Nervous system disorders** | | | | |
| **Unspecific altered peripheral perception** | | Paraesthesia<br>Dysesthesia | Hypoesthesia | Hyperesthesia |
| **Smell and taste disorder** | | Taste disorders (incl. ageusia in very rare cases) | Smell disorders (incl. anosmia) | |
| **Increased neurological activities** | Headache<br>Dizziness | Confusion and disorientation<br>Sleep disorders<br>Tremor<br>Vertigo | Abnormal dreams<br>Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo; ***in very rare cases leading to fall with injuries, esp. in elderly***)<br>Seizures of various clinical manifestations (incl. grand mal convulsions) | |
| **Decreased neurological activities** | | Somnolence | Disturbed attention<br>Speech disorders<br>Amnesia | |
| **Eye disorders** | | | | |
| **Eye disorders** | | Visual disturbances (especially in the course of CNS reactions) | | |
| **Ear and labyrinth disorders** | | | | |
| **Ear disorders** | | | Tinnitus | |

| Clinical description | Common<br>> 1 % to < 10 % | Uncommon<br>> 0.1 % to < 1 % | Rare<br>> 0.01 % to < 0.1 % | Very Rare<br>< 0.01 % |
|---|---|---|---|---|
| **Cardiovascular system disorders** | | | | |
| **Repolarisation disorders** | QT prolongation in patients with hypokalaemia | QT prolongation | | |
| **Unspecified dysrhythmias** | | Palpitations<br>Tachycardia | | Specified dysrhythmias |
| **Ventricular dysrhythmias** | | | Ventricular tachyarrhythmias | ***Torsade de Pointes**<br>*Cardiac arrest**<br>** (especially in patients with severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischemia)*** |
| **Nonspecific cardiovascular symptoms** | | Vasodilatation | Syncope<br>Hypertension<br>Hypotension | |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| **Nonspecific respiratory symptoms** | | Dyspnoea (including asthmatic conditions) | | |
| **Gastrointestinal disorders** | | | | |
| **Gastrointestinal symptoms** | Nausea<br>Vomiting<br>Gastrointestinal and abdominal pains | Anorexia<br>Constipation<br>Dyspepsia<br>Flatulence<br>Gastroenteritis (excl. erosive gastroenteritis)<br>Increased amylase | Dysphagia<br>Stomatitis | |
| **Antibiotic induced diarrheal disorders** | Diarrhoea | | Antibiotic associated colitis (in very rare cases associated with life threatening complications) | |
| **Hepatobiliary disorders** | | | | |
| **Mild to moderate hepatic reactions** | Increase in transaminases | Hepatic impairment (incl. LDH increase)<br>Increased bilirubin<br>Increased gamma-glutamyl-transferase<br>Increase in blood alkaline phosphatase | | |
| **Severe hepatic reactions** | | | Jaundice<br>Hepatitis (predominantly cholestatic) | ***Fulminant hepatitis potentially leading to life-threatening liver failure*** |
| **Skin and subcutaneous tissue disorders** | | | | |
| **Bullous skin reactions** | | | | ***Bullous skin reactions like Stevens-Johnson-Syndrome or Toxic*** |

| Clinical description | Common<br>> 1 % to < 10 % | Uncommon<br>> 0.1 % to < 1 % | Rare<br>> 0.01 % to < 0.1 % | Very Rare<br>< 0.01 % |
|---|---|---|---|---|
| | | | | ***Epidermal Necrolysis (potentially life threatening)*** |
| **Musculoskeletal, connective tissue and bone disorders** | | | | |
| **Tendon disorders** | | | Tendonitis | ***Tendon rupture*** |
| **Unspecific joint and muscular disorders** | | Arthralgia<br>Myalgia | Increased muscle tone and cramping | Arthritis<br>***Gait disturbance (caused by muscular, tendon or joint symptoms)*** |
| **Renal and urinary disorders** | | | | |
| **Renal impairment** | | ***Dehydration (caused by diarrhoea or reduced fluid intake)*** | Renal impairment<br>Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders) | |
| **General disorders and administration site conditions** | | | | |
| **General feeling of illness** | | Feeling unwell<br>Unspecific pain<br>Sweating | | |
| **Infusion site reactions** | Injection and infusion site reactions | Infusion site (thrombo-) phlebitis | | |
| **General disorders** | | | Oedema | |

**SPECIAL PRECAUTIONS:**

**General:** Quinolones may cause central nervous system (CNS) events, including: nervousness, agitation, insomnia, anxiety, nightmares or paranoia. (See WARNINGS and Information for patients.)

**Information for patients:**
To assure safe and effective use of AVELON, the following information and instructions should be communicated to the patient when appropriate:
Patients should be advised:

- that AVELON may produce changes in the electrocardiogram (QTc interval prolongation).
- that AVELON should be avoided in patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents.
- that AVELON may add to the QTc prolonging effects of other drugs such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants.
- to inform their medical practitioner of any personal or family history of QTc prolongation or proarrhythmic conditions such as recent hypokalemia, significant bradycardia, acute myocardial ischemia.
- to inform their medical practitioner of any other medications when taken concurrently with AVELON, including over-the-counter medications.
- to contact their medical practitioner if they experience palpitations or fainting spells while taking AVELON.
- that AVELON tablets may be taken with or without meals, and to drink fluids liberally.
- that AVELON may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other signs of an allergic reaction.
- to discontinue treatment; rest and refrain from exercise; and inform their medical practitioner if they experience pain, inflammation, or rupture of a tendon.

- that AVELON may cause dizziness and lightheadedness; therefore, patients should be cautioned to observe how they react to this drug before they operate a vehicle or machinery or engage in activities requiring mental alertness or coordination.
- that phototoxicity has been reported in patients receiving certain quinolones. There was no phototoxicity seen with AVELON at the recommended dose. In keeping with good medical practice, avoid excessive sunlight or artificial ultraviolet light (e.g. tanning beds). If sunburn-like reaction or skin eruptions occur, contact your medical practitioner. (See Photosensitivity Potential.)
- that convulsions have been reported in patients receiving quinolones, and they should notify their medical practitioner before taking AVELON if there is a history of this condition.
- that in some instances, hypersensitivity and allergic reactions occurred after the first administration and that 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 AVELON has to be discontinued, and medical treatment (e.g. treatment for shock) would be required.
- 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 AVELON 400 mg tablets is not recommended.

**KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:**

No specific countermeasures after accidental overdosage are recommended. General symptomatic therapy should be initiated. Concomitant administration of charcoal with a dose of 400mg oral or intravenous AVELON will reduce systemic availability of the drug by more than 80 % or 20 % respectively. The application of charcoal may be useful to prevent excessive increase of systemic exposure to AVELON in cases of oral overdose.

**IDENTIFICATION:**

**AVELON tablets:** Dull red coated oblong, convex tablet. One side is embossed “BAYER” and the other “M400”.
**AVELON IV:** Clear yellow solution.

**PRESENTATION:**

**AVELON tablets:** Blister packs of 5, 7 and 10 tablets
**AVELON IV:** 250 ml Polyolefin flexibag
**AVELON IV:** 250 ml Colourless glass bottle for infusion

**STORAGE INSTRUCTIONS:**

AVELON tablets:
Store below 25 °C in a dry place. Store in the manufacturer's original container.
KEEP OUT OF REACH OF CHILDREN.
AVELON IV:
Store below 25 ºC. Do not store below 8 ºC. At cool storage temperatures, precipitation may occur, which will re-dissolve at room temperature. It is therefore recommended not to store the infusion solution in a refrigerator. Protect from light. Keep the flexibags in the overwrap/pouch or the bottles in the outer cartons until required for use.
KEEP OUT OF REACH OF CHILDREN.

**REGISTRATION NUMBERS:**

| | |
|---|---|
| **South Africa** | |
| AVELON tablets: | 34/20.1.1/0008 |
| AVELON IV solution for infusion: | 36/20.1.1/0052 |
| **Botswana** | S2 |
| Tablet: | BOT 0400590 |
| IV: | BOT 0400633 |
| **Namibia** | |
| Tablet: | 04/20.1.1/0348 |
| IV: | 04/20.1.1/0349 |

**NAME AND ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:**

Bayer (Pty) Ltd
Registration No. 1968/011192/07
27 Wrench Road, Isando, 1609

**DATE OF PUBLICATION OF THIS PACKAGE INSERT:**

23 October 2008