**SCHEDULING STATUS** S4

## 1. NAME OF THE MEDICINE

**AVELON®** 400 mg film-coated tablet
**AVELON® IV** 400 mg/250 ml solution for Infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSTION

1 film-coated tablet contains 400 mg moxifloxacin (as hydrochloride).
Excipient with known effect: The film-coated tablet contains 68 mg lactose monohydrate (≈ 66 mg lactose) (see section 4.4).

1 bottle or 1 bag of 250 ml contains 400 mg moxifloxacin (as hydrochloride).
1 ml contains 1,6 mg moxifloxacin (as hydrochloride).
Excipients with known effect: 250 ml of solution for infusion contains 787 mg (34 mmol) sodium.
Sugar free.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet

Dull red coated oblong, convex tablet. One side is marked “BAYER” and the other “M400”.

Solution for infusion

Clear, yellow solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

**AVELON is indicated for the treatment of severe and/or complicated infections caused by moxifloxacin-sensitive bacteria where other antimicrobials, approved for a similar indication and to which the causative bacteria are sensitive, were considered not to be an appropriate treatment option, have failed, are contraindicated, or not tolerated.**

**AVELON is not indicated/approved for the initiation of treatment (first-line treatment) of infections described as mild/moderate/acute and uncomplicated, caused by bacteria sensitive to moxifloxacin, unless treatment with other appropriate antimicrobials, approved for a similar indication and to which the causative bacteria are sensitive, have failed, are contraindicated, or not tolerated.**

- Respiratory tract infections:
  AVELON tablets are indicated for the treatment of the following bacterial respiratory tract infections where treatment with other appropriate antimicrobials approved for a similar indication and to which the causative bacteria are sensitive have failed, are contraindicated or not tolerated:

- Acute exacerbations of chronic obstructive pulmonary disease (COPD) including chronic bronchitis (AECB) caused by *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae,* methicillin-sensitive *Staphylococcus aureus* or *Moraxella catarrhalis*.
- Community acquired pneumonia (CAP) of mild to moderate severity caused by *Streptococcus pneumoniae* (including CAP caused by penicillin-resistant strains and multi-drug resistant strains**),** *Haemophilus influenzae Mycoplasma pneumoniae, Chlamydophila pneumoniae***,** *Klebsiella pneumoniae,* methicillin-sensitive *Staphylococcus aureus* or *Moraxella catarrhalis.*
- Acute sinusitis caused by *Streptococcus pneumoniae, Haemophilus influenzae,* or *Moraxella catarrhalis.*
- **Uncomplicated pelvic inflammatory disease** (i.e. infections of female upper genital tract, including salpingitis and endometritis) (not caused by *Neisseria gonorrhoea)* where these infections are compliant with the indication statement, with special reference to the second part of the statement.
- **Severe and/or complicated skin and skin structure infections** (including diabetic foot infections) caused by methicillin-sensitive *Staphylococcus aureus, Streptococcus pyogenes, Enterococcus faecalis, Escherichia coli, Streptococcus agalactiae, Klebsiella pneumoniae, Proteus mirabilis, or Enterobacter cloacae.*
- **Severe and/or complicated intra-abdominal infections** including polymicrobial infections such as abscesses.

AVELON IV is indicated for the treatment of the following bacterial infections where these infections are compliant with the indication statement:

- Severe and/or complicated community acquired pneumonia (CAP), including CAP caused by multi-drug resistant strains.
- Severe and/or complicated skin and skin structure infections (including diabetic foot infections).
- Severe and/or 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 in severe and/or complicated infections before results of these tests are known; once results become available, appropriate therapy should be continued.

### 4.2 Posology and method of administration

Posology

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

Therapy may be initial intravenous administration, followed by oral administration of AVELON tablets as soon as the oral route is feasible.

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).

*Special Populations*
*Elderly patients*
No adjustment of dosage is required in the elderly.

*Children and adolescents*

The use of AVELON in children and adolescents below the age of 18 years is contraindicated (see section 4.3).

*Patients with hepatic impairment*
No dosage adjustment is required in patients with impaired liver function (see section 4.3 for use in patients with liver cirrhosis).

*Patients with renal impairment*
No dose adjustment is required in patients with renal impairment (including creatinine clearance < 30 mL/min/1,73m²) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis.

*Gender*
Dosage adjustments based on gender are not necessary.

Method of administration

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 (see section 6.6).

Duration of administration
The duration of treatment to contain and eradicate an infection depends upon the type and severity of the infection, immunological status, clinical response and bacteriological findings. In general, antibiotic therapy should continue for 3 to 4 days after the manifestations of the infection have cleared.

AVELON tablets

- Acute exacerbation of chronic obstructive pulmonary disease (COPD) including chronic bronchitis — 5 days
- Community acquired pneumonia — 7 to 14 days
- Acute sinusitis — 10 days
- Uncomplicated skin and skin structure infections — 7 days
- Uncomplicated pelvic inflammatory disease — 14 days
- Complicated skin and skin structure infections total treatment duration for sequential therapy (intravenous followed by oral therapy) — 7 to 21 days
- Complicated intra-abdominal infections total treatment duration for sequential therapy (intravenous followed by oral therapy) — 5 to 14 days

AVELON IV

- Community acquired pneumonia: The recommended total treatment duration for sequential administration (intravenous followed by oral therapy) — 7 to 14 days
- Complicated skin and skin structure infections total treatment duration for sequential therapy (intravenous followed by oral therapy) — 7 to 21 days
- Complicated intra-abdominal infections total treatment duration for sequential therapy (intravenous followed by oral therapy) — 5 to 14 days

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

## 4.3 Contraindications

- Known hypersensitivity to moxifloxacin or other quinolones or any of the excipients listed in section 6.1.

- A history of tendon, muscle, joint, nerve, central nervous system or psychiatric disorders especially those related to previous quinolone/fluoroquinolone use where alternative appropriate antibiotic choices are available.
- A history of convulsions, epilepsy or difficult to control epilepsy disorders.
- Aortic aneurysm and/or dissection or in patients with risk factors or conditions predisposing for aortic aneurysm and/or dissection where alternative choices are available.
- Myasthenia gravis.
- Concomitant use of fluoroquinolones with ACE inhibitors/Angiotensin-receptor blockers in patients with moderate to severe renal impairment (Creatine Clearance ≤ 30 ml/min) and in elderly patients.
- Patients below 18 years of age (there is evidence of damage to the cartilage of weight bearing joints in immature animals).
- Pregnancy and lactation (see section 4.6).
- Concomitant use with medicines that prolong the QT interval (see section 4.5).
- Congenital or documented acquired QT prolongation.
- Clinically relevant heart failure with reduced left-ventricular ejection fraction.
- Electrolyte disturbances, particularly in uncorrected hypokalaemia.
- Clinically relevant bradycardia.
- Previous history of symptomatic dysrhythmias.
- Patients with confirmed mitral valve and/or aortic valve regurgitation unless no safer appropriate alternative antibiotic is available, has failed, or is not well tolerated.

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 & B).

### 4.4 Special warnings and precautions for use

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 sections 4.3 and 4.6).

Hypersensitivity/allergic reactions

Hypersensitivity and allergic reactions may occur after the first administration.
Anaphylactic reactions can progress to a life-threatening shock, in some instances after the first administration. Hypersensitivity and allergic reactions, including life-threatening anaphylactic/anaphylactoid shock may occur with the first exposure of AVELON. In these cases the treatment with AVELON must be discontinued and appropriate medical treatment be instituted.

Prolongation of QTc interval and potentially QTc-prolongation-related clinical conditions

**AVELON HAS BEEN SHOWN TO PROLONG THE QT INTERVAL OF THE ELECTROCARDIOGRAM IN PATIENTS (SEE SECTION 4.3).**

**AVELON SHOULD BE AVOIDED IN PATIENTS WITH KNOWN PROLONGATION OF THE QT INTERVAL, PATIENTS WITH UNCORRECTED HYPOKALAEMIA AND PATIENTS RECEIVING CLASS IA (E.G. QUINIDINE, PROCAINAMIDE) OR CLASS III (E.G. AMIODARONE, SOTALOL) ANTI-DYSRHYTHMIC MEDICINES (SEE SECTION 4.3).**

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 AVELON-associated effects on the QT interval (see section 4.3).

As the magnitude of QT prolongation may increase with increasing concentrations of AVELON, 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 AVELON and QTc prolongation was observed. QT prolongation may lead to an increased risk of ventricular dysrhythmias including torsades de pointes. In patients with paired valid ECGs in Phase III clinical trials, the mean ± SD effect of AVELON 400mg on the QTc interval was 6 ± 26 msec (see section 4.3).

Therefore, treatment with AVELON should be avoided due to the lack of clinical experience with AVELON in these patient populations (see section 4.3):

- in patients with known prolongation of the QT interval
- in patients with uncorrected hypokalaemia
- in patients receiving class IA (e.g. quinidine, procainamide) or class III (e.g. amiodarone, sotalol) anti-dysrhythmic medicines

AVELON should be used with caution as an additive effect of AVELON on the QT interval cannot be excluded for the following conditions (see section 4.3):

- in patients treated concomitantly with medicines that prolong the QT interval such as cisapride, erythromycin, antipsychotics and tricyclic antidepressants.
- in patients with ongoing dysrhythmic conditions, such as clinically significant bradycardia, acute myocardial ischaemia.
- in patients with liver cirrhosis as pre-existing QT prolongation in these patients cannot be excluded.
- in women and elderly patients who, may be more susceptible to QTc-prolonging medicines.

<u>Aortic aneurysm and dissection</u>

There is some evidence of an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the elderly 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 aneurysmal disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissections, or in the presence of other risk factors or conditions predisposing aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known arthrosclerosis) (see section 4.3).

In case of sudden abdominal, chest, or back pain, patients should be advised to immediately consult a medical practitioner in an emergency department of a hospital.

<u>Mitral valve and/or aortic valve regurgitation</u>

There is some evidence, although inconclusive, of a possible association between fluoroquinolone use and mitral valve and/or aortic valve regurgitation. A thorough cardiovascular examination including an echocardiogram, should be performed before oral fluoroquinolones are prescribed. Fluoroquinolones should not be prescribed to patients with mitral valve and/or aortic valve regurgitation (see section 4.3).

<u>Concomitant use with ACE-inhibitors/Angiotensin-receptor blockers</u>

Concomitant use of fluoroquinolones and ACE inhibitors/Angiotensin-receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment

and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment, and monitored during treatment, with fluoroquinolone or ACE inhibitors/Angiotensin receptor blockers whether used separately and/or concomitantly.

Severe liver disorders

Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with AVELON (see section 4.8). Patients should be advised to contact their doctor immediately prior to continuing treatment if symptoms related to liver failure occur.

Serious bullous skin reactions

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with AVELON (see section 4.8). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Patients predisposed to seizures

Seizures may occur with AVELON therapy. It should be used with caution in patients with known or suspected CNS disorders which may predispose to seizures or lower the seizure threshold (see section 4.3).

Antibiotic-associated diarrhoea including colitis

Antibiotic-associated colitis/pseudomembranous colitis e.g. due to *Clostridium difficile*, 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 clinical situation adequate therapeutic measures should be initiated immediately. Medicines inhibiting peristalsis are contraindicated in patients who develop serious diarrhoea.

Patients with myasthenia gravis

AVELON should not be used in patients with myasthenia gravis (see section 4.3).

Tendinitis and tendon rupture

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 medicines also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species.

Tendinitis may occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. The risk of tendinitis and tendon rupture is increased in the elderly and in patients using corticosteroids. Tendinitis and/or tendon rupture may still occur for several months after completion of therapy.
Close monitoring of these patients is therefore necessary if they are prescribed AVELON. All patients should consult their medical practitioner if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with AVELON must be stopped immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon. The recovery process may be prolonged (weeks to months) and full recovery to the pre-treatment status may not occur.

Patients with pelvic inflammatory disease

AVELON tablets is not recommended for treatment 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.

Patients with MRSA infections

AVELON 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 (see section 5.1)

Interference with biological tests

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

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones including AVELON. Patients under treatment with AVELON should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop (see section 4.8). The recovery process of neuropathy may be prolonged (weeks to months) and full recovery to the pre-treatment status may not occur.

Psychiatric reactions

Psychiatric reactions may occur even after the first administration of fluoroquinolones, including AVELON. Patients who developed depression or psychotic reactions have progressed to suicidal thoughts and self-injurious behaviour such as suicide attempts (see section 4.8). In the event that the patient develops these reactions, AVELON should be discontinued and appropriate measures instituted. Caution is recommended if AVELON is to be used in psychotic patients or in patients with a history of psychiatric disease (see section 4.3).

Dysglycaemia

Disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with AVELON, usually in diabetic patients, receiving concomitant treatment with an oral hypoglycemic agent (e.g. sulfonylurea) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended (see section 4.8).

Patients of sodium diet

In patients for whom sodium intake is of medical concern (e.g. patients with congestive heart failure, renal failure, nephrotic syndrome) the additional sodium load of the solution for infusion should be taken into account. For sodium chloride content of the solution for infusion see section 2.

Information about excipients

Patients with the rare hereditary conditions of lactose or galactose intolerance e.g. galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption should not take AVELON tablets.
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 medicines and other forms of interaction**

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

**Antacids, minerals and multi-vitamins:** Concomitant ingestion of AVELON together with antacids, minerals and multivitamins may result in impaired absorption of AVELON 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 medicines (e.g. didanosine), and other preparations containing magnesium or aluminium, sucralfate and agents containing iron or zinc should be administered at least 4 hours before or 2 hours after ingestion of an oral AVELON dose.

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

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

**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.

**Warfarin:** *Changes in INR (International Normalized Ratio):* 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.

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

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

**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.

**Digoxin:** The pharmacokinetics of digoxin are significantly influenced by AVELON. After repeated dosing in healthy volunteers AVELON increased Cmax of digoxin by approximately 30 % at steady state without affecting AUC or trough levels. Increased clinical and laboratory monitoring of patients on digitalis therapy is advised.

**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 %.

**Charcoal:** Concomitant dosing of charcoal with a dose of 400 mg oral AVELON reduced systemic availability of AVELON by more than 80 %.

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

**Nonsteroidal anti-inflammatory medicines (NSAIDs):** The concomitant administration of a nonsteroidal anti-inflammatory medicine with a quinolone such as AVELON may increase the risks of CNS stimulation and convulsions.

**ACE inhibitors and angiotensin-receptor blockers:** Concomitant use of fluoroquinolones and ACE inhibitors/angiotensin-receptor blockers may precipitate acute kidney. The mechanism of kidney damage is unknown (see section 4.3).

### 4.6 Pregnancy and lactation

The use of AVELON in pregnancy and lactation is contraindicated (see section 4.3).

Pregnancy

The use of AVELON during pregnancy is contraindicated (see section 4.3). The safe use of AVELON in pregnancy has not been established. Joint injuries have been reported with quinolones. Animal studies have shown reproductive toxicity.

Lactation

The use of AVELON is contraindicated in lactation (see section 4.3). Mothers taking AVELON should not breastfeed their babies as quinolones are excreted in human milk. AVELON has been shown to cause lesions in the cartilage of the weight-bearing joints of immature animals.

### 4.7 Effects on ability to drive or use machines

AVELON may result in an impairment of the patient's ability to drive or operate machinery due to musculoskeletal and/or CNS reactions.

### 4.8 Undesirable effects

Adverse reactions based on all clinical studies with AVELON (oral and sequential therapy) sorted by CIOMS III categories of frequency are listed below:
Adverse reactions listed under "common" were observed with a frequency below 3 % with the exception of nausea and diarrhoea.
Adverse reactions derived from post-marketing reports are separated from clinical trial data (please refer to the adverse reaction list (below the table) provided under the heading “Data from post-marketing experience”).
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) and very rare (< 1/10 000).

Data from clinical trials

| Common | Uncommon | Rare | Very Rare |
|---|---|---|---|
| Infections and Infestations | | | |
| Mycotic superinfections | | | |
| Blood and Lymphatic System Disorders | | | |

| Common | Uncommon | Rare | Very Rare |
|---|---|---|---|
| | Anaemia<br>Leukopenia(s)<br>Neutropenia<br>Thrombocytopenia<br>Thrombocythaemia<br>Prolonged prothrombin time / Increased INR | Abnormal partial thromboplastin time (aPTT) | Increased prothrombin level / decreased INR prothrombin level / INR abnormal |
| Immune System Disorders | | | |
| | 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 | | | |
| | Hyperlipidaemia | Hyperglycaemia<br>Hyperuricaemia | Hypoglycaemia, particularly in diabetic patients. |
| Psychiatric Disorders | | | |
| | Anxiety reactions<br>Psychomotor hyperactivity/ agitation | Emotional lability<br>Depression (culminating in self-injurious behaviour, such as suicidal ideation/thoughts or suicide attempts)<br>Hallucinations | Depersonalisation<br>Psychotic reactions (culminating in self-injurious behaviour, such as suicidal ideation/thoughts or suicide attempts) |
| Nervous System Disorders | | | |
| Headache<br>Dizziness | Paraesthesia and Dysaesthesia<br>Taste disorders (incl. ageusia in very rare cases)<br>Confusion and disorientation<br>Sleep disorders<br>Tremor<br>Vertigo<br>Somnolence | Hypoaesthesia<br>Smell disorders (incl. anosmia)<br>Abnormal dreams<br>Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo)<br>Seizures of various clinical manifestations (incl. grand mal convulsions)<br>Disturbed attention<br>Speech disorders<br>Amnesia<br>Peripheral neuropathy and polyneuropathy | Hyperaesthesia |
| 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 | | | |

| Common | Uncommon | Rare | Very Rare |
|---|---|---|---|
| | | Tinnitus<br>Hearing impairment including deafness (usually reversible) | |
| Cardiovascular System Disorders | | | |
| QT prolongation in patients with hypokalaemia | QT prolongation<br>Palpitations<br>Tachycardia<br>Vasodilatation | Ventricular tachydysrhythmias<br>Syncope<br>Hypertension<br>Hypotension | Unspecified dysrhythmias |
| Respiratory, thoracic and mediastinal Disorders | | | |
| | Dyspnoea (including asthmatic conditions) | | |
| Gastrointestinal Disorders | | | |
| Nausea<br>Vomiting<br>Gastrointestinal and abdominal pains<br>Diarrhoea | Decreased appetite and food intake<br>Constipation<br>Dyspepsia<br>Flatulence<br>Gastroenteritis (excl. erosive gastroenteritis)<br>Increased amylase | Dysphagia<br>Stomatitis<br>Antibiotic-associated colitis / pseudomembranous colitis (in very rare cases associated with life-threatening complications) | Clostridium difficile-associated disease (CDAD) |
| Hepatobiliary Disorders | | | |
| Increase in transaminases | Hepatic impairment (incl. LDH increase)<br>Increased bilirubin<br>Increased gamma-glutamyl-transferase<br>Increase in blood alkaline phosphatase | Jaundice<br>Hepatitis (predominantly cholestatic) | Fulminant hepatitis potentially leading to life-threatening liver failure (incl. fatal cases) |
| Skin and subcutaneous tissue Disorders | | | |
| | | | Bullous skin reactions like Stevens-Johnson-Syndrome or Toxic epidermal necrolysis (potentially life-threatening) |
| Musculoskeletal, Connective Tissue and Bone Disorders | | | |
| | Arthralgia<br>Myalgia | Tendinitis<br>Increased muscle tone and cramping<br>Muscular weakness | Tendon rupture<br>Arthritis<br>Gait disturbance (caused by muscular, tendon or joint symptoms)<br>Exacerbation of symptoms of myasthenia gravis |
| Renal and Urinary Disorders | | | |
| | Dehydration (caused by | Renal impairment | |

| Common | Uncommon | Rare | Very Rare |
|---|---|---|---|
| | diarrhoea or reduced fluid intake) | 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<br>Unspecific pain<br>Sweating<br>Infusion site (thrombophlebitis) | Oedema | |

<u>The following adverse reactions have a higher frequency in the subgroup of IV/oral sequentially treated patients</u>
Common: Increased gamma-glutaryl-transferase
Uncommon: Ventricular tachydysrythmias, hypotension, oedema, antibiotic-associated colitis (in very rare cases associated with life-threatening complications), seizures of various clinical manifestations (including grand mal convulsions), hallucinations, renal impairment and renal failure (due to dehydration especially in elderly with pre-existing renal disorders).

<u>Data from post-marketing experience</u>
Adverse reactions derived from post-marketing reports**:**
**Metabolic and Nutrition Disorders**
Hyperglycaemia, hypoglycaemic coma

**Psychiatric Disorders**
Behavioural disturbances: Potential culmination of depression and psychotic reactions in self-endangering behaviour

**Nervous System Disorders**
Increased neurological activities: Disturbed coordination leading to fall with injuries, especially in the elderly; Guillain-Barré Syndrome

**Cardiovascular System Disorders**
Ventricular dysrhythmias: Torsade de Pointes, cardiac arrest (especially in patients with severe underlying dysrhythmic conditions such as clinically significant bradycardia, acute myocardial ischaemia); aortic aneurysm and dissection

**Hepatobiliary Disorders**
Severe hepatic reactions: Fulminant hepatitis potentially leading to life-threatening liver failure (incl. fatal cases)

**Skin and Subcutaneous Tissue Disorders**
Bullous skin reactions: Bullous skin reactions like Stevens Johnson Syndrome or toxic epidermal necrolysis (potentially life-threatening)

**Musculoskeletal, Connective Tissue and Bone Disorders**
Tendon disorders: Tendinitis and tendon rupture
Unspecific joint and muscular disorders: Gait disturbance (caused by muscular, tendon or joint symptoms), exacerbation of symptoms of myasthenia gravis

**Renal and urinary disorders**
Renal impairment: Dehydration (caused by diarrhoea or reduced fluid intake)

Cases of mitral valve and/or aortic regurgitation were reported in patients treated with oral fluoroquinolones. Due to insufficient post-marketing information in the reported cases, it is unknown whether fluoroquinolone use was the causative factor, or a contributory factor or played no role in the reported cases where mitral valve and/or aortic valve regurgitation was diagnosed.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

### 4.9 Overdose

Adverse reactions may be exaggerated or exacerbated.
No specific countermeasures after accidental overdosage are recommended. General symptomatic and supportive therapy should be initiated. Concomitant administration of charcoal with a dose of 400 mg oral or intravenous AVELON will reduce systemic availability of the medicine by more than 80 % and 20 %, respectively. AVELON causes QT-prolongation in a dose-dependent manner. Patients should be carefully monitored.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Quinolone antibacterials, fluoroquinolones, ATC code: J01MA14

Moxifloxacin is a fluoroquinolone antibacterial with a broad spectrum of bactericidal action.

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.

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.

| **Frequently resistant organisms** |
|---|
| Aerobic Gram-positive micro-organisms<br>Enterococcus faecalis |
| Aerobic Gram-negative micro-organisms<br>Enterobacter cloacae<br>Escherichia coli<br>Klebsiella oxytoca<br>Proteus mirabilis |
| Anaerobic micro-organisms<br>Bacteroides fragilis |
| **Inherently resistant organisms** |
| Aerobic Gram-negative micro-organisms<br>Pseudomonas aeruginosa |
| **Resistant organisms** |

| |
|---|
| *Staphylococus aureus* (methicillin/ofloxacin resistant strains)<br>Coagulase negative Staphylococci (S. cohnii, S. epidermidis, S. haemolyticus, S. hominis, S. saprophyticus, S. simulans) methicillin-resistant strains. |

**5.2 Pharmacokinetic properties**

Absorption and bioavailability

*AVELON tablets*
Following oral administration, moxifloxacin is absorbed rapidly and almost completely. The absolute bioavailability amounts to approximately 91 % after oral administration of a 400 mg dose.

Pharmacokinetics are linear in the range of 50 to 1 200 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 to 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.

Distribution

Moxifloxacin is distributed to extravascular spaces. Exposure to medicine in terms of AUC ($AUC_{norm}$ = 6 kg.h/L) is high; the volume of distribution at steady state amounts to $V_{ss}$ of 2 L/kg. In saliva peak concentrations are similar to those of plasma may be reached. Due to low protein binding (approximately 45 %) high free peak concentrations > 10 x MIC are observed. In *in-vitro and ex-vivo* experiments, the degree of protein binding within the moxifloxacin plasma concentration range of 0,02 to 2 mg/L remained the same at approximately 45 %, independent of the concentration of the medicine. Moxifloxacin is mainly bound to serum albumin.
In tissues like the lung (epithelial fluid, alveolar macrophages, lung biopsy tissue), the sinuses (maxillary and ethmoid sinus, nasal polyps) and inflamed lesions (cantharide blister fluid); concentrations exceeding those of the plasma are reached.
The peak concentrations and site vs. plasma concentration ratios for various target tissues yielded comparable results for both modes of medicine administration after a single dose of 400 mg moxifloxacin.

Metabolism

Moxifloxacin undergoes Phase II biotransformation and is excreted via renal and biliary/faecal pathways as unchanged medicine as well as the 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.

Elimination

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 to 53 mL/min suggesting partial tubular reabsorption of the medicine from the kidneys. Approximately 19 % of the dose is excreted unchanged into the urine and approximately 25 % in the faeces. Approximately 2,5 % is recovered as M1 in the urine and 36 % in the faeces, respectively. About 14 % is recovered as M2 in the urine.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

AVELON tablets
Croscarmellose sodium
Ferric oxide red
Hypromellose 15 cP
Lactose monohydrate
Macrogol 4000
Magnesium stearate
Microcrystalline cellulose
Titanium dioxide

AVELON IV
Hydrochloric acid 1N (for pH-adjustment)
Sodium chloride
Sodium hydroxide solution 2N (for pH-adjustment)
Water for injection.

### 6.2 Incompatibilities

The following co-infusions 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).

### 6.3 Shelf life

Tablets: 5 years
Flexibag: 3 years
Glass bottle:5 years

### 6.4 Special precautions for storage

AVELON tablets
Store at or below 25 °C in a dry place. Store in the manufacturer's original container

AVELON IV
Store at or below 25 ºC. Do not store below 15 ºC. At temperatures below 15 ºC precipitation may occur, which will re-dissolve at room temperature (15 ºC to 25 ºC). 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.
AVELON IV should be inspected visually for particles prior to administration. Only clear solution free from particles should be used.

### 6.5 Nature and content of container

AVELON tablets
Cartons containing colourless transparent or white opaque polypropylene/aluminium blisters or colourless transparent polyvinyl chloride/polyvinylidene chloride/aluminium blisters or polyamide/aluminium/polyvinyl chloride/aluminium blisters.
The film-coated tablets are available in packs of 5, 7, and 10 film-coated tablets.

AVELON IV
Polyolefine bags with polypropylene port sealed in aluminium foil overwrap.
Colourless glass bottles (type 2) with a chlorobutyl or bromobutyl rubber stopper as closure. The 250 ml bottle is available in packs of 1 bottle.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

The following co-infusions 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.

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

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

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

## 8. REGISTRATION NUMBERS

| | |
|---|---|
| AVELON: | 34/20.1.1/0008 |
| AVELON IV: | 36/20.1.1/0052 |

## 9. DATE OF FIRST AUTHORISATION

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|---|---|
| AVELON: | 20/02/2001 |
| AVELON IV: | 17/05/2002 |

## 10. DATE OF REVISION OF THE TEXT

3 September 2020