This document is the approved product information for Axitinib Accord, with the changes since the previous procedure affecting the product information (EMEA/H/C/006206/0000) tracked.

For more information, see the European Medicines Agency’s website: <https://www.ema.europa.eu/en/medicines/human/epar/axitinib-accord>

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

# NAME OF THE MEDICINAL PRODUCT

Axitinib Accord 1 mg film-coated tablets

Axitinib Accord 3 mg film-coated tablets

Axitinib Accord 5 mg film-coated tablets

# QUALITATIVE AND QUANTITATIVE COMPOSITION

Axitinib Accord 1 mg film-coated tablets

Each film-coated tablet contains 1 mg of axitinib.

Axitinib Accord 3 mg film-coated tablets

Each film-coated tablet contains 3 mg of axitinib.

Axitinib Accord 5 mg film-coated tablets

Each film-coated tablet contains 5 mg of axitinib.

Excipients with known effect

*Axitinib Accord 1 mg film-coated tablet*

Each film-coated tablet contains 54.2 mg of lactose.

*Axitinib Accord 3 mg film-coated tablet*

Each film-coated tablet contains 32.5 mg of lactose.

*Axitinib Accord 5 mg film-coated tablet*

Each film-coated tablet contains 54.2 mg of lactose.

For the full list of excipients, see section 6.1.

# PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Axitinib Accord 1 mg film-coated tablets

Red colored, modified capsule shaped biconvex film-coated tablets debossed with 'S14' on one side and plain on other side. The size of the tablet is approximately 9.1 ± 0.2 mm X 4.6 ± 0.2 mm.

Axitinib Accord 3 mg film-coated tablets

Red colored, round, biconvex film-coated-tablet debossed with 'S95' on one side and plain on the other side. The size of the tablet is approximately 5.3 ± 0.3 X 2.6 mm ± 0.3 mm.

Axitinib Accord 5 mg film-coated tablets

Red colored, triangular shaped biconvex film-coated tablets debossed with 'S15' on one side and plain on other side. The size of the tablet is approximately 6.4 ± 0.3 mm X 6.3 ± 0.3 mm.

# CLINICAL PARTICULARS

## **Therapeutic indications**

Axitinib Accord is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine.

## **Posology and method of administration**

Treatment with Axitinib Accord should be conducted by a physician experienced in the use of anticancer therapies.

Posology

The recommended dose of axitinib is 5 mg twice daily.

Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs that cannot be managed by concomitant medicinal products or dose adjustments.

If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.

Dose adjustments

Dose increase or reduction is recommended based on individual safety and tolerability.

Patients who tolerate the axitinib starting dose of 5 mg twice daily with no adverse reactions > Grade 2 (i.e. without severe adverse reactions according to the Common Terminology Criteria for Adverse Events [CTCAE] version 3.0) for two consecutive weeks may have their dose increased to 7 mg twice daily unless the patient’s blood pressure is > 150/90 mmHg or the patient is receiving antihypertensive treatment. Subsequently, using the same criteria, patients who tolerate an axitinib dose of 7 mg twice daily may have their dose increased to a maximum of 10 mg twice daily. Other products are available for the increased dose of 7 mg.

Management of some adverse reactions may require temporary or permanent discontinuation and/or dose reduction of axitinib therapy (see section 4.4). When dose reduction is necessary, the axitinib dose may be reduced to 3 mg twice daily and further to 2 mg twice daily.

Dose adjustment is not required on the basis of patient age, race, gender, or body weight.

Concomitant strong CYP3A4/5 inhibitors

Co-administration of axitinib with strong CYP3A4/5 inhibitors may increase axitinib plasma concentrations (see section 4.5). Selection of an alternate concomitant medicinal product with no or minimal CYP3A4/5 inhibition potential is recommended.

Although axitinib dose adjustment has not been studied in patients receiving strong CYP3A4/5 inhibitors, if a strong CYP3A4/5 inhibitor must be co‑administered, a dose decrease of axitinib to approximately half the dose (e.g. the starting dose should be reduced from 5 mg twice daily to 2 mg twice daily) is recommended. Management of some adverse reactions may require temporary or permanent discontinuation of axitinib therapy (see section 4.4). If co‑administration of the strong inhibitor is discontinued, a return to the axitinib dose used prior to initiation of the strong CYP3A4/5 inhibitor should be considered (see section 4.5).

Concomitant strong CYP3A4/5 inducers

Co-administration of axitinib with strong CYP3A4/5 inducers may decrease axitinib plasma concentrations (see section 4.5). Selection of an alternate concomitant medicinal product with no or minimal CYP3A4/5 induction potential is recommended.

Although axitinib dose adjustment has not been studied in patients receiving strong CYP3A4/5 inducers, if a strong CYP3A4/5 inducer must be co‑administered, a gradual dose increase of axitinib is recommended. Maximal induction with high-dose strong CYP3A4/5 inducers has been reported to occur within one week of treatment with the inducer. If the dose of axitinib is increased, the patient should be monitored carefully for toxicity. Management of some adverse reactions may require temporary or permanent discontinuation and/or dose reduction of axitinib therapy (see section 4.4). If co‑administration of the strong inducer is discontinued, the axitinib dose should be immediately returned to the dose used prior to initiation of the strong CYP3A4/5 inducer (see section 4.5).

Special populations

Elderly (≥ 65 years)

No dose adjustment is required (see sections 4.4 and 5.2).

Renal impairment

No dose adjustment is required (see section 5.2). Virtually no data are available regarding axitinib treatment in patients with a creatinine clearance of < 15 mL/min.

Hepatic impairment

No dose adjustment is required when administering axitinib to patients with mild hepatic impairment (Child-Pugh class A). A dose decrease is recommended when administering axitinib to patients with moderate hepatic impairment (Child-Pugh class B) (e.g. the starting dose should be reduced from 5 mg twice daily to 2 mg twice daily). Axitinib has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of Axitinib Accord in children and adolescents < 18 years have not been established. No data are available.

Method of administration

Axitinib is for oral use. The tablets should be taken orally twice daily approximately 12 hours apart with or without food (see section 5.2). They should be swallowed whole with a glass of water.

## **Contraindications**

Hypersensitivity to axitinib or to any of the excipients listed in section 6.1.

## **Special warnings and precautions for use**

Specific safety events should be monitored before initiation of, and periodically throughout, treatment with axitinib as described below.

Cardiac failure events

In clinical studies with axitinib for the treatment of patients with RCC, cardiac failure events (including cardiac failure, cardiac failure congestive, cardiopulmonary failure, left ventricular dysfunction, ejection fraction decreased, and right ventricular failure) were reported (see section 4.8).

Signs or symptoms of cardiac failure should periodically be monitored throughout treatment with axitinib. Management of cardiac failure events may require temporary interruption or permanent discontinuation and/or dose reduction of axitinib therapy.

Hypertension

In clinical studies with axitinib for the treatment of patients with RCC, hypertension was very commonly reported (see section 4.8).

In a controlled clinical study, the median onset time for hypertension (systolic blood pressure

> 150 mmHg or diastolic blood pressure > 100 mmHg) was within the first month of the start of axitinib treatment and blood pressure increases have been observed as early as 4 days after starting axitinib.

Blood pressure should be well-controlled prior to initiating axitinib. Patients should be monitored for hypertension and treated as needed with standard antihypertensive therapy. In the case of persistent hypertension, despite use of antihypertensive medicinal products, the axitinib dose should be reduced. For patients who develop severe hypertension, temporarily interrupt axitinib and restart at a lower dose once the patient is normotensive. If axitinib is interrupted, patients receiving antihypertensive medicinal products should be monitored for hypotension (see section 4.2).

In case of severe or persistent arterial hypertension and symptoms suggestive of posterior reversible encephalopathy syndrome (PRES) (see below), a diagnostic brain magnetic resonance image (MRI) should be considered.

Thyroid dysfunction

In clinical studies with axitinib for the treatment of patients with RCC, events of hypothyroidism and, to a lesser extent, hyperthyroidism, were reported (see section 4.8).

Thyroid function should be monitored before initiation of, and periodically throughout, treatment with axitinib. Hypothyroidism or hyperthyroidism should be treated according to standard medical practice to maintain euthyroid state.

Arterial embolic and thrombotic events

In clinical studies with axitinib, arterial embolic and thrombotic events (including transient ischemic attack, myocardial infarction, cerebrovascular accident and retinal artery occlusion) were reported (see section 4.8).

Axitinib should be used with caution in patients who are at risk for, or who have a history of, these events. Axitinib has not been studied in patients who had an arterial embolic or thrombotic event within the previous 12 months.

Venous embolic and thrombotic events

In clinical studies with axitinib, venous embolic and thrombotic events (including pulmonary embolism, deep vein thrombosis, and retinal vein occlusion/thrombosis) were reported (see section 4.8).

Axitinib should be used with caution in patients who are at risk for, or who have a history of, these events. Axitinib has not been studied in patients who had a venous embolic or thrombotic event within the previous 6 months.

Elevation of haemoglobin or haematocrit

Increases in haemoglobin or haematocrit, reflective of increases in red blood cell mass, may occur during treatment with axitinib (see section 4.8, polycythaemia). An increase in red blood cell mass may increase the risk of embolic and thrombotic events.

Haemoglobin or haematocrit should be monitored before initiation of, and periodically throughout, treatment with axitinib. If haemoglobin or haematocrit becomes elevated above the normal level, patients should be treated according to standard medical practice to decrease haemoglobin or haematocrit to an acceptable level.

Haemorrhage

In clinical studies with axitinib, haemorrhagic events were reported (see section 4.8).

Axitinib has not been studied in patients who have evidence of untreated brain metastasis or recent active gastrointestinal bleeding, and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the axitinib dose.

Aneurysms and artery dissections

The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating Axitinib Accord, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Gastrointestinal perforation and fistula formation

In clinical studies with axitinib, events of gastrointestinal perforation and fistulas were reported (see section 4.8).

Symptoms of gastrointestinal perforation or fistula should be periodically monitored for throughout treatment with axitinib.

Wound healing complications

No formal studies of the effect of axitinib on wound healing have been conducted.

Treatment with axitinib should be stopped at least 24 hours prior to scheduled surgery. The decision to resume axitinib therapy after surgery should be based on clinical judgment of adequate wound healing.

Posterior reversible encephalopathy syndrome (PRES)

In clinical studies with axitinib, events of PRES were reported (see section 4.8).

PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. In patients with signs or symptoms of PRES, temporarily interrupt or permanently discontinue axitinib treatment. The safety of reinitiating axitinib therapy in patients previously experiencing PRES is not known.

Proteinuria

In clinical studies with axitinib, proteinuria, including that of Grade 3 and 4 severity, was reported (see section 4.8).

Monitoring for proteinuria before initiation of, and periodically throughout, treatment with axitinib is recommended. For patients who develop moderate to severe proteinuria, reduce the dose or temporarily interrupt axitinib treatment (see section 4.2). Axitinib should be discontinued if the patient develops nephrotic syndrome.

Liver-related adverse reactions

In a controlled clinical study with axitinib for the treatment of patients with RCC, liver-related adverse reactions were reported. The most commonly reported liver-related adverse reactions included increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and blood bilirubin (see section 4.8). No concurrent elevations of ALT (> 3 times the upper limit of normal [ULN]) and bilirubin (> 2 times the ULN) were observed.

In a clinical dose-finding study, concurrent elevations of ALT (12 times the ULN) and bilirubin (2.3 times the ULN), considered to be drug-related hepatotoxicity, were observed in 1 patient who received axitinib at a starting dose of 20 mg twice daily (4 times the recommended starting dose).

Liver function tests should be monitored before initiation of, and periodically throughout, treatment with axitinib.

Hepatic impairment

In clinical studies with axitinib, the systemic exposure to axitinib was approximately two-fold higher in subjects with moderate hepatic impairment (Child‑Pugh class B) compared to subjects with normal hepatic function. A dose decrease is recommended when administering axitinib to patients with moderate hepatic impairment (Child‑Pugh class B) (see section 4.2).

Axitinib has not been studied in patients with severe hepatic impairment (Child‑Pugh class C) and should not be used in this population.

Elderly (≥ 65 years) and race

In a controlled clinical study with axitinib for the treatment of patients with RCC, 34 % of patients treated with axitinib were ≥ 65 years of age. The majority of patients were White (77 %) or Asian (21 %). Although greater sensitivity to develop adverse reactions in some older patients and Asian patients cannot be ruled out, overall, no major differences were observed in the safety and effectiveness of axitinib between patients who were ≥ 65 years of age and non-elderly, and between white patients and patients of other races.

No dosage adjustment is required on the basis of patient age or race (see sections 4.2 and 5.2).

Excipients

*Lactose*

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

*Sodium*

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

## **Interaction with other medicinal products and other forms of interaction**

## *In vitro* data indicate that axitinib is metabolised primarily by CYP3A4/5 and, to a lesser extent, CYP1A2, CYP2C19, and uridine diphosphate-glucuronosyltransferase (UGT) 1A1.

## CYP3A4/5 inhibitors

## Ketoconazole, a strong inhibitor of CYP3A4/5, administered at a dose of 400 mg once daily for 7 days, increased the mean area under the curve (AUC) 2‑fold and Cmax 1.5‑fold of a single 5‑mg oral dose of axitinib in healthy volunteers. Co‑administration of axitinib with strong CYP3A4/5 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, erythromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) may increase axitinib plasma concentrations. Grapefruit may also increase axitinib plasma concentrations. Selection of concomitant medicinal products with no or minimal CYP3A4/5 inhibition potential is recommended. If a strong CYP3A4/5 inhibitor must be co‑administered, a dose adjustment of axitinib is recommended (see section 4.2).

CYP1A2 and CYP2C19 inhibitors

CYP1A2 and CYP2C19 constitute minor (< 10 %) pathways in axitinib metabolism. The effect of strong inhibitors of these isozymes on axitinib pharmacokinetics has not been studied. Caution should be exercised due to the risk of increased axitinib plasma concentrations in patients taking strong inhibitors of these isozymes.

CYP3A4/5 inducers

Rifampicin, a strong inducer of CYP3A4/5, administered at a dose of 600 mg once daily for 9 days, reduced the mean AUC by 79 % and Cmax by 71 % of a single 5 mg dose of axitinib in healthy volunteers.

Co‑administration of axitinib with strong CYP3A4/5 inducers (e.g. rifampicin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital, and Hypericum perforatum [St. John’s wort]) may decrease axitinib plasma concentrations. Selection of concomitant medicinal products with no or minimal CYP3A4/5 induction potential is recommended. If a strong CYP3A4/5 inducer must be co-administered, a dose adjustment of axitinib is recommended (see section 4.2).

In vitro studies of CYP and UGT inhibition and induction

In vitro studies indicated that axitinib does not inhibit CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or UGT1A1 at therapeutic plasma concentrations.

In vitro studies indicated that axitinib has a potential to inhibit CYP1A2. Therefore, co‑administration of axitinib with CYP1A2 substrates may result in increased plasma concentrations of CYP1A2 substrates (e.g. theophylline).

In vitro studies also indicated that axitinib has the potential to inhibit CYP2C8. However, co‑administration of axitinib with paclitaxel, a known CYP2C8 substrate, did not result in increased plasma concentrations of paclitaxel in patients with advanced cancer, indicating lack of clinical CYP2C8 inhibition.

In vitro studies in human hepatocytes also indicated that axitinib does not induce CYP1A1, CYP1A2, or CYP3A4/5. Therefore co-administration of axitinib is not expected to reduce the plasma concentration of co‑administered CYP1A1, CYP1A2, or CYP3A4/5 substrates in vivo.

In vitro studies with P-glycoprotein

In vitro studies indicated that axitinib inhibits P‑glycoprotein. However, axitinib is not expected to inhibit P‑glycoprotein at therapeutic plasma concentrations. Therefore, co‑administration of axitinib is not expected to increase the plasma concentration of digoxin, or other P-glycoprotein substrates, in vivo.

## **Fertility, pregnancy and lactation**

Pregnancy

There are no data regarding the use of axitinib in pregnant women. Based on the pharmacological properties of axitinib, it may cause foetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity including malformations (see section 5.3). Axitinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with this medicinal product.

Women of childbearing potential must use effective contraception during and up to 1 week after treatment.

Breast-feeding

It is unknown whether axitinib is excreted in human milk. A risk to the suckling child cannot be excluded. Axitinib should not be used during breast-feeding.

Fertility

Based on non‑clinical findings, axitinib has the potential to impair reproductive function and fertility in humans (see section 5.3).

## **Effects on ability to drive and use machines**

Axitinib has minor influence on the ability to drive and use machines. Patients should be advised that they may experience events such as dizziness and/or fatigue during treatment with axitinib.

## **Undesirable effects**

Summary of the safety profile

The following risks, including appropriate action to be taken, are discussed in greater detail in section 4.4: cardiac failure events, hypertension, thyroid dysfunction, arterial thromboembolic events, venous thromboembolic events, elevation of haemoglobin or haematocrit, haemorrhage, gastrointestinal perforation and fistula formation, wound healing complications, PRES, proteinuria, and elevation of liver enzymes.

The most common (≥ 20 %) adverse reactions observed following treatment with axitinib were diarrhoea, hypertension, fatigue, decreased appetite, nausea, weight decreased, dysphonia, palmar-plantar erythrodysaesthesia (hand-foot) syndrome, haemorrhage, hypothyroidism, vomiting, proteinuria, cough, and constipation.

Tabulated list of adverse reactions

Table 1 presents adverse reactions reported in a pooled dataset of 672 patients who received axitinib in clinical studies for the treatment of patients with RCC (see section 5.1). Post‑marketing adverse reactions identified in clinical studies are also included.

The adverse reactions are listed by system organ class, frequency category and grade of severity. Frequency categories are defined as: very common (≥ 1/10), 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), and not known (cannot be estimated from the available data). The current safety database for axitinib is too small to detect rare and very rare adverse reactions.

Categories have been assigned based on absolute frequencies in the pooled clinical studies data. Within each system organ class, adverse reactions with the same frequency are presented in order of decreasing seriousness.

**Table 1. Adverse reactions reported in RCC studies in patients who received axitinib (N = 672)**

| **System organ class** | **Frequency category** | **Adverse reactionsa** | **All Gradesb%** | **Grade 3b %** | **Grade 4b %** |
| --- | --- | --- | --- | --- | --- |
| Blood and lymphatic system disorders | Common | Anaemia | 6.3 | 1.2 | 0.4 |
| Thrombocytopenia | 1.6 | 0.1 | 0 |
| Polycythaemiac | 1.5 | 0.1 | 0 |
| Uncommon | Neutropaenia | 0.3 | 0.1 | 0 |
| Leukopaenia | 0.4 | 0 | 0 |
| Endocrine disorders | Very common | Hypothyroidismc | 24.6 | 0.3 | 0 |
| Common | Hyperthyroidismc | 1.6 | 0.1 | 0.1 |
| Metabolism and nutrition disorders | Very common | Decreased appetite | 39.0 | 3.6 | 0.3 |
| Common | Dehydration | 6.7 | 3.1 | 0.3 |
| Hyperkalaemia | 2.7 | 1.2 | 0.1 |
| Hypercalcaemia | 2.2 | 0.1 | 0.3 |
| Nervous system disorders | Very common | Headache | 16.2 | 0.7 | 0 |
| Dysgeusia | 11.5 | 0 | 0 |
| Common | Dizziness | 9.1 | 0.6 | 0 |
| Uncommon | Posterior reversible encephalopathy syndromee | 0.3 | 0.1 | 0 |
| Ear and labyrinth disorders | Common | Tinnitus | 3.1 | 0 | 0 |
| Cardiac disorders | Common | Cardiac failure eventsc,d,f | 1.8 | 0.3 | 0.7 |
| Vascular disorders | Very common | Hypertensiong | 51.2 | 22.0 | 1.0 |
| Haemorrhagec,d,h | 25.7 | 3.0 | 1.0 |
| Common | Venous embolic and thrombotic eventsc,d,i | 2.8 | 0.9 | 1.2 |
| Arterial embolic and thrombotic eventsc,d,j | 2.8 | 1.2 | 1.3 |
| Not known | Aneurysms and artery dissectionsd | - | - | - |
| Respiratory, thoracic and mediastinal disorders | Very common | Dyspnoead | 17.1 | 3.6 | 0.6 |
| Cough | 20.4 | 0.6 | 0 |
| Dysphonia | 32.7 | 0 | 0.1 |
| Common | Oropharyngeal pain | 7.4 | 0 | 0 |
| Gastrointestinal disorders | Very common | Diarrhoea | 55.4 | 10.1 | 0.1 |
| Vomiting | 23.7 | 2.7 | 0.1 |
| Nausea | 33.0 | 2.2 | 0.1 |
| Abdominal pain | 14.7 | 2.5 | 0.3 |
| Constipation | 20.2 | 1.0 | 0 |
| Stomatitis | 15.5 | 1.8 | 0 |
| Dyspepsia | 11.2 | 0.1 | 0 |
| Common | Upper abdominal pain | 9.4 | 0.9 | 0 |
| Flatulence | 4.5 | 0 | 0 |
| Haemorrhoids | 3.3 | 0 | 0 |
| Glossodynia | 2.8 | 0 | 0 |
| Gastrointestinal perforation and fistulac,k | 1.9 | 0.9 | 0.3 |
| Hepatobiliary disorders | Common | Hyperbilirubinaemia | 1.3 | 0.1 | 0.1 |
| Cholecystitisn | 1.0 | 0.6 | 0.1 |
| Skin and subcutaneous tissue disorders | Very common | Palmar‑plantar erythrodysaesthesia (hand‑foot syndrome) | 32.1 | 7.6 | 0 |
| Rash | 14.3 | 0.1 | 0 |
| Dry skin | 10.1 | 0.1 | 0 |
| Common | Pruritus | 6.0 | 0 | 0 |
| Erythema | 3.7 | 0 | 0 |
| Alopecia | 5.7 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | Very common | Arthralgia | 17.7 | 1.9 | 0.3 |
| Pain in extremity | 14.1 | 1.0 | 0.3 |
| Common | Myalgia | 8.2 | 0.6 | 0.1 |
| Renal and urinary disorders | Very common | Proteinuria1 | 21.1 | 4.8 | 0.1 |
| Common | Renal failurem | 1.6 | 0.9 | 0.1 |
| General disorders and administration site conditions | Very common | Fatigue | 45.1 | 10.6 | 0.3 |
| Asthaeniad | 13.8 | 2.8 | 0.3 |
| Mucosal inflammation | 13.7 | 1.0 | 0 |
| Investigations | Very common | Weight decreased | 32.7 | 4.9 | 0 |
| Common | Lipase increased | 3.7 | 0.7 | 0.7 |
| Alanine aminotransferase increased | 6.5 | 1.2 | 0 |
| Amylase increased | 3.4 | 0.6 | 0.4 |
| Aspartate aminotransferase increased | 6.1 | 1.0 | 0 |
| Alkaline phosphatase increased | 4.8 | 0.3 | 0 |
| Creatinine increased | 5.7 | 0.4 | 0 |
| Thyroid stimulating hormone increased | 7.9 | 0 | 0 |

a Adverse reactions are according to treatment-emergent, all causality frequency.

b National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0

c See Description of selected adverse reactions section.

d Fatal (Grade 5) cases were reported.

e Including Leukoencephalopathy.

f Including cardiac failure, cardiac failure congestive, cardiopulmonary failure, ejection fraction decreased, left ventricular dysfunction and right ventricular failure.

g Including accelerated hypertension, blood pressure increased, hypertension and hypertensive crisis.

h Including activated partial thromboplastin time prolonged, anal haemorrhage, arterial haemorrhage, blood urine present, central nervous system haemorrhage, cerebral haemorrhage, coagulation time prolonged, conjunctival haemorrhage, contusion, diarrhea haemorrhagic, dysfunctional uterine bleeding, epistaxis, gastric haemorrhage, gastrointestinal haemorrhage, gingival bleeding, haematemesis, haematochezia, haematocrit decreased, haematoma, haematuria, haemoglobin decreased, haemoptysis, haemorrhage, haemorrhage coronary artery, haemorrhage urinary tract, haemorrhoidal haemorrhage, haemostasis, increased tendency to bruise, international normalized ratio increased, lower gastrointestinal haemorrhage, melaena, petechiae, pharyngeal haemorrhage, prothrombin time prolonged, pulmonary haemorrhage, purpura, rectal haemorrhage, red blood cell count decreased, renal haemorrhage, scleral haemorrhage, scrotal haematocoele, splenic haemotoma, splinter haemorrhage, subarachnoid haemorrhage, tongue haemorrhage, upper gastrointestinal haemorrhage and vaginal haemorrhage.

i Including Budd-Chiari syndrome, deep vein thrombosis, jugular vein thrombosis, pelvic venous thrombosis, pulmonary embolism, retinal vein occlusion, retinal vein thrombosis, subclavian vein thrombosis, venous thrombosis, and venous thrombosis limb.

j Including acute myocardial infarction, embolism, myocardial infarction, retinal artery occlusion and transient ischaemic attack.

k Gastrointestinal perforation and fistula includes the following preferred terms: abdominal abscess, anal abscess, anal fistula, fistula, gastrointestinal anastomotic leak, gastrointestinal perforation, large intestine perforation, oesophagobronchial fistula and peritonitis.

l Proteinuria includes the following preferred terms: protein urine, protein urine present and proteinuria.

m Including acute renal failure

n Cholecystitis includes Cholecystitis acute, Cholecystitis, Cholecystitis infective.

Description of selected adverse reactions

*Cardiac failure events (see section 4.4)*

In a controlled clinical study with axitinib (N = 359) for the treatment of patients with RCC, cardiac failure events were reported in 1.7 % patients receiving axitinib, including cardiac failure (0.6 %), cardiopulmonary failure (0.6 %), left ventricular dysfunction (0.3 %), and right ventricular failure (0.3 %). Grade 4 cardiac failure adverse reactions were reported in 0.6 % of patients receiving axitinib. Fatal cardiac failure was reported in 0.6 % of patients receiving axitinib.

In monotherapy studies with axitinib (N = 672) for the treatment of patients with RCC, cardiac failure events (including cardiac failure, cardiac failure congestive, cardiopulmonary failure, left ventricular dysfunction, ejection fraction decreased, and right ventricular failure) were reported in 1.8 % patients receiving axitinib. Grade 3/4 cardiac failure events were reported in 1.0 % patients and fatal cardiac failure events were reported in 0.3 % patients receiving axitinib.

Thyroid dysfunction (see section 4.4)

In a controlled clinical study with axitinib for the treatment of patients with RCC, hypothyroidism was reported in 20.9 % of patients and hyperthyroidism was reported in 1.1 % of patients. Thyroid stimulating hormone (TSH) increased was reported as an adverse reaction in 5.3 % of patients receiving axitinib. During routine laboratory assessments, in patients who had TSH < 5 μU/mL before treatment, elevations of TSH to ≥ 10 μU/mL occurred in 32.2 % of patients receiving axitinib.

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, hypothyroidism was reported in 24.6 % of patients receiving axitinib. Hyperthyroidism was reported in 1.6 % of patients receiving axitinib.

*Venous embolic and thrombotic events (see section 4.4)*

In a controlled clinical study with axitinib for the treatment of patients with RCC, venous embolic and thrombotic adverse reactions were reported in 3.9 % of patients receiving axitinib, including pulmonary embolism (2.2 %), retinal vein occlusion/thrombosis (0.6 %) and deep vein thrombosis (0.6 %). Grade 3/4 venous embolic and thrombotic adverse reactions were reported in 3.1 % of patients receiving axitinib. Fatal pulmonary embolism was reported in one patient (0.3 %) receiving axitinib.

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, venous embolic and thrombotic events were reported in 2.8 % of patients receiving axitinib. Grade 3 venous embolic and thrombotic events were reported in 0.9 % of patients. Grade 4 venous embolic and thrombotic events were reported in 1.2 % of patients. Fatal venous embolic and thrombotic events were reported 0.1 % patients receiving axitinib.

*Arterial embolic and thrombotic events (see section 4.4)*

In a controlled clinical study with axitinib for the treatment of patients with RCC, arterial embolic and thrombotic adverse reactions were reported in 4.7 % of patients receiving axitinib, including myocardial infarction (1.4 %), transient ischemic attack (0.8 %) and cerebrovascular accident (0.6 %). Grade 3/4 arterial embolic and thrombotic adverse reactions were reported in 3.3 % of patients receiving axitinib. A fatal acute myocardial infarction and cerebrovascular accident was reported in one patient each (0.3 %). In monotherapy studies with axitinib (N = 850), arterial embolic and thrombotic adverse reactions (including transient ischemic attack, myocardial infarction, and cerebrovascular accident) were reported in 5.3 % of patients receiving axitinib.

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, arterial embolic and thrombotic events were reported in 2.8 % of patients receiving axitinib. Grade 3 arterial embolic and thrombotic events were reported in 1.2 % of patients. Grade 4 arterial embolic and thrombotic events were reported in 1.3 % of patients. Fatal arterial embolic and thrombotic events were reported in 0.3 % patients receiving axitinib.

*Polycythaemia (see Elevation of haemoglobin or haematocrit in section 4.4)*

In a controlled clinical study with axitinib for the treatment of patients with RCC, polycythaemia was reported in 1.4 % of patients receiving axitinib. Routine laboratory assessments detected elevated haemoglobin above ULN in 9.7 % of patients receiving axitinib. In four clinical studies with axitinib for the treatment of patients with RCC (N = 537), elevated haemoglobin above ULN was observed in 13.6 % receiving axitinib.

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, polycythaemia was reported in 1.5 % of patients receiving axitinib.

*Haemorrhage (see section 4.4)*

In a controlled clinical study with axitinib for the treatment of patients with RCC that excluded patients with untreated brain metastasis, haemorrhagic adverse reactions were reported in 21.4 % of patients receiving axitinib. The haemorrhagic adverse reactions in patients treated with axitinib included epistaxis (7.8 %), haematuria (3.6 %), haemoptysis (2.5 %), rectal haemorrhage (2.2 %), gingival bleeding (1.1 %), gastric haemorrhage (0.6 %), cerebral haemorrhage (0.3 %) and lower gastrointestinal haemorrhage (0.3 %). Grade > 3 haemorrhagic adverse reactions were reported in 3.1 % of patients receiving axitinib (including cerebral haemorrhage, gastric haemorrhage, lower gastrointestinal haemorrhage and haemoptysis). Fatal haemorrhage was reported in one patient (0.3 %) receiving axitinib (gastric haemorrhage). In monotherapy studies with axitinib (N = 850), haemoptysis was reported in 3.9 % of patients; Grade > 3 haemoptysis was reported in 0.5% of patients.

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, haemorrhagic events were reported in 25.7 % of patients receiving axitinib. Grade 3 haemorrhagic adverse reactions were reported in 3 % of patients. Grade 4 haemorrhagic adverse reactions were reported in 1 % of patients and fatal haemorrhage were reported in 0.4 % of patients receiving axitinib.

Gastrointestinal perforation and fistula formation (see section 4.4)

In a controlled clinical study with axitinib for the treatment of patients with RCC, gastrointestinal perforation-type events were reported in 1.7 % of patients receiving axitinib, including anal fistula (0.6 %), fistula (0.3 %) and gastrointestinal perforation (0.3 %).In monotherapy studies with axitinib (N = 850), gastrointestinal perforation-type events were reported in 1.9% of patients and fatal gastrointestinal perforation was reported in one patient (0.1 %).

In pooled clinical studies with axitinib (N = 672) for the treatment of patients with RCC, gastrointestinal perforation and fistula were reported in 1.9% of patients receiving axitinib.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2013/03/WC500139752.doc).

## **Overdose**

There is no specific treatment for axitinib overdose.

In a controlled clinical study with axitinib for the treatment of patients with RCC, one patient inadvertently received a dose of 20 mg twice daily for 4 days and experienced dizziness (Grade 1).

In a clinical dose finding study with axitinib, subjects who received starting doses of 10 mg twice daily or 20 mg twice daily experienced adverse reactions which included hypertension, seizures associated with hypertension, and fatal haemoptysis.

In cases of suspected overdose, axitinib should be withheld and supportive care instituted.

# PHARMACOLOGICAL PROPERTIES

## **Pharmacodynamic properties**

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EK01

Mechanism of action

Axitinib is a potent and selective tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)‑1, VEGFR‑2 and VEGFR‑3. These receptors are implicated in pathologic angiogenesis, tumour growth, and metastatic progression of cancer. Axitinib has been shown to potently inhibit VEGF-mediated endothelial cell proliferation and survival. Axitinib inhibited the phosphorylation of VEGFR‑2 in xenograft tumour vasculature that expressed the target in vivo and produced tumour growth delay, regression, and inhibition of metastases in many experimental models of cancer.

Effect on QTc interval

In a randomised, 2‑way crossover study, 35 healthy subjects were administered a single oral dose of axitinib (5 mg) in the absence and presence of 400 mg ketoconazole for 7 days. Results of this study indicated that axitinib plasma exposures up to two‑fold greater than therapeutic levels expected following a 5 mg dose, did not produce clinically‑significant QT interval prolongation.

Clinical efficacy and safety

The safety and efficacy of axitinib were evaluated in a randomised, open-label, multicenter Phase 3 study. Patients (N = 723) with advanced RCC whose disease had progressed on or after treatment with one prior systemic therapy, including sunitinib, bevacizumab, temsirolimus, or cytokine-containing regimens were randomised (1:1) to receive axitinib (N = 361) or sorafenib (N = 362). The primary endpoint, progression-free survival (PFS), was assessed using a blinded independent central review. Secondary endpoints included objective response rate (ORR) and overall survival (OS).

Of the patients enrolled in this study, 389 patients (53.8 %) had received one prior sunitinib‑based therapy, 251 patients (34.7 %) had received one prior cytokine-based therapy (interleukin‑2 or interferon‑alpha), 59 patients (8.2 %) had received one prior bevacizumab‑based therapy, and 24 patients (3.3 %) had received one prior temsirolimus‑based therapy. The baseline demographic and disease characteristics were similar between the axitinib and sorafenib groups with regard to age, gender, race, Eastern Cooperative Oncology Group (ECOG) performance status, geographic region, and prior treatment.

In the overall patient population and the two main subgroups (prior sunitinib treatment and prior cytokine treatment), there was a statistically significant advantage for axitinib over sorafenib for the primary endpoint of PFS (see Table 2 and Figures 1, 2 and 3). The magnitude of median PFS effect was different in the subgroups by prior therapy. Two of the subgroups were too small to give reliable results (prior temsirolimus treatment or prior bevacizumab treatment). There were no statistically significant differences between the arms in OS in the overall population or in the subgroups by prior therapy.

**Table 2. Efficacy results**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Endpoint / study population** | **axitinib** | **sorafenib** | **HR (95% CI)** | **p-value** |
| **Overall ITT** | **N = 361** | **N = 362** |  |  |
| Median PFS a,b in months  (95% CI) | 6.8 (6.4, 8.3) | 4.7 (4.6, 6.3) | 0.67 (0.56, 0.81) | < 0.0001c |
| Median OSd in months  (95% CI) | 20.1 (16.7, 23.4) | 19.2 (17.5, 22.3) | 0.97 (0.80, 1.17) | NS |
| ORRb,e % (95% CI) | 19.4 (15.4, 23.9) | 9.4 (6.6, 12.9) | 2.06f (1.41, 3.00) | 0.0001g |
| **Prior sunitinib treatment** | **N = 194** | **N = 195** |  |  |
| Median PFSa,b in months  (95% CI) | 4.8 (4.5, 6.5) | 3.4 (2.8, 4.7) | 0.74 (0.58, 0.94) | 0.0063h |
| Median OSd in months  (95% CI) | 15.2 (12.8, 18.3) | 16.5 (13.7, 19.2) | 1.00 (0.78, 1.27) | NS |
| ORRb,e % (95% CI) | 11.3 (7.2, 16.7) | 7.7 (4.4, 12.4) | 1.48f (0.79, 2.75) | NS |
| **Prior cytokine treatment** | **N = 126** | **N = 125** |  |  |
| Median PFSa,b in months  (95% CI) | 12.0 (10.1, 13.9) | 6.6 (6.4, 8.3) | 0.52 (0.38, 0.72) | < 0.0001h |
| Median OSd in months  (95% CI) | 29.4 (24.5, NE) | 27.8 (23.1, 34.5) | 0.81 (0.56, 1.19) | NS |
| ORRb,e% (95% CI) | 32.5 (24.5, 41.5) | 13.6 (8.1, 20.9) | 2.39f (1.43-3.99) | 0.0002i |

CI = Confidence interval, HR = Hazard ratio (axitinib/sorafenib); ITT: Intent-to-treat; NE: not estimable; NS: not statistically significant; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival.

a Time from randomisation to progression or death due to any cause, whichever occurs first. Cutoff date: 03 June 2011.

b Assessed by independent radiology review according to Response Evaluation Criteria in Solid Tumours (RECIST).

c One-sided p-value from a log-rank test of treatment stratified by ECOG performance status and prior therapy.

d Cutoff date: 01 November 2011.

e Cutoff date: 31 August 2010.

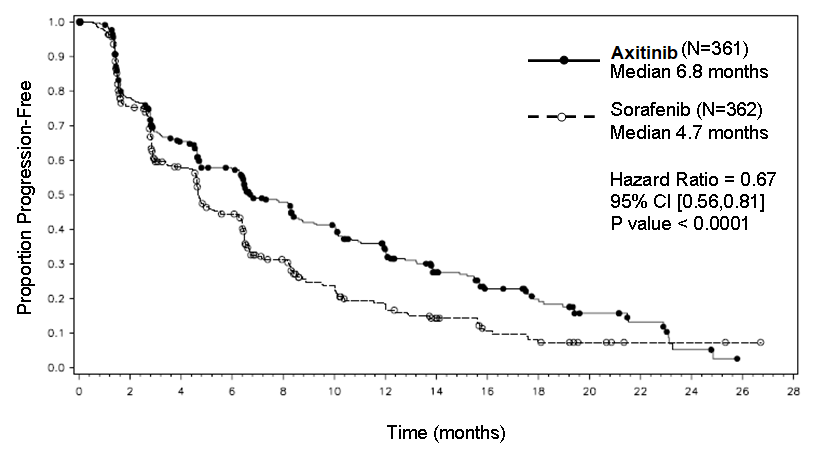
f Risk ratio is used for ORR. A risk ratio > 1 indicated a higher likelihood of responding in the axitinib a rm; a risk ratio < 1 indicated a higher likelihood of responding in the sorafenib arm.

g One-sided p-value from Cochran-Mantel-Haenszel test of treatment stratified by ECOG performance status and prior therapy.

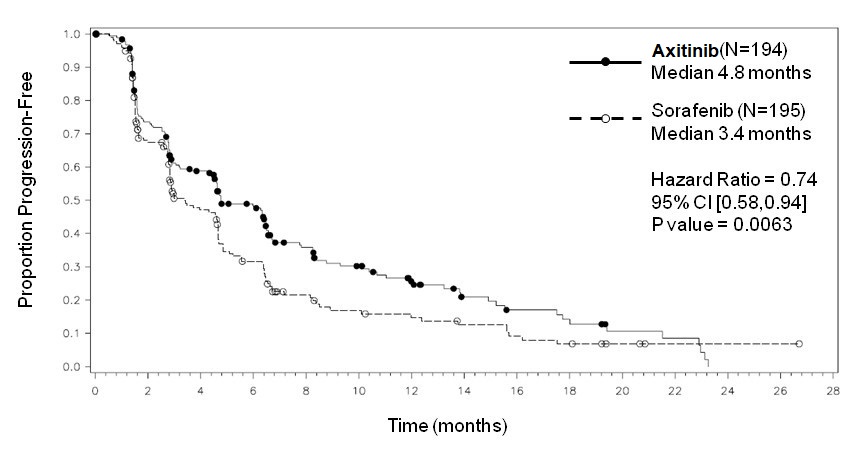
h One-sided p‑value from a log-rank test of treatment stratified by ECOG performance status.

i One-sided p‑value from Cochran-Mantel-Haenszel test of treatment stratified by ECOG performance status.

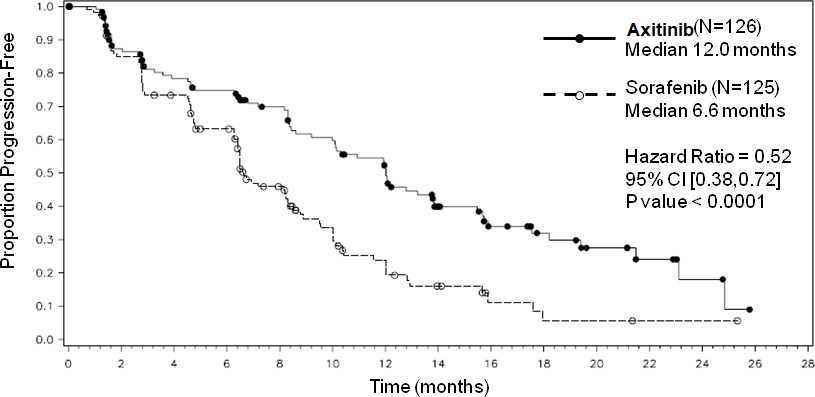
# Figure 1. Kaplan-Meier curve of progression-free survival by independent assessment for the overall population



**Figure 2. Kaplan-Meier curve of progression-free survival by independent assessment for the prior sunitinib subgroup**



**Figure 3. Kaplan-Meier curve of progression-free survival by independent assessment for the prior cytokine subgroup**



Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with axitinib in all subsets of the paediatric population for treatment of kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumour of the kidney) (see section 4.2 for information on paediatric use).

## **Pharmacokinetic properties**

After oral administration of axitinib tablets, the mean absolute bioavailability is 58 % compared to intravenous administration. The plasma half‑life of axitinib ranges from 2.5 to 6.1 hours. Dosing of axitinib at 5 mg twice daily resulted in less than two‑fold accumulation compared to administration of a single dose. Based on the short half-life of axitinib, steady state is expected within 2 to 3 days of the initial dose.

Absorption and distribution

Peak axitinib concentrations in plasma are generally reached within 4 hours following oral administration of axitinib with median Tmax ranging from 2.5 to 4.1 hours. Administration of axitinib with a moderate fat meal resulted in 10 % lower exposure compared to overnight fasting. A high fat, high-calorie meal resulted in 19 % higher exposure compared to overnight fasting. Axitinib may be administered with or without food (see section 4.2).

The average Cmax and AUC increased proportionally over an axitinib dosing range of 5 to 10 mg. *In vitro* binding of axitinib to human plasma proteins is > 99 % with preferential binding to albumin and moderate binding to α1-acid glycoprotein. At the 5 mg twice daily dose in the fed state, the geometric mean peak plasma concentration and 24‑hour AUC were 27.8 ng/mL and 265 ng.h/mL, respectively, in patients with advanced RCC. The geometric mean oral clearance and apparent volume of distribution were 38 L/h and 160 L, respectively.

Biotransformation and elimination

Axitinib is metabolised primarily in the liver by CYP3A4/5 and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1.

Following oral administration of a 5 mg radioactive dose of axitinib, 30-60 % of the radioactivity was recovered in faeces and 23 % of the radioactivity was recovered in urine. Unchanged axitinib, accounting for 12 % of the dose, was the major component identified in faeces. Unchanged axitinib was not detected in urine; the carboxylic acid and sulfoxide metabolites accounted for the majority of radioactivity in urine. In plasma, the N‑glucuronide metabolite represented the predominant radioactive component (50 % of circulating radioactivity) and unchanged axitinib and the sulfoxide metabolite each accounted for approximately 20 % of the circulating radioactivity.

The sulfoxide and N-glucuronide metabolites show approximately 400‑fold and 8000‑fold less *in vitro* potency, respectively, against VEGFR-2 compared to axitinib.

Special populations.

*Elderly, gender, and race*

Population pharmacokinetic analyses in patients with advanced cancer (including advanced RCC) and healthy volunteers indicate that there are no clinically relevant effects of age, gender, body weight, race, renal function, UGT1A1 genotype, or CYP2C19 genotype.

*Paediatric population*

Axitinib has not been studied in patients < 18 years of age.

*Hepatic impairment*

*In vitro* and *in vivo* data indicate that axitinib is primarily metabolised by the liver.

Compared to subjects with normal hepatic function, systemic exposure following a single dose of axitinib was similar in subjects with mild hepatic impairment (Child‑Pugh class A) and higher (approximately two‑fold) in subjects with moderate hepatic impairment (Child‑Pugh class B). Axitinib has not been studied in subjects with severe hepatic impairment (Child‑Pugh class C) and should not be used in this population (see section 4.2 for dose adjustment recommendations).

*Renal impairment*

Unchanged axitinib is not detected in the urine.

Axitinib has not been studied in subjects with renal impairment. In clinical studies with axitinib for the treatment of patients with RCC, patients with serum creatinine > 1.5 times the ULN or calculated creatinine clearance < 60 mL/min were excluded. Population pharmacokinetic analyses have shown that axitinib clearance was not altered in subjects with renal impairment and no dose adjustment of axitinib is required.

## **Preclinical safety data**

Repeat dose toxicity

Major toxicity findings in mice and dogs following repeated dosing for up to 9 months were the gastrointestinal, haematopoietic, reproductive, skeletal and dental systems, with No Observed Adverse Effect Levels (NOAEL) approximately equivalent to or below expected human exposure at the recommended clinical starting dose (based on AUC levels).

Carcinogenicity

Carcinogenicity studies have not been performed with axitinib.

Genotoxicity

Axitinib was not mutagenic or clastogenic in conventional genotoxicity assays in vitro. A significant increase in polyploidy was observed in vitro at concentrations > 0.22 µg/mL, and an elevation in micronucleated polychromatic erythrocytes was observed in vivo with No Observed Effect Level (NOEL) 69‑fold the expected human exposure. Genotoxicity findings are not considered clinically relevant at exposure levels observed in humans.

Reproduction toxicity

Axitinib-related findings in the testes and epididymis included decreased organ weight, atrophy or degeneration, decreased numbers of germinal cells, hypospermia or abnormal sperm forms, and reduced sperm density and count. These findings were observed in mice at exposure levels approximately 12‑fold the expected human exposure, and in dogs at exposure levels below the expected human exposure. There was no effect on mating or fertility in male mice at exposure levels approximately 57‑fold the expected human exposure. Findings in females included signs of delayed sexual maturity, reduced or absent corpora lutea, decreased uterine weights and uterine atrophy at exposures approximately equivalent to the expected human exposure. Reduced fertility and embryonic viability were observed in female mice at all doses tested, with exposure levels at the lowest dose approximately 10‑fold the expected human exposure.

Pregnant mice exposed to axitinib showed an increased occurrence of cleft palate malformations and skeletal variations, including delayed ossification, at exposure levels below the expected human exposure. Perinatal and postnatal developmental toxicity studies have not been conducted.

Toxicity findings in immature animals

Reversible physeal dysplasia was observed in mice and dogs given axitinib for at least 1 month at exposure levels approximately six-fold higher than the expected human exposure. Partially reversible dental caries were observed in mice treated for more than 1 month at exposure levels similar to the expected human exposure. Other toxicities of potential concern to paediatric patients have not been evaluated in juvenile animals.

# PHARMACEUTICAL PARTICULARS

## **List of excipients**

Tablet core

Lactose

Cellulose, Microcrystalline (E460)

Silica, Colloidal anhydrous

Hydroxypropylcellulose (300–600 mPa\*s)

Croscarmellose sodium (E 468)

Talc

Magnesium stearate (E 470b)

Tablet film-coating

Hypromellose 2910 (15 mPa\*s) (E464)

Lactose monohydrate

Titanium Dioxide (E171)

Triacetin

Iron Oxide Red (E172)

## **Incompatibilities**

Not applicable.

## **Shelf life**

Blister and bottle pack: 2 years

Shelf life after first opening of bottle: 1 mg - 45 days and 3, 5 mg - 30 days

## **Special precautions for storage**

This medicinal product does not require any special temperature storage conditions.

OPA/Aluminium/PVC/Aluminium blister:

Store in the original package in order to protect from moisture.

HDPE bottle:

Keep the bottle tightly closed to protect from moisture.

## **Nature and content of container**

Axitinib Accord 1 mg film-coated tablet

OPA/Aluminium/PVC/Aluminium blister containing 14 film-coated tablets. Each pack contains 28 or 56 film-coated tablets or perforated unit dose blisters of 28 x 1 or 56 x 1 film-coated tablets.

HDPE bottle with a silica gel desiccant and a polypropylene child resistant closure containing 180 film-coated tablets.

Axitinib Accord 3 mg film-coated tablet

OPA/Aluminium/PVC/Aluminium blister containing 14 film-coated tablets. Each pack contains 28 or 56 film-coated tablets or perforated unit dose blisters of 28 x 1 or 56 x 1 film-coated tablets.

HDPE bottle with a silica gel desiccant and a polypropylene child resistant closure containing 60 film-coated tablets.

Axitinib Accord 5 mg film-coated tablet

OPA/Aluminium/PVC/Aluminium blister containing 14 film-coated tablets. Each pack contains 28 or 56 film-coated tablets or perforated unit dose blisters of 28 x 1 or 56 x 1 film-coated tablets.

HDPE bottle with a silica gel desiccant and a polypropylene child resistant closure containing 60 film-coated tablets.

Not all pack sizes may be marketed.

## **Special precautions for disposal**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

# MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.

World Trade Center, Moll de Barcelona, s/n

Edifici Est, 6a Planta

08039 Barcelona

Spain

# MARKETING AUTHORISATION NUMBER(S)

# 1 mg Film-coated tablet

# EU/1/24/1847/001 28 tablets

# EU/1/24/1847/002 28 x 1 tablets (unit dose)

# EU/1/24/1847/003 56 tablets

# EU/1/24/1847/004 56 x 1 tablets (unit dose)

# EU/1/24/1847/005 180 tablets (bottle)

# 3 mg Film-coated tablet

# EU/1/24/1847/006 28 tablets

# EU/1/24/1847/007 28 x 1 tablets (unit dose)

# EU/1/24/1847/008 56 tablets

# EU/1/24/1847/009 56 x 1 tablets (unit dose)

# EU/1/24/1847/010 60 tablets (bottle)

# 5 mg Film-coated tablet

# EU/1/24/1847/011 28 tablets

# EU/1/24/1847/012 28 x 1 tablets (unit dose)

# EU/1/24/1847/013 56 tablets

# EU/1/24/1847/014 56 x 1 tablets (unit dose)

# EU/1/24/1847/015 60 tablets (bottle)

# DATE OF FIRST AUTHORISATION

Date of first authorisation: 19 September 2024.

# DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.

**ANNEX II**

1. **MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
2. **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
3. **OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
4. **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

# MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

APIS Labor GmbH

Resslstraβe 9, 9065 Ebenthal in Kärnten,

Austria

Accord Healthcare Polska Sp.z.o.o

ul Lutomierska 50,95-200

Pabianice, Poland

Accord Healthcare single member S.A.

64th Km National Road Athens, Lamia,

Schimatari, 32009, Greece

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

# CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product

Characteristics, section 4.2).

# OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

* **Periodic safety update reports (PSURs)**

The requirements for submission of PSURsfor this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

# CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

* **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

* At the request of the European Medicines Agency;
* Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

**A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON FOR 1 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Axitinib Accord 1 mg film-coated tablets

axitinib

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 1 mg axitinib.

**3. LIST OF EXCIPIENTS**

Contains lactose. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film‑coated tablet

28 film‑coated tablets

28 x 1 film‑coated tablets

56 film‑coated tablets

56 x 1 film‑coated tablets

**5. METHOD AND ROUTE OF ADMINISTRATION**

Read the package leaflet before use.

Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

This medicinal product does not require any special temperature storage conditions.

Store in the original package in order to protect from moisture.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Accord Healthcare S.L.U.

World Trade Center, Moll de Barcelona s/n, Edifici Est, 6a Planta,

08039, Barcelona,

Spain

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/24/1847/001

EU/1/24/1847/002

EU/1/24/1847/003

EU/1/24/1847/004

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Axitinib Accord 1 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER – HUMAN READABLE DATA**

PC

SN

NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOR 1 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Axitinib Accord 1 mg tablets

axitinib

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Accord

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

Oral use

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**UNIT DOSE BLISTER PACK (28 x 1 TABLETS, 56 x 1 TABLETS) FOR 1 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Axitinib Accord 1 mg tablets

axitinib

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Accord

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

Oral use

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**OUTER CARTON AND LABEL FOR HDPE BOTTLE FOR 1 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Axitinib Accord 1 mg film-coated tablets

axitinib

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 1 mg axitinib.

**3. LIST OF EXCIPIENTS**

Contains lactose. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film‑coated tablet

180 film-coated tablets

**5. METHOD AND ROUTE OF ADMINISTRATION**

Read the package leaflet before use.

Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

After first opening of the bottle: use within 45 days

**9. SPECIAL STORAGE CONDITIONS**

This medicinal product does not require any special temperature storage conditions.

Keep the bottle tightly closed to protect from moisture.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Accord Healthcare S.L.U.

World Trade Center, Moll de Barcelona s/n, Edifici Est, 6a Planta,

08039, Barcelona,

Spain

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/24/1847/005

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Axitinib Accord 1 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER – HUMAN READABLE DATA**

PC

SN

NN

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON FOR 3 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Axitinib Accord 3 mg film-coated tablets

axitinib

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 3 mg axitinib.

**3. LIST OF EXCIPIENTS**

Contains lactose. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film‑coated tablet

28 film‑coated tablets

28 x 1 film‑coated tablets

56 film‑coated tablets

56 x 1 film‑coated tablets

**5. METHOD AND ROUTE OF ADMINISTRATION**

Read the package leaflet before use.

Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

This medicinal product does not require any special temperature storage conditions.

Store in the original package in order to protect from moisture.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Accord Healthcare S.L.U.

World Trade Center, Moll de Barcelona s/n, Edifici Est, 6a Planta,

08039, Barcelona,

Spain

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/24/1847/006

EU/1/24/1847/007

EU/1/24/1847/008

EU/1/24/1847/009

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Axitinib Accord 3 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER – HUMAN READABLE DATA**

PC

SN

NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOR 3 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Axitinib Accord 3 mg tablets

axitinib

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Accord

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

Oral use

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**UNIT DOSE BLISTER PACK (28 x 1 TABLETS, 56 x 1 TABLETS) FOR 3 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Axitinib Accord 3 mg tablets

axitinib

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Accord

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

Oral use

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**OUTER CARTON AND LABEL FOR HDPE BOTTLE FOR 3 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Axitinib Accord 3 mg film-coated tablets

axitinib

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 3 mg axitinib.

**3. LIST OF EXCIPIENTS**

Contains lactose. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablets

60 film-coated tablets

**5. METHOD AND ROUTE OF ADMINISTRATION**

Read the package leaflet before use.

Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

After first opening of the bottle: use within 30 days

**9. SPECIAL STORAGE CONDITIONS**

This medicinal product does not require any special temperature storage conditions.

Keep the bottle tightly closed to protect from moisture.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Accord Healthcare S.L.U.

World Trade Center, Moll de Barcelona s/n, Edifici Est, 6a Planta,

08039, Barcelona,

Spain

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/24/1847/010

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Axitinib Accord 3 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER – HUMAN READABLE DATA**

PC

SN

NN

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON FOR 5 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Axitinib Accord 5 mg film-coated tablets

axitinib

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 5 mg axitinib.

**3. LIST OF EXCIPIENTS**

Contains lactose. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film‑coated tablet

28 film‑coated tablets

28 x 1 film‑coated tablets

56 film‑coated tablets

56 x 1 film‑coated tablets

**5. METHOD AND ROUTE OF ADMINISTRATION**

Read the package leaflet before use.

Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

This medicinal product does not require any special temperature storage conditions.

Store in the original package in order to protect from moisture.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Accord Healthcare S.L.U.

World Trade Center, Moll de Barcelona s/n, Edifici Est, 6a Planta,

08039, Barcelona,

Spain

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/24/1847/011

EU/1/24/1847/012

EU/1/24/1847/013

EU/1/24/1847/014

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Axitinib Accord 5 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER – HUMAN READABLE DATA**

PC

SN

NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOR 5 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Axitinib Accord 5 mg tablets

axitinib

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Accord

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

Oral use

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**UNIT DOSE BLISTER PACK (28 x 1 TABLETS, 56 x 1 TABLETS) FOR 5 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Axitinib Accord 5 mg tablets

axitinib

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Accord

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

Oral use

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**OUTER CARTON AND LABEL FOR HDPE BOTTLE FOR 5 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Axitinib Accord 5 mg film-coated tablets

axitinib

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 5 mg axitinib.

**3. LIST OF EXCIPIENTS**

Contains lactose. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablets

60 film-coated tablets

**5. METHOD AND ROUTE OF ADMINISTRATION**

Read the package leaflet before use.

Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

After first opening of the bottle: use within 30 days

**9. SPECIAL STORAGE CONDITIONS**

This medicinal product does not require any special temperature storage conditions.

Keep the bottle tightly closed to protect from moisture.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Accord Healthcare S.L.U.

World Trade Center, Moll de Barcelona s/n, Edifici Est, 6a Planta,

08039, Barcelona,

Spain

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/24/1847/015

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Axitinib Accord 5 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER – HUMAN READABLE DATA**

PC

SN

NN

**B. PACKAGE LEAFLET**

**Package leaflet: Information for the patient**

**Axitinib Accord 1 mg film-coated tablets**

**Axitinib Accord 3 mg film-coated tablets**

**Axitinib Accord 5 mg film-coated tablets**

axitinib

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

* Keep this leaflet. You may need to read it again.
* If you have any further questions, ask your doctor, pharmacist or nurse.
* This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
* If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**

1. What Axitinib Accord is and what it is used for
2. What you need to know before you take Axitinib Accord
3. How to take Axitinib Accord
4. Possible side effects
5. How to store Axitinib Accord
6. Contents of the pack and other information
7. **What Axitinib Accord is and what it is used for**

Axitinib Accord is a medicine containing the active substance axitinib. Axitinib reduces the blood supply to the tumour and slows down the growth of cancer.

Axitinib Accord is indicated for the treatment of advanced kidney cancer (advanced renal cell carcinoma) in adults, when another medicine (called sunitinib or a cytokine) is no longer stopping disease from progressing.

If you have any questions about how this medicine works or why this medicine has been prescribed for you, ask your doctor.

1. **What you need to know before you take Axitinib Accord**

**Do not take Axitinib Accord:**

If you are allergic to axitinib or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.

**Warnings and precautions**

**Talk to your doctor or nurse before taking Axitinib Accord**

* **If you have high blood pressure.**

Axitinib Accord can raise your blood pressure. It is important to check your blood pressure before you take this medicine, and regularly while you are taking it. If you have high blood pressure (hypertension) you may be treated with medicines to reduce the blood pressure. Your doctor should make sure that your blood pressure is under control before starting Axitinib Accord treatment, and while on treatment with this medicine.

* **If you have thyroid gland problems.**

Axitinib Accord can cause thyroid gland problems. Tell your doctor if you get tired more easily, generally feel colder than other people, or your voice deepens whilst taking this medicine. Your thyroid function should be checked before you take Axitinib Accord and regularly while you are taking it. If your thyroid gland is not producing enough thyroid hormone before, or while on treatment with this medicine, you should be treated with thyroid hormone replacement.

* **If you have had a recent problem with blood clots in your veins and arteries (types of blood vessels), including stroke, heart attack, embolism, or thrombosis.**

Get emergency help right away and call your doctor if you get symptoms such as chest pain or pressure; pain in your arms, back, neck or jaw; shortness of breath; numbness or weakness on one side of your body; trouble talking; headache; vision changes; or dizziness while on treatment with this medicine.

* **If you suffer from bleeding problems**.

Axitinib Accord may increase your chance of bleeding. Tell your doctor if you have any bleeding, coughing up of blood or bloody sputum while on treatment with this medicine.

* **If you have or have had an aneurysm (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall.**
* **If during treatment with this medicine you get severe stomach (abdominal) pain or stomach pain that does not go away.**

Axitinib Accord may increase the risk of developing a hole in the stomach or intestine or formation of fistula (abnormal tube-like passage from one normal body cavity to another body cavity or the skin).

Tell your doctor if you have severe abdominal pain while on treatment with this medicine.

* **If you are going to have an operation or if you have an unhealed wound.**

Your doctor should stop Axitinib Accord at least 24 hours before your operation as it may affect wound healing. Your treatment with this medicine should be restarted when the wound has adequately healed.

* **If during treatment with this medicine, you get symptoms such as headache, confusion, seizures (fits), or changes in vision with or without high blood pressure.**

Get emergency help right away and call your doctor. This could be a rare neurological side effect named posterior reversible encephalopathy syndrome.

* **If you have liver problems.**

Your doctor should do blood tests to check your liver function before and during treatment with Axitinib Accord.

* **If during treatment with this medicine, you get symptoms such as excessive tiredness, swelling of the abdomen, legs or ankles, shortness of breath, or protruding neck veins.**

Axitinib Accord may increase the risk of developing heart failure events. Your doctor should monitor for signs or symptoms of heart failure events periodically throughout treatment with axitinib.

**Use in children and adolescents**

Axitinib Accord is not recommended for people aged under 18. This medicine has not been studied in children and adolescents.

**Other medicines and Axitinib Accord**

Some medicines may affect Axitinib Accord, or be affected by it. Please tell your doctor, pharmacist or nurse about all the medicines you have recently taken, are currently taking, or plan to take, including medicines obtained without a prescription, vitamins, and herbal medicines. The medicines listed in this leaflet may not be the only ones that could interact with Axitinib Accord.

The following medicines may increase the risk of side effects with Axitinib Accord:

* ketoconazole or itraconazole, used to treat fungal infections;
* clarithromycin, erythromycin or telithromycin, antibiotics used to treat bacterial infections;
* atazanavir, indinavir, nelfinavir, ritonavir or saquinavir, used to treat HIV infections/AIDS;
* nefazodone, used to treat depression.

The following medicines may reduce the effectiveness of Axitinib Accord:

* rifampicin, rifabutin or rifapentin, used to treat tuberculosis (TB);
* dexamethasone, a steroid medicine prescribed for many different conditions, including serious illnesses;
* phenytoin, carbamazepine or phenobarbital, anti-epileptics used to stop seizures or fits;
* St. John’s wort (*Hypericum perforatum*), a herbal product used to treat depression.

You **should not** take these medicines during your treatment with Axitinib Accord. If you are taking any of them, tell your doctor, pharmacist or nurse. Your doctor may change the dose of these medicines, change the dose of Axitinib Accord, or switch you to a different medicine.

Axitinib Accord may increase side effects associated with theophylline, used to treat asthma or other lung diseases.

**Axitinib Accord with food and drink**

Do not take this medicine with grapefruit or grapefruit juice, as it may increase the chance of side effects.

**Pregnancy and breast-feeding**

* If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before taking this medicine.
* Axitinib Accord could harm an unborn baby or breast-fed baby.
* Do not take this medicine during pregnancy. Talk to your doctor before taking it if you are pregnant or might become pregnant.
* Use a reliable method of contraception while you are taking Axitinib Accord and up to 1 week after the last dose of this medicine, to prevent pregnancy.
* Do not breast-feed during treatment with Axitinib Accord. If you are breast-feeding, your doctor should discuss with you whether to discontinue breast-feeding or discontinue Axitinib Accord treatment.

**Driving and using machines**

If you experience dizziness and/or feel tired while on treatment with Axitinib Accord, take special care when driving or using machines.

**Axitinib Accord contains lactose**

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

**Axitinib Accord contains sodium**

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

1. **How to take Axitinib Accord**

Always take this medicine exactly as your doctor has told you. You should check with your doctor, pharmacist or nurse if you are not sure.

The recommended dose is 5 mg twice a day. Your doctor may subsequently increase or decrease your dose depending on how you tolerate treatment with Axitinib Accord. Other products are available for the increased dose of 7 mg.

Swallow the tablets whole with water, with or without food. Take the Axitinib Accord doses approximately 12 hours apart.

**If you take more Axitinib Accord than you should**

If you accidentally take too many tablets or a higher dose than you need, contact a doctor for advice right away. If possible, show the doctor the pack, or this leaflet. You may require medical attention.

**If you forget to take Axitinib Accord**

Take your next dose at your regular time. Do not take a double dose to make up for the forgotten tablets.

**If you vomit while taking Axitinib Accord**

If you vomit, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.

**If you stop taking Axitinib Accord**

If you are not able to take this medicine as your doctor prescribed or you feel you do not need it anymore, contact your doctor right away.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse

1. **Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Some side effects could be serious. You must immediately contact your doctor if you experience any of those following serious side effects (see also section 2 “What you need to know before you take Axitinib Accord”):**

* **Heart failure events.** Tell your doctor if you experience excessive tiredness, swelling of the abdomen, legs, or ankles, shortness of breath, or protruding neck veins.
* **Blood clots in your veins and arteries (types of blood vessels), including stroke, heart attack, embolism, or thrombosis.** Get emergency help right away and call your doctor if you get symptoms such as chest pain or pressure; pain in your arms, back, neck or jaw; shortness of breath; numbness or weakness on one side of your body; trouble talking; headache; vision changes: or dizziness.
* **Bleeding.** Tell your doctor right away if you have any of these symptoms or a serious bleeding problem during treatment with Axitinib Accord: black tarry stools, coughing up of blood or bloody sputum, or change in your mental status.
* **Hole in the stomach or intestine or formation of fistula (abnormal tube-like passage from one normal body cavity to another body cavity or the skin)**. Tell your doctor if you have severe abdominal pain.
* **Severe increase in blood pressure (hypertensive crisis).** Tell your doctor if you have a very high blood pressure, severe headache, or severe chest pain.
* **Reversible swelling of the brain (posterior reversible encephalopathy syndrome).** Get emergency help right away and call your doctor if you get symptoms such as headache, confusion, seizures (fits), or changes in vision with or without high blood pressure.

Other side effects with Axitinib Accord may include:

# Very common: may affect more than 1 in 10 people

* High blood pressure, or increases in blood pressure
* Diarrhoea, feeling or being sick (nausea or vomiting), stomach ache, indigestion, soreness of the mouth, tongue or throat, constipation
* Shortness of breath, cough, hoarseness
* Lack of energy, feeling weak or tired
* Under-active thyroid gland (may show in your blood tests)
* Redness and swelling of the palms of the hands or soles of the feet (hand-foot syndrome), skin rash, dryness of the skin
* Joint pain, pain in hands or feet
* Loss of appetite
* Protein in the urine (may show in your urine tests)
* Weight loss
* Headache, taste disturbance or loss of taste

**Common: may affect up to 1 in 10 people**

* Dehydration (loss of body fluids)
* Kidney failure
* Flatulence (wind), haemorrhoids, bleeding from gums, bleeding from the rectum, a burning or stinging sensation in the mouth
* Hyper-active thyroid gland (may show in your blood tests)
* Sore throat or nose and throat irritation
* Muscle pain
* Nose bleeding
* Skin itching, redness of the skin, hair loss
* Ringing/sound in the ears (tinnitus)
* Reduction in the number of red blood cells (may show in your blood tests)
* Reduction in the number of blood platelets (cells that help blood to clot) (may show in your blood tests)
* Presence of red blood cells in the urine (may show in your urine tests)
* Changes in the levels of different chemicals/enzymes in the blood (may show in your blood tests)
* Increase in the number of red blood cells (may show in your blood tests)
* Swelling of the abdomen, legs, or ankles, protruding neck veins, excessive tiredness, shortness of breath (signs of heart failure events)
* Fistula (abnormal tube like passage from one normal body cavity to another body cavity or the skin)
* Dizziness
* Inflammation of the gall bladder

**Uncommon: may affect up to 1 in 100 people**

* Reduction in the number of white blood cells (may show in your blood tests)

**Not known: frequency cannot be estimated from the available data**

* An enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections).

**Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2013/03/WC500139752.doc). By reporting side effects you can help provide more information on the safety of this medicine.

**5. How to store Axitinib Accord**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the blister foil or bottle after “EXP”. The expiry date refers to the last day of the month.

This medicine does not require any special temperature storage conditions.

OPA/Aluminium/PVC/Aluminium blister:

Store in the original package in order to protect from moisture.

HDPE bottle:

Keep the bottle tightly closed to protect from moisture.

Do not use any pack that is damaged or shows signs of tampering.

Bottle pack:

After first opening of the bottle:

1mg: use within 45 days.

3mg and 5mg: use within 30 days.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

1. **Contents of the pack and other information**

**What Axitinib Accord contains**

* The active substance is axitinib. Axitinib Accord film-coated tablets come in different strengths.

Axitinib Accord 1 mg: each tablet contains 1 mg axitinib

Axitinib Accord 3 mg: each tablet contains 3 mg axitinib

Axitinib Accord 5 mg: each tablet contains 5 mg axitinib

* The other ingredients are lactose, Cellulose, Microcrystalline (E460), silica colloidal anhydrous, hydroxypropylcellulose (300–600 mPa\*s), croscarmellose sodium (E 468), talc, magnesium stearate (E 470b), hypromellose 2910 (15 mPas) (E464), lactose monohydrate, titanium dioxide (E171), triacetin, and iron oxide red (E172) (see section 2 Axitinib Accord contains lactose).

**What Axitinib Accord looks like and contents of the pack**

Axitinib Accord 1 mg film-coated tablets are red colored, modified capsule shaped biconvex film-coated tablets debossed with 'S14' on one side and plain on other side. The size of the tablet is approximately 9.1 ± 0.2 mm X 4.6 ± 0.2 mm. Axitinib Accord 1 mg is available in bottles of 180 tablets and blisters of 14 tablets. Each blister pack contains 28 tablets or 56 tablets or perforated unit dose blisters of 28 x 1 or 56 x 1 tablets.

Axitinib Accord 3 mg film-coated tablets are red colored, round, biconvex film-coated tablet debossed with 'S95' on one side and plain on the other side. The size of the tablet is approximately 5.3 ± 0.3 X 2.6 mm ± 0.3 mm. Axitinib Accord 3 mg is available in bottles of 60 tablets and blisters of 14 tablets. Each blister pack contains 28 tablets or 56 tablets or perforated unit dose blisters of 28 x 1 or 56 x 1 tablets.

Axitinib Accord 5 mg film-coated tablets are red colored, triangular shaped biconvex film-coated tablets debossed with 'S15' on one side and plain on other side. The size of the tablet is approximately 6.4 ± 0.3 mm X 6.3 ± 0.3 mm. Axitinib Accord 5 mg is available in bottles of 60 tablets and blisters of 14 tablets. Each blister pack contains 28 tablets or 56 tablets or perforated unit dose blisters of 28 x 1 or 56 x 1 tablets.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**

Accord Healthcare S.L.U.

World Trade Center, Moll de Barcelona, s/n,

Edifici Est, 6a Planta,

08039 Barcelona,

Spain

**Manufacturer**

APIS Labor GmbH

Resslstraβe 9

9065 Ebenthal in Kärnten,

Austria

Accord Healthcare Polska Sp.z.o.o

ul Lutomierska 50,95-200

Pabianice, Poland

Accord Healthcare single member S.A.

64th Km National Road Athens, Lamia,

Schimatari, 32009, Greece

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

AT / BE / BG / CY / CZ / DE / DK / EE / ES / FI / FR / HR / HU / IE / IS / IT / LT / LV / LU / MT / NL / NO / PL / PT / RO / SE / SI / SK

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**This leaflet was last revised in {MM/YYYY}**

Detailed information on this medicine is available on the European Medicines Agency website: <https://www.ema.europa.eu>.