AXITINIB RISK MANAGEMENT PLAN

Risk Management Plan (RMP) *Version number*: 10.2

Data lock point for this RMP: 30 October 2018

Date of final sign off: 16 May 2019

Rationale for submitting an updated RMP:

The Marketing Authorisation Holder (MAH) is providing an updated RMP with a revised list of safety concerns to align with the new Good Pharmacovigilance Practice (GVP) Module V guidelines (Rev.2). On 06 September 2018, in the Final Assessment Report (FAR), the Pharmacovigilance and Risk Assessment Committee (PRAC) Rapporteur provided its final recommendation as regards the MAH's proposal presented in PSUR No. 9 to remove certain 'important identified and potential risks' and one missing information. The updates are in line with the new GVP Module V (Rev.2) guidelines and new RMP template issued on 31 October 2018 EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.2.

Summary of significant changes in this RMP:

RMP Part	RMP Module/Annex	Last RMP Approved (opinion date)	RMP Version number	Major change (s) in Version 10.2
PART I PRODUCT OVERVIEW	Not applicable	27 March 2015	9.0	Alignment with the GVP Module V Rev.2 requirements including addition of Hyperlink to the Product Information Additional monitoring in the EU updated
PART II SAFETY SPECIFICATION	PART II.Module SI Epidemiology of the Indications and Target Populations	27 March 2015	9.0	No major updates.
	PART II.Module SII Non-Clinical Part of the Safety Specification	27 March 2015	9.0	No major updates. The Module was aligned with the GVP Module V Rev.2 requirements.
	PART II.Module SIII Clinical Trial Exposure	27 March 2015	9.0	The list of studies evaluated for all indications was updated. The clinical trial (CT) exposure was updated.
	PART II.Module SIV Populations Not Studied in Clinical Trials	27 March 2015	9.0	Alignment with the GVP Module V Rev.2 requirements.
	PART II.Module SV Post-Authorisation Experience	27 March 2015	9.0	Alignment with the GVP Module V Rev.2 requirements. The post-authorisation exposure was updated.
	PART II.Module SVI Additional EU Requirements for the Safety Specification	27 March 2015	9.0	Alignment with the GVP Module V Rev.2 requirements.

RMP Part	RMP Module/Annex	Last RMP Approved (opinion date)	RMP Version number	Major change (s) in Version 10.2
	PART II.Module SVII Identified and Potential Risks	27 March 2015	9.0	Removal of the safety concerns in line with the GVP Module V Rev.2 and minor change in the presentation of the missing information as per agreement with the PRAC Rapporteur.
	PART II.Module SVIII Summary of the safety concerns	27 March 2015	9.0	Updated according to the list of safety concerns presented in Module SVII.
PART III PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)		27 March 2015	9.0	Updated according to the list of safety concerns presented in Module SVII.
PART IV PLAN FOR POST-AUTHORISATION EFFICACY STUDIES		27 March 2015	9.0	Alignment with the GVP Module V Rev.2 requirements.
PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)		27 March 2015	9.0	Updated according to the changes made to the safety concerns in Module VII.
PART VI SUMMARY OF THE RISK MANAGEMENT PLAN		27 March 2015	9.0	The text has been updated as per current template accompanying GVP Module V Rev.2.
PART VII ANNEXES TO THE RISK MANAGEMENT PLAN	**ANNEX 1** Eudravigilance interface			
	~~**ANNEX 2** Current or proposed SmPC/PIL~~	~~27 March 2015~~	~~9.0~~	Removed as per alignment with the GVP Module V Rev.2.
	~~**ANNEX 3** Worldwide marketing authorisation by country~~	~~27 March 2015~~	~~9.0~~	Removed as per alignment with the GVP Module V Rev.2.
	~~**ANNEX 4** Synopsis of clinical trial programme~~	~~27 March 2015~~	~~9.0~~	Removed as per alignment with the GVP Module V Rev.2.
	ANNEX ~~5~~ 2 ~~Synopsis of pharmacoepidemiological study programme~~ Tabulated summary of planned ongoing and completed pharmacovigilance study programme	09 September 2013	7.0	Minor editorial changes.

RMP Part	RMP Module/Annex	Last RMP Approved (opinion date)	RMP Version number	Major change (s) in Version 10.2
	ANNEX ~~6~~ 3 Protocols for proposed and on-going and completed studies in the pharmacovigilance plan ~~studies in Part III~~	09 September 2013	7.0	Minor editorial changes.
	ANNEX ~~7~~ 4 Specific adverse event follow-up forms	27 March 2015	9.0	Minor editorial changes.
	ANNEX ~~8~~ 5 Protocols for proposed and on-going studies in RMP Part IV	09 September 2013	7.0	Minor editorial changes.
	ANNEX ~~9~~ 6 ~~Synopsis of newly available study reports in Parts III IV~~ Details of proposed additional risk minimisation activities (if applicable)	09 September 2013	7.0	Minor editorial changes.
	ANNEX ~~10~~ 7 ~~Details of proposed additional risk minimisation measures~~ Other supporting data	Not applicable	10.2	CT and PM tables for each safety concern were provided.
	~~**ANNEX 11** Mock-up examples~~	~~09 September 2013~~	~~7.0~~	Removed as per alignment with the GVP Module V Rev.2.
	ANNEX ~~12~~ 8 ~~Other supporting data~~ Summary of changes to the Risk Management Plan over time	Not applicable	10.2	References removed; list of changes over time added as per alignment with the GVP Module V Rev.2. Minor change in the presentation of the missing information.

Other RMP versions under evaluation: None

Details of the currently approved RMP:

Version number: 9.0

Approved with procedure: EMEA/H/C/002406/IB/0012/G

Date of approval (opinion date): 27/03/2015

QPPV name[1]: Françoise Dumas-Sillan

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

LIST OF ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
ADR	Adverse Drug Reaction
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ATE	Arterial Embolic and Thrombotic Event
AUC	Area Under the Curve
BID	Twice Daily
BMI	Body Mass Index
CNT	Cytoreductive Nephrectomy
CrCL	Creatinine Clearance
CTCAE v3.0	Common Terminology Criteria for Adverse Events, Version 3.0
CTD	Common Technical Document
DCA	Data Capture Aid
ECOG	Eastern Cooperative Oncology Group
eCTD	Electronic Common Technical Document
EU	European Union
GI	Gastrointestinal
hERG	Human Ether-a-go-go
HIV	Human Immunodeficiency Virus
HMG Co A	3-Hydroxy-3-Methylglutaryl Coenzyme A
IARC	International Agency for Research on Cancer
ICSR	Individual Case Safety Report
IFN	Interferon
IL-2	Interleukin-2
IMS	IMS Health Prescribing Insights Medical
MAH	Market Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
mRCC	Metastatic Renal Cell Carcinoma
ONJ	Osteonecrosis of the Jaw
OR	Odds Ratio
PL	Package Leaflet
PRES	Posterior Reversible Encephalopathy Syndrome
PT	Preferred Term
RCC	Renal Cell Carcinoma
RMM	Risk Minimisation Measure
RMP	Risk Management Plan
RR	Relative Risk
Rx%	Prescriptions
SAE	Serious Adverse Event (s)
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
TCE	Trichloroethylene

ULN	Upper Limit of Normal
UK	United Kingdom
US	United States
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
VTE	Venous Embolic and Thrombotic Event

TABLE OF CONTENTS

LIST OF TABLES

PART I. PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	Axitinib
Pharmacotherapeutic group(s) (ATC Code)	L01XE17
Marketing Authorisation Holder	Pfizer Europe MA EEIG
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	Inlyta
Marketing authorisation procedure	Centralised
Brief description of the product:	Chemical class: Axitinib is a small molecule kinase inhibitor.
	Summary of mode of action: Axitinib potently and selectively inhibits the tyrosine kinase of VEGFR-1, -2, and -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 inhibited metastases in many experimental models of cancer.
	Important information about its composition: N/A
Hyperlink to the Product Information:	Product information
Indication(s) in the EEA	Current: Axitinib is indicated for the treatment of adult patients with advanced RCC after failure of prior treatment with sunitinib or a cytokine.
	Proposed: N/A

Dosage in the EEA	Current: **Recommended Dose:** The recommended starting oral dose of axitinib is 5 mg BID. Axitinib may be taken with or without food. **Dose Modification:** Dose increase or reduction is recommended based on individual safety and tolerability. Subjects who tolerate the axitinib starting dose of 5 mg BID with no adverse reactions >Grade 2 (ie, without severe adverse reactions according to the CTCAE v3.0) for 2 consecutive weeks, may have their dose increased to 7 mg BID unless the subject's blood pressure is >150/90 mm Hg or the subject is receiving antihypertensive medication. Subsequently, using the same criteria, dose may be increased to a maximum of 10 mg BID. Management of some adverse drug reactions may require temporary or permanent discontinuation and/or dose reduction of axitinib therapy. When dose reduction is necessary, the axitinib dose may be reduced to 3 mg BID and further to 2 mg BID. Dose adjustment is not required based on subject age, race, gender, or body weight.
	Proposed: N/A
Pharmaceutical forms and strengths	Current: Axitinib tablets are supplied as follows: 1 mg oval tablets: Red film-coated tablets, debossed with "Pfizer" on 1 side and "1 XNB" on the other. 3 mg round tablets: Red film-coated tablets, debossed with "Pfizer" on 1 side and "3 XNB" on the other. 5 mg triangular tablets: Red film-coated tablets, debossed with "Pfizer" on 1 side and "5 XNB" on the other. 7 mg diamond shaped tablets: Red film-coated tablets, debossed with "Pfizer" on 1 side and "7 XNB" on the other.
	Proposed: N/A
Is/will the product be subject to additional monitoring in the EU?	No

ATC = Anatomical Therapeutic Chemical; BID = Twice Daily; CTCAE = Common Terminology Criteria for Adverse Events v3.0; EEA = European Economic Area; EU = European Union; INN = International Non-Proprietary Name; N/A = Not Applicable; RCC = Renal Cell Carcinoma; VEGF = Vascular Endothelial Growth Factor; VEGFR = Vascular Endothelial Growth Factor Receptor.

PART II. SAFETY SPECIFICATION

Module SI. Epidemiology of the Indication(s) and Target Population (s)

Indication:

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

RCC accounts for 2-3% of all cancers, and occurs most frequently in Western countries. In 2012, there were an estimated 84,400 incident RCC cases and 34,700 deaths from kidney cancer in the European Union (EU).[1] About 25-30% of patients with RCC have advanced disease at the time of diagnosis.[2,3] Advanced RCC is associated with a high quality of life burden and drastically reduced survival – only about 2.3% to 22.5% of advanced RCC patients survive for 5 years or more[4,5,6,7] as compared to 92.6% of patients with localised cancer (SEER 2018).[7] More detailed information on the incidence and prevalence of advanced RCC, associated mortality and demographic profile of advanced RCC patient population is presented below.

Incidence:

Incidence data specific to advanced RCC are lacking, but can be derived from any stage RCC incidence estimates by applying the proportion of cases that present with metastatic disease at diagnosis. The International Agency for Research on Cancer (IARC) maintains a cancer incidence database called GLOBOCAN; these data are derived from population-based cancer registries throughout the world. Although the GLOBOCAN database contains information on "kidney cancer", RCC accounts for 90-95% of kidney neoplasms[8,9] thus, GLOBOCAN incidence estimates are reasonably applicable to RCC. Gupta et al. obtained country-specific metastatic RCC incidence estimates using the data on any RCC incidence from the 2002 IARC GLOBOCAN database assuming that 25-30% (mean 27.5%) of all new RCC patients present with metastatic disease.[2]

Since the analysis of GLOBOCAN 2002 data was published by Gupta et al., IARC has made 2012 estimates of cancer incidence and mortality available.[10] The table below contains the 2012 incidence estimates assuming that 27.5% of the new RCC patients present with metastatic disease.

Region	Country	Estimated Age-Adjusted Incidence Rate Of Metastatic RCC in 2012 (per 100,000)		Estimated Total Number of Incident Metastatic RCC Cases in 2012
		Males	Females	
North/ Central America	Canada	3.3	1.9	1534
	Mexico	1.3	0.7	1059
	United States	4.4	2.3	16011

Region	Country	Estimated Age-Adjusted Incidence Rate Of Metastatic RCC in 2012 (per 100,000)		Estimated Total Number of Incident Metastatic RCC Cases in 2012
		Males	Females	
Europe	Belgium	3.3	1.6	485
	Denmark	2.7	1.3	207
	Finland	2.6	1.8	243
	France	3.9	1.6	3031
	Germany	3.9	2.1	5119
	Italy	3.6	1.3	3108
	Portugal	2.0	0.8	276
	Spain	3.1	1.3	1780
	Sweden	2.2	1.3	309
	UK	3.0	1.6	2671
	European Union-28	3.4	1.6	23434
Australia and Asia	Australia	3.5	1.7	963
	Japan	2.1	0.8	4628
	Korea (Republic of)	3.2	1.3	1554
	Singapore	2.0	0.9	110
South America	Argentina	3.2	1.4	1119
	Brazil	1.1	0.6	1720

RCC = Renal Cell Carcinoma; UK = United Kingdom.

Based on the Canadian Cancer Society's Steering Committee on Cancer Statistics,[11] the number of incident metastatic kidney cancer cases in 2012 was estimated as 1540 (ie, 27.5% of 5600 kidney cancer cases), which is consistent with the GLOBOCAN estimate above.

Prevalence:

The table below presents 2012 GLOBOCAN 5-year prevalence estimates for selected countries.[10] Given that RCC accounts for up to 95% of kidney neoplasms,[8] these kidney cancer prevalence estimates reasonably approximate RCC prevalence estimates.

Region	Country	Estimated 5-year prevalence of RCC in 2012 (per 100,000)		Estimated Total Number of Incident Metastatic RCC Cases in 2012
		Males	Females	
North/ Central America	Canada	73.7	44.1	17041
	Mexico	15.7	8.6	10047
	United States	90.9	51.0	178013
Europe	Belgium	78.2	40.2	5257
	Denmark	51.9	26.6	1799
	Finland	63.7	50.0	2558
	France	92.9	41.5	34302
	Germany	104.1	61.8	58591
	Italy	96.1	41.6	35627
	Portugal	47.5	21.5	3097
	Spain	65.1	29.8	18693
	Sweden	49.6	31.2	3188
	UK	55.6	31.2	22366
	European Union-28	77.2	40.0	248799

Region	Country	Estimated 5-year prevalence of RCC in 2012 (per 100,000)		Estimated Total Number of Incident Metastatic RCC Cases in 2012
		Males	Females	
Australia and Asia	Australia	70.7	36.2	9889
	Japan	64.8	30.3	51524
	Korea (Republic of)	63.7	27.1	18512
	Singapore	26.8	12.5	866
South America	Argentina	44.6	21.5	10152
	Brazil	12.8	7.7	15272

RCC = Renal Cell Carcinoma; UK = United Kingdom.

Demographics of the Population in the Authorised Proposed Indication – Age, Gender, Racial and/or Ethnic Origin and Risk Factors for the Disease

In the metastatic RCC incidence estimates (based on GLOBOCAN data) provided above, incidence in males is twice the incidence in females on average. The recently updated guidelines on RCC from the European Association of Urology note a 1.5-fold increase in RCC incidence in males as compared with females, with greatest incidence seen in patients aged 60-70 years.[1] These trends are generally supported by individual studies, as described in the examples below.

In a retrospective cohort study of 5654 United States (US) and European patients with RCC, 67% were male and median age at diagnosis was 61 years.[12]

In an analysis of 11,182 advanced RCC patients registered in the US SEER database, 65% were male, almost 69% were over 60 years of age, and 85.5% were white.[13]

In a smaller study of 308 advanced RCC patients previously untreated with systemic therapy who were enrolled in clinical trials at the US Cleveland Clinic Foundation between 1987 and 2002, 73% of patients were males, and median age at advanced RCC diagnosis was 54 years (range 23 to 76 years).[14]

Risk Factors for the Disease

RCC Risk Factors

In addition to increasing age and male sex, recently published reviews of the epidemiology of RCC suggest that smoking, obesity, and hypertension are established risk factors for RCC, while diet, and occupational exposures to specific carcinogens may also contribute to its aetiology; a minor proportion of RCC is attributed to rare genetic factors.[15,16]

Smoking

Cigarette smoking is a well-established risk factor for RCC. In a 2005 meta-analysis of 19 case-control studies of 8032 cases and 13,800 controls and 5 cohort studies of 1,457,754 participants, the relative risk (RR) for lifetime smoking status was 1.54 (95% CI: 1.42, 1.68) for males and 1.22 [95% Confidence Interval (CI): 1.09, 1.36) for females.[17] A dose-relationship was evident; the RRs for the highest dose (≥21 cigarettes per day) was 2.03

(95% CI: 1.51, 2.74) for men and 1.58 (95% CI: 1.14, 2.20) for women. Results were similar between European and North American studies and between population-based case-control and cohort studies. In a recent meta-analysis of 14 studies of smoking and RCC mortality, current smoking was significantly associated with overall mortality (hazard ratio [HR] = 1.57, 95% CI: 1.20, 2.06) and with death from RCC (HR=1.50, 95% CI: 1.10, 2.05).[9]

Passive smoking has also been shown to increase risk for RCC. Among never-smokers identified in a US population-based case-control study, the odds ratio (OR) for at least 20 years of home exposure to environmental tobacco smoke as compared with no home exposure was 2.18 (95% CI: 1.14, 4.18).[18]

Obesity

Excess body weight is considered an established risk factor for RCC. In a 2008 meta-analysis of 12 observational cohort studies of renal cancer, the RR for every 5 kg/m^2 increase in body mass index (BMI) was 1.24 (95% CI: 1.15, 1.34) for males and 1.34 (95% CI: 1.25, 1.43) for females.[19] Results were similar among European/Australian, North American, and Asian studies.

Hypertension

The effects of hypertension and antihypertensive medication use on RCC are difficult to tease apart because most patients with diagnosed hypertension are treated. Nonetheless, several large observational cohort studies have shown an independent association between hypertension and RCC; all effect estimates presented were derived from multivariate analyses that adjusted for factors such as age, BMI, blood pressure medication use, and smoking status. In a study of 363,992 Swedish male construction workers identified during 1971-1992 (759 cases of RCC were observed), there was a dose-response relationship between the risk of RCC and diastolic blood pressure ($p<0.001$); a similar, but not statistically significant trend was observed for systolic blood pressure.[20] Compared with men with a diastolic blood pressure of <70 mm Hg, men with a diastolic blood pressure of ≥110 mm Hg had a 2.2-fold increased risk of RCC (95% CI: 1.1, 4.5). Compared with men with a systolic blood pressure of <120 mm Hg, men with a systolic blood pressure of ≥160 mm Hg had a 1.7-fold increased risk of RCC (95% CI: 1.1, 2.6).

The overall relationship between blood pressure and RCC, as well as the relationship in the absence of antihypertensive medication use, were assessed in a population-based Norwegian study of 36,728 women and 35,688 men.[21] Among women (94 RCC cases were observed), those with a diastolic blood pressure of ≥105 mm Hg were 1.6 times as likely to be diagnosed with RCC as compared with those with a diastolic blood pressure of <85 mm Hg (95% CI: 0.8, 3.5); those with a systolic blood pressure of ≥170 mm Hg were 2.0 times as likely to be diagnosed with RCC as compared with those with a systolic blood pressure of <130 mm Hg (95% CI: 0.9, 4.6). Among women who reported never using a blood pressure medication, the RRs were 1.7 (95% CI: 0.6, 5.0) and 3.4 (95% CI: 1.3, 8.9) for diastolic and systolic blood pressure, respectively. Among men, no association between blood pressure and renal cell cancer risk was observed.

In the European Prospective Investigation into Cancer and Nutrition (EPIC), 225 RCC cases were observed among 254,935 men and women recruited from 8 European countries during 1992-1998[22] with information on blood pressure and antihypertensive medication use. Among women, those with a diastolic blood pressure of >100 mm Hg were 1.9 times as likely to be diagnosed with renal cancer as compared with those with a diastolic blood pressure of <80 mm Hg (95% CI: 1.0, 3.6); those with a systolic blood pressure of >160 mm Hg were 2.6 times as likely to be diagnosed with renal cancer as compared with those with a systolic blood pressure of <120 mm Hg (95% CI: 1.4, 5.0). There was a trend in the RR across all categories of each blood pressure measure. Among men, those with a diastolic blood pressure of >100 mm Hg were 3.1 times as likely to be diagnosed with renal cancer as compared with those with a diastolic blood pressure of <80 mm Hg (95% CI: 1.7, 5.6); those with a systolic blood pressure of >160 mm Hg were 2.4 times as likely to be diagnosed with RCC as compared with those with a systolic blood pressure of <120 mm Hg (95% CI: 1.1, 5.2). As with women, there was a trend in the RR across all categories of each blood pressure measure. These effect estimates were not appreciably different between users and non-users of antihypertensive medications, except for users with poorly controlled blood pressure.

A study published by Flaherty et al. (2005) reported on the association between blood pressure and RCC risk in the US Nurses' Health Study (118,191 women) and Health Professionals Follow-Up Study (48,953 men) cohorts.[23] In the Nurses' Health study cohort (156 RCC cases were observed), hypertension was associated with a 1.9-fold increase in renal cell cancer risk (95% CI: 1.4, 2.7). In the Health Professionals Follow-Up Study cohort (110 RCC cases were observed), hypertension was associated with a 1.8-fold increase in RCC risk (95% CI: 1.2, 2.7). Use of thiazide diuretics was not found to be independently associated with RCC risk.

Diabetes

Some studies have shown an association between diabetes and RCC, but it is not clear whether diabetes affects RCC risk independently from hypertension and obesity.[24]

Diet

Although the variation in RCC incidence worldwide and increasing rates in Asia suggests that diet may play a role in RCC development, epidemiology studies of diet, such as studies evaluating fat, meat, fish, or alcohol intake, and RCC risk have produced inconsistent results.[15] In a pooled analysis of 13 cohort studies that followed a total of 530,469 women and 244,483 men, Lee et al. observed an adjusted RR estimate of 0.68 (95% CI: 0.54, 0.87) for high fruit/vegetable intake (≥600 grams/day) as compared with low fruit/vegetable intake (<200 grams/day).[25] However, a subsequent report on 27,062 Finnish male smokers enrolled in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study showed no association between fruit/vegetable intake and RCC risk.[26] In another analysis of the same group of pooled studies (encompassing 530,469 women and 244,483 men) described above, there was no statistically significant difference in renal cell cancer risk between those in the highest and lowest quintiles of total fat intake, after adjustment for BMI, alcohol use, and fruit/vegetable intake.[27]

Occupational Exposures

Studies of exposure to trichloroethylene (TCE), an industrial solvent used to degrease metal, suggest an association with risk of RCC. In a recent meta-analysis of 15 cohort and 13 case-control studies, the RR estimate was 1.3 (95% CI: 1.2, 1.5) for the association between TCE exposure and kidney cancer.[28] Other occupational exposures, such as lead, glass fibres, mineral wood fibres, and brick dust, require further study.[15]

Genetic Factors

As reviewed by Ljungberg et al. (2011) and Qayyum et al. (2013), first-degree relatives of RCC cases have twice the risk of RCC as compared with patients with no immediate family history.[15,24] There is some evidence of low susceptibility conferred by genetic metabolic variants, along with rare germline mutations that are associated with early-onset, bilateral, and/or multifocal RCC; mutations in the von Hippel-Lindau gene are the most common of these rare mutations, affecting 1 in 36,000 births.

The Main Existing Treatment Options

Traditional cancer treatments such as radiation therapy and chemotherapy are not as effective with this type of cancer. Among the main, currently approved drugs for the treatment of advanced RCC, there are cytokines (interleukin-2 [IL-2] and interferon alfa [IFN-α]), agents targeting the VEGF-pathway (sunitinib, sorafenib, bevacizumab in combination with IFN-α, pazopanib, axitinib and cabozantinib), mTOR-inhibitors (everolimus and temsirolimus) and check point inhibitors (e.g. ipilimumab and nivolumab).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

The mortality burden of advanced RCC is significant. While 5-year survival can be up to 92.6% for patients with localised kidney and renal pelvis cancer,[7] it ranges from 8% to 22.5% among patients with advanced RCC,[4,5,6,7,29] and can be significantly lower in sub-populations of untreated patients, e.g. as low as 2.3% in patients without cytoreductive nephrectomy.[29] The table below summarises the findings of the studies that reported on the advanced RCC mortality:

Study	N	Treatment	Survival				
			1-Year	2-Year	3-Year	5-Year	Median
US							
Motzer, 2002 [5]	463	INF-α[a]	54%	30%	19%	10%	13 mo
Mekhail, 2005 [14]	308	Any	57%	-	-	-	14.8 mo
2008-2014 SEER 18 registries [7]	N/A	Any	-	-	-	11.6%	-
1988-2004 SEER 9 registries [10]	2447 2925	CNT[b] No CNT[b]	53.6% 18.5%	36.3% 7.4%	-	19.4% 2.3%	-
1988-2004 SEER 17 registries [13]	3443 7739	CNT[b] No CNT[b]	-	-	-	-	10.5 mo 3.75 mo
Heng, 2009 [30]	645	Anti-VEGF[a]	-	47%	~35%	-	22 mo

Study	N	Treatment	Survival				
			1-Year	2-Year	3-Year	5-Year	Median
Europe							
Negrier, 2000 [4]	281	IL-2	41%	22%	--	8%	10 mo
Aass, 2005 [31]	161[c] 159	INF-α-2° INF-α-2° +13CRA	~53% ~59%	~26% ~41%	~16% ~25%	~8% ~10%	13.2 mo 17.3 mo
Sant, 2009 [32]	69,522 (all stages)	Any	72%	--	58%	51%	--
Wahlgren, 2013 [33]	2753	Any	-	-	21%	13%	10.9 mo
Japan							
Naito, 2009 [6]	1,463	Any	64.2%	-	35.2%	22.5%	21.4 mo
Takagi, 2013 [34]	86	Targeted therapy	-	-	-	-	38 mo
International mRCC Database Consortium (Canada, US, Singapore, Denmark, South Korea)							
Harshman 2012 [35]	1,673	Anti-VEGF	-	44-51%[d]	-	-	20.2 mo
Canada							
Canadian Cancer Registry database at Statistics Canada 2011 [36]	N/A	Any	-	-	-	67%[e]	-

a. With or without nephrectomy or any other therapy.
b. CNT, with or without any other therapy.
c. 1-, 2-, 3- and 5-year survival estimated from the figure presented in Aass, 2005.[31]
d. 2-year conditional survival, ie, the probability of surviving an additional 2 years, conditional on surviving 0-18 months following treatment initiation.
e. 5-year relative survival ratio, ie, the ratio of observed 5-year survival to the survival expected for people in the same general population; excludes data from Quebec.

13CRA = 13-Cis-Retinoic Acid; CNT = Cytoreductive Nephrectomy; IL-2 = Interleukin-2; INF = Interferon; mRCC = Metastatic Renal Cell Carcinoma; N = Number of Patients; mo = Months; SEER = Surveillance, Epidemiology, and End Results; US = United States; VEGF = Vascular Endothelial Growth Factor.

Important Co-morbidities:

No data on the prevalence of medical co-morbidities in the population of patients with advanced RCC were identified. Table 1 summarizes the data on co-morbidities among patients with any RCC. Specific search terms were "metastatic renal cell carcinoma" or "mRCC" or "RCC" or "renal cell carcinoma" or "renal cancer" or "kidney cancer" and "comorbid" or "comorbidity" or "anaemia" or "decreased haemoglobin" or "cardiovascular" or "diabetes" or "hypertension" or "high blood pressure" or "hypothyroidism" or "thyroid function" or "thyroid."

Table 1. Co-morbidity in the Advanced Renal Cell Carcinoma/Any Renal Cell Carcinoma Patient Population

Important Co-morbidity in the RCC Population	Prevalence, Mortality and Co-Prescribed Medicinal Products
Anaemia	Prevalence Anaemia is common in RCC patients. In a study of 1046 RCC cases (593 localised and 453 metastatic) undergoing nephrectomy between 1989 and 2001 at a single US institution, anaemia (defined as preoperative haematocrit less than 40% in men and less than 36% in women) was present in 52.1% of the subjects.[37] In a small study of 37 patients diagnosed with RCC between 1987 and 1995 in a single UK hospital, anaemia was present in 46% of the cases.[38] In a recent study of 968 patients with metastatic RCC from 13 international centres, 56% had a baseline haemoglobin concentration that was less than the lower limit of normal.[39] Mortality Anaemia is associated with shorter survival times and increased risk of mortality in patients. Based on a comprehensive literature review by Caro et al., patients with RCC who have anaemia have a mortality rate that is 1.9-fold higher than those without anaemia.[40] Co-prescribed medications Anaemia can be effectively treated with erythropoietin.
Cardiovascular disease	Prevalence In a large population-based study that included 1259 patients aged 50 years or older who were diagnosed with kidney cancer (includes RCC and renal pelvis carcinoma) in 1995-2002 in southern Netherlands, the prevalence of heart and vascular disease varied by age from 14% to 39% in males and from 6% to 27% in females.[41] Of the 368 RCC patients in a Danish population-based case-control study conducted in 1989-1991, 11.7% had a history of angina pectoris, 7.1% had a prior MI, and 3.5% had a history of stroke.[42] In a recent study of 8633 Danish residents with RCC, 6.1% had a prior MI, 5.2% had congestive heart failure, and 8.4% had cerebrovascular disease.[43] Mortality No data on cardiovascular mortality are available for the RCC patient population. Co-prescribed medications Medications that may be prescribed for coronary heart disease patients include beta blockers, ACE inhibitors, calcium channel blockers, diuretics, nitrates, and statins.

Table 1. Co-morbidity in the Advanced Renal Cell Carcinoma/Any Renal Cell Carcinoma Patient Population

Important Co-morbidity in the RCC Population	Prevalence, Mortality and Co-Prescribed Medicinal Products
Diabetes	Prevalence In a Danish population-based case-control study conducted in 1989-1991, 6.3% of the 368 RCC patients had a history of diabetes.[42] In a large population-based study that included 1259 patients aged 50 years or older who were diagnosed with kidney cancer (includes RCC and renal pelvis carcinoma) from 1995 to 2002 in southern Netherlands, the prevalence of diabetes varied by age from 8% to 21%.[41] In a recent study of 8633 Danish residents with RCC, 2.6-6.2% had a history of diabetes.[43] In a study of 1761 Italian patients with RCC, 8.9% had a prior diabetes diagnosis.[44] Mortality In a study of 1604 Italian patients with non-metastatic RCC (152 with prior diagnosis of diabetes), diabetes was not significantly associated with RCC- or non-RCC-related mortality.[44] Co-prescribed medications Most commonly, patients with diabetes are treated with oral antihyperglycemics, insulin, HMG CoA-reductase inhibitors (statins), antiplatelets, and antihypertensives.
Hypertension	Prevalence Studies suggest that a significant proportion of patients with RCC have a history of arterial hypertension and that blood pressure returns to normal or decreases following nephrectomy.[45] The reported estimates of hypertension prevalence in RCC population vary from ~ 29% to 79%.[38,42,45,46,47] Mortality No data on hypertension-associated mortality are available for RCC patient population. Co-prescribed medications Medications that may be prescribed for hypertensive patients include alpha blockers, ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, central alpha agonists, diuretics, and renin inhibitors.
Thyroid disorders	Prevalence Literature suggests that history of thyroid disorders is common in RCC patients. For instance, in an epidemiological study of 247 women diagnosed with RCC in a single US cancer centre between 1981 and 1985, 19% had a prior history of thyroid disorders, including hypothyroidism, nodular thyroid, goitre, hyperthyroidism, and carcinoma of the thyroid.[48] In a Danish population-based case-control study of RCC risk factors, a history of thyroid disorders was present in 6.5% of 368 histologically verified RCC cases.[42] Mortality No data on mortality in association with thyroid disorders in RCC patients are available. Co-prescribed medications Thyroid hormone supplements may be used to treat thyroid disorders. Standard treatment for hypothyroidism involves daily use of the synthetic thyroid hormone levothyroxine.

ACE = Angiotensin Converting Enzyme; HMG Co A = 3-Hydroxy-3-Methylglutaryl-coenzyme A; MI = Myocardial Infarction; RCC = Renal Cell Carcinoma; UK = United Kingdom; US = United States.

Module SII. Non-Clinical Part of the Safety Specification

The non-clinical safety profile of axitinib was evaluated in vitro and in vivo in mice and dogs. The mouse and dog were selected as the rodent and non-rodent species, respectively, for general toxicity studies because they demonstrated the ability to assess potential toxicities from both primary and secondary pharmacological targets, exposure profiles were sufficient, and there was representation of most major metabolism pathways observed in humans. Consistent with the intended clinical route of administrations, the toxicity studies were conducted using the oral administration route. Repeat-dose toxicity studies up to 39 weeks of daily dosing were conducted and were considered relevant to the dosing regimen in the clinic. In addition, safety pharmacology, genetic toxicity, and reproductive toxicity studies were conducted.

Based on the non-clinical safety studies conducted with axitinib, the primary target organ toxicities were observed in the gastrointestinal, hematopoietic (primarily erythroid), musculoskeletal, heart, and reproductive systems. Other findings related to administration of axitinib included effects on the exocrine pancreas and hemodynamic effects (elevated blood pressure, reduced heart rate). Axitinib was also associated with the potential for fertility and developmental effects. In genetic toxicity tests, axitinib was identified as an aneugen but not a mutagen.

Table 2. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Toxicology Findings	
Gastrointestinal Effects on the alimentary tract were observed in dogs treated for ≥14 days and in mice given axitinib for 13 or 26 weeks. Gastrointestinal effects in the dog were indicative of widespread toxicity to the alimentary tract following repeat dosing, including abnormal faecal excretions, and chronic active inflammation, ulcerations, haemorrhage and/or necrosis of the oral, stomach or intestinal mucosa. Mucosal hyperplasia and/or inflammation in the cecum or colon were observed following repeat dosing in the mouse. Changes in mice and dogs were partially to fully reversible following a 4-week recovery period after 13 weeks of treatment (CTD Module 2.4.4.11.1).	Axitinib has the potential to cause gastrointestinal toxicity in humans. See PART II.SVII.3.1.2 Gastrointestinal Perforation and Fistula and PART II.SVII.3.1.3 Haemorrhage.
Haematopoietic Haematopoietic effects were observed in the mouse and dog treated for ≥14 days, primarily reflected by an effect on the erythron including bone marrow hypocellularity, but also as effects on coagulative potential and lymphopoietic organs (e.g. lymphoid atrophy of the thymus and spleen). Following 13 weeks of axitinib-treatment in mice and dogs and a subsequent 4-week recovery period, all haematopoietic effects were reversible (CTD Module 2.4.4.11.2).	Axitinib has the potential to cause haematolymphopoietic effects in humans; however it has not been considered to be a safety concern requiring further actions in the RMP.

Table 2. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Toxicology Findings	
Musculoskeletal Musculoskeletal changes observed following repeat-dosing included a thickening of the physeal growth plate in the mouse and dog and incisor tooth odontopathies in the mouse. Partial to full reversibility of effects on the growth plate and teeth were observed after a 4-week recovery period following 13 weeks of axitinib administration (CTD Module 2.4.4.11.3).	Axitinib has the potential to have an effect on bone growth in a paediatric population in a state of active growth; bone effects in adult patients whose growth plates are inactive have not been reported; however this has not been considered to be a safety concern requiring further actions in the RMP.
Pancreatic A decrease in zymogen granules and concomitant increase in acinar cells in the pancreas were observed in dogs after 28 days of axitinib administration. (CTD Module 2.4.4.11.6.3).	Axitinib may have potential effects on the exocrine pancreas based on non-clinical safety studies in the dog. See PART II.SVII.3.1.6 Effects on the Exocrine Pancreas for events in humans in clinical studies.
Reproductive and Developmental toxicity Male and Female Reproductive Organs Effects on male (testicular degeneration/atrophy and/or decreased number of germ cells/hypospermia) and female (decreased corpora lutea and/or uterine atrophy) reproductive organs were observed in the mouse and dog administered axitinib for ≥28 days. Testicular effects were fully reversible after an 8-week recovery period following 38-weeks of axitinib administration, and female reproductive effects were partially reversible after 13-weeks of treatment and a 4-week recovery period. Fertility Results of a fertility assessment completed in the mouse as part of a fertility and early embryonic development study identified effects on sperm density and count in males without an effect on mating and fertility. Fertility and early embryonic development were affected in female mice (CTD Module 2.4.4.11.4). Embryo-foetal toxicity Axitinib administration was associated with developmental effects in a mouse embryofoetal development study with effects on ossification (skeletal variations) and occurrences of cleft palate (CTD Module 2.4.4.11.5).	Axitinib may impair reproductive function and fertility in humans, based on results of non-clinical safety studies. Neovascularization is a critical component of embryonic and foetal development. As such, axitinib may cause foetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women using axitinib. See PART II.SVII.3.1.10 Reproductive and Developmental Toxicity for events in humans in clinical studies.
Cardiovascular The potential for haemodynamic changes (increased blood pressure, changes in heart rate) was identified in conscious, telemetered mice, rats, and dogs following repeat-dose administration. Lower heart weights were present in male mice after ≥14 days of axitinib administration with no histologic or functional correlate; similar effects were not observed in female mice or dogs (CTD Module 2.4.4.11.6.1).	Consistent with expected pharmacology, axitinib is known to cause elevations in blood pressure. Heart rate changes may also be observed. See PART II.SVII.3.1.8 Congestive Heart Failure/Cardiomyopathy and PART II.SVII.3.1.9 Torsade de pointes due to QT prolongation for events in humans in clinical studies.

Table 2. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Toxicology Findings	
Genotoxicity Axitinib was identified as an aneugen but not a mutagen in genetic toxicity studies (CTD Module 2.4.4.11.6.5).	Axitinib has aneugenic potential, but a no effect level was established at AUC exposures approximately 70-fold above those observed in humans at the recommended human starting dose.

AUC = Area Under the Curve

The non-clinical studies included in Module 4 and summarised in Module 2.4, 2.6.2, 2.6.4, and 2.6.6 of the Electronic Common Technical Document (eCTD) are considered appropriate to support the intended indication of axitinib for the treatment of adults with advanced RCC after failure of prior systemic treatment. Carcinogenicity and pre- and postnatal development studies are planned to support a terminated clinical study (A4061071 [also referred to as AP311736][2] in patients with RCC being treated in the adjuvant setting).

[2] This is a co-sponsored study by Pfizer and SFJ Pharmaceuticals (sponsorship varies according to country). In this study a total of 724 patients were randomized to receive axitinib or placebo (363 in axitinib arm versus 361 in placebo arm; 4 patients – 3 in axitinib arm and 1 in placebo arm - were randomized and not treated). The Clinical Study Report is available upon request.

Module SIII. Clinical Trial Exposure

Cumulative Clinical Trial Exposure

Clinical trial exposure data are being provided for completed[3] studies as of 30 October 2018. The clinical trial exposure data are provided for 3 different pools of subjects.

- All single-agent clinical trials in the approved indication of advanced RCC (N=672, Pool A).
- Randomized single-agent, clinical trials for advanced RCC (N=494, Pool B).
- All completed[3] clinical trial data for all indications, single-agent and combination studies (does not include completed studies in healthy volunteers) (N=2528, Pool C).

Populations for Analysis of Clinical Trial Data in this RMP

- Pool A: Single-agent clinical trials (5) in the approved indication of advanced RCC (Phase 3 RCC Study A4061032, Phase 2 RCC Studies A4061012, A4061023 and A4061035, and Phase 3 Study A4061051 second-line);
- Pool B: The population from axitinib single-agent, randomised, clinical trials (2) for advanced RCC (Phase 3 RCC Study A4061032 and Study A4061051 second-line);
- Pool C: All completed[3] clinical trial data (26[4]) for all indications, single-agent and combination studies (does not include completed studies in healthy volunteers) (A4061032, A4061012, A4061023, A4061035 and A4061051 second-line, A4060010, A4061022, A4061044, A4061011, A4061014, A4061015, A4061027, A4061046 and A4061051 first-line and the newly added A4061010, A4061013, A4061016, A4061019, A4061020, A4061028, A4061030, A4061034, A4061038, A4061039, A4061055 and A4061058).

In addition, exposure in clinical studies in special populations (hepatic impairment) is provided in Table 7.

Exposure to axitinib for patients with advanced RCC and for all patients in all completed single-agent and combination axitinib studies by duration of exposure, dose, and demographic characteristics is shown in Table 3 through Table 6.

These studies enrolled more male than female patients, and the patients were predominantly Caucasian and Asian, with very few Black patients. Patients under 18 years of age were excluded from the studies, but the studies included a substantial proportion of patients ≥65 years of age.

[3] All studies included in the analysis of data from clinical trial in this RMP had completed enrollment and protocol specified follow-up periods as of the cut-off date, although patients may still be monitored for safety.

[4] Study A4061051 includes patients with 2 lines of therapies: first- and second-line.

Table 3. Duration of Exposure

Duration of Exposure [a]	Patients	Person-Time (months) [b]
Phase 2 and 3 Studies of Single-Agent Axitinib in Subjects with Advanced RCC [c]		
≥1 month	634	9488.1
≥3 months	530	9276.1
≥6 months	427	8812.2
≥12 months	265	7435.1
≥24 months	124	5034.2
≥36 months	53	3003.6
Total	**672**	**9509.0**
Phase 2 and 3 Studies of Single-Agent Axitinib in Subjects in Randomised Advanced RCC Studies [d]		
≥1 month	472	6985.5
≥3 months	384	6804.5
≥6 months	314	6489.5
≥12 months	190	5435.9
≥24 months	83	3650.2
≥36 months	40	2422.1
Total	**494**	**6997.8**
Phase 1, 2 and 3 All Completed Clinical Trials [e]		
≥1 month	2296	26883.6
≥3 months	1726	25756.2
≥6 months	1225	23524.6
≥12 months	666	18777.7
≥24 months	289	12468.3
≥36 months	145	8255.7
Total	**2528**	**27014.0**

a. Duration includes time when temporarily withdrew from study but re-started at later date; one month is defined to be 30.44 days.
b. Exposure (person-time) is based on overall exposure.
c. Studies include: A4061012, A4061023, A4061032, A4061035, and A4061051 second-line.
d. Studies include: A4061032, A4061051 second-line.
e. Studies include: A4060010, A4061010, A4061011, A4061012, A4061013, A4061014, A4061015, A4061016, A4061019, A4061020, A4061022, A4061023, A4061027, A4061028, A4061030, A4061032, A4061034, A4061035, A4061038, A4061039, A4061044, A4061046, A4061051 first-line, A4061051 second-line, A4061055, and A4061058.
Source: Clinical database, programming table reference: RMP-October 2018 Tables 1.1.1, 1.1.2 and 1.1.3.
RCC = Renal Cell Carcinoma.

Table 4. By Dose

Dose of Exposure (per day) [a]	Persons	Person-Time (months) [b]
Phase 2 and 3 Studies of Single-Agent Axitinib in Subjects with Advanced RCC [c]		
<6 mg	1	0.03
6 – 8 mg	1	6.41
10 mg	403	5664.68
12 – 14 mg	128	1768.33
15 mg	1	8.18
16 – 18 mg	8	150.69
20 mg	128	1884.20
30 mg	1	19.81

Table 4. By Dose

Dose of Exposure (per day) [a]	Persons	Person-Time (months) [b]
40 mg	1	6.70
Total	**672**	**9509.03**
Phase 2 and 3 Studies of Single-Agent Axitinib in Subjects in Randomised Advanced RCC Studies [d]		
<6 mg	1	0.03
6 – 8 mg	1	6.41
10 mg	272	3722.04
12 – 14 mg	96	1384.49
15 mg	0	0
16 – 18 mg	1	101.71
20 mg	121	1756.60
30 mg	1	19.81
40 mg	1	6.70
Total	**494**	**6997.80**
Phase 1, 2 and 3 All Completed Clinical Trials [e]		
<6 mg	284	3181.83
6 – 8 mg	64	663.11
10 mg	1461	13086.79
11 mg	2	23.65
12 – 14 mg	305	3971.12
15 mg	15	116.33
16 – 18 mg	13	241.75
20 mg	370	5619.91
22 mg	1	30.19
30 mg	7	51.48
35 mg	1	5.52
40 mg	4	12.39
60 mg	1	9.95
Total	**2528**	**27014.03**

a. Maximum total daily dose during participation in the study.
b. Duration includes time when subject temporarily withdrew from study but re-started at a later date; one month is defined as 30.44 days.
c. Studies include: A4061012, A4061023, A4061032, A4061035, and A4061051 second-line.
d. Studies include: A4061032, A4061051 second-line.
e. Studies include: A4060010, A4061010, A4061011, A4061012, A4061013, A4061014, A4061015, A4061016, A4061019, A4061020, A4061022, A4061023, A4061027, A4061028, A4061030, A4061032, A4061034, A4061035, A4061038, A4061039, A4061044, A4061046, A4061051 first-line, A4061051 second-line, A4061055, and A4061058.
Source: Clinical database, programming table reference: RMP-October 2018 Tables 2.1.1, 2.1.2 and 2.1.3.
RCC = Renal Cell Carcinoma.

Table 5. By Age Group and Gender

Age Group	Persons		Person-Time (months) [a]	
	Male	Female	Male	Female
Phase 2 and 3 Studies of Single-agent Axitinib in Subjects with Advanced RCC [b]				
<18	0	0	0	0
18 – 44	53	23	509.4	383.2
45 – 64	281	109	4174.6	1906.1
65 – 74	117	45	1482.3	456.9

Table 5. By Age Group and Gender

Age Group	Persons		Person-Time (months) [a]	
	Male	Female	Male	Female
75 – 84	31	11	386.1	170.0
≥ 85	1	1	31.7	8.6
Total	**483**	**189**	**6584.2**	**2924.8**
Phase 2 and 3 Studies of Single-agent Axitinib in Subjects in Randomised Advanced RCC Studies [c]				
<18	0	0	0	0
18 – 44	42	16	403.0	271.4
45 – 64	207	81	3006.1	1494.6
65 – 74	86	33	982.1	366.5
75 – 84	21	7	314.1	128.2
≥ 85	1	0	31.7	0
Total	**357**	**137**	**4737.1**	**2260.7**
Phase 1, 2 and 3 All Completed Clinical Trials [d]				
<18	0	0	0	0
18 – 44	119	109	1174.5	1255.0
45 – 64	930	525	11099.6	5456.2
65 – 74	401	233	3939.9	2244.6
75 – 84	137	66	1136.1	635.2
≥ 85	4	4	44.4	28.5
Total	**1591**	**937**	**17394.5**	**9619.5**

a. Duration includes time when temporarily withdrew from study but re-started at later date; one month is defined to be 30.44 days.
b. Studies include: A4061012, A4061023, A4061032, A4061035 and A4061051 second-line.
c. Studies include: A4061032, A4061051 second-line.
d. Studies include: A4060010, A4061010, A4061011, A4061012, A4061013, A4061014, A4061015, A4061016, A4061019, A4061020, A4061022, A4061023, A4061027, A4061028, A4061030, A4061032, A4061034, A4061035, A4061038, A4061039, A4061044, A4061046, A4061051 first-line, A4061051 second-line, A4061055, and A4061058.
Source: Clinical database, programming table reference: RMP-October 2018 Tables 3.1.1, 3.1.2 and 3.1.3.
RCC = Renal Cell Carcinoma.

Table 6. By Ethnic or Racial Origin

Ethnic/Racial Origin	Persons	Person-Time (months) [a]
Phase 2 and 3 Studies of Single-agent Axitinib in Subjects with Advanced RCC [b]		
Caucasian	388	4370.1
Black	1	23.5
Asian	277	5055.5
Other	6	60.0
Total	**672**	**9509.0**
Phase 2 and 3 Studies of Single-agent Axitinib in Subjects in Randomised Advanced RCC Studies [c]		
Caucasian	278	3045.8
Black	1	23.5
Asian	210	3873.4
Other	5	55.2
Total	**494**	**6997.8**

Table 6. By Ethnic or Racial Origin

Ethnic/Racial Origin	Persons	Person-Time (months) [a]
Phase 1, 2 and 3 All Completed Clinical Trials [d]		
Caucasian	1743	16878.5
Black	54	336.5
Asian	675	9122.9
Other	64	672.4
Not Listed or Race Not Collected	1	3.7
Total	**2528**	**27014.0**

a. Duration includes time when temporarily withdrew from study but re-started at later date; one month is defined to be 30.44 days.
b. Studies include A4061012, A4061023, A4061032, A4061035 and A4061051 second-line.
c. Studies include: A4061032, A4061051 second-line.
d. Studies include: A4060010, A4061010, A4061011, A4061012, A4061013, A4061014, A4061015, A4061016, A4061019, A4061020, A4061022, A4061023, A4061027, A4061028, A4061030, A4061032, A4061034, A4061035, A4061038, A4061039, A4061044, A4061046, A4061051 first-line, A4061051 second-line, A4061055, and A4061058.
Source: Clinical database, programming table reference: RMP-October 2018 Tables 4.1.1, 4.1.2 and 4.1.3.
RCC = Renal Cell Carcinoma.

Data from special populations were available from study A4061036, a phase 1 study to evaluate the pharmacokinetics in subjects with impaired hepatic function, in which patients received a single dose of axitinib (Table 7). There are no data from clinical studies in other special populations.

Table 7. Special Populations

Special Populations	Persons	Person-Time (months) [a]
Hepatic impairment	16	0.52

a. Duration includes the time when a patient temporarily withdrew from the study but re-started at a later date; one month is defined as 30.44 days. All patients received a single 5-mg oral dose of the study treatment (AG-013736) on Day 1, therefore the exposure for the patients with hepatic impairment accounted to 16/30.44=0.52.
Source: A4061036 CSR.

Module SIV. Populations Not Studied In Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Populations excluded from the clinical program include paediatric patients below the age of 18 years and women who were pregnant or lactating or women of child bearing potential who were not protected from becoming pregnant. In addition, patients with recent cardiovascular or thromboembolic disease, severe hepatic or renal impairment, severe medical conditions, human immunodeficiency virus or acquired immunodeficiency syndrome, were excluded; therefore it is unknown whether they would be at greater risk of Adverse Events (AEs).

Table 8. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criterion	Reason for Being an Exclusion Criterion	Missing Information / Justification for not Being a Missing Information or a Contraindication
ECOG Performance Status of >1	Poor performance status increases risk of dropping out from the clinical studies, which can jeopardise the scientific integrity of the study.	Is it considered to be included as missing information? No Rationale: There are no data suggesting the possibility of a worse benefit/risk profile for axitinib in patients with ECOG Performance Status>1.
Paediatric patients<18 years old	Increased risk of damage to growth plates consistent with mechanism of action.	Is it considered to be included as missing information? Yes. Rationale: Lack of data for axitinib in paediatric patients. The intended indication, advanced RCC, is a disease that has extremely limited applicability to paediatric patients in that the disease occurs for the most part in the adult population. The SmPC Section 4.2 states that safety and efficacy of axitinib in children and adolescents (<18 years) have not been established.
Women who were pregnant or lactating or women of child bearing potential who were not protected from becoming pregnant	To minimise increased risk of birth defects due to mechanism of action of axitinib.	Is it considered to be included as missing information? Yes. Rationale: Lack of data for axitinib in women who were pregnant or lactating or women of child bearing potential who were not protected from becoming pregnant. The SmPC Section 4.6 states that axitinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with this medicinal product and that axitinib should not be used during breast-feeding.

Table 8. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criterion	Reason for Being an Exclusion Criterion	Missing Information / Justification for not Being a Missing Information or a Contraindication
Severe hepatic impairment and moderate and severe renal impairment (creatinine clearance <60 mL/min)	To ensure uniformity of clinical trial population and exclude patients with significant co-morbidities potentially adversely impacting clinical trial results e.g. increased risk of excessively high drug exposure.	Is it considered to be included as missing information? Yes. Rationale: The SmPC Section 5.2 states that axitinib has not been studied in subjects with severe hepatic impairment (Child-Pugh class C) and should not be used in this population. The SmPC states (Section 5.2) that 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.
Subjects with recent major surgery, active gastrointestinal bleeding, evidence of brain metastases, recent cardiovascular or thromboembolic disease, severe medical conditions, HIV or AIDS	Increased risk of delayed wound healing, bleeding, and thromboembolic events. Presence of HIV or AIDS can increase the risk of dropping out from study, which can jeopardise the scientific integrity of the clinical studies.	Is it considered to be included as missing information? Yes. Rationale: The SmPC Section 4.4 states that 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. The SmPC Section 4.4 states that axitinib should be used with caution in patients who are at risk for, or who have a history of venous and arterial embolic and thrombotic events.
Subjects currently using or anticipating the need for treatment with drugs that are known strong CYP3A4 inhibitors or inducers	Increased risk of drug-drug interactions, potentially resulting in higher or lower drug exposure than expected in absence of strong CYP3A4 inhibitor or inducer.	Is it considered to be included as missing information? No. Rationale: The SmPC Section 4.5 states that selection of concomitant medicinal products with no or minimal CYP3A4/5 inhibition or induction potential is recommended.

AIDS = Acquired Immune Deficiency Syndrome; CYP = Cytochrome P450; ECOG = Eastern Cooperative Oncology Group; HIV = Human Immunodeficiency Virus; RCC = Renal Cell Carcinoma; SmPC = Summary of Product Characteristics; ULN = Upper Limit of Normal.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Table 9. Limitations of ADR Detection

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
Which are Rare (≥1/10,000 to <1/1,000) and Very rare (<1/10,000)	Overall 2528 subjects with solid tumours were exposed to axitinib monotherapy in Phase 1, 2 and 3 completed studies	Rare or very rare ADRs occurring in more than 3,000 patients were not observed in the clinical development programme.
Due to prolonged exposure	Only a limited number of patients with advanced RCC were exposed to axitinib for >5 years.	A long-term safety analysis of patients treated in clinical studies was conducted. Two (2) populations were evaluated (patients with advanced RCC vs. advanced solid tumours). In single-agent studies with advanced solid tumours, conducted in a variety of tumours, 145 patients continued to receive axitinib for ≥3 years. In advanced RCC single-agent studies, 53 patients continued to receive axitinib for ≥3 years. Overall, the long-term analysis of the safety profile of axitinib was consistent with the information described in the SmPC.[49] The safety of axitinib in patients receiving long-term treatment with axitinib in clinical trials will continue to be monitored in on-going clinical trials and post-authorisation experience.
Which have a long latency	Because of short life span expected among patients with advanced RCC, ADRs associated with a long latency period are difficult to observe in this population.	Patients with earlier stage RCC (potentially curable patients) were studied in an adjuvant treatment of RCC trial (terminated Pfizer study A4061071), which did not identify any detection of ADRs associated with a long latency period. Due to the fact that most patients have advanced disease, the potential impact of delayed effects is not likely to be high. The potential for delayed effects of axitinib will continue to be monitored in post-authorisation experience.

ADR = Adverse Drug Reaction; RCC = Renal Cell Carcinoma; SmPC = Summary of Product Characteristics.

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 10. Exposure of Special Populations Included or not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program. Axitinib has not been studied in pregnant or breast feeding women. The safety database for axitinib does not include any reports in pregnant and breast feeding women. Studies in animals have shown reproductive toxicity including malformations. The SmPC states that axitinib may cause foetal harm when administered to a pregnant woman. Axitinib is not expected to be administered to pregnant and breast feeding women in the post-marketing setting.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment	Axitinib has been studied in subjects with mild (Child-Pugh Class A, n = 8 subjects in Study A4061036[5]) and moderate (Child-Pugh Class B, n = 8 subjects in Study A4061036) hepatic impairment, but has not been studied in subjects with severe (Child-Pugh Class C) hepatic impairment. Compared to healthy volunteers with normal hepatic function, mild hepatic impairment did not alter axitinib plasma exposure, but the systemic exposure of axitinib was higher (approximately 2-fold) in subjects with moderate hepatic impairment (Child-Pugh Class B) (CTD Module 2, Section 2.7.2.3.9.1.1; CTD Module 5, A4061036). The SmPC states that the axitinib dose should be decreased in patients with moderate hepatic impairment (CTD Module 2, Section 2.7.2.3.9.1.1), while axitinib should not be used in patients with severe hepatic impairment.
• Patients with renal impairment	Axitinib parent drug is not detected in the urine (CTD Module 2, Section 2.6.4.5.4.3; CTD Module 4, AG013736-PDM-043; CTD Module 2, Section 2.7.2.2.2.1.1; CTD Module 5, A4061003). Axitinib has not been studied in subjects with moderate and severe renal impairment (CTD Module 2, Section 2.7.2.3.9.1.2). Studies conducted in subjects with advanced RCC excluded subjects with serum creatinine >1.5 ULN or calculated creatinine <60 mL/min. However, in Study A4061032, subjects could be categorised as having renal impairment based on their creatinine clearance at baseline and at any time on the study. There were 73 patients with moderate renal impairment and 4 patients with severe renal impairment at baseline, and there were 101 subjects with moderate renal impairment and 10 subjects with severe renal impairment at any time on the study. Population pharmacokinetic analyses have shown that axitinib clearance was not altered in subjects with renal impairment and no dose adjustment of axitinib is recommended (CTD Module 2, Section 2.7.2.3.5.1; CTD Module 5, PMAR-00079).

[5] Subjects in the Phase 2 or Phase 3 studies in RCC patients could not be categorized for hepatic impairment since the information needed for calculating the Child Pugh score were not captured on the Case Report Form for studies in patients.

Table 10. Exposure of Special Populations Included or not in Clinical Trial Development Programmes

Type of special population	Exposure
• Patients with other relevant comorbidities	Subjects with other relevant co-morbidities such as subjects with recent major surgery, active gastrointestinal bleeding, evidence of brain metastases, recent cardiovascular or thromboembolic disease, severe medical conditions, HIV or AIDS/immunocompromised patients, were not included in the clinical development program.
Population with relevant different ethnic origin	Axitinib studies included both Asian and Caucasian populations, although there were few Black patients in the clinical trials. There were 429 Asian, 40 Black, and 8 patients from other not further detailed ethnic origin reporting serious ADRs in axitinib clinical trials. Other not further detailed ethnicities were reported in 20 patients. No clinically significant differences between Asian and Caucasian populations have been found. Therefore, no clinically significant differences in safety profile of axitinib are expected among patients of other racial and/or ethnic origins.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Other • Paediatric patients	Not included in the clinical development program. Axitinib has not been studied in patients <18 years of age. The intended indication, advanced RCC, is a disease that has extremely limited applicability to paediatric patients in that the disease occurs for the most part in the adult population. Axitinib is not expected to be administered to paediatric subjects in the post-marketing setting. The SmPC states that the safety and efficacy of axitinib in children and adolescents (<18 years) have not been established.
• Elderly patients	Elderly patients were studied in clinical trials of axitinib. In the advanced RCC studies, 206 of the 672 patients (30.6%) were ≥65 years of age (162 with age between 65 and 74 years, 42 with age between 75 and 84 years and 2 aged more than 85 years), and in all completed Phase 1, 2 and 3 trials, 845 of the 2528 patients (33.4%) were ≥65 years of age (634 with age between 65 and 74 years, 203 with age between 75 and 84 years and 8 aged more than 85 years).

AIDS = Acquired Immune Deficiency Syndrome; HIV = Human Immunodeficiency Virus; RCC = Renal Cell Carcinoma; SmPC = Summary of Product Characteristics; ULN = Upper Limit of Normal.

Module SV. Post-Authorisation Experience

Based on the estimates of exposure to commercial axitinib, a total of 78,484 patients worldwide are estimated to have been exposed to axitinib since axitinib was approved.

Based on ongoing safety surveillance of post-marketing reports, axitinib is used primarily in adult patients with advanced RCC after failure of prior treatment with sunitinib or a cytokine. Due to limited available evidence regarding the axitinib use in paediatric patients (≤17 years of age), the benefit-risk profile of the axitinib use in paediatric patients is not known. Therefore, it will continue to be considered missing information.

Routine monitoring indicates that the most commonly reported off-label indications are Adenoid cystic carcinoma, Lung neoplasm malignant, and Thyroid cancer metastatic. The total number of cases from the use in these indications is low and the AEs reported in association with these uses are consistent with the known safety profile of axitinib.

The post-marketing exposure in special populations (paediatric and elderly population) is included in Table 11.

Based on the available evidence regarding the populations of pregnant or lactating women, patients with severe hepatic impairment and moderate and severe renal impairment, patients with recent major surgery, patients with active peptic ulcer disease, patients with evidence of brain metastases, spinal cord compression, or carcinomatous meningitis, the benefit-risk profile of the axitinib use in these populations is unknown. Therefore, the use in these populations will continue to be considered missing information. A detailed discussion of the axitinib use in these special populations considered missing information is included in Module SVII.

SV.1. Post-Authorisation Exposure

SV.1.1. Method Used to Calculate Exposure

This estimate is based on axitinib use in the US through 30 October 2018 and was obtained from several sources including specialty pharmacies, Group Purchasing Organizations (GPOs), and exception accounts, all of which have direct communication links to IQVIA (former IMS, IMS Health Prescribing Insights Medical); IQVIA cleans and summarizes the data for Pfizer. Non-US IQVIA Standard Unit data are utilized to derive a US and non-US factor. The factor is then applied to the US new patient starts to estimate Global Patients. The split of exposure by age, gender, region, formulation and dose is based on the prescriptions (Rx%) for the respective categories. The Rx% is multiplied by the total patients in order to calculate the required breakdown of exposure. The Rx% is available for a relatively short duration and varies with the time interval covered by them. The Rx% for age, gender and average daily dose is available for 3 years (from third quarter 2015 to second quarter 2018) and formulation, region data covers a time interval of 6 years (from third quarter 2012 to second quarter 2018).

Of note, the global total patient exposure is based on US new patient data. Free patient volume is added to the US estimate only. Free patients include uninsured patients covered by Pfizer's patient assistance programs as well as hardship approvals under Medicare D.

SV.1.2. Exposure

Axitinib received first regulatory approval in the US on 27 January 2012. It is estimated that 78,484 patients were exposed to axitinib from the first regulatory approval in the US on 27 January 2012 through 30 October 2018.

The cumulative estimated exposures (total global patients) by indication, gender, age group, dose, formulation, and region based on Pfizer internal sales data (extrapolated to the cut-off date of 30 October 2018) and factored, as applicable, by data from IQVIA for the period from 27 January 2012 to 30 October 2018 are summarised in Table 11.

Table 11. Cumulative Estimated Exposure for Axitinib (Oral Formulation)

Indication	Sex			Age (Years)			Dose					Region			
	Male	Female	Unk	0-16	17-65	> 65	1 mg	5 mg	3 mg	7 mg	Unk [a]	EU	US	Japan	ROW
Overall	**49,566**	**27,924**	**994**	**0**	**33,623**	**44,862**	**26,703**	**51,259**	**0**	**11**	**511**	**26,491**	**17,932**	**31,033**	**3,028**
Malignant neoplasm of kidney, except renal pelvis	44,815	23,575	994	0	31,006	38,379	21,485	47,645	0	0	254	23,419	15,853	27,435	2,677
Neoplasm of uncertain or unknown behaviour of urinary organs	4,677	4,092	0	0	2,360	6,409	5,218	3,551	0	0	0	2,960	2,003	3,467	338
Total Others	74	257	0	0	257	74	0	63	0	11	257	112	76	131	13

a. Strength was not available.
Total sum of patients may differ due to rounding in calculations.
EU = Europe; ROW = Rest of World; Unk = Unknown; US = United States.

Module SVI. Additional EU Requirements for the Safety Specification

SVI.1. Potential for Misuse for Illegal Purposes

Based on the preclinical studies there was no evidence to suggest that axitinib has the potential for abuse. There are no underlying pharmacological mechanisms, or neural or behavioural signs and symptoms that suggest that axitinib would induce drug-seeking behaviour. There have been no known reports of drug abuse or drug dependence associated with the use of axitinib in clinical trials and post-marketing experience.

Module SVII. Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Not applicable as this is not an initial submission.

SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

None.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

No new safety concerns were identified.

Previous regulatory request: PSUR No. 9 assessment procedure (EMEA/H/C/PSUSA/00010022/201801)

In accordance with GVP Module V - Risk management systems (Rev.2) (effective date 31 March 2017) and as part of the PSUR No. 9 assessment procedure (EMEA/H/C/PSUSA/00010022/201801), the MAH proposed to remove a number of risks from the list of safety concerns. On 06 September 2018 in the Final Assessment Report (FAR), the Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteur provided its final recommendation as regards the MAH's proposal presented in PSUR No. 9 to remove certain 'important identified and potential risks' and one missing information. Additionally, the important potential risk of QT prolongation is renamed to Torsade de pointes due to QT prolongation as per the PRAC's request.

The important identified risks agreed upon by the PRAC to be removed from the list of safety concerns are: Elevation of haemoglobin or haematocrit, Hypertension, Proteinuria, Thyroid dysfunction, Overexposure in patients with a history of hepatic or hepatobiliary disorders, Palmar-Plantar Erythrodysaesthesia, Fatigue and asthenic conditions, Overexposure with CYP3A inhibitors, Hepatic disorders, and Neutropenia/Cytopenia.

The important potential risks agreed upon by the PRAC to be removed from the list of safety concerns are: Wound healing complications, Microangiopathy and Drug-drug interactions with CYP1A2, CYP2C8 and P-glycoprotein substrates. Additionally, the important potential risk of QT prolongation is renamed to Torsade de pointes due to QT prolongation as per the PRAC's request.

The missing information agreed upon by the PRAC to be removed from the list of safety concerns is: Risks in subjects with recent myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure,

cerebrovascular accident or transient ischemic attack, deep vein thrombosis or pulmonary embolism.

SVII.3. Details of Important Identified, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risks:

SVII.3.1.1. Arterial Embolic and Thrombotic Events

Table 12. Arterial Embolic and Thrombotic Events[a]

Potential mechanism	Postulated mechanisms of ATE include inhibiting VEGF action causing hypertension, hypothyroidism, endothelial cell damage leading to thrombosis, or increasing blood viscosity by an overproduction of erythropoietin. ATE (myocardial infarction, TIA, ischaemic stroke) have been reported as drug reactions of other kinase inhibitors of VEGFR (e.g. pazopanib).[50,51] In addition, a hypercoagulable or prothrombotic state occurs in malignancies due to the ability of tumour cells to activate the coagulation system.[52]
Evidence source and strength of evidence	Evidence Source: Axitinib clinical trials and post-marketing reports. Strength of evidence: Arterial embolic and thrombotic events have been reported for other VEGFI, and have been reported in axitinib clinical trials and in the post-marketing setting.
Characterisation of the risk	All-causality AEs suggestive of ATE occurred in 6.3% (95% CI 4.54, 8.35) of subjects in All Single-agent Advanced RCC Studies. The frequency was similar in All Completed Clinical Trials (ie, in any indication including advanced RCC): 6.1% (95% CI: 5.23, 7.14). All Single-Agent Advanced RCC Studies The frequency of individual Preferred Terms (PTs) that potentially could represent or lead to ATE events, the seriousness and the outcome are provided in Annex 7 (Table 1). Myocardial infarction is the most commonly reported PT (11 occurrences). Fatal (Grade 5) events were reported in 8 (1.2%) subjects. Of the 42 subjects with potential ATE-related events, 29 (69.0%) had Grade 3 or 4 events and 8 (19.0%) had Grade 5 (fatal). All causality AEs of ATE by grade is provided in Annex 7 (Table 2). Post-authorisation Data There were 306 cases (containing 320 relevant events; 310 of which were deemed to be serious) for patients treated with axitinib that were potentially indicative of ATE. The most commonly reported event is Myocardial infarction (81, all serious). The frequency of the individual PTs, the seriousness and the outcome are provided in Annex 7 (Table 3).
Risk factors and risk groups	Cancer patients have an increased risk of ATE. Increasing age, smoking, hypertension, hypercholesterolemia, polycythaemia, and a history of ATE are other recognised predisposing risk factors for ATE.[53]
Preventability	There are no known specific preventive measures to reduce the risk of thromboembolic events in patients treated with axitinib.
Impact on the risk-benefit balance of the product	These events may be serious and lead to hospitalisation and may be fatal.

Table 12. Arterial Embolic and Thrombotic Events[a]

Public health impact	Considering the epidemiology of ATE in the mRCC population, it is unlikely the risk in patients on axitinib will have a major impact on overall public health as compared with ATE in general.

a. MedDRA (v 21.1) - Embolic and thrombotic events, arterial [Standardised MedDRA Query (SMQ) narrow], Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ narrow).
AE = Adverse Event; ATE = Arterial Embolic and Thrombotic Event; CI = Confidence Interval; PT = Preferred Term; mRCC = metastatic Renal Cell Carcinoma; TIA = Trans Ischaemic Attack; VEGFI = Vascular Endothelial Growth Factor Inhibitor; VEGFR = Vascular Endothelial Growth Factor Receptor.

SVII.3.1.2. Gastrointestinal Perforation and Fistula

Table 13. Gastrointestinal Perforation and Fistula[a]

Potential mechanism	The mechanism underlying gastrointestinal perforation and fistula in cancer patients with anti-VEGF treatment is known to be associated with VEGF inhibition. VEGF inhibition on capillary beds of intestinal villi may directly contribute to perforation by inducing the regression of normal blood vessels.[54] In normal adult mice, inhibition of VEGF signalling for 2-3 weeks causes regression of 34-46% of capillaries of intestinal villi.[55]
Evidence source and strength of evidence	Evidence Source: Axitinib clinical trials and post-marketing reports. Strength of evidence: In non-clinical studies, gastrointestinal toxicity to the alimentary tract was observed following repeat dosing, including haemorrhage and/or necrosis of the oral, stomach or intestinal mucosa. Gastrointestinal (GI) perforation and fistula have been reported in axitinib clinical trials and in the post-marketing setting.
Characterisation of the risk	All-causality AEs suggestive of gastrointestinal perforation or fistula occurred in 1.9% (95% CI: 1.03, 3.29) of subjects in All Single-agent Advanced RCC Studies. The frequency was similar in All Completed Clinical Trials (ie, in any indication including advanced RCC): 2.0 % (95% CI: 1.51, 2.64). All Single Agent Advanced RCC Studies The frequency of individual PTs that potentially could represent or lead to gastrointestinal perforation and fistula-related events, the seriousness and the outcome are provided in Annex 7 (Table 4). Anal abscess and Anal fistula are the most commonly reported PTs (4 occurrences each). There were no fatal (Grade 5) events reported. Of the 13 subjects with potential gastrointestinal perforation and fistula-related events, 7 (53.8%) had Grade 3 or 4 events and none had Grade 5. All causality AEs of gastrointestinal perforation and fistula-related events by grade is provided in Annex 7 (Table 5). Post-authorisation Data There were 69 cases (containing 80 relevant events; 77 of which were deemed to be serious) for patients treated with axitinib that were potentially indicative of gastrointestinal perforation and fistula-related events. The most commonly reported events are Gastrointestinal perforation and Intestinal perforation (16 each, all serious). The frequency of the individual PTs, the seriousness and the outcome are provided in Annex 7 (Table 6).
Risk factors and risk groups	Higa et al. suggest that acute conditions involving the bowel, including tumour at the site of perforation, acute diverticulitis, bowel obstruction and carcinomatosis, as well as radiation, may be associated with an increased risk of developing gastrointestinal perforation.[50] Risk factors for fistula formation in subjects with RCC who are treated with anti angiogenic agents are unknown.

Table 13. Gastrointestinal Perforation and Fistula[a]

Preventability	Other than a theoretical risk in patients with intra-abdominal malignancy, it is not known which patients may be at increased risk of developing gastrointestinal perforation following exposure to axitinib. There are no known specific preventive measures to reduce the incidence, or decrease the severity of perforation in individual patients treated with axitinib; however, signs and symptoms of gastrointestinal perforation should be assessed and treated.
Impact on the risk-benefit balance of the product	Depending on the location and severity of the event, the impact on an individual patient's quality of life may vary considerably. Gastrointestinal perforations are life-threatening emergencies and warrant prompt medical/surgical intervention. Fistulas can cause considerable patient morbidity and can have a profound impact on an individual patient's quality of life and may require prompt surgical/medical intervention to prevent or manage life-threatening complications.
Public health impact	Gastrointestinal perforations and fistulas are often serious, lead to hospitalisation, and may be associated with a fatal outcome. Considering the incidence of the event and the incidence of RCC in the population, the impact on overall public health is expected to be low.

a. MedDRA (v 21.1) - Gastrointestinal perforation (SMQ narrow) or PTs: Fistula, Tumour perforation.
AE = Adverse Event; CI = Confidence Interval; GI = Gastrointestinal; PT = Preferred Term; RCC = Renal Cell Carcinoma; VEGF = Vascular Endothelial Growth Factor.

SVII.3.1.3. Haemorrhage

Table 14. Haemorrhage[a]

Potential mechanism	Haemorrhage has been associated with the use of VEGF/VEGFR inhibitors, e.g. bevacizumab, pazopanib, sorafenib, and sunitinib. The mechanism of action that causes haemorrhage is currently unknown; however, haemorrhage may, in some cases be a function of an anti-tumour effect, specifically for highly vascularised tumours. Inhibition of VEGF could diminish the regenerative capacity of endothelial cells and cause defects that expose pro-coagulant phospholipids on the luminal plasma membrane or underlying matrix, leading to thrombosis or haemorrhage.[56] For subjects receiving axitinib, 2 distinct patterns of bleeding have occurred. The first is minor haemorrhage, most commonly CTCAE Grade 1 epistaxis. The second is serious haemorrhagic events. During the axitinib program, SAEs involving haemorrhage have occurred, including rectal haemorrhage and intracranial haemorrhage (cerebral and subarachnoid).
Evidence source and strength of evidence	Evidence Source: Axitinib clinical trials and post-marketing reports. Strength of evidence: Haemorrhage has been reported with other Tyrosine Kinase Inhibitors (TKIs) and has been reported in axitinib clinical trials and in the post-marketing setting.

Table 14. Haemorrhage[a]

Characterisation of the risk	All-causality AEs suggestive of haemorrhage occurred in 26.9% (95% CI: 23.61, 30.46) of subjects in All Single agent Advanced RCC Studies. The frequency was similar in All Completed Clinical Trials (ie, in any indication including advanced RCC): 27.9% (95% CI: 26.15, 29.68). All Single-Agent Advanced RCC Studies The frequency of individual PTs that potentially could represent or lead to haemorrhage, the seriousness and the outcome are provided in Annex 7 (Table 7). Epistaxis is the most commonly reported PT (65 occurrences). Fatal (Grade 5) events were reported in 4 subjects (0.6%). Of the 181 subjects with potential haemorrhage-related events, 30 (16.6%) had Grade 3 or 4 events and 4 (2.2%) had Grade 5. All causality AEs of haemorrhage-related events by grade is provided in Annex 7 (Table 8). Post-authorisation Data There were 489 cases (containing 571 relevant events; 334 of which were deemed to be serious) for patients treated with axitinib that were potentially indicative of haemorrhage-related events. The most commonly reported event is Epistaxis (87, 11 serious). The frequency of the individual PTs, the seriousness and the outcome are provided in Annex 7 (Table 9).
Risk factors and risk groups	From clinical trials data in subjects with advanced RCC, tissues with tumour involvement appear to be more likely to haemorrhage than uninvolved tissues.
Preventability	There are no known specific measures to prevent haemorrhagic events in patients treated with axitinib. Routine assessment of haemorrhagic events should include serial complete blood counts and physical examinations.
Impact on the risk-benefit balance of the product	The majority of the events encompassed within this risk are low CTCAE grade, reversible, manageable and the patients recover. Depending on the location of the event and the rapidity of treatment, the impact on an individual may vary considerably.
Public health impact	In clinical trials, all-causality haemorrhages were reported with very common frequency and most were mild to moderate in severity in patients with advanced RCC. Thus, the potential for a significant impact on public health is low.

a. MedDRA (v 21.1) - Haemorrhage laboratory terms (SMQ narrow and broad), Haemorrhage terms (excl laboratory terms) (SMQ narrow and broad).
AE = Adverse Event; CI = Confidence Interval; CTCAE = Common Terminology Criteria for Adverse Events v3.0; PT = Preferred Term; RCC = Renal Cell Carcinoma; SAE = Serious Adverse Event; TKI = Tyrosine Kinase Inhibitor; VEGF = Vascular Endothelial Growth Factor; VEGFR = Vascular Endothelial Growth Factor Receptor.

SVII.3.1.4. Posterior Reversible Encephalopathy Syndrome

Table 15. Posterior Reversible Encephalopathy Syndrome[a]

Potential mechanism	Hinchey et al. attributed PRES to sudden elevations in systemic blood pressure exceeding the autoregulatory capability of the brain vasculature with subsequent breakdown of the blood-brain barrier and transudation of fluid and petechial haemorrhages.[57] Ozkan et al. reported PRES associated with the VEGF inhibitor, bevacizumab, and suggested the mechanism to be vasospasm, hypertensive encephalopathy and vasogenic oedema induced by endothelial dysfunction and a disrupted blood-brain barrier.[58]

Table 15. Posterior Reversible Encephalopathy Syndrome[a]

Evidence source and strength of evidence	Evidence Source: Axitinib clinical trials, post-marketing reports, and literature reports of other multi targeted agents with anti-VEGFR activity. Strength of evidence: PRES has been reported in clinical trials and in the post-marketing setting and may be related to the known adverse reaction of hypertension with axitinib.
Characterisation of the risk	All-causality AEs of PRES occurred in 0.3% (95% CI: 0.04, 1.07) of subjects in All Single-agent Advanced RCC Studies. The frequency was similar in All Completed Clinical Trials (ie, in any indication including advanced RCC): 0.5% (95% CI: 0.27, 0.88). All Single-Agent Advanced RCC Studies Leukoencephalopathy is the only reported PT (2 occurrences); the seriousness and the outcome are provided in Annex 7 (Table 10). There were no fatal (Grade 5) events reported. Of the 2 subjects with potential PRES-related events, 1 had Grade 3 and none had Grade 5. All causality AEs of PRES-related events by grade is provided in Annex 7 (Table 11). Post-authorisation Data There were 87 cases (containing 87 relevant events; all of which were deemed to be serious) for patients treated with axitinib that were potentially indicative of PRES-related events. The most commonly reported event is Posterior reversible encephalopathy syndrome (67, all serious). The frequency of the individual PTs, the seriousness and the outcome are provided in Annex 7 (Table 12).
Risk factors and risk groups	PRES has been most frequently observed with acute increases in blood pressure, which may account for its occurrence in patients with uncontrolled hypertension, renal failure or eclampsia.[50,59,60,61]
Preventability	Control of blood pressure during and after axitinib administration and patient monitoring may help prevent the syndrome.
Impact on the risk-benefit balance of the product	Signs and symptoms may be severe and are usually treatable and reversible. There is the potential for a profound negative effect on individual patient's quality of life as long-lasting or even permanent neurologic dysfunction may remain.
Public health impact	Because the event is expected to be uncommon, a substantial impact on public health is not expected. The event can be serious, lead to hospitalisation, and may be associated with a fatal outcome.

a. MedDRA (v 21.1) - PTs: Encephalopathy, Leukoencephalopathy, Posterior reversible encephalopathy syndrome.
AE = Adverse Event; CI = Confidence Interval; PRES = Posterior Reversible Encephalopathy Syndrome; PT = Preferred Term; RCC = Renal Cell Carcinoma; VEGF = Vascular Endothelial Growth Factor; VEGFR = Vascular Endothelial Growth Factor Receptor.

SVII.3.1.5. Venous Embolic and Thrombotic Events

Table 16. Venous Embolic and Thrombotic Event [a]

Potential mechanism	VTE are considered an adverse effect of other medicinal products that block the action of VEGF; however the aetiology is not well understood. As with ATE, postulated mechanisms include inhibiting VEGF action causing endothelial cell damage leading to thrombosis, or increasing blood viscosity by an overproduction of erythropoietin.
Evidence source and strength of evidence	Evidence Source: Axitinib clinical trials and post-marketing reports. Strength of evidence: Venous Embolic and Thrombotic Events have been reported for other VEGFI, and have been reported in axitinib clinical trials and in the post-marketing setting.
Characterisation of the risk	All-causality AEs suggestive of venous embolic and thrombotic events (VTE) occurred in 3.1% (95% CI: 1.94, 4.74) of subjects in All Single-agent Advanced RCC Studies. The frequency was similar in All Completed Clinical Trials (ie, in any indication including advanced RCC): 5.1% (95% CI: 4.24, 5.99). All Single-Agent Advanced RCC Studies The frequency of individual PTs that potentially could represent or lead to VTE, the seriousness and the outcome are provided in Annex 7 (Table 13). Pulmonary embolism is the most frequently reported PT (9 occurrences). A fatal (Grade 5) event was reported in 1 subject (0.1%). Of the 21 subjects with potential VTE-related events, 14 (66.7%) had Grade 3 or 4 and 1 (4.8%) had Grade 5. All causality AEs of VTE-related events by grade is provided in Annex 7 (Table 14). Post-authorisation Data There were 66 cases (containing 70 relevant events; 64 of which were deemed to be serious) for patients treated with axitinib that were potentially indicative of VTE-related events. The most commonly reported event is Pulmonary embolism (39, all serious). The frequency of the individual PTs, the seriousness and the outcome are provided in Annex 7 (Table 15).
Risk factors and risk groups	Cancer patients have an increased risk of VTE. No other risk factor for VTE has been identified in axitinib studies.
Preventability	There are no known specific preventive measures to reduce the risk of thromboembolic events in patients treated with axitinib.
Impact on the risk-benefit balance of the product	The majority of the events encompassed within this risk are reversible and manageable. However VTE can lead to hospitalisation or can be fatal.
Public health impact	In clinical trials with axitinib, all-causality AEs of VTE were reported with common frequency in patients with advanced RCC. VTE are often serious, lead to hospitalisation, and may be associated with a fatal outcome. Considering the epidemiology of VTE in the mRCC population, it is unlikely the risk in patients on axitinib will have a major impact on overall public health as compared with VTE in general.

a. MedDRA (v 21.1) - Embolic and thrombotic events, venous (SMQ narrow).
AE = Adverse Event; ATE = Arterial Embolic and Thrombotic Event; CI = Confidence Interval; PT = Preferred Term; RCC = Renal Cell Carcinoma; VEGF = Vascular Endothelial Growth Factor; VEGFI = Vascular Endothelial Growth Factor Inhibitor; VTE = Venous Embolic and Thrombotic event.

SVII.3.1.6. Effects on the Exocrine Pancreas

Table 17. Effects on the Exocrine Pancreas [a]

Potential mechanism	Pancreatic zymogen granule depletion with acinar cell proliferation or increased acinar cell apoptosis was observed in dogs following repeat-dose administration.
Evidence source and strength of evidence	Evidence Source: Axitinib clinical trials and post-marketing reports. Strength of evidence: In non-clinical studies, a decrease in zymogen granules and concomitant increase in acinar cells in the pancreas were observed after 28 days of axitinib administration.
Characterisation of the risk	All-causality AEs suggestive of effects on the exocrine pancreas occurred in 5.7% (95% CI: 4.03, 7.68) of subjects in All Single-agent Advanced RCC Studies. The frequency was similar in All Completed Clinical Trials (ie, in any indication including advanced RCC): 3.0% (95% CI: 2.38, 3.75). All Single-Agent Advanced RCC Studies The frequency of individual PTs that potentially could represent or lead to effects on exocrine pancreas, the seriousness and the outcome are provided in Annex 7 (Table 16). Lipase increased (25 occurrences) and Amylase increased (24 occurrences) were the only reported PTs. No fatal (Grade 5) events were reported. Of the 38 subjects with potential effects on exocrine pancreas-related events, 12 (31.6%) had Grade 3 or 4 events and none had Grade 5. All causality AEs of exocrine pancreas-related events by grade is provided in Annex 7 (Table 17). Post-authorisation Data There were 36 cases (containing 42 relevant events; 27 of which were deemed to be serious) for patients treated with axitinib that were potentially indicative of effects on exocrine pancreas. The most commonly reported event is Pancreatitis (16, all serious). The frequency of the individual PTs, the seriousness and the outcome are provided in Annex 7 (Table 18).
Risk factors and risk groups	No risk group has been identified.
Preventability	It is not known which patients may be at increased risk of developing pancreatitis following exposure to axitinib. There are no known specific preventive measures to reduce the incidence, or decrease the severity of pancreatitis in individual patients treated with axitinib.
Impact on the risk-benefit balance of the product	The majority of events associated with this risk are low CTCAE grade, reversible, manageable and the patients recover. However, treatment may include hospitalisation.
Public health impact	In clinical trials, all causality events suggestive of effects on the exocrine pancreas were reported with common frequency in patients with advanced RCC. No fatal cases were reported. The potential effect on public health is likely to be low at this time.

a. MedDRA (v 21.1) - PTs: Amylase increased, Exocrine pancreatic function test abnormal, Lipase increased, Oedematous pancreatitis, Pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising, Pancreatitis relapsing.
AE = Adverse Event; CI = Confidence Interval; CTCAE = Common Terminology Criteria for Adverse Events v3.0; PT = Preferred Term; RCC = Renal Cell Carcinoma.

SVII.3.1.7. Renal Failure

Table 18. Renal Failure [a]

Potential mechanism	The mechanism of action effecting renal function is unknown. Since VEGF is expressed both in podocytes in the glomerulus and tubular cells, kidney injury may result from a direct toxicity of axitinib to glomeruli and renal tubules due to its anti-VEGFR effect.
Evidence source and strength of evidence	Evidence Source: Axitinib clinical trials and post-marketing reports. Strength of evidence: Most cases of renal failure in the clinical trial and safety database involved known risk factors which may have contributed to the development of renal failure.
Characterisation of the risk	All-causality AEs suggestive of renal failure occurred in 27.8% (95% CI: 24.47, 31.38) of subjects in All Single agent Advanced RCC Studies. The frequency was similar in All Completed Clinical Trials (ie, in any indication including advanced RCC): 22.7% (95% CI: 21.09, 24.39). All Single-Agent Advanced RCC Studies The frequency of individual PTs that potentially could represent or lead to renal failure, the seriousness and the outcome are provided in Annex 7 (Table 19). Proteinuria is the most frequently reported PT (132 occurrences). A fatal (Grade 5) event was reported in 1 subject (0.1%). Of the 187 subjects with potential renal failure-related events, 51 (27.3%) had Grade 3 or 4 events and 1 (0.5%) had Grade 5. All causality AEs of renal failure by grade is provided in Annex 7 (Table 20). Post-authorisation Data There were 810 cases (containing 867 relevant events; 246 of which were deemed to be serious) for patients treated with axitinib that were potentially indicative of renal failure. The most commonly reported event is Proteinuria (519, 35 serious). The frequency of the individual PTs, the seriousness and the outcome are provided in Annex 7 (Table 21).
Risk factors and risk groups	In a retrospective review of 108 Korean patients with RCC, 39.8% developed chronic kidney disease post-surgery.[62] Risk factors identified for renal failure include advanced age; chronic infection; diabetes; hypertension; heart failure; immune disorders, such as lupus, IgA nephropathy and scleroderma; hepatic disease; prostate gland enlargement; and bladder outlet obstruction. Risk factors for prerenal acute renal failure include dehydration, heart failure, sepsis, and severe blood loss.
Preventability	Monitor signs and symptoms of renal impairment. Standard assessments should be utilised.
Impact on the risk-benefit balance of the product	The majority of events associated with this risk are low CTCAE grade, reversible, manageable, and most patients recover. However renal failure generally led to hospitalisation and may be associated with a fatal outcome.
Public health impact	Considering the seriousness and possible fatal outcome, there is moderate potential for impact on public health.

a. MedDRA (v 21.1) - Acute renal failure (SMQ narrow and broad).
AE = Adverse Event; CI = Confidence Interval; CTCAE = Common Terminology Criteria for Adverse Events v3.0; PT = Preferred Term; RCC = Renal Cell Carcinoma; VEGFR = Vascular Endothelial Growth Factor Receptor.

SVII.3.1.8. Congestive Heart Failure/Cardiomyopathy

Table 19. Congestive Heart Failure/Cardiomyopathy [a]

Potential mechanism	Mechanistically disruption of VEGF–VEGFR signalling in the heart may induce cardiac dysfunction by preventing compensatory hypertrophy; VEGF is relevant to capillary density in the myocardium and critical for stem-cell differentiation into cardiomyocytes.[63,64] In the murine model, disruption of VEGF–VEGFR signalling during imposition of the pressure load was shown to reduce capillary density, which in turn was associated with contractile dysfunction, fibrosis and heart failure. Thus, inhibition of VEGF–VEGFR signalling in the heart may become relevant to patients with poorly controlled hypertension. TKI-induced changes to the thyroid function may cause cardiac toxicity. Triiodothyronine has a direct effect on the cardiomyocytes. Any T3 depletion could cause changes at the nuclear level of the myocyte level by influencing T3-regulated transcription of genes that encode Ca^{2+}-ATPase exchanger, Na^{+}/K^{+}-ATPase and voltage-gated potassium channels. Moreover, T3 exerts important non-nuclear functions on the myocyte which include ion channels for sodium, potassium and calcium.[65] Low serum T3 levels have been shown to be the single and the most significant predictor of cardiovascular and all-cause mortalities in adults with heart disease.[66] Triiodothyronine also directly affects vascular smooth muscle cells, promoting relaxation.[67] Hypothyroidism was shown to increase vascular resistance[67,68] and to exert endothelial dysfunction due to reduced nitric oxide availability.[69,70]
Evidence source and strength of evidence	Evidence Source: Axitinib clinical trials and post-marketing reports. Strength of evidence: Congestive heart failure/Cardiomyopathy has been reported with other TKIs and has been reported in axitinib clinical trials and in the post-marketing setting.
Characterisation of the risk	All-causality AEs suggestive of congestive heart failure/cardiomyopathy occurred in 1.8% (95% CI: 0.93, 3.10) of subjects in All Single-agent Advanced RCC Studies. The frequency was similar in All Completed Clinical Trials (ie, in any indication including advanced RCC): 1.3% (95% CI: 0.90, 1.83). All Single-Agent Advanced RCC Studies The frequency of individual PTs that potentially could represent or lead to congestive heart failure/cardiomyopathy, the seriousness and the outcome are provided in Annex 7 (Table 22). Cardiac failure is the most frequently reported PT (5 occurrences). Fatal (Grade 5) events were reported in 3 subjects (0.4%). Of the 12 subjects with potential congestive heart failure/cardiomyopathy-related events, 6 (50.0%) had Grade 3 or 4 events and 3 (25%) had Grade 5. All causality AEs of cardiac failure by grade is provided in Annex 7 (Table 23). Post-authorisation Data There were 96 cases (containing 97 relevant events; 89 of which were deemed to be serious) for patients treated with axitinib that were potentially indicative of congestive heart failure/cardiomyopathy. The most commonly reported event is Cardiac failure (55, all serious). The frequency of the individual PTs, the seriousness and the outcome are provided in Annex 7 (Table 24).
Risk factors and risk groups	In cases of congestive heart failure/cardiomyopathy, for which medical history was reported, most patients had a personal or family history of coronary artery disease and/or one or more risk factors, including cigarette smoking, hypertension, hyperlipidaemia, diabetes, advanced age, and obesity.
Preventability	Close monitoring for signs or symptoms of cardiac failure periodically throughout treatment with axitinib is recommended. Management of cardiac failure events may require temporary interruption or permanent discontinuation and/or dose reduction of axitinib therapy.

Table 19. Congestive Heart Failure/Cardiomyopathy [a]

Impact on the risk-benefit balance of the product	These events may be serious and lead to hospitalisation and may be fatal.
Public health impact	In clinical trials, all-causality events suggestive of congestive heart failure/cardiomyopathy were reported with common frequency in patients with advanced RCC, including Grade 3 or 4 AEs, which were reported with common frequency. All-causality events suggestive of congestive heart failure/cardiomyopathy are often serious, lead to hospitalisation, and may be associated with a fatal outcome. Considering the incidence and severity of this risk, this can have a moderate impact on public health.

a. MedDRA (v 21.1) – PTs: Acute left ventricular failure, Acute right ventricular failure, Cardiac failure, Cardiac failure acute, Cardiac failure chronic, Cardiac failure congestive, Cardiac failure high output, Cardiac output decreased, Cardio-respiratory distress, Cardiogenic shock, Cardiomyopathy acute, Cardiopulmonary failure, Central venous pressure increased, Chronic left ventricular failure, Chronic right ventricular failure, Congestive cardiomyopathy, Cor pulmonale, Cor pulmonale acute, Cor pulmonale chronic, Diastolic dysfunction, Ejection fraction abnormal, Ejection fraction decreased, Left ventricular dysfunction, Left ventricular failure, Low cardiac output syndrome, Myocardial depression, Neonatal cardiac failure, Oedema due to cardiac disease, Right ventricular dysfunction, Right ventricular failure, Systolic dysfunction, Ventricular dysfunction, Ventricular failure.
AE = Adverse Event; CI = Confidence Interval; PT = Preferred Term; RCC = Renal Cell Carcinoma; TKI = Tyrosine Kinase Inhibitor; VEGF = Vascular Endothelial Growth Factor; VEGFR = Vascular Endothelial Growth Factor Receptor.

Important Potential Risks

SVII.3.1.9. Torsade de Pointes due to QT Prolongation

Table 20. Torsade de Pointes due to QT Prolongation [a]

Potential mechanism	QT prolongation and/or Torsade de pointes is reported with other VEGF inhibitors, which are multi-targeted kinase inhibitors. Sunitinib, for example, has been shown to inhibit the human ether-a-go-go (hERG) potassium channels, which can result in QT prolongation leading to Torsade de pointes. However, axitinib is a selective tyrosine kinase inhibitor and the potential mechanism of action may be different.
Evidence source and strength of evidence	Evidence Source: Axitinib clinical trials and post-marketing reports. Strength of evidence: QT prolongation and/or Torsade de pointes has been reported with other VEGFI. QT prolongation may lead to ventricular arrhythmias such as Torsade de pointes. However, the relationship between axitinib administration and Torsade de pointes due to QT prolongation is not yet established.

Table 20. Torsade de Pointes due to QT Prolongation [a]

Characterisation of the risk	All-causality AEs reporting suggestive of QT prolongation occurred in 3.3% (95% CI: 2.06, 4.91) of subjects in All Single-agent Advanced RCC Studies. The frequency was the same in All Completed Clinical Trials (ie, in any indication including advanced RCC): 3.3% (95% CI: 2.66, 4.10). All Single-Agent Advanced RCC Studies The frequency of individual PTs that potentially could represent or lead to QT prolongation/Torsade de pointes, the seriousness and the outcome are provided in Annex 7 (Table 25). Syncope is the most frequently reported PT (10 occurrences). Fatal (Grade 5) events were reported in 3 subjects (0.4%). Of the 22 subjects with potential QT prolongation-related events, 12 (54.5%) had Grade 3 or 4 events and 3 (25%) had Grade 5. All causality AEs of QT prolongation by grade is provided in Annex 7 (Table 26). Although there are reports suggestive of QT prolongation, as of 30 October 2018, there are no cases of Torsade de Pointes reported following use of axitinib. Post-authorisation Data There were 68 cases (containing 72 relevant events; 65 of which were deemed to be serious) for patients treated with axitinib that were potentially indicative of QT prolongation/Torsade de pointes. The most commonly reported event is Loss of consciousness (32, all serious). The frequency of the individual PTs, the seriousness and the outcome are provided in Annex 7 (Table 27).
Risk factors and risk groups	No risk factors have been identified. Theoretically patients who have baseline QT interval prolongation, cardiac disease, or receive other medications that cause QT interval prolongation may be at increased risk of Torsade de pointes.
Preventability	Axitinib should be used with caution in patients with a history of QT prolongation and specific cardiac events and on certain concomitant treatments.
Impact on the risk-benefit balance of the product	The majority of events associated with this risk are reversible, manageable, and the patients recover. Cases of syncope account for the largest number of events in this risk and it is unclear that these cases of syncope are related to QT prolongation. QT prolongation can lead to potentially fatal arrhythmia/Torsade de pointes. No cases of torsade de pointes have been observed in axitinib exposed patients. The potential effect on individual patient's quality of life is considered to be very low at this time.
Public health impact	The potential public health impact with this risk is considered to be low at this time.

a. MedDRA (v 21.1) – Torsade de pointes/QT prolongation (SMQ narrow and broad).
AE = Adverse Event; CI = Confidence Interval; PT = Preferred Term; RCC = Renal Cell Carcinoma; VEGF = Vascular Endothelial Growth Factor.

SVII.3.1.10. Reproductive and Developmental Toxicity

Table 21. Reproductive and Developmental Toxicity [a]

Potential mechanism	Formation of the corpus luteum requires angiogenesis. Inhibition of VEGFR has been demonstrated to perturb this process in non-clinical species. There are no clinical data to suggest that this affects reproduction or results in ovarian failure. In a fertility study in mice, axitinib did not affect mating or fertility rate when administered orally twice daily to males at any dose tested up to 50 mg/kg/dose following at least 70 days of administration (approximately 57 times the AUC in patients at the recommended starting dose). In female mice, reduced fertility and embryonic viability were observed at all doses tested (≥15 mg/kg/dose administered orally twice daily) following at least 15 days of treatment with axitinib (approximately 10 times the AUC in patients at the recommended starting dose). Effects on male and female reproductive organs were observed in the mouse and dog following repeat-dose administration of axitinib.
Evidence source and strength of evidence	Evidence Source: Axitinib clinical trials and post-marketing reports. Strength of evidence: Non-clinical studies identified effects on male and female reproductive organs with axitinib administration for ≥28 days. However, the relationship between axitinib administration and reproductive and developmental toxicity in humans is not yet established.
Characterisation of the risk	All-causality AEs suggestive of reproductive and developmental toxicity occurred in 0.3% (95% CI: 0.04, 1.07) of subjects in All Single-agent Advanced RCC Studies. The frequency was similar in All Completed Clinical Trials (ie, in any indication including advanced RCC): 0.4% (95% CI: 0.19, 0.73). All Single-Agent Advanced RCC Studies The frequency of individual PTs that potentially could represent or lead to reproductive and developmental toxicity, the seriousness and the outcome are provided in Annex 7 (Table 28). Macroglossia and Nipple infection were the only reported PTs. No fatal (Grade 5) events were reported. Of the 2 subjects with potential reproductive and developmental toxicity-related events, none has Grade 3 or 4 or Grade 5. All causality AEs of reproductive and developmental toxicity by grade is provided in Annex 7 (Table 29). Post-authorisation Data There were 2 cases of Paternal exposure timing unspecified, which on review were not indicative of reproductive or developmental toxicity. The frequency of the individual PTs, the seriousness and the outcome are provided in Annex 7 (Table 30).
Risk factors and risk groups	No risk group has been identified.
Preventability	Developmental toxicity is a potential risk for the embryo/foetus exposed to axitinib and is described in the product information. Patients are advised to avoid becoming pregnant during treatment with axitinib. Both male and female patients should be counselled to use effective birth control during treatment with axitinib. Female patients should also be advised against breast feeding while receiving axitinib.
Impact on the risk-benefit balance of the product	Since there were no relevant AEs reported, the potential effect on individual patients or the embryo/foetus cannot be determined at this time.

Table 21. Reproductive and Developmental Toxicity [a]

Public health impact	The potential effect on public health cannot be precisely determined at this time.

a. MedDRA (v 21.1) – Congenital, familial and genetic disorders (SMQ narrow), Foetal disorders (SMQ narrow), Lactation related topics (incl neonatal exposure through breast milk) (SMQ narrow), Neonatal disorders (SMQ narrow), Pregnancy, labour and delivery complications and risk factors (excl abortions and stillbirth) (SMQ narrow), Termination of pregnancy and risk of abortion (SMQ narrow) and PTs Ovarian failure, Infertility female.
AE = Adverse Event; AUC = Area Under the Curve; CI = Confidence Interval; PT = Preferred Term; RCC = Renal Cell Carcinoma; VEGFR = Vascular Endothelial Growth Factor Receptor.

SVII.3.1.11. Carcinogenicity

The clinical trial database does not distinguish between carcinogenicity events related to the progression of the malignancy under study being treated by axitinib and second primary malignancies. During a review of second malignancy cases, every case of second malignancy reported during Pfizer clinical trials was categorised as serious and included in the Pfizer safety database. It is Pfizer practice to add the MedDRA PT Second primary malignancy to every such case as appropriate in the Pfizer safety database. Therefore, frequency information related to the potential risk of carcinogenicity is based on the cases found in the safety database from the relevant clinical trials where the PT Second primary malignancy is included.

Table 22. Carcinogenicity [a]

Potential mechanism	Carcinogenicity studies have not been conducted with axitinib. Axitinib was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay and was not clastogenic in the in vitro human lymphocyte chromosome aberration assay. Axitinib was genotoxic in the in vivo mouse bone marrow micronucleus assay.
Evidence source and strength of evidence	Evidence Source: Axitinib clinical trials and post-marketing reports. Strength of evidence: Pre-clinical carcinogenicity study and spontaneous reports of second primary malignancy. However, the relationship between axitinib administration and carcinogenicity in humans is not yet established.

Table 22. Carcinogenicity [a]

Characterisation of the risk	All-causality AEs possibly suggestive of carcinogenicity (ie, reporting PTs in the malignant or unspecified tumours SMQ or the PT Secondary primary malignancy) occurred in 1.6% (95% CI: 0.82, 2.91) of subjects in All Single-agent Advanced RCC Studies. The frequency was similar in All Completed Clinical Trials (ie, in any indication including advanced RCC): 1.8% (95% CI: 1.34, 2.42). All Single-Agent Advanced RCC Studies The frequency of individual PTs that potentially could represent or lead to carcinogenicity, the seriousness and the outcome are provided in Annex 7 (Table 31). Neoplasm is the most frequently reported PT (2 occurrences). A fatal (Grade 5) event was reported in 1 subject (0.1%). Of the 11 subjects with potential carcinogenicity-related events, 2 (18.2%) had Grade 3 or 4 events and 1 (9.1%) Grade 5. All causality AEs of carcinogenicity by grade is provided in Annex 7 (Table 32). All PTs were reported as a single event except for the PT Neoplasm which was reported in 2 cases. One fatal (Grade 5) case was reported with the PT Bone cancer. Post-authorisation Data There were 2399 cases containing 2429 events (of which 363 were deemed to be serious) for patients treated with axitinib that were potentially indicative of carcinogenicity. The most commonly reported event was Metastatic renal cell carcinoma (1080, 88 serious). The frequency of the individual PTs, the seriousness and the outcome are provided in Annex 7 (Table 33). A review of all reports suggestive of carcinogenicity identified only 26 that were consistent with a second primary malignancy [Second primary malignancy (26), Prostate cancer (3), Brain neoplasm, Malignant melanoma and Squamous cell carcinoma (2 each), Acute promyelocytic leukaemia, Bladder neoplasm, Bone cancer, Breast cancer, Breast cancer stage I, Cervix carcinoma, Colon cancer metastatic, Gastric cancer, Glioblastoma, Laryngeal cancer, Leukaemia, Lung adenocarcinoma, Neoplasm malignant, Oral neoplasm, Plasma cell myeloma, Squamous cell carcinoma of skin, Testis cancer (1 each). The remaining reports were consistent with progression of disease.
Risk factors and risk groups	No risk groups have been identified.
Preventability	There are no known preventive measures.
Impact on the risk-benefit balance of the product	As the potential for carcinogenicity in axitinib treated patients is not known at this time, the potential effect on individual patient's quality of life cannot be determined. In general, secondary malignancies can have a significant impact on the individual patient.
Public health impact	Overall information available does not suggest that patients treated with axitinib have an increased risk of second neoplasms. Neoplasms that have been reported have not been singular or unusual in type. The impact on overall public health is considered to be low.

a. MedDRA (v 21.1) –Malignant or unspecified tumours (SMQ narrow), Malignant tumours (SMQ narrow), Tumours of unspecified malignancy (SMQ narrow) and PTs: Myelodysplastic syndrome, Second primary malignancy.
AE = Adverse Event; CI = Confidence Interval; PT = Preferred Term; RCC = Renal Cell Carcinoma; SMQ = Standardised MedDRA Query.

SVII.3.1.12. Osteonecrosis of the Jaw

Table 23. Osteonecrosis of the Jaw [a]

Potential mechanism	ONJ is considered an adverse reaction of certain multi-targeted medicinal products that block the action of VEGF; however, the aetiology is not well understood. A reasonable hypothesis would be that potent anti-antigenic activity might amplify the inhibition of bone remodelling exerted by aminophosphonates entrapped within the osteonecrotic mineral matrix and antagonise mucosal healing which may result in exposure of bone to infectious agents.
Evidence source and strength of evidence	Evidence Source: Axitinib clinical trials and post-marketing reports. Strength of evidence: Osteonecrosis of the jaw has been reported with other VEGFI. However, the relationship between axitinib administration and Osteonecrosis of the jaw is not yet established.
Characterisation of the risk	All-causality AEs of ONJ were reported in only 1 subject (0.1%, 95% CI: 0.00, 0.83) in All Single-agent Advanced RCC Studies. The frequency was similar in All Completed Clinical Trials (ie, in any indication including advanced RCC): 0.2% (95% CI: 0.04, 0.40). All Single-Agent Advanced RCC Studies Osteonecrosis of the jaw is the only reported PT (1 occurrence, Grade 2); the seriousness and the outcome are provided in Annex 7 (Table 34). All causality AEs of ONJ by grade is provided in Annex 7 (Table 35). Post-authorisation Data There were 10 cases (containing 10 relevant events; all of which were deemed to be serious) for patients treated with axitinib that were potentially indicative of ONJ. Osteonecrosis of jaw (10, all serious) is the only PT reported. The frequency of the individual PTs, the seriousness and the outcome are provided in Annex 7 (Table 36).
Risk factors and risk groups	Risk factors for osteonecrosis of the jaw include bisphosphonates, diabetes, alcoholism, cigarette smoking, obesity, hyperlipidaemia, pancreatitis, chemotherapy with L-asparaginase, radiotherapy, receipt of parenteral steroids, jaw trauma, and dental procedures.
Preventability	Caution should be exercised when axitinib and IV bisphosphonates are used either simultaneously or sequentially.
Impact on the risk-benefit balance of the product	The incidence of ONJ in axitinib treated patients appears to be low. In general, ONJ can have a significant impact on the individual patient.
Public health impact	Considering the incidence of the event and the incidence of RCC in the population, the impact on overall public health is expected to be low.

a. Osteonecrosis (SMQ narrow).
AE = Adverse Event; CI = Confidence Interval; PT = Preferred Term; ONJ = Osteonecrosis of the jaw; RCC = Renal cell cancer; VEGF = Vascular Endothelial Growth Factor; VEGFI = Vascular Endothelial Growth Factor Inhibitor.

SVII.3.2. Presentation of the Missing Information

SVII.3.2.1. Risks in Pregnant and Lactating Women

Table 24. Missing Information: Risks in Pregnant and Lactating Women

Risk-benefit impact	Anticipated risk/consequence of the missing information: No MAH-sponsored clinical studies have investigated the use of axitinib in pregnant women nor has it been adequately studied outside of the clinical program. Studies in animals have shown reproductive toxicity including foetal malformations. Based on the pharmacological properties of axitinib, it may cause foetal harm when administered to a pregnant woman. No MAH-sponsored clinical studies have been conducted in humans to assess the effect of axitinib on milk production, its presence in breast milk, or its effects on the breast-fed child. It is unknown whether axitinib is excreted in human milk. Based upon the available evidence from non-clinical data, a potential risk of foetal malformations may be anticipated in pregnant and lactating women with the use of axitinib. The routine pharmacovigilance is sufficient to characterize this risk in pregnant and lactating women.

SVII.3.2.2. Risks in Paediatric Subjects

Table 25. Missing Information: Risks in Paediatric Subjects

Risk-benefit impact	Population in need of further characterisation: MAH-sponsored clinical trials with axitinib have not included paediatric patients and there has been very limited reported post-marketing experience of paediatric patients who were administered axitinib. It is not known whether there is any difference in the safety and pharmacokinetic profiles of paediatric patients versus adult treated with axitinib. Paediatric patients treated with axitinib could have a different safety profile from adult axitinib patients, therefore this population needs further characterization.

SVII.3.2.3. Risks in Subjects with Moderate and Severe Renal Impairment (Serum Creatinine >1.5 times the ULN or Calculated Creatinine Clearance <60 mL/min)

Table 26. Missing Information: Risks in Subjects with Moderate and Severe Renal Impairment (Serum Creatinine >1.5 times the ULN or Calculated Creatinine Clearance <60 mL/min)

Risk-benefit impact	Population in need of further characterisation: MAH-sponsored clinical trials with axitinib have not included patients with moderate and severe renal impairment (serum creatinine >1.5 times the ULN or calculated creatinine clearance <60 mL/min) and there has been very limited reported post-marketing experience of patients with severe renal impairment who were administered axitinib. It is not known whether there is any difference in the safety and pharmacokinetic profiles of patients with normal renal function versus those who have moderate and severe renal impairment among axitinib treated patients. Axitinib patients with moderate and severe renal impairment could have a different PK and safety profile from patients without moderate and severe renal impairment, therefore this population needs further characterization.

ULN = Upper Limit of Normal, PK = Pharmacokinetic.

SVII.3.2.4. Risks in Subjects with Severe Hepatic Impairment (Child Pugh Class C)

Table 27. Missing Information: Risks in Subjects with Severe Hepatic Impairment (Child Pugh Class C)

Risk-benefit impact	Population in need of further characterisation: MAH-sponsored clinical trials with axitinib have not included patients with severe hepatic impairment, and no data exists from post-marketing experience regarding the patients with severe hepatic impairment who were administered axitinib. It is not known whether there is any difference in the safety and pharmacokinetic profiles of patients with normal hepatic function versus those who have severe hepatic impairment (Child-Pugh class C) among axitinib treated patients. Axitinib patients with severe hepatic impairment could have a different PK and safety profile from patients without hepatic impairment and therefore this population needs further characterization.

PK = Pharmacokinetic.

SVII.3.2.5. Risks in Subjects with Brain Metastasis, Spinal Cord Compression, or Carcinomatous Meningitis

Table 28. Missing Information: Risks in Subjects with Brain Metastasis, Spinal Cord Compression, or Carcinomatous Meningitis

Risk-benefit impact	Population in need of further characterisation: In MAH-sponsored clinical trials, axitinib has not been studied in patients who have evidence of untreated brain metastasis, spinal cord compression, or carcinomatous meningitis. In post-marketing experience, there has been very limited reports from patients who have evidence of untreated brain metastasis, or spinal cord compression, or carcinomatous meningitis. It is not known whether there is any difference in the safety and pharmacokinetic profiles of patients who have evidence of untreated brain metastasis, spinal cord compression, or carcinomatous meningitis. This population could have a different safety profile from patients without evidence of untreated brain metastasis, spinal cord compression, or carcinomatous meningitis. The routine pharmacovigilance is sufficient to characterize this risk in patients with evidence of untreated brain metastasis, spinal cord compression, or carcinomatous meningitis.

PK = Pharmacokinetic.

SVII.3.2.6. Risks in Subjects with Active Peptic Ulcer Disease

Table 29. Missing Information: Risks in Subjects with Active Peptic Ulcer Disease

Risk-benefit impact	Anticipated risk/consequence of the missing information: In MAH-sponsored clinical trials, axitinib has not been studied in patients with active peptic ulcer disease. No data exist regarding the use of axitinib in patients with active peptic ulcer disease from post-marketing experience. It is not known whether there is any difference in the safety profile of axitinib in patients with active peptic ulcer disease. Based on the known safety profile of axitinib, this population may be at higher risk of gastrointestinal bleeding and perforation. The routine pharmacovigilance is sufficient to characterize this risk in patients with active peptic ulcer disease.

SVII.3.2.7. Risks in Subjects with a Recent Major Surgery (within 4 weeks) or Radiation Therapy (within 2 weeks)

Table 30. Missing Information: Risks in Subjects with a Recent Major Surgery (within 4 weeks) or Radiation Therapy (within 2 weeks)

Risk-benefit impact	Anticipated risk/consequence of the missing information: In MAH-sponsored clinical trials, axitinib has not been studied in patients with a recent major surgery (within 4 weeks) or radiation therapy (within 2 weeks). In post-marketing experience, there has been very limited reports from patients with a recent major surgery (within 4 weeks) or radiation therapy (within 2 weeks). Based on the known safety profile of axitinib, there is a potential risk of wound healing complications in patients with a recent major surgery. The routine pharmacovigilance is sufficient to characterize this risk in patients with a recent major surgery (within 4 weeks) or radiation therapy (within 2 weeks).

Module SVIII. Summary of the Safety Concerns

Table 31. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	• Arterial embolic and thrombotic events • Gastrointestinal perforation and fistula • Haemorrhage • Posterior Reversible Encephalopathy Syndrome • Venous Embolic and Thrombotic Event • Effects on the exocrine pancreas • Renal failure • Congestive heart failure/cardiomyopathy
Important potential risks	• Torsade de pointes due to QT prolongation • Reproductive and developmental toxicity • Carcinogenicity • Osteonecrosis of the jaw
Missing information	• Risks in pregnant and lactating women • Risks in paediatric subjects • Risks in subjects with moderate and severe renal impairment (serum creatinine >1.5 times the ULN or calculated creatinine clearance <60 mL/min) • Risks in subjects with severe hepatic impairment (Child-Pugh Class C) • Risks in subjects with brain metastasis, spinal cord compression, or carcinomatous meningitis • Risks in subjects with active peptic ulcer disease • Risks in subjects with a recent major surgery (within 4 weeks) or radiation therapy (within 2 weeks)

ULN = Upper Limit of Normal.

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

There are no studies specifically focused on safety risks, but safety data will continue to be collected in ongoing studies.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaire for QT prolongation/Torsade de pointes:

To obtain structured follow up information for the important potential risk of Torsade de pointes due to QT prolongation, a Data Capture Aid (DCA) is being used by prescribers containing specific questions for QT related AEs. The DCA is provided in Annex 4.

Other forms of routine pharmacovigilance activities for safety concerns:

None.

III.2. Additional Pharmacovigilance Activities

There are no category 1, 2 and 3 studies for axitinib.

III.3. Summary Table of Additional Pharmacovigilance Activities

There are no category 1, 2 and 3 studies for axitinib.

III.3.1. On-Going and Planned Additional Pharmacovigilance Activities

None.

PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES

There are no post-authorization efficacy studies (PAES) that are a specific obligation by the competent authorities and/or condition of the MA.

PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

V.1. Routine Risk Minimisation Measures

Table 32. Description of Routine Risk Minimisation Measures By Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Important Identified Risks	
ATE	Routine risk communication: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2. What you need to know before you take Inlyta: Warnings and precautions PL Section 4. Possible side effects
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Special warnings and precautions for ATE are included in SmPC Section 4.4. Undesirable effects associated with ATE are included in SmPC Section 4.8. Information about ATE is present in Section 2 and Section 4 of the PL. Other routine risk minimisation measures beyond the Product Information: None.
Gastrointestinal perforation and fistula	Routine risk communication: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2. What you need to know before you take Inlyta: Warnings and precautions PL Section 4. Possible side effects
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Special warnings and precautions for gastrointestinal perforation and fistula are included in SmPC Section 4.4. Undesirable effects associated with gastrointestinal perforation and fistula are included in SmPC Section 4.8. Information about gastrointestinal perforation and fistula is present in Section 2 and Section 4 of the PL. Other routine risk minimisation measures beyond the Product Information: None.
Haemorrhage	Routine risk communication: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2. What you need to know before you take Inlyta: Warnings and precautions PL Section 4. Possible side effects

Table 32. Description of Routine Risk Minimisation Measures By Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Haemorrhage *Cont'd*	Routine risk minimisation activities recommending specific clinical measures to address the risk: Special warnings and precautions for haemorrhage are included in SmPC Section 4.4. Undesirable effects associated with haemorrhage are included in SmPC Section 4.8. Information about haemorrhage is present in Section 2 and Section 4 of the PL. Other routine risk minimisation measures beyond the Product Information: None.
PRES	Routine risk communication: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2. What you need to know before you take Inlyta: Warnings and precautions PL Section 4. Possible side effects
	Routine risk minimisation activities recommending specific clinical measures to address the risk Special warnings and precautions for PRES are included in SmPC Section 4.4. Undesirable effects associated with PRES are included in SmPC Section 4.8. Information about PRES is present in Section 2 and Section 4 of the PL. Other routine risk minimisation measures beyond the Product Information: None.
VTE	Routine risk communication: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2. What you need to know before you take Inlyta: Warnings and precautions PL Section 4. Possible side effects
	Routine risk minimisation activities recommending specific clinical measures to address the risk Special warnings and precautions for VTE are included in SmPC Section 4.4. Undesirable effects associated with VTE are included in SmPC Section 4.8. Information about VTE is present in Section 2 and Section 4 of the PL. Other routine risk minimisation measures beyond the Product Information: None.

Table 32. Description of Routine Risk Minimisation Measures By Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Effects on the exocrine pancreas	Routine risk communication: SmPC Section 4.8 Undesirable effects
	Routine risk minimisation activities recommending specific clinical measures to address the risk Undesirable effects associated with effects on the exocrine pancreas are included in SmPC Section 4.8. Other routine risk minimisation measures beyond the Product Information: None.
Renal failure	Routine risk communication: SmPC Section 4.2 Posology and method of administration SmPC Section 4.8 Undesirable effects SmPC Section 5.2 Pharmacodynamic properties PL Section 4. Possible side effects
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Posology and method of administration information related to renal failure is included in SmPC Section 4.2. Undesirable effects associated with renal failure are included in SmPC Section 4.8. Pharmacodynamic properties for renal failure are included in SmPC Section 5.2. Information about renal failure is present in Section 4 of the PL. Other routine risk minimisation measures beyond the Product Information: None.
Congestive heart failure/ cardiomyopathy	Routine risk communication: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2. What you need to know before you take Inlyta: Warnings and precautions PL Section 4. Possible side effects
	Routine risk minimisation activities recommending specific clinical measures to address the risk Special warnings and precautions for congestive heart failure/cardiomyopathy are included in SmPC Section 4.4. Undesirable effects associated with congestive heart failure/cardiomyopathy are included in SmPC Section 4.8. Information about congestive heart failure/cardiomyopathy is present in Section 2 and Section 4 of the PL. Other routine risk minimisation measures beyond the Product Information: None.

Table 32. Description of Routine Risk Minimisation Measures By Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Important Potential Risks	
Torsade de pointes due to QT prolongation	Routine risk communication: No risk minimisation measures identified.
	Routine risk minimisation activities recommending specific clinical measures to address the risk None. Other routine risk minimisation measures beyond the Product Information: None.
Reproductive and developmental toxicity	Routine risk communication: SmPC Section 4.6 Fertility, pregnancy and lactation SmPC Section 5.3 Pre-clinical safety data PL Section 2. What you need to know before you take Inlyta: Warnings and precautions
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Information related to reproductive and developmental toxicity is included in SmPC Section 4.6. Pre-clinical safety data for reproductive and developmental toxicity is included in SmPC Section 5.3. Information about reproductive and developmental toxicity is present in Section 2 of the PL. Other routine risk minimisation measures beyond the Product Information: None.
Carcinogenicity	Routine risk communication: No risk minimisation measures identified.
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Osteonecrosis of the jaw	No risk minimisation measures identified.

Table 32. Description of Routine Risk Minimisation Measures By Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Missing Information	
Risks in pregnant and lactating women	Routine risk communication: SmPC Section 4.6 Fertility, pregnancy and lactation SmPC Section 5.3 Pre-clinical safety data PL Section 2. What you need to know before you take Inlyta: Warnings and precautions
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Information related to risks in pregnant and lactating women is included in SmPC Section 4.6. Pre-clinical safety data for risks in pregnant and lactating women is included in SmPC Section 5.3. Information about risks in pregnant and lactating women is present in Section 2 of the PL. Other routine risk minimisation measures beyond the Product Information: None.
Risks in paediatric subjects	Routine risk communication: SmPC Section 4.2 Posology and method of administration PL Section 2. What you need to know before you take Inlyta: Warnings and precautions
	Routine risk minimisation activities recommending specific clinical measures to address the risk Posology and method of administration for paediatric subjects is included in SmPC Section 4.2. Information about risk in paediatric subjects is present in Section 2 of the PL. Other routine risk minimisation measures beyond the Product Information: None.
Risks in subjects with moderate and severe renal impairment (serum creatinine >1.5 times the ULN or calculated creatinine clearance <60 mL/min)	Routine risk communication: SmPC Section 4.2 Posology and method of administration SmPC Section 5.2 Pharmacodynamic properties
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Posology and method of administration for subjects with moderate and severe renal impairment (information about patients with serum creatinine >1.5 times the ULN or calculated creatinine clearance <60 mL/min) is included in SmPC Section 4.2. Pharmacodynamic properties for subjects with moderate and severe renal impairment (information about patients with serum creatinine >1.5 times the ULN or calculated creatinine clearance <60 mL/min) are included in SmPC Section 5.2. Other routine risk minimisation measures beyond the Product Information: None.

Table 32. Description of Routine Risk Minimisation Measures By Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Risks in subjects with severe hepatic impairment (Child-Pugh Class C)	Routine risk communication: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 5.2 Pharmacodynamic properties PL Section 2. What you need to know before you take Inlyta: Warnings and precautions
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Posology and method of administration for subjects with severe hepatic impairment (Child-Pugh Class C) is included in SmPC Section 4.2. Special warnings and precautions for risk in subjects with severe hepatic impairment (Child-Pugh Class C) are included in SmPC Section 4.4. Pharmacodynamic properties for subjects with severe hepatic impairment (Child-Pugh Class C) are included in SmPC Section 5.2. Information about subjects with severe hepatic impairment (Child-Pugh Class C) is present in Section 2 of the PL. Other routine risk minimisation measures beyond the Product Information: None.
Risks in subjects with brain metastasis, spinal cord compression, or carcinomatous meningitis	Routine risk communication: SmPC Section 4.4 Special warnings and precautions for use
	Routine risk minimisation activities recommending specific clinical measures to address the risk Special warnings and precautions about risks in subjects with brain metastasis are included in SmPC Section 4.4. Other routine risk minimisation measures beyond the Product Information: None.

Table 32. Description of Routine Risk Minimisation Measures By Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Risks in subjects with active peptic ulcer disease	Routine risk communication: Although the SmPC does not contain any specific wording related to peptic ulcer disease, SmPC Section 4.4 Special warnings and precautions for use includes the warnings about gastrointestinal perforation and haemorrhage. PL Section 2. What you need to know before you take Inlyta: Warnings and precautions PL Section 4. Possible side effects
	Routine risk minimisation activities recommending specific clinical measures to address the risk Special warnings and precautions about gastrointestinal perforation and haemorrhage are included in SmPC Section 4.4. Information related to risks in subjects with active peptic ulcer disease is present in Section 2 and Section 4 of the PL. Other routine risk minimisation measures beyond the Product Information: None.
Risks in subjects with a recent major surgery (within 4 weeks) or radiation therapy (within 2 weeks)	Routine risk communication: SmPC Section 4.4 Special warnings and precautions for use PL Section 2. What you need to know before you take Inlyta: Warnings and precautions
	Routine risk minimisation activities recommending specific clinical measures to address the risk Axitinib has not been studied in patients with a recent major surgery (within 4 weeks) or radiation therapy (within 2 weeks). Special warnings and precautions about risk of wound healing complications to stop axitinib at least 24 hours prior to scheduled surgery are included in SmPC Section 4.4. Information related to risk of wound healing complications is present in Section 2 of the PL. Other routine risk minimisation measures beyond the Product Information: None.

ATE = Arterial Embolic and Thrombotic Event; PL = Package Leaflet; PRES = Posterior Reversible Encephalopathy Syndrome; SmPC = Summary of Product Characteristics; ULN = Upper Limit of Normal; VTE = Venous Thrombotic and Embolic Event.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in PART V.1 Routine Risk Minimisation Measures are sufficient to manage the safety concerns of the medicinal product.

V.3. Summary of Risk Minimisation Measures

Routine risk minimisation actions include the use of SmPC and PL to address the safety concerns, as summarised in Table 33 below. There are no additional risk minimisation measures (RMMs) proposed.

Table 33. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures (RMMs)	Pharmacovigilance Activities
Important Identified Risks		
ATE	Routine RMMs: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2. What you need to know before you take Inlyta: Warnings and precautions PL Section 4. Possible side effects Additional risk minimisation measures: None.	Routine
Gastrointestinal perforation and fistula	Routine RMMs: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2. What you need to know before you take Inlyta: Warnings and precautions PL Section 4. Possible side effects Additional risk minimisation measures: None.	Routine
Haemorrhage	Routine RMMs: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 What you need to know before you take Inlyta: Warnings and precautions PL Section 4. Possible side effects Additional risk minimisation measures: None.	Routine
PRES	Routine RMMs: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2. What you need to know before you take Inlyta: Warnings and precautions PL Section 4. Possible side effects Additional risk minimisation measures: None.	Routine
VTE	Routine RMMs: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2, What you need to know before you take Inlyta: Warnings and precautions PL Section 4. Possible side effects Additional risk minimisation measures: None.	Routine

Table 33. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures (RMMs)	Pharmacovigilance Activities
Effects on the exocrine pancreas	Routine RMMs: SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: None.	Routine
Renal failure	Routine RMMs: SmPC Section 4.2 Posology and method of administration SmPC Section 4.8 Undesirable effects SmPC Section 5.2 Pharmacodynamic properties PL Section 4. Possible side effects Additional risk minimisation measures: None.	Routine
Congestive heart failure/ cardiomyopathy	Routine RMMs: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2. What you need to know before you take Inlyta: Warnings and precautions PL Section 4. Possible side effects Additional risk minimisation measures: None.	Routine
Important Potential Risks		
Torsade de pointes due to QT prolongation	Routine RMMs: No risk minimisation measures identified. Additional risk minimisation measures: None.	Routine
Reproductive and developmental toxicity	Routine RMMs: SmPC Section 4.6 Fertility, pregnancy and lactation SmPC Section 5.3 Pre-clinical safety data PL Section 2. What you need to know before you take Inlyta: Warnings and precautions Additional risk minimisation measures: None.	Routine
Carcinogenicity	Routine RMMs: No risk minimisation measures identified. Additional risk minimisation measures: None.	Routine
Osteonecrosis of the jaw	No risk minimisation measures identified.	Routine

Table 33. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures (RMMs)	Pharmacovigilance Activities
Missing Information		
Risks in pregnant and lactating women	Routine RMMs: SmPC Section 4.6 Fertility, pregnancy and lactation SmPC Section 5.3 Pre-clinical safety data PL Section 2. What you need to know before you take Inlyta: Warnings and precautions Additional risk minimisation measures: None.	Routine
Risks in paediatric subjects	Routine RMMs: SmPC Section 4.2 Posology and method of administration PL Section 2. What you need to know before you take Inlyta: Warnings and precautions Additional risk minimisation measures: None.	Routine
Risks in subjects with moderate and severe renal impairment (serum creatinine >1.5 times the ULN or calculated creatinine clearance <60 mL/min)	Routine RMMs: SmPC Section 4.2 Posology and method of administration SmPC Section 5.2 Pharmacodynamic properties Additional risk minimisation measures: None.	Routine
Risks in subjects with severe hepatic impairment (Child-Pugh Class C)	Routine RMMs: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 5.2 Pharmacodynamic properties PL Section 2. What you need to know before you take Inlyta: Warnings and precautions Additional risk minimisation measures: None.	Routine
Risks in subjects with brain metastasis, spinal cord compression, or carcinomatous meningitis	Routine RMMs: SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures: None.	Routine

Table 33. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures (RMMs)	Pharmacovigilance Activities
Risks in subjects with active peptic ulcer disease	Routine RMMs: Although the SmPC does not contain any specific wording related to peptic ulcer disease, SmPC Section 4.4 (Special warnings and precautions for use) includes the warnings about gastrointestinal perforation and haemorrhage. PL Section 2. What you need to know before you take Inlyta: Warnings and precautions PL Section 4. Possible side effects Additional risk minimisation measures: None.	Routine
Risks in subjects with a recent major surgery (within 4 weeks) or radiation therapy (within 2 weeks)	Routine RMMs: SmPC Section 4.4 Special warnings and precautions for use (for wound healing complications) PL Section 2. What you need to know before you take Inlyta: Warnings and precautions (for wound healing complications) Additional risk minimisation measures: None.	Routine

ATE = Arterial Embolic and Thrombotic Event; PRES = Posterior Reversible Encephalopathy Syndrome; SmPC = Summary of Product Characteristics; ULN = Upper Limit of Normal; VTE = Venous Thrombotic and Embolic Event.

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Inlyta

This is a summary of the risk management plan (RMP) for Inlyta. The RMP details important risks of Inlyta, how these risks can be minimised, and how more information will be obtained about Inlyta's risks and uncertainties (missing information).

Inlyta's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Inlyta should be used.

This summary of the RMP for Inlyta should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

There are no new important safety concerns identified with axitinib, however changes to the current ones are included in updates of Inlyta's RMP.

I. The Medicine and What It Is Used For

Inlyta is authorised for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine. It contains axitinib as the active substance and it is given by oral route of administration.

Further information about the evaluation of Inlyta's benefits can be found in Inlyta's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage

https://www.ema.europa.eu/en/medicines/human/EPAR/inlyta

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Inlyta, together with measures to minimise such risks and the proposed studies for learning more about Inlyta's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the public (eg with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Inlyta is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Inlyta are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Inlyta. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

Table 34. List of Important Risks and Missing Information

Important identified risks	• Arterial embolic and thrombotic events • Gastrointestinal perforation and fistula • Haemorrhage • Posterior Reversible Encephalopathy Syndrome • Venous Embolic and Thrombotic Event • Effects on the exocrine pancreas • Renal failure • Congestive heart failure/cardiomyopathy
Important potential risks	• Torsade de pointes due to QT prolongation • Reproductive and developmental toxicity • Carcinogenicity • Osteonecrosis of the jaw
Missing information	• Risks in pregnant and lactating women • Risks in paediatric subjects • Risks in subjects with moderate and severe renal impairment (serum creatinine >1.5 times the ULN or calculated creatinine clearance <60 mL/min) • Risks in subjects with severe hepatic impairment (Child-Pugh Class C) • Risks in subjects with brain metastasis, spinal cord compression, or carcinomatous meningitis • Risks in subjects with active peptic ulcer disease • Risks in subjects with a recent major surgery (within 4 weeks) or radiation therapy (within 2 weeks)

ULN = Upper Limit of Normal

II.B. Summary of Important Risks

Table 35. Important Identified Risk: Arterial Embolic and Thrombotic Events

Evidence for linking the risk to the medicine	Evidence Source: Inlyta clinical trials and post-marketing reports. Strength of evidence: Arterial embolic and thrombotic events have been reported for other VEGFI, and have been reported in Inlyta clinical trials and in the post-marketing setting.
Risk factors and risk groups	Cancer patients have an increased risk of ATE. Increasing age, smoking, hypertension, hypercholesterolemia, polycythaemia, and a history of ATE are other recognised predisposing risk factors for ATE.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 What you need to know before you take Inlyta: Warnings and precautions PL Section 4. Possible side effects Additional risk minimisation measures: None.

Table 36. Important Identified Risk: Gastrointestinal perforation and fistula

Evidence for linking the risk to the medicine	Evidence Source: Inlyta clinical trials and post-marketing reports. Strength of evidence: In non-clinical studies, gastrointestinal toxicity to the alimentary tract was observed following repeat dosing, including haemorrhage and/or necrosis of the oral, stomach or intestinal mucosa. Gastrointestinal perforation and fistula have been reported in Inlyta clinical trials and in the post-marketing setting.
Risk factors and risk groups	Acute conditions involving the bowel, including tumour at the site of perforation, acute diverticulitis, bowel obstruction and carcinomatosis, as well as radiation, may be associated with an increased risk of developing gastrointestinal perforation.[50] Risk factors for fistula formation in subjects with RCC who are treated with anti angiogenic agents are unknown.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 What you need to know before you take Inlyta: Warnings and precautions PL Section 4. Possible side effects Additional risk minimisation measures: None.

Table 37. Important Identified Risk: Haemorrhage

Evidence for linking the risk to the medicine	Evidence Source: Inlyta clinical trials and post-marketing reports. Strength of evidence: Haemorrhage has been reported with other TKIs and has been reported in Inlyta clinical trials and in the post-marketing setting.
Risk factors and risk groups	From clinical trials data in subjects with advanced RCC, tissues with tumour involvement appear to be more likely to haemorrhage than uninvolved tissues.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 What you need to know before you take Inlyta: Warnings and precautions PL Section 4. Possible side effects Additional risk minimisation measures: None.

Table 38. Important Identified Risk: Posterior Reversible Encephalopathy Syndrome

Evidence for linking the risk to the medicine	Evidence Source: Inlyta clinical trials and post-marketing reports. Strength of evidence: PRES has been reported in clinical trials and in the post-marketing setting and may be related to the known adverse reaction of hypertension with Inlyta.
Risk factors and risk groups	PRES has been most frequently observed with acute increases in blood pressure, which may account for its occurrence in patients with uncontrolled hypertension, renal failure or eclampsia.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 What you need to know before you take Inlyta: Warnings and precautions PL Section 4. Possible side effects Additional risk minimisation measures: None.

Table 39. Important Identified Risk: Venous Embolic and Thrombotic Events

Evidence for linking the risk to the medicine	Evidence Source: Inlyta clinical trials and post-marketing reports. Strength of evidence: Venous embolic and thrombotic events have been reported for other VEGFI, and have been reported in Inlyta clinical trials and in the post-marketing setting.
Risk factors and risk groups	Cancer patients have an increased risk of VTE. No other risk factor for VTE has been identified in Inlyta studies.

Table 39. Important Identified Risk: Venous Embolic and Thrombotic Events

Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 What you need to know before you take Inlyta: Warnings and precautions PL Section 4. Possible side effects Additional risk minimisation measures: None.

Table 40. Important Identified Risk: Effects on the Exocrine Pancreas

Evidence for linking the risk to the medicine	Evidence Source: Inlyta clinical trials and post-marketing reports. Strength of evidence: In non-clinical studies, a decrease in zymogen granules and concomitant increase in acinar cells in the pancreas were observed after 28 days of Inlyta administration.
Risk factors and risk groups	No risk group has been identified.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: None.

Table 41. Important Identified Risk: Renal Failure

Evidence for linking the risk to the medicine	Evidence Source: Inlyta clinical trials and post-marketing reports. Strength of evidence: Most cases of renal failure in the clinical trial and in the post-marketing setting involved known risk factors which may have contributed to the development of renal failure.
Risk factors and risk groups	In a retrospective review of 108 Korean patients with RCC, 39.8% developed chronic kidney disease post-surgery.[62] Risk factors identified for renal failure include advanced age; chronic infection; diabetes; hypertension; heart failure; immune disorders, such as lupus, IgA nephropathy and scleroderma; hepatic disease; prostate gland enlargement; and bladder outlet obstruction. Risk factors for prerenal acute renal failure include dehydration, heart failure, sepsis, and severe blood loss.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.8 Undesirable effects SmPC Section 5.2 Pharmacokinetic properties PL Section 4. Possible side effects Additional risk minimisation measures: None.

Table 42. Important Identified Risk: Congestive Heart Failure/Cardiomyopathy

Evidence for linking the risk to the medicine	Evidence Source: Inlyta clinical trials and post-marketing reports. Strength of evidence: Congestive heart failure/cardiomyopathy has been reported with other TKIs and has been reported in Inlyta clinical trials and in the post-marketing setting.
Risk factors and risk groups	In cases of congestive heart failure/cardiomyopathy, for which medical history was reported, most patients had a personal or family history of coronary artery disease and/or one or more risk factors, including cigarette smoking, hypertension, hyperlipidaemia, diabetes, advanced age, and obesity.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 What you need to know before you take Inlyta: Warnings and precautions PL Section 4. Possible side effects Additional risk minimisation measures: None.

Table 43. Important Potential Risk: Torsade de pointes due to QT Prolongation

Evidence for linking the risk to the medicine	Evidence Source: Inlyta clinical trials and post-marketing reports. Strength of evidence: QT prolongation has been reported with other VEGFI. However, the relationship between Inlyta administration and QT Prolongation leading to Torsade de pointes is not yet established.
Risk factors and risk groups	No risk factors have been identified. Theoretically patients who have baseline QT interval prolongation, cardiac disease, or receive other medications that cause QT interval prolongation may be at increased risk.
Risk minimisation measures	Routine risk minimisation measures No risk minimisation measures identified. Additional risk minimisation measures: None.

Table 44. Important Potential Risk: Reproductive and Developmental Toxicity

Evidence for linking the risk to the medicine	Evidence Source: Inlyta clinical trials and post-marketing reports. Strength of evidence: Non-clinical studies identified effects on male and female reproductive organs with Inlyta administration for ≥28 days. However, the relationship between Inlyta administration and reproductive and developmental toxicity in humans is not yet established.
Risk factors and risk groups	No risk group has been identified.

Table 44. Important Potential Risk: Reproductive and Developmental Toxicity

Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6 Fertility, pregnancy and lactation SmPC Section 5.3 Pre-clinical safety data PL Section 2. What you need to know before you take Inlyta: Warnings and precautions Additional risk minimisation measures: None.

Table 45. Important Potential Risk: Carcinogenicity

Evidence for linking the risk to the medicine	Evidence Source: Inlyta clinical trials and post-marketing reports. Strength of evidence: Pre-clinical carcinogenicity study and spontaneous reports of second primary malignancy. However, the relationship between Inlyta administration and carcinogenicity in humans is not yet established.
Risk factors and risk groups	No risk group has been identified.
Risk minimisation measures	Routine risk minimisation measures: No risk minimisation measures identified. Additional risk minimisation measures: None.

Table 46. Important Potential Risk: Osteonecrosis of the Jaw

Evidence for linking the risk to the medicine	Evidence Source: Inlyta clinical trials and post-marketing reports. Strength of evidence: Osteonecrosis of the jaw has been reported with other VEGFI. However, the relationship between Inlyta administration and osteonecrosis of the jaw is not yet established.
Risk factors and risk groups	Risk factors for osteonecrosis of the jaw include bisphosphonates, diabetes, alcoholism, cigarette smoking, obesity, hyperlipidaemia, pancreatitis, chemotherapy with L-asparaginase, radiotherapy, receipt of parenteral steroids, jaw trauma, and dental procedures.
Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None.

Table 47. Missing Information: Risks in Pregnant and Lactating Women

Risk minimisation measures	Information regarding use during pregnancy and lactation is provided in the SmPC Section 4.6 and 5.3 and PL Section 2.

Table 48. Missing Information: Risks in Paediatric Subjects

Risk minimisation measures	Information regarding use in paediatric patients is provided in the SmPC Section 4.2 and PL Section 2.

Table 49. Missing Information: Risks in Subjects with Moderate and Severe Renal Impairment (Serum Creatinine >1.5 times the ULN or Calculated Creatinine Clearance <60 mL/min)

Risk minimisation measures	Information regarding use in patients with renal impairment is provided in the SmPC Section 4.2 and 5.2.

Table 50. Missing Information: Risks in Subjects with Severe Hepatic Impairment (Child-Pugh Class C)

Risk minimisation measures	Information regarding use in patients with hepatic impairment is provided in the SmPC Section 4.2, 4.4 and 5.2 and PL Section 2.

Table 51. Missing Information: Risks in Subjects with Brain Metastasis, Spinal Cord Compression, or Carcinomatous Meningitis

Risk minimisation measures	Information regarding use in patients with brain metastasis is provided in the SmPC Section 4.4.

Table 52. Missing Information: Risks in Subjects with Active Peptic Ulcer Disease

Risk minimisation measures	Although the SmPC does not contain any specific wording related to peptic ulcer disease, SmPC, Section 4.4 includes the warnings about gastrointestinal perforation and haemorrhage; PL Section 2 and Section 4.

Table 53. Missing Information: Risks in Subjects with a Recent Major Surgery (within 4 weeks) or Radiation Therapy (within 2 weeks)

Risk minimisation measures	Information regarding use in patients with wound healing complications is provided in the SmPC Section 4.4; PL Section 2.

II.C. Post-Authorisation Development Plan

II.C.1. Studies which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Inlyta.

II.C.2. Other Studies in Post-Authorisation Development Plan

There are no studies required for Inlyta.

PART VII. ANNEXES

Annex 1 – EudraVigilance Interface

Annex 2 – Tabulated Summary of Planned, On-going, and Completed Pharmacovigilance Study Programme

Annex 3 – Protocols for Proposed, On-going, and Completed Studies in the Pharmacovigilance Plan

Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms

Annex 5 – Protocols for Proposed and On-going Studies in RMP Part IV

Annex 6 – Details of Proposed Additional Risk Minimisation Activities (if applicable)

Annex 7 – Other Supporting Data (Including Referenced Material)

Annex 8 – Summary of Changes to the Risk Management Plan over Time

REFERENCES

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ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

[redacted]

Instructions for use:

Select questions as needed to obtain any DCA-defined information described below that was not included in the initial report.

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting special follow-up activities: _____

QT Interval/Torsades de Pointes Follow-up Questions

Please provide additional details on a separate page if needed, and reference the question number.

1. Is the reported adverse event a:

- ☐ New event
- ☐ Recurrence *(please provide details on previous events)*
- ☐ Exacerbation of underlying condition *(please provide details)*

Details:

2. Please specify whether the patient has a history of any of the following: *(please specify date of onset / resolution)*

- ☐ Eating disorder
- ☐ Protein diets
- ☐ Laxative abuse
- ☐ Gastroplasty/ileojejunal bypass
- ☐ Celiac disease
- ☐ Acute nervous system injury
- ☐ CVA
- ☐ Hemorrhage
- ☐ Pheochromocytoma
- ☐ Hypothyroidism
- ☐ Impaired renal function
- ☐ Impaired liver function
- ☐ Bradycardia
- ☐ 2nd Degree AV block
- ☐ 3rd Degree AV block
- ☐ Recent therapeutic atrial fibrillation conversion
- ☐ MI
- ☐ Cardiomyopathy
- ☐ Mitral valve prolapse
- ☐ Recent heart surgery
- ☐ Recent catheterization or intracoronary dye
- ☐ Congenital long QT syndrome
- ☐ Concurrent hypothermia
- ☐ History of VT/VEA
- ☐ Other *(please specify)*

Details:

3. Please mark whether the patient was taking any of the following medications at the time of the adverse event or within one month prior to the onset of the adverse event: *(Please provide the specific dates of administration, dosage, and timing in relation to product)*

Antiarrhythmic Drugs:
- ☐ Quinidine
- ☐ Disopyramide
- ☐ Procainamide
- ☐ Sotalol
- ☐ Amiodarone
- ☐ Ibutilide
- ☐ Dofetilide
- ☐ Other *(Please specify)*

Antibiotics:
- ☐ Erythromycin
- ☐ Clarithromycin
- ☐ Fluconazole
- ☐ Ketoconazole
- ☐ Amantadine
- ☐ Pentamidine
- ☐ Other *(Please specify)*

Psychiatric Medications:
- ☐ Tricyclics
- ☐ Tetracyclics,
- ☐ Other Antidepressants *(Please specify)*
- ☐ Thioridazine
- ☐ Haloperidol
- ☐ Sertindole
- ☐ Phenothiazines
- ☐ Other Antipsychotics *(Please specify)*

Antihistamines:
- ☐ Astemizole
- ☐ Other *(Please specify)*

Serotonin Receptor Antagonists:
- ☐ Ketanserin
- ☐ Other *(Please specify)*

Diuretics:
- ☐ Indapamide
- ☐ Triamterene
- ☐ Hydrochlorothiazide,
- ☐ Other *(Please specify)*

- ☐ Laxatives: *(Please specify)*

Inotropics:
- ☐ Amrinone
- ☐ Milrinone
- ☐ Other *(Please specify)*

	Details:

4. Were any of the following laboratory tests or diagnostic studies performed? *Please specify laboratory data with units, date of test, and reference ranges; and please provide printouts and photographs if available:*

	Before Drug	On Drug	After Drug Stopped
Was an ECG or rhythm strip done?	☐ No ☐ Yes *(provide date)*	☐ No ☐ Yes *(provide date)*	☐ No ☐ Yes *(provide date)*
What was the actual QT interval?			
What was the QTc?			
Correction formula used?			
What was the corresponding heart rate?			
Was the ECG or rhythm strip automated and/or interpreted?	☐ Automated computer read out? ☐ Read by a physician? ☐ Read by cardiologist?	☐ Automated computer read out? ☐ Read by a physician? ☐ Read by cardiologist?	☐ Automated computer read out? ☐ Read by a physician? ☐ Read by cardiologist?

Other Tests

Laboratory Test	Date Performed	Results with units if applicable	Reference Ranges if applicable
☐ Potassium			
☐ Magnesium			
☐ Calcium			
☐ Thyroid studies			
☐ Other relevant tests *(please specify)*:			

Revision History

Revision	Effective Date	Summary of Revisions
1.0	22-May-2014	New DCA

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable as no additional risk minimisation measures identified.