Part VI: Summary of the risk management plan

Summary of risk management plan for Fotivda (Tivozanib Hydrochloride)

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

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

This summary of the RMP for Fotivda 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).

Important new concerns or changes to the current ones will be included in updates of Fotivda's RMP.

I. The medicine and what it is used for

Fotivda is authorised for the first line treatment of adult patients with advanced renal cell carcinoma (RCC) and for adult patients who are VEGFR and mammalian target of rapamycin (mTOR) pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for advanced RCC (see SmPC for the full indication). It contains Tivozanib Hydrochloride as the active substance and it is given by oral administration.

Further information about the evaluation of Fotivda's benefits can be found in Fotivda's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/fotivda.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Fotivda, together with measures to minimise such risks and the proposed studies for learning more about Fotivda'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 patient (e.g. 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 Fotivda is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Fotivda are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Fotivda. 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 (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Hypertension Arterial embolic and thrombotic events Venous embolic and thrombotic events Congestive heart failure (CHF) Haemorrhage Proteinuria Hand-foot skin reaction (HFSR) Posterior reversible encephalopathy syndrome (PRES)
Important potential risks	QT prolongation Hepatic effects GI perforation and fistula Reproductive and developmental toxicity Wound healing complications Overdose
Missing information	Use during lactation

II.B Summary of important risks

Important identified risk: Hypertension

<table>
<tr><td>Evidence for linking the risk to the medicine</td><td>Non-clinical: Transient increase in blood pressure after a single oral dose of 3 mg/kg/day was seen in monkeys. A maximum increase of 14 to 19 mmHg was seen 90 minutes post-dose.
Clinical trials (DLP of 20 January 2015): The overall frequency of hypertension TEAEs among tivozanib hydrochloride-treated patients in the core RCC monotherapy studies was 49.4%.

UPDATE as of DLP 23 Feb 2021:
Clinical trials: The overall frequency of hypertension TEAEs among tivozanib hydrochloride-treated patients in the TIVO-3 study was 40.5%.

Post-marketing experience (DLP of 23 Feb 2021): Cumulative data from the post-marketing experience revealed 31 reports of Hypertension (hypertension, n=22, blood pressure increased, n=3, blood pressure diastolic increased n=1, hypertensive crisis n=3, hypertensive heart disease n=1, and accelerated hypertension=1). No new safety issues have been identified from these post-marketing cases.

Class effect:
<table>
<tr><td>Sorafenib</td><td>▪ 29% (all grades); 11% (Grade 3/4) (Rini et al., 2011; USPI NEXAVAR (sorafenib))
▪ > 10% (all grades) (SmPC NEXAVAR (sorafenib))
▪ 16-36% (all grades); 1-10% (Grade 3/4) (Beck et al., 2011; Di Lorenzo, Carteni, et al., 2009; Escudier, Eisen, et al., 2009; Garcia et al., 2010; Hutson et al., 2008; Kane et al., 2006; Procopio et al., 2011; Procopio et al., 2007)</td></tr>
<tr><td>Sunitinib</td><td>▪ 34% (all grades) (SmPC SUTENT (sunitinib)); 13% (Grade 3); (USPI SUTENT (sunitinib malate))
▪ 22-61% (all grades); 5-18% (Grade ≥ 3) (Ansari et al., 2010; Escudier, Roigas, et al., 2009; Gore et al., 2009; Hutson et al., 2008; Motzer et al., 2009; Rini et al., 2008; Tomita et al., 2010; Uemura et al., 2010; Yildiz et al., 2011)</td></tr>
<tr><td>Axitinib</td><td>▪ 40% (all grades); 16% (Grade 3/4) (Rini et al., 2011; USPI INLYTA (axitinib)) 45-84% (all grades); 15-70% (Grade ≥ 3) (Rini et al., 2009; Rixe et al., 2007; Tomita et al., 2011)</td></tr>
<tr><td>Pazopanib</td><td>▪ Hypertension: 41% (all grades); 10% (Grade 3); <1% (Grade 4) (SmPC VOTRIENT (pazopanib))
▪ 40-41% (all grades); 4-9% (Grade 3); 0% (Grade 4) (Hutson et al., 2010; Sternberg et al., 2010)</td></tr>
</table></td></tr>
<tr><td>Risk factors and risk groups</td><td>The potential risk groups for hypertension or its complications are patients with uncontrolled hypertension and patients who may have ingested an overdose of tivozanib hydrochloride.</td></tr>
<tr><td>Risk minimisation measures</td><td>Routine risk minimisation measures:
SmPC section 4.2, 4.4, 4.8, 4.9
PL section 2, 3, 4
Prescription only medication and use is restricted to physicians experienced in the treatment of RCC.
Additional risk minimisation measures: No risk minimisation measures</td></tr>
<tr><td colspan="2">Important identified risk: Arterial embolic and thrombotic events</td></tr>
</table>

<table>
<tr><td>Evidence for linking the risk to the medicine</td><td>Clinical trials (DLP of 20 January 2015): The overall frequency of treatment-emergent arterial embolic and thrombotic events among tivozanib hydrochloride-treated patients in the core RCC monotherapy studies was 3.3%, and the frequency of Grade ≥ 3 events was 2.5%.

UPDATE as of DLP 23 Feb 2021:
Clinical trials: The overall frequency of treatment-emergent arterial embolic and thrombotic events (ischemic stroke) among tivozanib hydrochloride-treated patients in the TIVO-3 study was 1.2%.

Post-marketing experience (DLP of 23 Feb 2021): Cumulative data from the post-marketing experience revealed 8 reports of arterial embolic and thrombotic events (myocardial infarction, n=2, acute myocardial infarction, n=3, retinal artery thrombosis, n=1, pelvic venous thrombosis, n=1, peripheral arterial occlusive disease n=1). The safety information from post marketing data is consistent with the reported safety data in clinical trials.

Class effect:
<table>
<tr><td>Sorafenib</td><td>▪ ATE: 1% (Grade 3/4) (USPI NEXAVAR (sorafenib))
▪ Cardiac ischemia/infarction: 3-5% (all grades) (Escudier, Eisen, et al., 2009; Hutson et al., 2008; SmPC NEXAVAR (sorafenib))</td></tr>
<tr><td>Sunitinib</td><td>▪ Cerebrovascular accident (CVA), transient ischemic attack (TIA): <1%, MI: <10%, fatal ATE has been reported (SmPC SUTENT (sunitinib))
▪ Treatment-related fatal MI: 1% (SmPC SUTENT (sunitinib))
▪ MI: 3% (all grades); 3% (Grade ≥ 3) (Yildiz et al., 2011)</td></tr>
<tr><td>Axitinib</td><td>▪ ATE: 2% (all grades); 1% (Grade 3/4)
▪ Fatal CVA: < 1%
▪ TIA: 1% (all grades) (USPI INLYTA (axitinib))</td></tr>
<tr><td>Pazopanib</td><td>▪ ATE: 3% (MI/ischemia 2%, CVA < 1%, TIA < 1% - 1%) (Sternberg et al., 2010; USPI VOTRIENT (pazopanib))
▪ Ischemic stroke: < 1% (all grades); 0% (Grade 3); < 1% (Grade 4)
TIA: < 1% (all grades); < 1% (Grade 3); 0% (Grade 4)
CVA: < 1% (all grades); < 1% (Grade 3); < 1% (Grade 4)
Myocardial ischemia: < 1% (all grades); < 1% (Grade 3); 0% (Grade 4)
MI: < 1% (all grades); < 1% (Grade 3); < 1% (Grade 4) (SmPC VOTRIENT (pazopanib))</td></tr>
</table></td></tr>
<tr><td>Risk factors and risk groups</td><td>Risk factors for arterial embolic and thrombotic events include malignant disease, age > 65 years, hypertension, diabetes mellitus, and prior thromboembolic disease.</td></tr>
<tr><td>Risk minimisation measures</td><td>Routine risk minimisation measures:
SmPC section 4.4, 4.8
PL section 2, 4
Prescription only medication and use is restricted to physicians experienced in the treatment of RCC.
Additional risk minimisation measures: No risk minimisation measures</td></tr>
<tr><td colspan="2">Important identified risk: Venous embolic and thrombotic events</td></tr>
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<tr><td>Evidence for linking the risk to the medicine</td><td>Clinical trials (DLP of 20 January 2015): The overall frequency of treatment-emergent venous embolic and thrombotic events among tivozanib hydrochloride-treated patients in the core RCC monotherapy studies was 2%, and the frequency of Grade ≥ 3 events was 0.9%.

UPDATE as of DLP 23 Feb 2021:
Clinical trials: The overall frequency of treatment-emergent venous embolic and thrombotic events (pulmonary embolism) among tivozanib hydrochloride-treated patients in the TIVO-3 study was 2.9%.

Post-marketing experience (DLP of 23 Feb 2021): Data from the post-marketing experience revealed 3 reports of venous embolism and thrombotic events (Pulmonary embolism n=3). The safety information from post marketing data is consistent with the reported safety data in clinical trials.

Class effect:
<table>
<tr><td>Sorafenib</td><td>▪ Thromboembolism <1% (USPI NEXAVAR (sorafenib))</td></tr>
<tr><td>Sunitinib</td><td>▪ Venous thromboembolic event (VTE): 3% (all grades)
▪ 2% pulmonary embolism (PE) all grades, 2% deep venous thrombosis (DVT) (all grades) (USPI SUTENT (sunitinib malate))</td></tr>
<tr><td>Axitinib</td><td>▪ VTE: 3.9% (all grades), 3.1% (Grade ≥3)
▪ PE: 2.2%, fatal PE 0.3%, DVT: 0.6%, Retinal vein occlusion/thrombosis: 0.6% (SmPC INLYTA (axitinib))</td></tr>
<tr><td>Pazopanib</td><td>▪ VTE: 1% (all grades), <1% (Grade ≥ 3) (SmPC VOTRIENT (pazopanib))</td></tr>
</table></td></tr>
<tr><td>Risk factors and risk groups</td><td>Risk factors for venous embolic and thrombotic events include advanced age, race (higher prevalence in Caucasians and African Americans), and presence of risk factors, such as cancer, surgery, trauma, inherited thrombophilic states, prior VTE or ATE, obesity, cardiac or respiratory failure, and immobilisation (Connelly-Frost et al., 2013; Weber, 2014).
A number of factors for VTE in malignancy have been implicated, including tumour-induced hypercoagulability, vascular injury from surgical treatment, chemotherapy, radiation, and venous stasis due to immobilisation. The risk did not appear to increase with added co-morbidity burden (A. B. Smith et al., 2014).</td></tr>
<tr><td>Risk minimisation measures</td><td>Routine risk minimisation measures:
SmPC section 4.4, 4.8
PL section 2, 4
Prescription only medication and use is restricted to physicians experienced in the treatment of RCC.
Additional risk minimisation measures: No risk minimisation measures</td></tr>
<tr><td colspan="2">Important identified risk: Congestive heart failure (CHF)</td></tr>
<tr><td>Evidence for linking the risk to the medicine</td><td>Clinical trials (DLP of 20 January 2015): Among tivozanib hydrochloride-treated patients in the core RCC monotherapy studies, the overall frequency of CHF TEAEs was 1% (7/674).

UPDATE as of DLP 23 Feb 2021:
Clinical trials: There was no new data pertaining to clinical trials since the product approval.

Post-marketing experience (DLP of 23 Feb 2021): Data from the post-marketing experience revealed no report of CHF.
Class effect:
<table>
<tr><td>Sorafenib</td><td>▪ CHF: 2% (all grades) (SmPC NEXAVAR (sorafenib))</td></tr>
<tr><td>Sunitinib</td><td>▪ CHF: <1% (all grades) (SmPC SUTENT (sunitinib))</td></tr>
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<tr><td></td><td>▪ Grade 3 LVEF dysfunction and/or CHF: 7% (Di Lorenzo, Autorino, et al., 2009).
▪ CHF: 4% (all grades); 2% (Grade ≥ 3) (Richards et al., 2011).</td></tr>
<tr><td>Axitinib</td><td>No information found</td></tr>
<tr><td>Pazopanib</td><td>▪ Cardiac dysfunction such as decreased LVEF and CHF: 0.6% (USPI VOTRIENT (pazopanib))
▪ CHF: 0.5% (SmPC VOTRIENT (pazopanib))</td></tr>
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</td></tr>
<tr><td>Risk factors and risk groups</td><td>Cardiotoxicity from TKI treatment is a risk factor for CHF. History of coronary artery disease (OR=18; 95% CI=4-160) and history of hypertension (OR=3; 95% CI=1.5-80) are significant predictors of CHF (Di Lorenzo, Autorino, et al., 2009).</td></tr>
<tr><td>Risk minimisation measures</td><td>Routine risk minimisation measures:
SmPC section 4.4, 4.8
PL section 2, 4
Prescription only medication and use is restricted to physicians experienced in the treatment of RCC.
Additional risk minimisation measures: No risk minimisation measures</td></tr>
<tr><td colspan="2">Important identified risk: Haemorrhage</td></tr>
<tr><td>Evidence for linking the risk to the medicine</td><td>Clinical trials (DLP of 20 January 2015): The overall frequency of haemorrhage TEAEs among tivozanib hydrochloride-treated patients in the core RCC monotherapy studies was 10.4%.

UPDATE as of DLP 23 Feb 2021:
Clinical trials: There was no new data pertaining to clinical trials since the product approval.

Post-marketing experience (DLP of 23 Feb 2021): Cumulative data from the post-marketing experience revealed 6 reports of haemorrhage (haemorrhage n=1, anal haemorrhage and skin haemorrhage n=1, subdural haematoma n=1, post-procedural haemorrhage n=1, gastrointestinal haemorrhage n=1, and epistaxis n=1). The safety information from post marketing data is consistent with the reported safety data in clinical trials.

Class effect:
<table>
<tr><td>Sorafenib</td><td>▪ Haemorrhagic events: 18% (all grades); 3% (Grade 3/4); 1% (Grade 5) (USPI NEXAVAR (sorafenib))
▪ Haemorrhage (including GI, respiratory tract, and cerebral) (all grades): Very common (> 10%) (SmPC NEXAVAR (sorafenib))
▪ Bleeding (all grades): 12-21% (Di Lorenzo, Carteni, et al., 2009; Hutson et al., 2008; Je et al., 2009).</td></tr>
<tr><td>Sunitinib</td><td>▪ 26-39% (all grades); 5% (Grade ≥ 3) (SmPC SUTENT (sunitinib))
▪ 19-26% (all grades); 3% (Grade ≥ 3) (Je et al., 2009)
▪ Epistaxis: 6-42% (all grades); 0-1% (Grade ≥ 3) (Ansari et al., 2010; Gore et al., 2009; Motzer et al., 2009; Tomita et al., 2010; Uemura et al., 2010; Yildiz et al., 2011)</td></tr>
<tr><td>Axitinib</td><td>▪ 16% (all grades); 1% (Grade 3/4); < 1% (Grade 5) (USPI INLYTA (axitinib))
▪ Epistaxis: 10-16% (all grades); 0% (Grade 3/4) (Rini et al., 2009; Rixe et al., 2007)
▪ Cerebral haemorrhage: 3% (all grades) (Tomita et al., 2011)
▪ Haematuria 6%; rectal haemorrhage 4%, GI haemorrhage 2% (Rixe et al., 2007)</td></tr>
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<tr><td></td><td><table>
<tr><td>Pazopanib</td><td>▪ Haemorrhagic events: 13% (all grades) (Sternberg et al., 2010; USPI VOTRIENT (pazopanib))
▪ Epistaxis: 4% (all grades); <1 % (Grade 3); 0% (Grade 4)
▪ Other events (all grades) each reported < 1%: oesophageal haemorrhage, GI haemorrhage, hematemesis, haematochezia, haemoptysis (1%), haemorrhage, haemorrhage urinary tract, haemorrhoidal haemorrhage, menorrhagia, metrorrhagia, mouth haemorrhage, pulmonary haemorrhage, rectal haemorrhage, retroperitoneal haemorrhage, upper GI haemorrhage, vaginal haemorrhage.
▪ Grade 3 events (each reported < 1%): GI haemorrhage, upper GI haemorrhage, rectal haemorrhage.
▪ Grade 4 events: no events in RCC patients; oesophageal haemorrhage in soft tissue sarcoma patients (< 1%) (SmPC VOTRIENT (pazopanib))</td></tr>
</table></td></tr>
<tr><td>Risk factors and risk groups</td><td>The potential risk groups for haemorrhage include subjects with prior history of bleeding or subjects receiving anti-coagulant therapy or anti-platelet treatments including aspirin.
Risk of bleeding might be higher and more relevant in the older and frailer population, in whom even a Grade 2 bleed is of clinical importance (Je et al., 2009).</td></tr>
<tr><td>Risk minimisation measures</td><td>Routine risk minimisation measures:
SmPC section 4.4, 4.8
PL section 2, 4
Prescription only medication and use is restricted to physicians experienced in the treatment of RCC.
Additional risk minimisation measures: No risk minimisation measures</td></tr>
<tr><td colspan="2">Important identified risk: Proteinuria</td></tr>
<tr><td>Evidence for linking the risk to the medicine</td><td>Non-clinical: Increases in urinary albumin, urobilinogen and other proteins were observed in rats.
Clinical trials (DLP of 20 January 2015): The overall frequency of proteinuria TEAEs among tivozanib hydrochloride-treated patients in the core RCC monotherapy studies was 8.9%.

UPDATE as of DLP 23 Feb 2021:
Clinical trials: The overall frequency of proteinuria TEAEs among tivozanib hydrochloride-treated patients in the TIVO-3 study was 6.4%.

Post-marketing experience (DLP of 23 Feb 2021): Cumulative data from the post-marketing experience revealed 2 reports of proteinuria (proteinuria, n=2). The safety information from post marketing data is consistent with the reported safety data in clinical trials.

Class effect:
<table>
<tr><td>Sorafenib</td><td>▪ 7% (all grades); 2% (Grade 3) (USPI NEXAVAR (sorafenib))</td></tr>
<tr><td>Sunitinib</td><td>▪ 1-10% (all grades) (SmPC SUTENT (sunitinib))</td></tr>
<tr><td>Axitinib</td><td>▪ 11% (all grades); 3% (Grade 3) (SmPC INLYTA (axitinib))
▪ 8-58% (all grades); 0-9% (Grade ≥ 3) (Rixe et al., 2007; Tomita et al., 2011)</td></tr>
<tr><td>Pazopanib</td><td>▪ 12% (all grades); 3% (Grade 3); 0% (Grade 4) (SmPC VOTRIENT (pazopanib))</td></tr>
</table></td></tr>
<tr><td>Risk factors and risk groups</td><td>Risk factors for proteinuria include high systolic and diastolic blood pressure.</td></tr>
<tr><td>Risk minimisation measures</td><td>Routine risk minimisation measures:</td></tr>
</table>

<table>
<tr><td></td><td>SmPC section 4.4, 4.8
PL section 2, 4
Prescription only medication and use is restricted to physicians experienced in the treatment of RCC.
Additional risk minimisation measures: No risk minimisation measures</td></tr>
<tr><td colspan="2">Important identified risk: Hand-foot skin reaction (HFSR)</td></tr>
<tr><td>Evidence for linking the risk to the medicine</td><td>Clinical trials (DLP of 20 January 2015): Among tivozanib hydrochloride-treated patients in the core RCC monotherapy studies, the overall frequency of HFSR TEAEs was 11%; the frequency of Grade ≥ 3 HFSR TEAEs was 1.5%.

UPDATE as of DLP 23 Feb 2021:
Clinical trials: The overall frequency of HFSR TEAEs among tivozanib hydrochloride-treated patients in the TIVO-3 study was 15.6%.

Post-marketing experience (DLP of 23 Feb 2021): Cumulative data from the post-marketing experience revealed 16 reports of HFSR (palmar-plantar erythrodysaesthesia syndrome, n=16). The safety information from post marketing data is consistent with the reported safety data in clinical trials.

Class effect:
<table>
<tr><td>Sorafenib</td><td>▪ 37-51% (all grades); 16% (Grade 3/4) (Massey et al., 2015; Rini et al., 2011; USPI NEXAVAR (sorafenib))
▪ 21-79% (all grades); 4-31% (Grade ≥ 3) (Beck et al., 2011; Di Lorenzo, Carteni, et al., 2009; Escudier, Eisen, et al., 2009; Garcia et al., 2010; Hutson et al., 2008; Procopio et al., 2011; Procopio et al., 2007)</td></tr>
<tr><td>Sunitinib</td><td>▪ 29% (all grades); 8% (Grade ≥ 3) (USPI SUTENT (sunitinib malate))
▪ 21-53% (all grades); Grade ≥ 3: 5-18% (Ansari et al., 2010; Escudier, Roigas, et al., 2009; Gore et al., 2009; Hutson et al., 2008; Motzer et al., 2009; Rini et al., 2008; Tomita et al., 2010; Uemura et al., 2010; Yildiz et al., 2011)</td></tr>
<tr><td>Axitinib</td><td>▪ 32% (all grades); 8% (Grade 3); 0% (Grade 4) (SmPC INLYTA (axitinib))
▪ 27% (all grades); 5% (Grade 3/4) (Rini et al., 2011; USPI INLYTA (axitinib))
▪ 7-75% (all grades); 16-22% (Grade ≥ 3) (Rini et al., 2009; Rixe et al., 2007; Tomita et al., 2011)</td></tr>
<tr><td>Pazopanib</td><td>▪ 9-18% (all grades); 3% (Grade 3); 0% (Grade 4) (Massey et al., 2015; SmPC VOTRIENT (pazopanib))
▪ 11% (all grades); 2% (Grade ≥ 3); 0% (Grade 4) (Hutson et al., 2008)</td></tr>
</table></td></tr>
<tr><td>Risk factors and risk groups</td><td>The risk group might include patients receiving concomitant therapy with agents known to cause HFS, such as capecitabine, 5-FU, doxorubicin, and IL-2. However, according to a meta-analysis of 33 randomised studies of TKIs with VEGFR inhibitory activity, the risk of HFSR when such TKIs were used as a component of a combination regimen involving a conventional chemotherapeutic agent was not different from TKI use as monotherapy (Massey et al., 2015).
The risk for developing HFSR or HFS depends on patient social, work and home life. Patients whose jobs require a significant amount of walking or hand friction are at greater risk of developing these skin toxicities and use of caustic cleaning solutions and hot water are also contributors (W. Smith & Abou-Alfa, 2010). Experience from clinical practice has shown that HFSR tends to be more severe in younger, 'more-active' patients (Edmonds et al., 2012).</td></tr>
<tr><td>Risk minimisation measures</td><td>Routine risk minimisation measures:</td></tr>
</table>

<table>
<tr><td></td><td>SmPC section 4.4, 4.8
PL section 2, 4
Prescription only medication and use is restricted to physicians experienced in the treatment of RCC.
Additional risk minimisation measures: No risk minimisation measures</td></tr>
<tr><td colspan="2">Important identified risk: Posterior reversible encephalopathy syndrome (PRES)</td></tr>
<tr><td>Evidence for linking the risk to the medicine</td><td>Clinical trials (DLP of 23 Feb 2019): Data from clinical trials revealed 4 reports of PRES.
UPDATE as of DLP 23 Feb 2021:
Clinical trials: There was no new data pertaining to clinical trials post the DLP of 23 Feb 2019.

Post-marketing experience (DLP of 23 Feb 2021): Cumulative data from the post-marketing experience revealed 4 reports of PRES. The safety information from post marketing data is consistent with the reported safety data in clinical trials.

Class effect:<table><tr><td>Sorafenib</td><td>▪ Reversible posterior leukoencephalopathy syndrome (RPLS): uncommon (0.1-1%, all grades)
Encephalopathy: frequency not known, reported during post-marketing
(SmPC NEXAVAR (sorafenib))</td></tr><tr><td>Sunitinib</td><td>▪ PRES: rare (0.01-0.1%) in gastrointestinal stromal tumour (GIST), metastatic RCC, and pancreatic neuroendocrine tumour (pNET) clinical trials (SmPC SUTENT (sunitinib))</td></tr><tr><td>Axitinib</td><td>▪ RPLS: < 1% (all grades) (USPI INLYTA (axitinib))
▪ PRES (including leukoencephalopathy): 0.3% (all grades); 0.1% (Grade 3); 0% (Grade 4)</td></tr><tr><td>Pazopanib</td><td>▪ PRES/RPLS: frequency not known, reported during post-marketing (SmPC VOTRIENT (pazopanib))</td></tr></table></td></tr>
<tr><td>Risk factors and risk groups</td><td>Hypertension is one of the most common conditions associated with PRES, being present in 6-72% of cases (Legriel et al., 2011). Therefore, risk factors for PRES/RPLS include uncontrolled hypertension and non-compliance with anti-hypertensive treatment.</td></tr>
<tr><td>Risk minimisation measures</td><td>Routine risk minimisation measures:
SmPC section 4.4, 4.8
PL section 2, 4
Prescription only medication and use is restricted to physicians experienced in the treatment of RCC.
Additional risk minimisation measures: No risk minimisation measures</td></tr>
<tr><td colspan="2">Important potential risk: QT prolongation</td></tr>
<tr><td>Evidence for linking the risk to the medicine</td><td>Clinical trials (DLP of 20 January 2015): Among tivozanib hydrochloride-treated patients in the core RCC monotherapy studies, 1 patient (0.1%) experienced an event of QT prolongation.
UPDATE as of DLP 23 Feb 2021:
Clinical trials: There was no new data pertaining to clinical trials since the product approval.

Post-marketing experience (DLP of 23 Feb 2021): Cumulative data from the post-marketing experience revealed 2 reports of QT prolongation (electrocardiogram QT prolonged, n=1 and Ventricular tachycardia, n=1). The safety information from post marketing data is consistent with the reported safety data in clinical trials.

Class effect:<table><tr><td>Sorafenib</td><td>▪ rare (0.01-0.1%) (all grades) (SmPC NEXAVAR (sorafenib))
▪ 5% (all grades) (Schmidinger et al., 2008)</td></tr></table></td></tr>
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<table>
<tr><td></td><td><table>
<tr><td>Sunitinib</td><td>▪ QT prolonged: < 1% (all grades)
▪ Torsade de pointes: < 0.1% (SmPC SUTENT (sunitinib))
▪ <1%-4% (Hutson et al., 2010; Tomita et al., 2010; Uemura et al., 2010; Yildiz et al., 2011)
▪ 5% (all grades) (Schmidinger et al., 2008)</td></tr>
<tr><td>Axitinib</td><td>No information found</td></tr>
<tr><td>Pazopanib</td><td>▪ QT prolonged: < 1% (all grades); <1% (Grade 3); 0% (Grade 4) (SmPC VOTRIENT (pazopanib))
▪ Torsade de pointes < 1% (all grades) (USPI VOTRIENT (pazopanib))</td></tr>
</table></td></tr>
<tr><td>Risk factors and risk groups</td><td>Patients with a history of QT prolongation or using any other medication that may affect the QT interval (Bronte et al., 2015).</td></tr>
<tr><td>Risk minimisation measures</td><td>Routine risk minimisation measures:
SmPC section 4.4, 4.8, 5.1
PL section 2, 4
Prescription only medication and use is restricted to physicians experienced in the treatment of RCC.
Additional risk minimisation measures: No risk minimisation measures</td></tr>
<tr><td colspan="2">Important potential risk: Hepatic effects</td></tr>
<tr><td>Evidence for linking the risk to the medicine</td><td>Clinical trials (DLP of 20 January 2015): The overall frequency of hepatic effects TEAEs among tivozanib hydrochloride-treated patients in the core RCC monotherapy studies was 9.5%. Hepatic effects TEAEs of Grade ≥ 3 were reported in 4.2% of tivozanib hydrochloride-treated patients.

UPDATE as of DLP 23 Feb 2021:
Clinical trials: There was no new data pertaining to clinical trials since the product approval.

Post-marketing experience (DLP of 23 Feb 2021): Cumulative data from the post-marketing experience revealed 4 reports of hepatic effects (gamma-glutamyltransferase increased and blood alkaline phosphatase increased, n=1, hepatic infection bacterial, n=1, hepatotoxicity, n=1, and Aspartate aminotransferase increased, n=1). The safety information from post marketing data is consistent with the reported safety data in clinical trials.

Class effect:<table>
<tr><td>Sorafenib</td><td>▪ ALT increased: 22% (all grades); 2% (Grade 3/4)
AST increased: 25% (all grades); 1% (Grade 3/4)
ALP increased: 34% (all grades); 1% Grade 3/4
(USPI NEXAVAR (sorafenib))
▪ Drug induced hepatitis: rare (0.01-0.1%) (all grades)
Increase in transaminases (all grades): Common (1-10%)
Increase in bilirubin and jaundice (all grades): Uncommon (< 1%)
Increase in blood ALP (all grades): Uncommon (< 1%)
(SmPC NEXAVAR (sorafenib))
▪ Transaminase elevation: 5-6% (all grades); 0-2% (Grade 3/4) (Di Lorenzo, Carteni, et al., 2009; Procopio et al., 2011)</td></tr>
<tr><td>Sunitinib</td><td>▪ ALT increased: 51%% (all grades); 3% (Grade 3/4)
AST increased: 56% (all grades); 2% (Grade 3/4)
▪ ALP increased: 46% (all grades); 2% (Grade 3/4)
Hepatic function abnormal/hepatic failure: < 1% (all grades), hepatitis <0.1% (all grades) (USPI SUTENT (sunitinib malate))</td></tr>
</table></td></tr>
</table>

		▪ ALT increased: 51% (all grades); 2-6% (Grade 3) AST increased: 43-67% (all grades); 2-10% (Grade 3/4) ALP increased: 33-57% (all grades); 2-5% (Grade 3/4) Bilirubin increased: 20-31% (all grades); 1-2% (Grade 3/4) (Ansari et al., 2010; Motzer et al., 2009; Tomita et al., 2010; Uemura et al., 2010)
	Axitinib	▪ Hyperbilirubinemia: 1.3% (all grades); 0.1% (Grade 3); 0.1% (Grade 4) ▪ ALT increased: 7-22% (all grades); 1.2% (Grade 3); < 1% (Grade 4) AST increased: 6-20% (all grades); ≤ 1% (Grade 3/4) ALP increased: 5-30% (all grades); ≤1% (Grade 3/4) (SmPC INLYTA (axitinib); USPI INLYTA (axitinib)) ▪ ALT increased: 23% (all grades); 3% (Grade ≥ 3). AST increased: 23% (all grades); 2% (Grade ≥ 3) ALP increased 17% (all grades); 0% (Grade ≥ 3) Lactate dehydrogenase increased 13% all grades; 0% (Grade ≥ 3) (Tomita et al., 2011)
	Pazopanib	▪ Hepatotoxicity: 2% (all grades); < 1% (Grade 3); < 1% (Grade 4) ALT increased: 21% (all grades); 7% (Grade 3); 1% (Grade 4) AST increased: 18% (all grades); 4% (Grade 3); < 1% (Grade 4) Hepatic function abnormal: 3% (all grades); 1% (Grade 3); < 1% Grade 4 Hyperbilirubinemia: 3% (all grades); < 1% (Grade 3); < 1% (Grade 4) Blood bilirubin increased: 5% (all grades); <1% (Grade 3); <1% (Grade 4) Hepatic enzyme increased: < 1% (all grades); < 1% (Grade 3); < 1% (Grade 4) Gamma glutamyltransferase (GGT) increased: 3% (all grades); < 1% (Grade 3); < 1% (Grade 4) Transaminase increased: < 1% (all grades); < 1% (Grade 3); 0% (Grade 4) Liver function test (LFT) abnormal: 1% (all grades); <1% (Grade 3); < 1% (Grade 4) (SmPC VOTRIENT (pazopanib)) ▪ ALT increased: 53% (all grades); 10% (Grade 3); 2% (Grade 4) AST increased: 53% (all grades); 7% (Grade 3); <1% (Grade 4) Bilirubin increased: 36% (all grades); 3% (Grade 3); <1% (Grade 4) (Sternberg et al., 2010; USPI VOTRIENT (pazopanib))
Risk factors and risk groups	Although the risk groups and risk factors for hepatic effects are unknown, VEGF inhibiting agents, both TKIs and antibodies have been found to induce transaminase elevations and sometimes dose limiting hepatotoxicity (Eskens & Verweij, 2006).	
Risk minimisation measures	**Routine risk minimisation measures**: SmPC section 4.2, 4.4, 4.8, 5.2 PL section 2, 3, 4 Prescription only medication and use is restricted to physicians experienced in the treatment of RCC. **Additional risk minimisation measures**: No risk minimisation measures	
Important potential risk: GI perforation and fistula		

<table>
<tr><td>Evidence for linking the risk to the medicine</td><td>Non-clinical: Slight to moderately severe gastric changes were seen in the 1.0 mg/kg/day group in monkeys. These gastric changes were characterised microscopically by dilated gastric glands, acute inflammation, hyperplasia of fundic and pyloric columnar epithelium, and decreased numbers of parietal and chief cells.
Clinical trials (DLP of 20 January 2015): Among tivozanib hydrochloride-treated patients in the core RCC monotherapy studies, the overall frequency of GI perforation and fistula TEAEs was less than 1% (1/674 [0.1%], PT = abdominal abscess); the frequency of Grade ≥ 3 GI perforation and fistula TEAEs was also less than 1% (1/674 [0.1%], PT = abdominal abscess).
UPDATE as of DLP 23 Feb 2021:
Clinical trials: There was no new data pertaining to clinical trials since the product approval.

Post-marketing experience (DLP of 23 Feb 2021): Cumulative data from the post-marketing experience revealed 6 reports of GI perforation and fistula, including duodenal ulcer n=1, gastrointestinal haemorrhage, gastric ulcer, haematemesis n=1, gastric ulcer n=1, intestinal obstruction n=1, diverticular perforation, diverticulitis n=1, and abdominal abscess n=1. The safety information from post marketing data is consistent with the reported safety data in clinical trials.

Class effect:
<table>
<tr><td>Sorafenib</td><td>▪ GI perforation: < 1% (all grades), including fatalities (SmPC NEXAVAR (sorafenib))</td></tr>
<tr><td>Sunitinib</td><td>▪ Intestinal perforation: < 1% (all grades), including fatalities
Anal fistula: < 1% (all grades)
(SmPC SUTENT (sunitinib))</td></tr>
<tr><td>Axitinib</td><td>▪ GI perforation and fistula: 1.9% (all), 0.9% (Grade 3), 0.3% (Grade 4) (SmPC INLYTA (axitinib))
▪ GI perforation: < 1% (all grades) (USPI INLYTA (axitinib))</td></tr>
<tr><td>Pazopanib</td><td>▪ Large intestine perforation: < 1% (all grades); < 1% (Grade 3);
0% (Grade 4)
Enterocutaneous fistula <1% (all grades); 0% (Grade 3); 0% (Grade 4)
Ileal perforation < 1% (all grades); 0% (Grade 3); < 1% (Grade 4)
(SmPC VOTRIENT (pazopanib))
▪ GI perforation or fistula: 0.9%; 0.3% (Grade 5) (USPI VOTRIENT (pazopanib))</td></tr>
</table></td></tr>
<tr><td>Risk factors and risk groups</td><td>The risk for GI perforation and fistula may be dose-dependent, as reported for bevacizumab (Hapani et al., 2009). Risk factors postulated to increase the risk of spontaneous bowel fistula include the history of peptic ulcer disease, diverticulitis, colitis, intestinal obstruction, tumour necrosis, recent sigmoidoscopy or colonoscopy, intact primary tumour, radiotherapy, higher cumulative dose, or emergency surgery while receiving bevacizumab (Abu-Hejleh et al., 2012).</td></tr>
<tr><td>Risk minimisation measures</td><td>Routine risk minimisation measures:
SmPC section 4.4, 4.8
PL section 2, 4
Prescription only medication and use is restricted to physicians experienced in the treatment of RCC.
Additional risk minimisation measures: No risk minimisation measures</td></tr>
<tr><td colspan="2">Important potential risk: Reproductive and developmental toxicity</td></tr>
</table>

Evidence for linking the risk to the medicine	**Non-clinical**: An increased incidence of early and late foetal resorptions, reduced foetal body weight and gross external and skeletal malformations was observed at doses ≥ 0.03 mg/kg in rats.
Risk factors and risk groups	Sexually active pre-menopausal female subjects.
Risk minimisation measures	**Routine risk minimisation measures**: SmPC section 4.6, 5.3 PL section 2 Prescription only medication and use is restricted to physicians experienced in the treatment of RCC. **Additional risk minimisation measures**: No risk minimisation measures
Important potential risk: Wound healing complications	
Evidence for linking the risk to the medicine	**Clinical trials (DLP of 20 January 2015)**: Among tivozanib hydrochloride-treated patients in the core RCC monotherapy studies, the overall frequency of wound healing complication TEAEs was 0.1%. There were no wound healing complication TEAEs of Grade ≥ 3 in tivozanib hydrochloride-treated patients. **UPDATE as of DLP 23 Feb 2021:** **Clinical trials**: There was no new data pertaining to clinical trials since the product approval. **Post-marketing experience**: Cumulative data from the post-marketing experience revealed 1 case of wound healing complications. The safety information from post marketing data is consistent with the reported safety data in clinical trials. **Class effect**: Cases reported with Sunitinib.
Risk factors and risk groups	The potential risk group for wound healing complications includes patients undergoing major surgical procedures.
Risk minimisation measures	**Routine risk minimisation measures**: SmPC section 4.4 PL section 2 Prescription only medication and use is restricted to physicians experienced in the treatment of RCC. **Additional risk minimisation measures**: No risk minimisation measures
Important potential risk: Overdose	
Evidence for linking the risk to the medicine	**Clinical trials (DLP of 20 Jan 2015):** There was a low incidence (1 patient, 0.1%) of tivozanib hydrochloride treated patients with an overdose. **UPDATE as of DLP 23 Feb 2021:** **Clinical trials:** There was no new data pertaining to clinical trials since the product approval **Post-marketing experience:** Data from the post-marketing experience revealed no reports of overdose.
Risk factors and risk groups	▪ Patients at increased risk of a severe outcome following overdose include patients with uncontrolled hypertension ▪ Patients with moderate and severe hepatic impairment ▪ Elderly patients
Risk minimisation measures	**Routine risk minimisation measures**: SmPC section 4.4 PL section 2 Prescription only medication and use is restricted to physicians experienced in the treatment of RCC. **Additional risk minimisation measures**: No risk minimisation measures
Missing information: Use during lactation	
Risk minimisation measures	**Routine risk minimisation measures**:

	SmPC section 4.6 PL section 2 Prescription only medication and use is restricted to physicians experienced in the treatment of RCC. **Additional risk minimisation measures**: No risk minimisation measures

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 Fotivda.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Fotivda.