Part VI: Summary of the risk management plan

Summary of risk management plan for Imatinib Koanaa (Imatinib)

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

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

This summary of the RMP for Imatinib Koanna 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 Imatinib Koanaa's RMP.

I. The medicine and what it is used for

Imatinib Koanaa is authorised for treatment of chronic myeloid leukaemia (CML), acute lymphoblastic leukaemia (ALL), myelodysplastic/myeloproliferative diseases (MDS/MPD), hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL), gastrointestinal stromal tumours (GIST) and dermatofibrosarcoma protuberans (DFSP) (see SmPC for the full indication). It contains Imatinib as the active substance and it is given by oral route.

Further information about the evaluation of Imatinib Koanaa's benefits can be found in Imatinib Koanaa'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/imatinib-koanaa.

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

Important risks of Imatinib Koanaa, together with measures to minimise such risks and the proposed studies for learning more about Imatinib Koanaa'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 are 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 Imatinib Koanaa is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Imatinib Koanaa are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken orally. 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 Imatinib Koanaa. 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	None
Important potential risks	Second primary Malignancy Tolerability during Pregnancy and Pregnancy Outcomes
Missing information	Paediatric patients: Long term follow up Paediatric patients below 2 years of age

II.B Summary of important risks

There are no important identified risks for imatinib.

Important potential risk: Second primary Malignancy	
Evidence for linking the risk to the medicine	The severity and nature of an identified malignancy will generally vary with the specific type of malignancy and the promptness with which it is identified and treated. No characteristic pattern has been identified with imatinib. Rebora et al (2010) used the Swedish Cancer Registry to assess the incidence rates of second primary cancers among CML patients. With a total of a 145 subsequent primary malignancies identified in 2,753 adult patients diagnosed with CML between 1970 and 1995, an increased incidence rate of second malignancy was found for all-site cancers (standardized incidence rate – SIR of 1.82, 95%CI: 1.53 – 2.14), stomach cancer (SIR = 2.76, 95%CI: 1.33 – 5.08), skin cancer (SIR = 5.36, 95%CI: 3.18 – 8.47), urogenital tract cancer (SIR = 1.61, 95%CI: 1.15 – 2.21), and lymphoid leukemia (SIR = 5.53, 95%CI: 1.79 – 12.89). Among 856 survivors of childhood ALL, 44 developed second primary neoplasms; 41 of them radiation-related. The risk of a second neoplasm was significantly higher in the 597 patients who received radiation therapy (irradiated group) than in the 259 patients who did not

	(p=0.04; estimated cumulative risk [+/-SE] at 20 years, 20.9+/-3.9% vs. 0.95+/-0.9%) (Pui et al 2003). Gabriele Gugliotta et al 2017, in a retrospective analysis of three clinical trials, 559 patients with CML indication were enrolled. Data was collected from 514 patients (309 males, 205 females) with median age at CML diagnosis was 59 years, median time for SPM diagnosis from CML diagnosis was 34 months. The most commonly experienced secondary malignancies included colon cancers (n=4), prostate cancers (n=3), breast cancers (n=2), central nervous system cancers (n=2), pancreatic cancers (n=2), liver cancers (n=2), non-Hodgkin lymphomas (n=2), and thyroid cancers (n=2). In conclusion, the analysis did not reveal a higher incidence of second primary malignancies; however, the outcome of second primary malignancies in such patients was worse than expected. Phan K et al 2014, the study examined the incidence of SPMs after GIST, particularly before (pre-imatinib era: 1992-2001) and after (imatinib era: 2002-2009), and factors related to the occurrence of SPMs. Imatinib mesylate was FDA-approved in 2002 for the treatment of unresectable and metastatic GISTs and has become the standard of care. There were significantly more patients in the imatinib era alive after follow-up (n=533, 63.99%) than in the pre-imatinib era (n=130, 22.41%, P<0.001). Overall, the rate of SPMs after GIST in the imatinib era was 7.07%, compared with the rate of 1.15% that occurred in the pre-imatinib era (P=0.030). The findings in the study demonstrate that patients after GIST are at increased risk of developing SPMs and that this risk is increased following the introduction of imatinib in 2002. The increased incidence of SPMs in the era of imatinib could be explained by the increased survival of patients with metastatic GIST and therefore more time to develop SPMs, however, further studies are needed to investigate this mechanism.
Risk factors and risk groups	Unknown
Risk minimisation measures	<u>Routine risk minimisation measures</u>: None. However, Section 5.3 of the SmPC provides details about the pre-clinical data on this safety concern. <u>Additional risk minimisation measures</u>: None

Important potential risk: Tolerability during Pregnancy and Pregnancy Outcomes	
Evidence for linking the risk to the medicine	Information on pregnancy in patients with CML in the pre-imatinib era is scarce. Several case reports have been published. Mubarak et al (2002) and Ali et al (2004) described in total 13 cases, all with normal outcome. No incidence rates are available. Singular reports described outcomes of pregnancy in women with ALL. Molkenboer et al (2005) presented 2 cases: one with missed abortion in 6th week and one with stillborn fetus

	at 22 weeks of pregnancy. Among 6 pregnancies in patients with ALL reported by Chelghoum et al (2005), 3 ended with therapeutic abortion and 3 with premature birth. In the general population, according to the Centers for Disease Control and Prevention [CDC (2008)], the overall prevalence of major defects was 3.0 per 100 in 2005 in the Metropolitan Atlanta Congenital Defects Program (MACDP). This program monitors the prevalence of all major structural or genetic defects at the time of delivery among live births, stillbirths, and pregnancies electively terminated after prenatal diagnosis of defects at >20 weeks' gestation in the five central counties of metropolitan Atlanta. MACDP defines major structural or genetic birth defects as conditions that 1) result from a malformation, deformation, or disruption in one or more parts of the body, a chromosomal abnormality, or a known clinical syndrome; 2) are present at birth; and 3) have a serious, adverse effect on health, development, or functional ability. EUROCAT is a European network of population-based registries for the epidemiologic surveillance of congenital anomalies that was started in 1979 and has surveyed more than 1.7 million births surveyed per year in Europe. It includes data from 43 registries in 23 countries and covers 29% of the European birth population. EUROCAT reported that the prevalence of all anomalies was 2.56 (95% CI: 2.55-2.58) per 100 births (live births (LB), fetal deaths/still births from 20 weeks gestation (FD) and termination of pregnancy for fetal anomaly following prenatal diagnosis (TOPFA)) (EUROCAT 2014). In the general population, spontaneous abortion is the most common complication of early pregnancy, its frequency decreasing with increasing gestational age. Eight to 20 percent of clinically recognized pregnancies at less than 20 weeks of gestation undergo spontaneous abortion with 80% of these occurring in the first 12 weeks of gestation. The overall risk of spontaneous abortion after 15 weeks is low (about 0.6%) for chromosomally and structurally normal fetuses, but varies with the presence of associated risk factors. Loss of unrecognized or subclinical pregnancies occurs in 13 to 26% of all pregnancies. If pre-implantation losses are considered, approximately 50% of fertilized oocytes do not result in a live birth (Tulandi and Al-Fozan 2013). Pye, Seonaid M et al 2008, in a retrospective study, 180 female patients were treated with imatinib, most of them were treated for CML. The timing of exposure to imatinib by trimester was available for 146 (81%) patients and majority were exposed during first trimester. Outcome data are known for 125 pregnancies. A total of 63 pregnancies resulted in the birth of normal live infants and 35 women underwent elective terminations. The abnormal pregnancy outcomes of the study include spontaneous abortion in 18, elective termination due to foetal abnormalities in 03, stillbirth with congenital anomaly in 01 and live birth with congenital anomaly in 08 pregnancies.
Risk factors and risk groups	Women of childbearing age becoming pregnant and/or requiring treatment with imatinib through pregnancy if treatment cannot be discontinued.
Risk minimisation measures	<u>Routine risk minimisation measures</u>: SmPC sections 4.6 and 5.3

	PL Section 2. SmPC Section 4.6 and PL Section 2 recommend that imatinib should not be used in pregnancy unless there is a clear necessity. Additional risk minimisation measures: None

Missing information: Paediatric patients: Long term follow up	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.9 PL Section 2 Additional risk minimisation measures: None

Missing information: Paediatric patients below 2 years of age	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2. There is no data in this population. Additional risk minimisation measures: None

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 Imatinib Koanaa.

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

There are no studies required for Imatinib Koanaa.