AYVAKYT® (avapritinib)

AYVAKYT® Advanced SM Patient Profiles

These patient profiles are fictional portrayals

INDICATION

AYVAKYT is indicated as a monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL), **after at least one systemic therapy.**[1]

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 of the Summary of Product Characteristics (SmPC) for how to report adverse reactions.

Abbreviated Prescribing Information can be found on page 12.

Leon

68-year-old male diagnosed with SM-AHN (low-risk MDS)

PATIENT HISTORY

- Leon had already received a diagnosis of an AHN (low-risk MDS), and presented with unexplained anaphylaxis, hepatosplenomegaly and bone pain
- Based on results from serum tryptase testing and bone marrow biopsy that confirmed the SM component to his disease, the patient received a revised diagnosis of SM-AHN (low-risk MDS)
- Initiated systemic treatment with a tyrosine kinase inhibitor but discontinued due to tolerability issues
- Baseline platelet count was 65 x 10^9/L

INTRODUCTION OF AYVAKYT

- The patient initiated AYVAKYT 200 mg once daily, and platelet counts were monitored every 2 weeks for the first 8 weeks as per dosing guidelines[1]
- Platelet count decreased to 45 x 10^9/L after 4 weeks of treatment
- Treatment was interrupted until platelet count recovered to >50 x 10^9/L, due to increased risk of intracranial haemorrhages, as per dosing guidelines[1]

TREATMENT EVOLUTION

- After 2 weeks, the platelet count did not improve, and the physician ordered a transfusion
- Platelet count improved to >50 x 10^9/L, and treatment was resumed at a reduced dose of 100 mg once daily with monitoring[1]
- After 6 months of treatment, repeated bone marrow biopsy showed a significant reduction in bone marrow mast cell aggregates, and a steady improvement in symptoms was reported

Monitoring platelet counts at initiation and regularly during treatment is important with AYVAKYT[1]

MDS=myelodysplastic syndrome; SM-AHN=systemic mastocytosis with an associated neoplasm

Celine

65-year-old female diagnosed with ASM

PATIENT HISTORY

- Celine presented with hepatosplenomegaly, rash, itching and fatigue
- The patient was diagnosed with ASM
- Initiated systemic treatment with interferon alfa
- The treating physician decided to switch therapies due to unstable serum tryptase levels and tolerability issues

INTRODUCTION OF AYVAKYT

- The patient initiated AYVAKYT 200 mg once daily and platelet counts were monitored every 2 weeks for the first 8 weeks, as per dosing guidelines[1]
- Platelet count at initiation was 188 x 10^9/L
- Mild (Grade 1) facial oedema and peripheral oedema were observed within a week. Platelet count was 140 x 10^9/L with no other cytopenias after 2 weeks of treatment
- The patient started to experience cognitive effects such as losing her keys and word-finding difficulty, so treatment was interrupted, as per dosing guidelines[1]

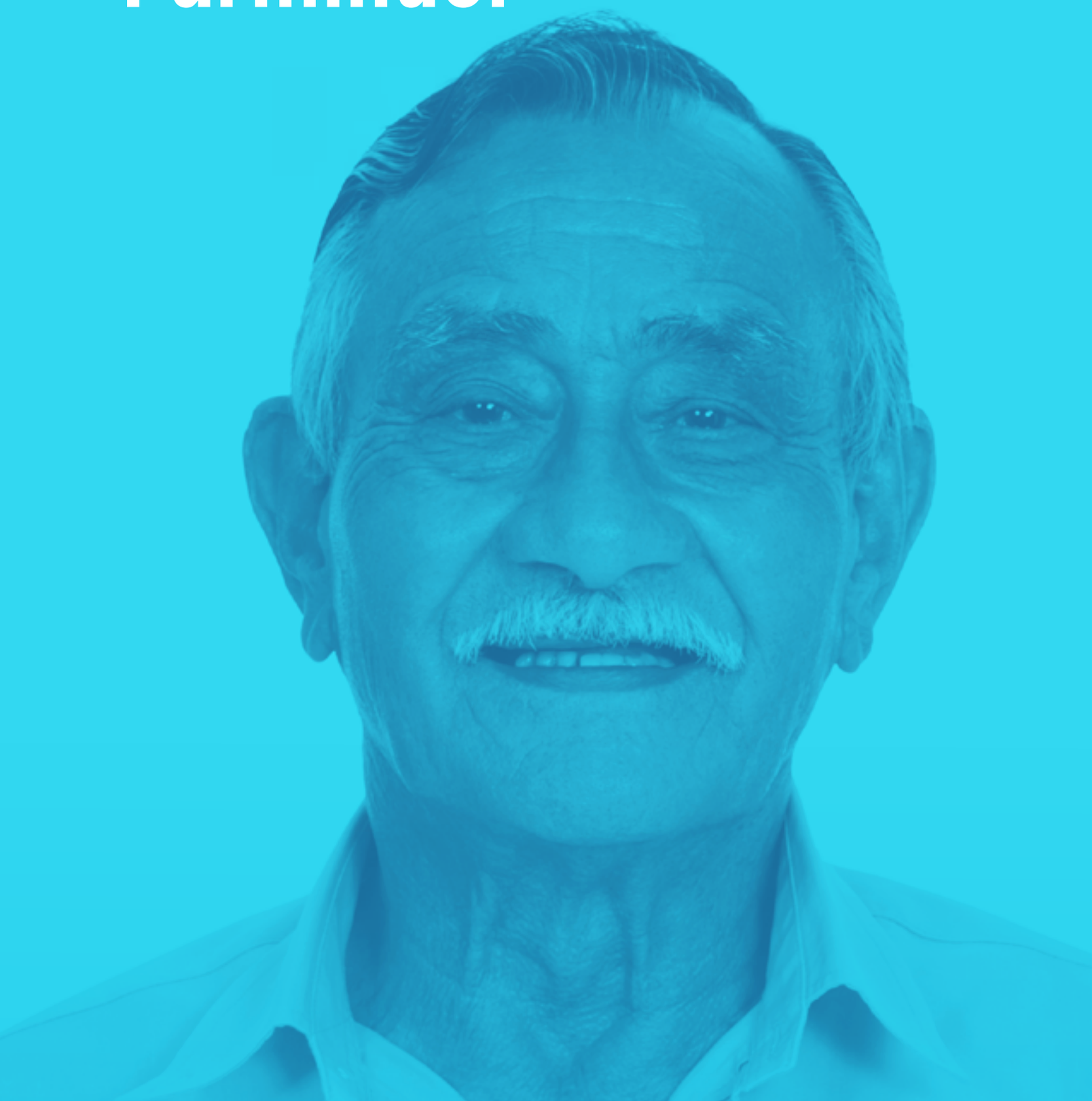
TREATMENT EVOLUTION

- After 2 weeks, the cognitive effects improved, and treatment was resumed at a reduced dose of 100 mg once daily with monitoring[1]
- The patient remained stable during the 1 year of treatment. She remained on AYVAKYT therapy at 100 mg once daily and was tolerating it well

Dose reduction and interruption are important strategies for patients treated with AYVAKYT[1]

ASM=aggressive systemic mastocytosis

Parminder



67-year-old male diagnosed with SM-AHN (SM-CMML-1)

PATIENT HISTORY

- Parminder presented with fatigue, mild ascites and maculopapular rash with 15% monocytes in circulating blood and 8% bone marrow blasts. No *KIT* mutation was detected by NGS, therefore a diagnosis of CMML-1 was made
- Initiated systemic treatment with azacitidine (x4 cycles); monocytes decreased and CBC normalised but no improvement in symptoms was observed
- Upon re-evaluation, serum tryptase, allele specific PCR testing for *KIT* D816V and bone marrow biopsy confirmed a revised diagnosis of SM-AHN (SM-CMML-1)

INTRODUCTION OF AYVAKYT

- The patient initiated AYVAKYT 200 mg once daily, and platelet counts were monitored every 2 weeks for the first 8 weeks, as per dosing guidelines[1]
- Worsening peripheral oedema (Grade 3) was observed after 3 months of treatment
- Treatment was interrupted until resolution to baseline, as per dosing guidelines[1]

TREATMENT EVOLUTION

- After 1 week, oedema resolved and treatment was resumed at a reduced dose of 100 mg once daily with monitoring[1]
- The patient remained stable during the 2 years of treatment. He remained on AYVAKYT therapy at 100 mg once daily and was tolerating it well

Treatment interruption with or without dose reduction may be considered to manage adverse reactions[1]

CBC=complete blood count; CMML=chronic myelomonocytic leukaemia; NGS=next-generation sequencing; PCR=polymerase chain reaction; SM-AHN=systemic mastocytosis with an associated neoplasm

Adrienne

64-year-old female diagnosed with MCL

PATIENT HISTORY

- Adrienne presented with night sweats, fatigue, dyspnoea on exertion and daily fevers
- Bone marrow biopsy aspirate smear showed spindle-shaped mast cells (30%). Serum tryptase measured at 388 ng/mL and the patient was *KIT* D816V positive upon PCR sequencing
- The patient was diagnosed with MCL
- Initiated systemic treatment with cladribine (x2 cycles) to cytoreduce abnormally high mast cell counts. In parallel, an allogenic consult was initiated
- Symptoms improved but the patient was ruled a poor candidate for bone marrow transplant due to the lack of available donors
- After discussing options with the patient, the treating physician decided to explore other therapies

INTRODUCTION OF AYVAKYT

- The patient initiated AYVAKYT 200 mg once daily, and platelet counts were monitored every 2 weeks for the first 8 weeks as per dosing guidelines[1]
- Platelet count at initiation was 95 x 10^9/L
- After 6 weeks of treatment, 5% of bone marrow mast cells were detected. Thrombocytopenia improved to Grade 1 (160 x 10^9/L)
- Grade 2 anaemia and Grade 2 periorbital oedema were observed, so treatment was interrupted for 1 week

TREATMENT EVOLUTION

- After 1 week, adverse reactions improved, and treatment was resumed at a reduced dose of 100 mg once daily with monitoring[1]
- After 1 year of treatment, repeated bone marrow biopsy showed an improvement in mast cell measures

MCL=mast cell leukaemia; PCR=polymerase chain reaction

Special warnings and precautions for use[1]

HAEMORRHAGES

AYVAKYT has been associated with an increased incidence of haemorrhagic adverse reactions, including serious and severe adverse reactions, like gastrointestinal haemorrhage and intracranial haemorrhage in patients with Advanced SM (see section 4.8 of the SmPC).

Routine surveillance of haemorrhagic adverse reactions must include physical examination. Complete blood counts, including platelets, and coagulation parameters must be monitored, particularly in patients with conditions predisposing to bleeding, and in those treated with anticoagulants (e.g. warfarin and phenprocoumon) or other concomitant medicinal products that increase the risk of bleeding.

INTRACRANIAL HAEMORRHAGES

Adverse reactions of intracranial haemorrhage occurred in patients who received AYVAKYT. Before initiating AYVAKYT the risk for intracranial haemorrhage should be carefully considered in patients with potential increased risk including those with thrombocytopenia, vascular aneurysm or a history of intracranial haemorrhage or cerebrovascular accident within the prior year.

Patients who experience clinically relevant neurological signs and symptoms (e.g. severe headache, vision problems, somnolence, and/or focal weakness) during treatment with AYVAKYT must interrupt dosing of AYVAKYT and inform their healthcare professional immediately. Brain imaging by magnetic resonance imaging (MRI) or computed tomography (CT) may be performed at the discretion of the physician based on severity and the clinical presentation.

For patients with observed intracranial haemorrhage during treatment with AYVAKYT, regardless of severity grade, AYVAKYT must be permanently discontinued (see section 4.2 of the SmPC).

Serious adverse reactions of intracranial haemorrhage were reported in patients with Advanced SM receiving AYVAKYT (see section 4.8 of the SmPC). The exact mechanism is unknown. The incidence of intracranial haemorrhage was higher in patients with platelet counts <50 x 10^9/L and in patients with a starting dose of ≥300 mg.

Considering the above, a platelet count must be performed prior to initiating therapy. **AYVAKYT is not recommended in patients with platelet counts <50 x 10^9/L**. Following treatment initiation, platelet counts must be performed every 2 weeks for the first 8 weeks regardless of baseline platelet count. After 8 weeks of treatment, monitor platelet counts every 2 weeks (or more frequently as clinically indicated) if values are less than 75 x 10^9/L, every 4 weeks if values are between 75 and 100 x 10^9/L, and as clinically indicated if values are greater than 100 x 10^9/L.

Manage platelet counts of <50 x 10^9/L by temporarily interrupting AYVAKYT. Platelet support may be necessary, and the recommended dose modification in Table 2 must be followed (see section 4.2 of the SmPC). Thrombocytopenia was generally reversible by reducing or interrupting AYVAKYT in clinical studies. The maximum dose for patients with AYVAKYT must not exceed 200 mg once daily.

COGNITIVE EFFECTS

Cognitive effects, such as memory impairment, cognitive disorder, confusional state and encephalopathy, can occur in patients receiving AYVAKYT (see section 4.8 of the SmPC). The mechanism of the cognitive effects is not known.

It is recommended that patients are clinically monitored for signs and symptoms of cognitive events such as new or increased forgetfulness, confusion and/or difficulty with cognitive functioning. Patients must notify their healthcare professional immediately if they experience new or worsening cognitive symptoms.

For patients with observed cognitive effects related to treatment with AYVAKYT, the recommended dose modification in Table 2 must be followed (see section 4.2 of the SmPC). In clinical studies, dose reductions or interruptions improved Grade ≥2 cognitive effects compared to no action.

FLUID RETENTION

In patients with Advanced SM, localised (facial, periorbital, peripheral, pulmonary oedema, pericardial and/or pleural effusion) or generalised oedema, and ascites have been observed with a frequency category of at least common (see section 4.8 of the SmPC). Other localised oedemas (laryngeal oedema) have been reported uncommonly.

Therefore, it is recommended that patients be evaluated for these adverse reactions including regular assessment of weight and respiratory symptoms. An unexpected rapid weight gain or respiratory symptoms indicating fluid retention must be carefully investigated and appropriate supportive care and therapeutic measures, such as diuretics, should be undertaken. For patients presenting with ascites, it is recommended to evaluate the aetiology of ascites.

QT INTERVAL PROLONGATION

Prolongation of QT interval has been observed in patients with Advanced SM treated with AYVAKYT in clinical studies. QT interval prolongation may induce an increased risk of ventricular arrhythmias, including Torsade de pointes.

AYVAKYT should be used with caution in patients with known QT interval prolongation or at risk of QT interval prolongation (e.g. due to concomitant medicinal products, pre-existing cardiac disease and/or electrolyte disturbances). Concomitant administration with strong or moderate CYP3A4 inhibitors should be avoided due to the increased risk of adverse reactions, including QT prolongation and related arrhythmias (see section 4.5 of the SmPC). If concomitant use of moderate CYP3A4 inhibitors cannot be avoided, see section 4.2 of the SmPC for dose modification instructions.

Interval assessments of QT by electrocardiogram (ECG) should be considered if AYVAKYT is taken concurrently with medicinal products that can prolong QT interval.

GASTROINTESTINAL DISORDERS

Diarrhoea, nausea and vomiting were the most commonly reported gastrointestinal adverse reactions in patients with Advanced SM (see section 4.8 of the SmPC). Patients who present with diarrhoea, nausea and vomiting should be evaluated to exclude disease-related aetiologies. Supportive care for gastrointestinal adverse reactions requiring treatment may include medicinal products with antiemetic, antidiarrheal or antacid properties.

The hydration status of patients experiencing gastrointestinal adverse reactions must be closely monitored and treated as per standard clinical practice.

LABORATORY TESTS

Treatment with AYVAKYT in patients with Advanced SM is associated with anaemia, neutropenia and/or thrombocytopenia. Complete blood counts must be performed on a regular basis during the treatment with AYVAKYT. See also intracranial haemorrhages above in this section and in section 4.8 of the SmPC.

Treatment with AYVAKYT is associated in patients with Advanced SM with elevations in bilirubin and liver transaminases (see section 4.8 of the SmPC). Liver function (transaminases and bilirubin) should be monitored regularly in patients receiving AYVAKYT.

CYP3A4 INHIBITORS AND INDUCERS

Co-administration with strong or moderate CYP3A inhibitors should be avoided because it may increase the plasma concentration of AYVAKYT (see sections 4.2 and 4.5 of the SmPC).

Co-administration with strong or moderate CYP3A inducers should be avoided because it may decrease the plasma concentrations of AYVAKYT (see section 4.5 of the SmPC).

PHOTOSENSITIVITY REACTION

Exposure to direct sunlight must be avoided or minimised due to the risk of phototoxicity associated with AYVAKYT. Patients must be instructed to use measures such as protective clothing and sunscreen with high sun protection factor (SPF).

SODIUM

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

Please refer to the SmPC for additional information on dosing and administration of AYVAKYT.

Abbreviated Prescribing Information (EN)

AYVAKYT 25 mg film-coated tablets
AYVAKYT 50 mg film-coated tablets
AYVAKYT 100 mg film-coated tablets
AYVAKYT 200 mg film-coated tablets
AYVAKYT 300 mg film-coated tablets
Active substance: avapritinib

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 of the Summary of Product Characteristics (SmPC) for how to report adverse reactions.

Qualitative and quantitative composition:
AYVAKYT 25 mg film-coated tablets
Each film-coated tablet contains 25 mg of avapritinib.
AYVAKYT 50 mg film-coated tablets
Each film-coated tablet contains 50 mg of avapritinib.
AYVAKYT 100 mg film-coated tablets
Each film-coated tablet contains 100 mg of avapritinib.
AYVAKYT 200 mg film-coated tablets
Each film-coated tablet contains 200 mg of avapritinib.
AYVAKYT 300 mg film-coated tablets
Each film-coated tablet contains 300 mg of avapritinib.

List of excipients:
Tablet core: microcrystalline cellulose, copovidone, croscarmellose sodium, magnesium stearate; tablet coat: talc, macrogol 3350, poly(vinyl alcohol), titanium dioxide (E171); printing ink (only 100 mg, 200 mg and 300 mg film-coated tablets): shellac glaze 45% (20% esterified) in ethanol, brilliant blue FCF (E133), titanium dioxide (E171), black iron oxide (E172), propylene glycol.

Therapeutic indications:
Unresectable or metastatic gastrointestinal stromal tumour (GIST)
AYVAKYT is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation.
Advanced systemic mastocytosis (AdvSM)
AYVAKYT is indicated as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL), after at least one systemic therapy.

Contraindications: Hypersensitivity to the active substance or to any of the excipients.

Undesirable effects:
Unresectable or metastatic GIST: *very common (≥ 1/10)*: anaemia, white blood cell count decreased, neutrophil count decreased, decreased appetite, memory impairment, cognitive disorder, dizziness, taste effect, lacrimation increased, abdominal pain, vomiting, diarrhoea, nausea, dryness, gastroesophageal reflux disease, hyperbilirubinaemia, hair colour changes, rash, oedema, fatigue, transaminases increased; common *(≥ 1/100, < 1/10)*: conjunctivitis, thrombocytopenia, lymphocyte count decreased, hypophosphataemia, hypokalaemia, hypomagnesaemia, hyponatraemia, dehydration, hypoalbuminaemia, hypocalcaemia, confusional state, depression, anxiety, insomnia, intracranial haemorrhage, mental impairment, neuropathy peripheral, somnolence, aphasia, hypokinesia, headache, balance disorder, speech disorder, tremor, ocular haemorrhage, vision blurred, conjunctival haemorrhage, photophobia, vertigo, hypertension, pleural effusion, dyspnoea, nasal congestion, cough, gastrointestinal haemorrhage, ascites, constipation, dysphagia, stomatitis, flatulence, salivary hypersecretion, palmar-plantar erythrodysaesthesia syndrome, photosensitivity reaction, skin hypopigmentation, pruritus, alopecia, myalgia, arthralgia, back pain, muscle spasms, acute kidney injury, blood creatinine increased, haematuria, asthenia, pyrexia, malaise, feeling cold, electrocardiogram QT prolonged, blood creatine phosphokinase increased, weight decreased, weight increased, blood lactate dehydrogenase increased; *uncommon (≥ 1/1.000, < 1/100)*: tumour haemorrhage, encephalopathy, pericardial effusion, hepatic haemorrhage.
Advanced systemic mastocytosis: *very common (≥ 1/10)*: thrombocytopenia, anaemia, neutropenia, taste effect, cognitive disorder, diarrhoea, nausea, hair colour changes, oedema, fatigue; *common (≥ 1/100, < 1/10)*: leukopenia, confusional state, headache, memory impairment, dizziness, neuropathy peripheral, intracranial haemorrhage, lacrimation increased, epistaxis, pleural effusion, vomiting, gastroesophageal reflux disease, ascites, dryness, constipation, abdominal pain, gastrointestinal haemorrhage, hyperbilirubinaemia, rash, alopecia, arthralgia, pain, weight increased, blood alkaline phosphatase increased, transaminase increased, electrocardiogram QT prolonged, contusion; uncommon *(≥ 1/1.000, < 1/100)*: pericardial effusion, photosensitivity reaction, acute kidney injury.

General classification for supply: Germany: medicinal product subject to medical prescription. Austria: available only on prescription and only in pharmacies, repeated dispensation prohibited.

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitor, ATC code: L01EX18.

Pharmaceutical entrepreneur/Marketing authorisation holder: Blueprint Medicines (Netherlands) B.V., Gustav Mahlerplein 2, 1082 MA Amsterdam, Netherlands.

Further information: For detailed information on warnings and precautions for use, interactions, pregnancy and lactation as well as undesirable effects, please refer to the published Summary of Product Characteristics. **Status:** March 2022

Notes

Notes

References:

1. AYVAKYT® (avapritinib). Summary of Product Characteristics; March 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/ayvakyt-epar-product-information_en.pdf.

blueprint™ MEDICINES

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