

Summary of the Risk Management Plan (RMP) for Ezmekly[®] (mirdametinib)

Dosage strength:	1 mg, 2 mg
Pharmaceutical Form:	capsules, dispersible tablets
Marketing Authorisation Number:	70387, 70392
Marketing Authorisation Holder	Merck (Schweiz) AG, Chamerstrasse 174, 6300 Zug
Based on EU RMP:	Version 1.0, sign-off date: 20 May 2025

Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Ezmekly is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation/Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisation.

Please note that the reference document which is valid and relevant for the effective and safe use of Ezmekly in Switzerland is the "Arzneimittelinformation/Information sur le médicament" (see www.swissmedic.ch) approved and authorised by Swissmedic. Merck (Schweiz) AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Ezmekly.

Part VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of the risk management plan for EZMEKLY

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

EZMEKLY's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how EZMEKLY should be used.

This summary of the RMP for EZMEKLY 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 EZMEKLY RMP.

1.1 I. The medicine and what it is used for

EZMEKLY as monotherapy is indicated for the treatment of symptomatic PN in adult and paediatric patients aged 2 years and above with neurofibromatosis type 1 who require systemic therapy. It contains mirdametinib as the active substance and it is given by the oral route.

Further information about the evaluation of EZMEKLY's benefits can be found in EZMEKLY EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage.

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

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

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

- 1) Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- 2) Important advice on the medicine's packaging;
- 3) The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- 4) 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 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 EZMEKLY is not yet available, it is listed under missing information below.

1.2.1 II.A List of important risks and missing information

Important risks of EZMEKLY 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 EZMEKLY. 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	Ocular events (RVO, RPED, Vision blurred) Ejection fraction decreased
Important potential risks	Embryo-foetal toxicity Physcal dysplasia Adverse effects on cardiac conduction Carcinogenicity
Missing information	Long term safety

1.2.2 II.B Summary of important risks

Important Identified Risk: Ocular events (RVO, RPED, Vision blurred)	
Evidence for linking the risk to the medicine	<p>Several MEK inhibitors have been reported to cause ocular toxicities, such as central serous retinopathy, RVO, or periorbital oedema. These ocular toxicities appear to be a class effect of MEK inhibition. MEK inhibitors have been reported to cause unique dose- and time-dependent MEKAR, which is an umbrella term that includes serous retinopathy, central serous chorioretinopathy, SRD, macular oedema, visual disturbance, retinopathy, chorioretinopathy, and blurred vision (Stjepanovic 2016). RVO is an uncommon but potentially serious adverse event reported in initial clinical trials of several MEK inhibitors (Han 2023).</p> <p>In Pool 1, Eye disorders were reported in 11 (19%) pediatric participants and 21 (28%) adult participants. In Pool 2, Eye disorders were reported in 55 (48.7%) participants.</p> <p>In Pool 1, RVO has been observed in 2 (3%) adult participants. RVO was not observed in paediatric participants. In Pool 2, RVO was observed in 3 (3%) adult participants with advanced cancers receiving mirdametinib at doses ≥ 5 mg BID. All participants who reported RVO had at least 1 predisposing factor including</p>

Important Identified Risk: Ocular events (RVO, RPED, Vision blurred)	
	<p>hypertension, diabetes, hypercholesterolemia, COVID-19 vaccination, advanced cancer, or concomitant medications.</p> <p>In Pool 1, Vision blurred was reported by 4 (7%) paediatric and 8 (11%) adult participants. In Pool 2, Vision blurred was reported in 16 (14.2%) participants.</p> <p>In Pool 1, asymptomatic RPED was reported in one (1%) adult participant and was not reported in any paediatric participant. In Pool 2, no participant reported RPED. One participant in the CUP with NF1 PN treated with mirdametinib 4 mg BID reported a nonserious event of RPED.</p>
Risk factors and risk groups	<p>RVO: A basic risk factor for RVO is advancing age. Further risk factors include systemic conditions such as hypertension, arteriosclerosis, diabetes mellitus, hyperlipidaemia, vascular cerebral stroke, blood hyperviscosity, and thrombophilia. A strong risk factor for RVO is metabolic syndrome (hypertension, diabetes mellitus, and hyperlipidemia). Individuals with end-organ damage caused by diabetes mellitus and hypertension have a greatly increased risk for RVO. Socioeconomic status seems to also be a risk factor. American blacks are more often diagnosed with RVO than non-Hispanic whites. Females are, according to some studies, at lower risk than men. The role of thrombophilic risk factors in RVO is still controversial. Congenital thrombophilic diseases including Factor V Leiden mutation, hyperhomocysteinaemia and anticardiolipin antibodies increase the risk of RVO (Kolar 2014). Further, hypercoagulability induced by systemic malignancy has also been associated with RVO (Mishra 2023). RVO is an uncommon but potentially serious adverse event reported in initial clinical trials of several MEK inhibitors (Han 2023). Cigarette smoking also increases the risk of RVO as do systemic inflammatory conditions like vasculitis and Behcet disease. Ophthalmic risk factors for RVO are ocular hypertension and glaucoma, higher ocular perfusion pressure, and changes in the retinal arteries (Kolar 2014). Additionally, COVID-19 vaccination has been associated with an increased risk of RVO (Li 2023), and oral contraceptives have been implicated in the pathogenesis of occlusive retinopathy (Somisetty 2023).</p> <p>Vision blurred and RPED: Age, glomerular filtration rate, and history of ocular disease (particularly inflammatory eye disease) were associated with a risk of MEK inhibitor-induced retinopathy in a study of 247 patients treated with cobimetinib and vemurafenib (Booth 2020). However, these patients were participants in an advanced melanoma study and the same conclusions may not necessarily be applicable to the NF1 population. Additionally, NF1 mutations place patients at risk for the development of glaucoma, choroidal abnormalities including reduced choroid thickness or altered choroidal circulation due to the presence of nodules, and infrequently, retinal alterations, which have been described in case reports as microvascular abnormalities. Finally, optic pathway glioma occurs frequently in patients with NF1, which can result in reduced visual acuity,</p>

Important Identified Risk: Ocular events (RVO, RPED, Vision blurred)	
	visual field defects, oedema of the papilla, proptosis, and strabismus (Abdolrahimzadeh 2016).
Risk minimisation measures	SmPC <ul style="list-style-type: none"> • Section 4.2: Posology and method of administration. • Section 4.4: Special warnings and precautions for use. • Section 4.8: Undesirable effects. PIL <ul style="list-style-type: none"> • Section 2: What you need to know before you take EZMEKLY. • Section 4: Possible serious side effects. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study

Important Identified Risk: Ejection fraction decreased	
Evidence for linking the risk to the medicine	<p>The MAPK signaling cascade is important for cardiac adaptation in response to stress; when inhibited, the heart cannot compensate by getting stronger or preventing cell death. Mice that lack ERK1/2 have normal cardiac size and function, but are more susceptible to cardiomyocyte apoptosis and suffer greater cardiac damage in response to insult (Lips 2004). This finding suggests that susceptibility to MEK inhibitor-associated injury does not occur due to drug exposure alone, but requires a second source of injury (e.g., hypertension, ischemia, or other toxic drug exposure) (Banks 2017). MEK inhibition alone at lower doses in the NF1 paediatric patient population is also associated with cardiac AEs, primarily cardiomyopathy/ejection fraction decrease and hypertension (Gross 2023).</p> <p>In Study MEK-NF-201, 20 events of asymptomatic ejection fraction decreased were observed in 15 (27%) paediatric participants, and 13 events were observed in 9 (16%) adult participants. The median (min, max) ejection fraction at baseline was similar between the cohorts: 65% (55%, 78%) in paediatric participants and 62% (55%, 80%) in adult participants. For those participants still receiving mirdametinib after 1 year, the median (min, max) ejection fraction was largely unchanged from baseline at 63.2% (50%, 77%) in paediatric, and 60% (53%, 67%) in adult participants. In Study MEK-NF-201, 1 participant in each cohort was observed to have an event of ejection fraction decreased with a >10% absolute value decrease from their baseline value to an ejection fraction <50%. All events were asymptomatic and no events of cardiomyopathy or left ventricular dysfunction were reported.</p>
Risk factors and risk groups	None have been identified.

Important Identified Risk: Ejection fraction decreased	
Risk minimisation measures	<p>SmPC</p> <ul style="list-style-type: none"> • Section 4.2: Posology and method of administration. • Section 4.4: Special warnings and precautions for use. • Section 4.8: Undesirable effects. <p>PIL</p> <ul style="list-style-type: none"> • Section 2: What you need to know before you take EZMEKLY. <p>Additional risk minimisation measures: None</p>
Additional pharmacovigilance activities	Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study

Important Potential Risk: Embryo-foetal toxicity	
Evidence for linking the risk to the medicine	<p>Significant embryo-foetal development toxicities were observed in both the rat and rabbit range-finding studies manifesting as foetal absorptions, post-implantation loss, and decreased foetal weights. The findings with mirdametinib are consistent with the embryo-foetal toxicity observed in nonclinical studies with other MEK inhibitors and are considered a class effect. Specifically, these findings from animal studies were noted with approved MEK inhibitors selumetinib (KOSELUGO SmPC), trametinib MEKINIST SmPC, binimetinib MEKTOVI SmPC, and cobimetinib (COTELLIC SmPC) which clearly highlight the class effect of these compounds related to potential foetal harm if these agents are administered to pregnant women.</p> <p>Mirdametinib was not genotoxic in a bacterial reverse mutation (Ames) assay or in an in vitro human lymphocyte chromosomal aberration assay but was equivocal in the in vivo micronucleus study and in vivo chromosomal aberrations study in rats. A genotoxicity risk in humans could not be excluded.</p> <p>One participant in Study MEK-NF-201 had a positive urine pregnancy test reported 31 days after the last dose of mirdametinib. The pregnancy ended in a first trimester spontaneous abortion.</p> <p>There was one case of a partner pregnancy reported for a 34-year-old male with NF1 PN treated with mirdametinib 4 mg BID. The outcome of the pregnancy is unknown.</p>
Risk factors and risk groups	Females of reproductive potential and their partners.
Risk minimisation measures	<p>SmPC</p> <ul style="list-style-type: none"> • Section 4.4: Special warnings and precautions for use. • Section 4.5: Interaction with other medicinal products and other forms of interaction. • Section 4.6: Fertility, pregnancy and lactation. • Section 5.3: Preclinical safety data.

Important Potential Risk: Embryo-foetal toxicity	
	<p>PIL</p> <ul style="list-style-type: none"> Section 2: What you need to know before you take EZMEKLY. <p>Additional risk minimisation measures: None</p>
Additional pharmacovigilance activities	Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study

Important Potential Risk: Physeal dysplasia	
Evidence for linking the risk to the medicine	Administration of mirdametinib to rats resulted in bone lesions that included necrosis of the metaphysis and the ossifying zone of the physis and thickening of the zone of hypertrophying cartilage of the physis. The expansion of chondrocytes in the physis may be a response to the metaphyseal necrosis and loss of osteoprogenitor cells. These changes are characterised by localised injury to bone, which appear to be due to local ischaemia and/or necrosis. Skeletal vascular changes may be present in these animals, resulting in disruption of endochondral ossification. Skeletal lesions, including bone necrosis, can result from Vitamin D intoxication (Haschek 1978). In the pivotal 1- and 3-month studies in rats, hypocellularity in the metaphyseal region of the distal portion of the femur and/or proximal portion of the tibia occurred in males only at 1 mg/kg/day and was reversible following cessation of dosing in the 1-month study. In addition, thickening of the bony trabeculae in the femoral/tibial metaphyseal region was evident in all males at 1.0 mg/kg/day in the 3-month study. Bone lesions, like those observed in rats, have not been seen in dogs, monkeys, or mice given mirdametinib.
Risk factors and risk groups	Paediatric patients with open growth plates
Risk minimisation measures	<p>SmPC</p> <ul style="list-style-type: none"> Section 5.3: Pre-clinical safety data. <p>Additional risk minimisation measures: None</p>

Important Potential Risk: Physeal dysplasia	
Additional pharmacovigilance activities	Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study

Important Potential Risk: Adverse effects on cardiac conduction	
Evidence for linking the risk to the medicine	<p>Mirdametinib reduced action potential duration at concentrations of 10 µM and 100 µM and reduced the maximum rate of depolarisation and amplitude at 100 µM. 10 µM is approximately 2500-fold higher than the unbound steady-state maximum concentration (C_{max,ss,u}) of mirdametinib at the clinical dose (2 mg/m² BID [maximum dose of 4 mg BID]) in Study MEK-NF-201.</p> <p>In a (GLP)-compliant in vitro study, mirdametinib and the metabolite PD-0315209 did not inhibit hERG current at a concentration of 10 µM. In a GLP-compliant in vitro assay using isolated canine Purkinje fibres, there was no meaningful effect on resting membrane potential at any tested concentrations of mirdametinib. Mirdametinib did reduce action potential duration at high concentrations of 10 µM and 100 µM and reduced the maximum rate of depolarisation and amplitude at 100 µM. 10 µM is approximately 2500-fold higher than the unbound steady-state maximum concentration (C_{max,ss,u}) of mirdametinib at the clinical dose (2 mg/m² BID [maximum dose of 4 mg BID]) in Study MEK-NF-201.</p> <p>In a GLP-compliant cardiovascular study in telemetered monkeys, there were no mirdametinib-related effects in blood pressure, heart rate, body temperature, or electrocardiography parameters, including QT interval, for 24 hours after single oral doses up to 10 mg/kg. Mirdametinib exposure at the 10 mg/kg dose was 10-fold higher than the unbound exposure (C_{max,ss,u}) of mirdametinib at the clinical dose (2 mg/m² BID [maximum dose of 4 mg BID]) in Study MEK-NF-201. In a secondary pharmacodynamic study conducted with mirdametinib at 1 and 10 µM against a panel of 87 targets, inhibition of the L-type calcium channel by 54% was observed at 10 µM (2500-fold higher than the human mirdametinib C_{max,ss,u} at the clinical dose).</p> <p>In a thorough QT study conducted in healthy participants, no clinically significant effect of mirdametinib at supratherapeutic exposures (up to 6-fold higher than the C_{max,ss} in Study MEK-NF-201) on baseline-adjusted QTcF or QTc prolongation was observed. There was also no statistically significant change observed in the QRS interval.</p>
Risk factors and risk groups	Patients with medical history of cardiac conduction disturbances or intercurrent illnesses associated with changes in cardiac conduction
Risk minimisation measures	None
Additional pharmacovigilance activities	Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study

Important Potential Risk: Carcinogenicity	
Evidence for linking the risk to the medicine	Mirdametinib was equivocal in the in vivo micronucleus study and in vivo chromosomal aberrations study in rats, and these findings may relate to a potential aneugenic mechanism that has been observed with other MEK inhibitors. Mirdametinib treatment resulted in equivocal findings in the in vivo genotoxicity studies in rats, was negative for carcinogenicity in transgenic mice, and the currently ongoing 2-year carcinogenicity study in rats is testing dose levels that will produce exposures below the therapeutic clinical exposure because of tolerability issues in rats.
Risk factors and risk groups	None identified
Risk minimisation measures	SmPC <ul style="list-style-type: none"> • Section 4.4: Special warnings and precautions for use. • Section 5.3: Pre-clinical safety data. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study

Missing Information: Long term safety	
Risk minimisation measures	None
Additional pharmacovigilance activities	Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study

1.2.3 II.C Post-authorisation development plan

1.2.3.1 II.C.1 Studies which are conditions of the marketing authorisation

None

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

Post-authorisation safety study to estimate the incidence of physeal dysplasia in patients aged 2 to < 18 years (paediatric cohort) with NF1 for the treatment of symptomatic PNs, based on the approved indication in the local labelling, treated with mirdametinib for up to 6 years. In addition, the study will further characterise the long-term safety in both adult and paediatric patients aged 2 years and above (adult and paediatric cohort) for the treatment of symptomatic PNs based on the approved indication in the local labelling, treated with mirdametinib for up to 6 years.