swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Ezmekly

International non-proprietary name: mirdametinib
Pharmaceutical form: Dispersible tablets
Dosage strength(s): 1 mg and 2 mg
Route(s) of administration: oral
Marketing authorisation holder: Merck (Schweiz) AG
Marketing authorisation no.: 70392
Decision and decision date: approved on 9 April 2026

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, definitions, abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

New active substance status
The applicant requested new active substance status for mirdametinib in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA. Orphan drug status was granted on 19 June 2025.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

Temporary authorisation for human medicinal products
The applicant requested temporary authorisation in accordance with Article 9*a* TPA.

2.2 Indication and dosage

2.2.1 Indication

Ezmekly is indicated as monotherapy for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric and adult patients with neurofibromatosis type 1 (NF1) aged 2 years and above.

2.2.2 Approved indication

Ezmekly as monotherapy is indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in adult and paediatric patients with neurofibromatosis type 1 (NF1) aged 2 years and above.

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dose of Ezmekly is 2 mg/m^2 of body surface area (BSA), twice daily (approximately every 12 hours) for the first 21 days of each 28-day cycle. The maximum dose is 4 mg twice daily.

For paediatric patients 2 to <6 years of age and for patients who are unable to swallow capsules whole, Ezmekly is also available as a 1 mg dispersible tablet formulation that can be dispersed in water. The recommended dose for patients with a BSA of less than 0.40 m^2 has not been established.

Body surface area (BSA)	Recommended dose
0.40 to 0.69 m^2	1 mg twice daily
0.70 to 1.04 m^2	2 mg twice daily
1.05 to 1.49 m^2	3 mg twice daily
≥ 1.50 m^2	4 mg twice daily

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	21 October 2025
Formal control completed	22 October 2025
Preliminary decision	17 December 2025
Response to preliminary decision	23 January 2026
Labelling corrections and/or other aspects	5 February 2026
Response to labelling corrections and/or other aspects	10 February 2026
Final decision	9 April 2026
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

Based on Art. 13 TPA Swissmedic has not assessed the primary data (e.g. study reports) submitted with this application and relies for its decision on the assessment of the foreign reference authority (European Medicines Agency). This SwissPAR relates to the assessment report *Ezmekly (mirdametinib), European Public Assessment Report (EPAR),* published on 20 August 2025, Procedure No. EMEA/H/C/006460/0000, issued by European Medicines Agency (EMA).

3 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority (European Medicines Agency). The quality aspects in this SwissPAR refer to the publicly available assessment report of EMA. (see section 2.3 Regulatory history (milestones)).

4 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority EMA (see section 2.3 Regulatory history (milestones)).

5 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and relies on the assessment of the foreign reference authority EMA (see section 2.3 Regulatory history (milestones)).

6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Ezmekly was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Ezmekly is authorized for a limited period of time; see the section "Indications/Possible uses." Healthcare professionals have to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

EZMEKLY, dispersible tablets

Composition

Active substances

Mirdametinibum

Excipients

Cellulosum microcristallinum (E460), carmellosum natricum conexum (E468), magnesii stearas (E572), sucralosum, aromatica (grape flavour).
Grape flavour: glucosi sirupus desiccatus, aromatica naturale, maydis amylum modificatum (E1422), triacetinum (E1518).
Each dispersible tablet contains a maximum of 0.6 mg of sodium.

Pharmaceutical form and active substance quantity per unit

Each dispersible tablet contains 1 mg of mirdametinib.
Oval, white to off-white dispersible tablets (approximately 6 mm × 9 mm) debossed with 'S' on one side.

Indications/Uses

Ezmekly as monotherapy is indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in adult and paediatric patients with neurofibromatosis type 1 (NF1) aged 2 years and above.
Due to incomplete documentation at the time of review of the application, this indication is authorized for a limited period (Art. 9a TPA). The temporary marketing authorization is strictly linked to the timely fulfilment of requirements. Once these requirements have been met, the temporary marketing authorization can be converted into an authorization without specific requirements.

Dosage/Administration

Treatment with Ezmekly should be initiated by a physician experienced in the diagnosis and the treatment of patients with NF1 related tumours.

Posology

The recommended dose of Ezmekly is 2 mg/m^2 of body surface area (BSA), twice daily (approximately every 12 hours) for the first 21 days of each 28-day cycle. The maximum dose is 4 mg twice daily (see Table 1).

Ezmekly is also available in a hard capsule formulation. It is recommended that the dispersible tablets be used in patients aged 2 to <6 years of age and in adults who are unable to swallow hard capsules whole. The recommended dose for patients with a BSA less than 0.40 m^2 has not been established.

Table 1: Recommended dose based on body surface area

Body surface area (BSA)	Recommended dose
0.40 to 0.69 m^2	1 mg twice daily
0.70 to 1.04 m^2	2 mg twice daily
1.05 to 1.49 m^2	3 mg twice daily
≥ 1.50 m^2	4 mg twice daily

Duration of treatment

Treatment with Ezmekly should continue until PN progression or the development of unacceptable toxicity.

Missed dose

If a dose of Ezmekly is missed, an additional dose is not to be taken. The patient should continue with the next scheduled dose.

Vomiting

If vomiting occurs after Ezmekly is administered, an additional dose is not to be taken. The patient should continue with the next scheduled dose. Manage events of vomiting as clinically indicated, including use of anti-emetics.

Dose adjustments

Dose reduction and/or interruption or permanent discontinuation of Ezmekly may be required based on individual safety and tolerability (see sections “Warning and Precautions” and “Undesirable effects”). Recommended dose reductions are given in Table 2. Permanently discontinue treatment in patients unable to tolerate Ezmekly after one dose reduction.

Table 2: Recommended dose reductions

Body surface area (BSA)	Reduced dose	
	Morning	Evening
0.40 to 0.69 m^2	1 mg once daily	
0.70 to 1.04 m^2	2 mg	1 mg
1.05 to 1.49 m^2	2 mg	2 mg
≥ 1.50 m^2	3 mg	3 mg

Management of patients according to the adverse reactions associated with this medicinal product are presented in Table 3.

Table 3: Recommended dose modifications for adverse reactions

Severity of adverse reactions[a]	Recommended dose modification for Ezmekly
Ocular toxicity (see sections "Warnings and precautions" and "Undesirable effects")	
Grade ≤ 2	Continue treatment. Consider ophthalmologic examinations every 2 to 4 weeks until improvement.
Grade ≥ 3	Interrupt treatment until improvement. If recovery occurs ≤14 days, resume at reduced dose (see Table 2). If recovery occurs in >14 days, consider discontinuation.
Any grade asymptomatic retinal pigment epithelium detachment (RPED)	Continue treatment. Ophthalmic assessment should be conducted every 3 weeks until resolution.
Symptomatic RPED	Interrupt treatment until resolution. Resume at reduced dose (see Table 2).
Retinal vein occlusion (RVO)	Discontinue treatment permanently.
Decreased left ventricular ejection fraction (LVEF) (see sections "Warnings and precautions" and "Undesirable effects")	
Asymptomatic, absolute decrease in LVEF less than 20% and greater than the lower limit of normal	Continue treatment.
Asymptomatic, absolute decrease in LVEF of 10% or greater from baseline and is less than the lower limit of normal.	Interrupt treatment until improvement. Resume at reduced dose (see Table 2).
For any absolute decrease in LVEF 20% or greater from baseline.	Discontinue treatment permanently.
Skin toxicity (see sections "Warnings and precautions" and "Undesirable effects")	
Grade 1 or 2 dermatitis acneiform or non-acneiform rash	Continue treatment.
Intolerable Grade 2 or Grade 3 dermatitis acneiform or non-acneiform rash	Interrupt treatment until improvement. Resume at reduced dose (see Table 2).
Grade 3 or Grade 4 dermatitis acneiform or non-acneiform rash	Interrupt treatment until improvement. Resume at reduced dose (see Table 2).
Other adverse reactions (see section "Undesirable effects")	
Intolerable Grade 2 or Grade 3	Interrupt treatment until improvement. Resume at reduced dose (see Table 2).
Grade 4	Interrupt treatment until improvement. Resume at reduced dose (see Table 2). Consider discontinuation.

[a] *National Cancer Institute Common Terminology Criteria for Adverse Events* (NCI CTCAE) version 5.0

Special populations

Elderly

No dose adjustment is recommended for patients who are aged 65 or over. Clinical data in patients aged 65 or over is limited.

Renal impairment

No dose adjustment is recommended in patients with mild or moderate renal impairment based on a population pharmacokinetic analysis. Ezmekly has not been studied in patients with severe renal

impairment (CrCL ≥ 15 to < 30 mL/min) or patients with end stage renal disease (ESRD), and therefore, no dose recommendations can be made (see section “Pharmacokinetics”).

Hepatic impairment

No dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin > upper limit of normal [ULN] to 1.5x ULN or total bilirubin ≤ ULN and aspartate amino transferase AST > ULN), based on a population pharmacokinetic analysis. Ezmekly has not been studied in patients with moderate or severe hepatic impairment, and therefore, no dose recommendation can be made (see section “Pharmacokinetics”).

Paediatric population

The safety and efficacy of Ezmekly in children below 2 years of age have not been established.
No data are available.
Ezmekly is not approved for use in patients under 2 years of age.

Method of administration

Ezmekly is for oral use.
The dispersible tablets can be taken with or without food (see section “Pharmacokinetics”).
Ezmekly dispersible tablets can be swallowed whole, or if dosing of whole dispersible tablets is not possible, dispersible tablets can be dispersed in water prior to oral administration via dosing cup. Ezmekly oral suspension can also be administered via an enteral feeding tube. Please see section “Information for handling” for instructions on preparation and administration of the oral suspension.
Ezmekly is also available as a hard capsule formulation. It is recommended that the dispersible tablets be used in patients aged 2 to < 6 and in adults who are unable to swallow hard capsules.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section “Composition”.

Warnings and precautions

Ocular toxicity

Patients should be advised to report any new visual disturbances. RVO (retinal vein occlusion) and RPED (retinal pigment epithelial detachment) were commonly reported in adult patients receiving Ezmekly in clinical studies (see section “Undesirable effects”).
A comprehensive ophthalmological evaluation prior to treatment initiation, at regular intervals during treatment, and at any time a patient reports new or worsening visual changes such as blurred vision is necessary in children, adolescents and adults. For ocular adverse reactions, mirdametinib therapy should be interrupted and then dose reduced or treatment permanently discontinued based on severity of the adverse reaction. If RVO is diagnosed, treatment with mirdametinib should be permanently discontinued. If symptomatic RPED is diagnosed, treatment with mirdametinib should be

interrupted until resolution and the dose reduced when treatment is resumed. In patients diagnosed with RPED without reduced visual acuity, treatment can be continued but ophthalmic assessment should be conducted every 3 weeks until resolution (see section “Dosage/Administration”).

Decreased left ventricular ejection fraction (LVEF)

Asymptomatic decrease in LVEF ≥ 10% from baseline occurred in 16% of adult patients and 27% of paediatric patients in the ReNeu study. All cases of decreased LVEF in adult or paediatric patients in the clinical studies were asymptomatic (see section “Undesirable effects”).
Patients with a history of impaired LVEF or a baseline ejection fraction that is below the institutional lower limit of normal (LLN) have not been studied. LVEF should be evaluated by echocardiogram before initiation of treatment to establish baseline values, every 3 months during the first year, then as clinically indicated thereafter. Prior to starting treatment, patients should have an ejection fraction above the institutional LLN.
Decreased LVEF can be managed using treatment interruption, dose reduction or treatment discontinuation (see section “Dosage/Administration”).

Skin toxicity

Skin adverse reactions, including rash (dermatitis acneiform and non-acneiform rashes), dry skin, pruritus, eczema, and hair changes have been reported in the ReNeu study (see section “Undesirable effects”).
Patients should contact their doctor or nurse if they experience any skin reactions. Supportive care, e.g. the use of emollient creams, should be initiated at first signs of skin toxicity. Mirdametinib therapy should be interrupted, the dose reduced or permanently discontinued based on severity of the adverse reaction (see section “Dosage/Administration”).

Carcinogenicity risk

A potential carcinogenicity risk in humans could not be excluded at the clinical exposure range (see section “Preclinical data”).

Women of childbearing potential/Contraception in females and males

Mirdametinib is not recommended in women of childbearing potential who are not using contraception (see sections “Interactions” and “Pregnancy, lactation”). Both male and female patients (of reproductive potential) should be advised to use effective contraception.

Excipients with known effect

Each dispersible tablet contains less than 1 mmol sodium (23 mg) per dose which means it is essentially ‘sodium-free’.

Interactions

No clinical interaction studies have been performed (see section “Pharmacokinetics”).

Effects of other medicinal products on mirdametinib pharmacokinetics

In vitro studies showed that mirdametinib is metabolised by multiple uridine diphosphate glucuronosyltransferase (UGT) and carboxyl esterase (CES) enzymes. No clinical studies assessing the effect of a strong inducer and inhibitor of these enzymes have been performed. Therefore, caution should be made when mirdametinib is concomitantly used with medicinal products known to either induce or inhibit these enzymes: probenecid, diclofenac (UGT inhibitors), rifampicin (UGT inducer) (see section “Pharmacokinetics”).
Cytochromes P450 do not contribute significantly to the metabolism of mirdametinib.
Based on in vitro studies, mirdametinib is a substrate for BCRP and P-gp transporters and its metabolite, M15, is a substrate for BCRP, but they are unlikely to be clinically relevant.
Mirdametinib and M15 are not substrates for the OATP1B1 and 1B3 transporters.

Effects of gastric acid reducing agents on mirdametinib

The combination of mirdametinib with proton-pump inhibitors, antacids, or H2-receptor antagonists is not expected to be clinically meaningful as mirdametinib does not exhibit pH dependent dissolution. Ezmekly can be used concomitantly with gastric pH modifying agents (i.e., H2-receptor antagonists and proton pump inhibitors) without restrictions.

Effects of mirdametinib on the pharmacokinetics of other medicinal products

Hormonal contraceptives

The effect of mirdametinib on the exposure of systemically acting hormonal contraceptives has not been evaluated. Therefore, use of an additional barrier method should be recommended to women using systemically acting hormonal contraceptives (see section “Pregnancy, lactation”).

Substrates of BCRP, OATP1B1, or OATP2B1

The M22 metabolite of mirdametanib inhibits BCRP, OATP1B1, and OATP2B1 *in vitro*. The effect of this inhibition at clinically relevant concentrations is unknown, but caution is recommended when substrates of BCRP, OATP1B1, or OATP2B1 are administered concomitantly with mirdametinib.

In vitro studies

At therapeutic concentrations *in vitro*, mirdametinib does not induce CYP1A2, 2B6, 2C8, 2C9, 2C19, or 3A4.
In vitro, mirdametinib, M15, and M22 are not inhibitors of CYP1A2, CYP2B6, CYP2C19, CYP2D6, or CYP3A4. Mirdametinib and M22 do not inhibit CYP2C8 or CYP2C9. M15 is an inhibitor of CYP2C8 and CYP2C9 *in vitro*, however there is a low potential for inhibition at clinically relevant concentrations.
In vitro, mirdametinib is not an inhibitor of the isoforms UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15 at clinically relevant concentrations. *In vitro*, M15 was not an

inhibitor of the isoforms UGT1A3, UGT1A4, UGT1A6, UGT2B15, or UGT2B17. M15 is an inhibitor of UGT1A1, UGT1A9, and UGT2B7 *in vitro*, however there is a low potential for inhibition at clinically relevant concentrations.
In vitro studies suggest that mirdametinib and its metabolite M15 do not inhibit BCRP, P-gp, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1, or MATE2K. M22 does not inhibit P-gp, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, or MATE2K.

Pregnancy, lactation

Women of childbearing potential/Contraception in females and males

Women of childbearing potential should be advised that Ezmekly may cause foetal harm and to avoid becoming pregnant while receiving Ezmekly. It is recommended that a pregnancy test should be performed on women of childbearing potential prior to initiating treatment. Both male and female patients (of reproductive potential) should be advised to use effective contraception during treatment and for 3 months and 6 months, respectively, after the last dose. The effect of mirdametinib on the exposure of systemically acting hormonal contraceptives has not been evaluated, therefore women using systemically acting hormonal contraceptives should be recommended to add a barrier method.

Pregnancy

There are limited data on the use of mirdametinib in pregnant women. In ReNeu, a pregnancy reported 31 days after the last dose of Ezmekly resulted in a first trimester spontaneous abortion. Studies in animals have shown reproductive toxicity (see section “Preclinical data”). Ezmekly should not be used during pregnancy and in women of childbearing potential not using contraception. If a female patient or a female partner of a male patient receiving Ezmekly becomes pregnant, she should be apprised of the potential risk to the foetus.

Breast-feeding

It is not known whether mirdametinib or its metabolites are excreted in human milk. A risk to the breast-fed child cannot be excluded, therefore breast-feeding should be discontinued during treatment with Ezmekly and should not be resumed for 1 week after the last dose.

Fertility

Based on findings in animals, Ezmekly may impair fertility in males and females of reproductive potential. The reversibility of the effects on male and female reproductive organs in animals is unknown (see section “Preclinical data”). There are no data on the effect of mirdametinib on human fertility. The potential risk for humans is unknown.

Effects on ability to drive and use machines

No corresponding study has been conducted. Ezmekly may have a moderate influence on the ability to drive and use machines. Fatigue and blurred vision have been reported during treatment with

mirdametinib (see section “Undesirable effects”). Patients who experience these symptoms should observe caution when driving or using machines.

Undesirable effects

Summary of the safety profile

In the combined adult pool of NF1 patients, the most common adverse reactions of any grade were dermatitis acneiform (83%), diarrhoea (55%), nausea (55%), blood creatine phosphokinase increased (47%), musculoskeletal pain (41%), vomiting (37%), and fatigue (36%). Adverse reactions leading to discontinuation in >1 adult patient were dermatitis acneiform, diarrhoea, nausea, rash, and vomiting. The following serious adverse reactions were reported: abdominal pain (3%), musculoskeletal pain (1.3%) and retinal vein occlusion (1.3%).
In the combined paediatric pool of NF1 patients, the most common adverse reaction of any grade were blood creatine phosphokinase increased (59%), diarrhoea (53%), dermatitis acneiform (43%), musculoskeletal pain (41%), abdominal pain (40%), vomiting (40%), and headache (36%). The following serious adverse reaction was reported: musculoskeletal pain (1.7%).

Tabulated list of adverse reactions

The safety profile of mirdametinib has been determined following evaluation of a combined safety population of 75 adult and 58 paediatric patients dosed at 2 mg/m^2 twice daily for the first 21 days of each 28-day cycle. This pool of patients comprised 114 patients (58 adult, 56 paediatric) in ReNeu (the pivotal dataset), and 19 patients (17 adult, 2 paediatric) in NF-106.
In the adult pool (N = 75), the median total duration of mirdametinib treatment was 18.7 months (range: 0.4 to 45.6 months).
In the paediatric pool (N = 58, including 32 patients aged ≥ 2 to 11 years), the median total duration of mirdametinib treatment was 21.9 months (range: 1.6 to 40.1 months).
Table 4 presents the adverse reactions identified in the safety population.
Adverse reactions are classified by MedDRA system organ class (SOC). Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000).

Table 4. Adverse reactions reported in the safety population

MedDRA SOC	MedDRA term	Adult pool (N=75)		Paediatric pool (N=58)	
		Overall frequency (All CTCAE grades)	Frequency of CTCAE grade 3 and above	Overall frequency (All CTCAE grades)	Frequency of CTCAE grade 3 and above
Infections and infestations	Paronychia	Common	-	Very common (33%)	-
Blood and lymphatic system disorders	Neutrophil count decreased	Common	Common	Very common (30%)	Very common (11%)
	Leukocyte count decreased	Common	-	Very common (39%)	-
Nervous system disorders	Headache	Very common (16%)	Common (1%)	Very common (36%)	Common (2%)
Eye disorders	Blurred vision	Common	-	Common	-
	Retinal vein occlusion	Common	Common	-	-
	RPED (retinal pigment epithelial detachment)	Common	-	-	-
Cardiac disorders	Ejection fraction decreased	Very common (12%)	-	Very common (26%)	Common (2%)
Gastrointestinal disorders	Diarrhoea	Very common (55%)	-	Very common (53%)	Common (5%)
	Nausea	Very common (55%)	-	Very common (29%)	-
	Vomiting	Very common (37%)	-	Very common (40%)	-
	Abdominal pain[a]	Very common (20%)	Common (4%)	Very common (40%)	Common (3%)
	Constipation	Very common (19%)	-	Very common (10%)	-
	Dry mouth	Common	-	-	-
	Stomatitis[b]	Common	-	Very Common (19%)	-
Hepatobiliary disorders	Blood alkaline phosphatase increased	Very common (14%)	-	Very common (24%)	-
	AST increased	Very common (16%)	-	Common	-
	ALT increased	Common	-	Very common (21%)	-
Skin and subcutaneous tissue disorders	Dermatitis acneiform	Very common (83%)	Common (7%)	Very common (43%)	Common (2%)
	Rash[c]	Very common (17%)	Common (1%)	Very common (33%)	Common (2%)
	Dry skin	Very common (13%)	-	Very common (17%)	-
	Alopecia	Very common (12%)	-	Very common (14%)	-

MedDRA SOC	MedDRA term	Adult pool (N=75)		Paediatric pool (N=58)	
		Overall frequency (All CTCAE grades)	Frequency of CTCAE grade 3 and above	Overall frequency (All CTCAE grades)	Frequency of CTCAE grade 3 and above
	Pruritus	Very common (13%)	-	Very common (12%)	-
	Eczema	Common	-	Very common (14%)	-
	Hair colour changes	Common	-	Very common (12%)	-
	Hair texture abnormal	Common	-	Common	-
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[d]	Very common (41%)	Common (7%)	Very common (41%)	Common (2%)
General disorders and administation site conditions	Fatigue	Very common (36%)	Common (1%)	Very common (12%)	-
	Oedema peripheral[e]	Very common (12%)	-	Common (5%)	-
Investigations	Blood creatine phosphokinase increased	Very common (47%)	Common (3%)	Very common (59%)	Common (5%)

[a] Abdominal pain includes abdominal pain and abdominal pain upper.

[b] Stomatitis includes stomatitis, mouth ulceration, aphthous ulcer.

[c] Rash includes rash, rash maculo-papular, rash pustular, rash erythematous, rash papular, exfoliative rash, papule, rash macular, rash pruritic.

[d] Musculoskeletal pain includes musculoskeletal pain, myalgia, pain in extremity, back pain, musculoskeletal chest pain, neck pain, non-cardiac chest pain, arthralgia, bone pain.

[e] Oedema peripheral includes oedema peripheral, peripheral swelling.

Description of specific adverse reactions and additional information

Ocular toxicity

In the ReNeu study, retinal vein occlustion (RVO) was observed in 3% of adult patients, including Grade 3 RVO in 1.7% of patients which resulted in permanent discontinuation. Asymptomatic Grade 1 retinal pigment epithelium detachment (RPED) occurred in 1.7% of patients and was managed without dose modification. Vision blurred was reported by 12% of adult patients. The median time to first onset of ocular toxicity in adults was 147 days. The median time to resolution was 267 days. In these adults, 38% of patients reported resolution of their ocular toxicity, while 25% reported resolution of events with sequelae.

Vision blurred was reported by 7% of paediatric patients. The median time to first onset of vision blurred was 161 days in paediatric patients. The median time to resolution was 29 days. All paediatric patients reported resolution of events of vision blurred (see sections “Dosage/Administration” and “Warnings and precautions”).

Decreased left ventricular ejection fraction (LVEF)

In the ReNeu study, asymptomatic decreased LVEF was reported in 16% of adults. Of these patients, only one reported an LVEF to < 50%, which led to discontinuation followed by return to normal values. Of the remaining adult patients with decreased LVEF, five had a dose interruption, and one patient had a dose reduction. The median time to first onset of decreased LVEF in adults was 70 days. Decreased LVEF resolved in 89% of adult patients.
In the ReNeu study, asymptomatic decreased LVEF was reported in 27% of paediatric patients. Of these patients, one reported an LVEF to < 50%, which returned to normal values without dose modification. One patient had a Grade 3 decreased LVEF that resolved without dose modification and another patient with Grade 2 decreased LVEF had a dose interruption. The remaining 12 patients’ events of decreased LVEF were Grade 2 and no action was taken with study treatment in response to any of these events. The median time to first onset of decreased LVEF in paediatric patients was 132 days. Decreased LVEF resolved in 67% of paediatric patients (see sections “Dosage/Administration” and “Warnings and precautions”).

Skin toxicity

In the ReNeu study, dermatitis acneiform and non-acneiform rashes occurred in 90% of adult patients. Grade 3 dermatitis acneiform and other rashes occurred in 9% and 1.7% of adult patients, respectively. Rashes resulted in discontinuations in 10% of adults and dose reductions in 10% of adults. The median time to first onset of rashes was 9 days in adult patients. The median time to resolution was 115 days. In these adult patients, 33 (64%) reported resolution of their rashes, 3 (6%) reported resolution with sequelae, and 8 (15%) reported that their rashes were resolving.
In the ReNeu study, dermatitis acneiform and non-acneiform rashes occurred in 70% of paediatric patients. Dermatitis acneiform and non-acneiform rashes of grade 3 occurred in 1.8% and 1.8%, respectively. Rashes resulted in discontinuations in 4% of paediatric patients and dose reductions in 4% of paediatric patients. Dermatitis acneiform occurred with a higher frequency in patients aged 12 to 17 years, while other rashes occurred with a higher frequency in patients aged 2 to 11 years. The median time to first onset of rashes in paediatric patients was 15 days. The median time to resolution was 155 days. In these paediatric patients, 27 (69%) reported resolution of their rashes and 3 (8%) reported that their rashes were resolving (see sections “Dosage/Administration” and “Warning and precautions”).

Musculoskeletal pain

In the ReNeu study, musculoskeletal pain (including musculoskeletal pain, myalgia, pain in extremity, back pain, musculoskeletal chest pain, neck pain, non-cardiac chest pain, arthralgia, and bone pain) were reported by 41% of adult and 41% of paediatric patients. Concomitant medications used to treat musculoskeletal pain included non-steroidal anti-inflammatory medicinal products, non-opioid analgesics and glucocorticoids. Treat musculoskeletal pain as clinically indicated.

AST and ALT increased

In the ReNeu study, laboratory shifts of ALT increased were observed in 9% of adult and 21% of paediatric patients. Laboratory shifts of AST increased were observed in 18% of adult and 9% of paediatric patients. All events were mild to moderate severity with no Grade 3 events reported. ALT and AST increased did not result in any discontinuations, dose reductions or interruptions. Monitor and manage increases in ALT and AST as clinically indicated.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no specific treatment for overdose. If overdose occurs, patients should be closely monitored for signs and symptoms of adverse reactions and treated supportively with appropriate monitoring as necessary. Dialysis is ineffective in the treatment of overdose

Properties/Effects

ATC code

L01EE05

Mechanism of action

Mirdametinib is a selective, non-competitive inhibitor of mitogen-activated protein kinase 1 and 2 (MEK1/2). Mirdametinib blocks MEK activity and the rat sarcoma (RAS)-rapidly accelerated fibrosarcoma (RAF)-MEK pathway. Therefore, MEK inhibition blocks proliferation and survival of tumour cells in which the RAF-MEK-extracellular related kinase (ERK) pathway is activated.

Clinical efficacy

The efficacy of mirdametinib was evaluated in 114 patients in ReNeu, a multi-centre, open-label, single-arm, Phase 2 study in patients ≥ 2 years of age with symptomatic inoperable NF1-PN causing significant morbidity. An inoperable PN was defined as a PN that cannot be completely surgically

removed without risk for substantial morbidity due: to encasement of or close proximity to vital structures, invasiveness, or high vascularity of the PN. Patients received Ezmekly 2 mg/m^2 orally twice daily for the first 21 days of each 28-day cycle until disease progression or unacceptable toxicity.

A total of 58 adult patients received Ezmekly. The median age was 34.5 years (range 18 to 69 years); 85% were Caucasian, 64% were female and 3.4% were greater than 65 years of age. Approximately half of the patients (53%) had a progressing PN at study entry, 48% had their tumour in the head and neck, and 69% had prior surgery. All patients had significant morbidities. The most commonly reported morbidities were pain (90%), disfigurement or major deformity (52%), and motor dysfunction (40%).

A total of 56 paediatric patients received Ezmekly. 57% were aged 2 to 11 years and 43% were aged 12 to 17 years. The median age was 10.0 years (range 2 to 17 years); 66% were Caucasian and 54% were female. Half of participants (50%) had their tumour in head and neck, most participants had a progressing PN at study entry (63%) and 36% had prior surgery. The majority of patients (96%) had significant morbidities. The most commonly reported morbidities were pain (70%), disfigurement or major deformity (50%) and motor dysfunction (27%).

The primary efficacy endpoint measure was confirmed objective response rate (ORR), defined as the percentage of patients with complete response (disappearance of the target PN) or confirmed partial response (≥ 20% reduction in PN volume confirmed at consecutive tumour assessments approximately every four cycles within 2-6 months during the 24-cycle treatment phase). Tumour response status was assessed by blinded independent central review (BICR) approximately every four cycles using volumetric magnetic resonance imaging (MRI) analysis. Objective response rate was evaluated per Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria with two consecutive assessments of partial response or complete response by a BICR within 2-6 months during the 24-cycle treatment phase.

A secondary efficacy objective was to determine the duration of response for patients who achieved a confirmed objective response.

Efficacy results are provided in Table 5. The median time to onset of response was 7.8 months (range: 4.0 months to 19.0 months) for the adult cohort and 7.9 months (range: 4.1 months to 18.8 months) for the paediatric cohort. The median duration of response was not reached for either cohort.

Table 5. Efficacy results in ReNeu

	Adult (N=58)	**Paediatric (N=56)**
Confirmed objective response rate per REiNS by BICR[a, b] n (%)	24 (41%)	29 (52%)
95% CI[c]	(29, 55)	(38, 65)
Confirmed complete response, n (%)	0	0
Confirmed partial response, n (%)	24 (41%)	29 (52%)
Duration of response		
DoR ≥ 12 months[d]	21 (88%)	26 (90%)
DoR ≥ 24 months[d]	12 (50%)	14 (48%)

Abbreviations: CI = confidence interval; BICR = blinded independent central review; REiNS = Response Evaluation in Neurofibromatosis and Schwannomatosis; DoR = duration of response

[a] Confirmed objective response was defined as two consecutive assessments of partial response or complete response assessed by a BICR within 2-6 months during the 24-cycle treatment phase.

[b] Patients who had no post-baseline MRI assessment or no confirmed objective response were treated as non-responders.

[c] Obtained using the Clopper-Pearson approach.

[d] Duration of response (data cut-off, June 2024) was assessed using the Kaplan-Meier approach.

Pharmacokinetics

Absorption

Following multiple oral doses at 2 mg/m^2 twice daily, the geomean [geometric % coefficient of variation (CV)] the maximum plasma concentration (C_{max}) and area under the curve at the last measurable concentration (AUC_{last}) in adult participants with NF1-PN were 188 (52%) ng/mL and 431 (43%) ng × h/mL, respectively. Following oral dosing, mirdametinib produced peak steady state plasma concentrations (T_{max}) approximately one hour post-dose.

Effect of food

In healthy adult subjects at a single dose of 20 mg, co-administration of mirdametinib with a high-fat, high-calorie meal resulted in 43% lower C_{max}, while the area under the concentration-time curve (AUC) was not significantly changed (AUC_{inf} decreased by 7%). The time to reach maximum concentration (T_{max}) was delayed by approximately 3 hours. The effect on C_{max} is not considered clinically relevant due to the absence of effect on overall exposure.

Distribution

Following a single oral dose of 4 mg [^{14}C]mirdametinib in healthy subjects, the mean apparent volume of distribution of mirdametinib was 255 L. Human plasma protein binding is > 99%. Mirdametinib is mainly bound to human serum albumin (>99%). Binding to α1-acid glycoprotein (AAG) ranged from 17.2% to 54.3%. The blood/plasma ratio for mirdametinib is 0.61.

Metabolism

Mirdametinib is highly metabolised via glucuronidation, hydrolysis and oxidation via uridine diphosphate glucuronosyltransferase (UGT) and carboxyl esterase (CES) enzymes, resulting in M22 (a secondary O-glucuronide metabolite) and M15 (a carboxylic acid metabolite), respectively. Less than 10% is excreted unchanged.

Elimination

In healthy adult subjects, following a single dose of 4 mg of radiolabelled mirdametinib, 68% of the dose was recovered in urine (0.7% unchanged) while 27% was recovered in faeces (8.7% unchanged in urine and faeces). The mean terminal half life is 28 hours. The apparent systemic clearance (CL/F) is 6.34 L/h.

Linearity

Mirdametinib exposures, as measured by C_{max} and AUC_{tau}, generally increased dose proportionally from 1 mg QD/BID to 30 mg BID. A linear relationship between dose and exposure was verified by population pharmacokinetic analyses over the dose range of 1 mg to 20 mg mirdametinib BID. The mean accumulation ratio ranged from 1.1 to 1.9 across dose levels from 1 to 30 mg.
Steady-state concentrations in patients with NF1-PN are achieved on average approximately 6 days following repeat administration.

Kinetics in specific patient groups

Based on population pharmacokinetic analysis, age (2 to 86 years), sex, and race (72% white, 11% black or African American, and 12% Asian) do not significantly influence the pharmacokinetics of mirdametinib.

Renal impairment

No formal pharmacokinetic studies have been conducted in patients with renal impairment. No data are available in patients with severe renal impairment or end stage renal disease (ESRD).
Patients with creatinine clearance indicative of mild or moderate renal impairment participated in mirdametinib clinical studies. Population pharmacokinetic analyses suggest that mild or moderate renal impairment (as estimated by creatinine clearance) do not impact mirdametinib exposure.

Hepatic impairment

No formal pharmacokinetic studies have been conducted in patients with hepatic impairment. Population pharmacokinetic analyses in patients with mild hepatic impairment indicate no meaningful effects on exposure.

Paediatric population

The pharmacokinetic profile in children is similar to that of adults.

Preclinical data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology.

Genotoxicity/Carcinogenicity

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 human could not be excluded at the clinical exposure range.
Mirdametinib was not carcinogenic in transgenic mice at a dose of 5 mg/kg/day (3 times the human exposure). Since a genotoxicity risk in humans could not be excluded at clinical exposure and the 2-year rat carcinogenicity study is performed at exposures below the clinical exposure, a carcinogenicity risk could not be excluded.

Repeat-dose toxicity

In oral, repeat dose toxicity studies conducted for up to 3 months in rats and dogs, the primary toxicities due to MEK inhibition were in the skin and gastrointestinal tract at doses below human exposure. In the 3-month rat study with mirdametinib, at doses approximately equivalent to the human exposure, rats showed dysplasia in femoral epiphyseal growth plate, metaphyseal hypocellularity of the bone marrow of long bones, and metaphyseal thickening of bone trabeculae of long bones. Male rats were more sensitive to these effects. These bone effects were not seen in other species (dogs, monkeys or mice). Reversibility of dysplasia in epiphyseal growth plate was not evaluated. In rats, systemic mineralization and ocular findings (corneal opacities and atrophy or thinning of the corneal epithelium) were observed in repeat dose toxicity studies at doses below human exposure.
Increases in liver enzymes (rats) and hepatocellular necrosis (rats, mice, and dogs) were observed at exposures similar to clinical exposure. In a 2-week study in cynomolgus monkeys, gallbladder toxicity was observed at exposures > 2.5-fold the human exposure.
CNS effects were observed in dogs in the 3-month study at exposures approximately 1.5 times the human exposure; these effects in dogs, including impaired balance and tremors, were reversible and there was no microscopic correlate.

Reproductive and developmental toxicity

In a male and female rat fertility study, mirdametinib at a dose up to 1.0 mg/kg/day (approximately equivalent to the human exposure at the recommended dose based on AUC) did not affect mating performance or fertility in both sexes. In a 3-month repeat-dose toxicology study in rats, mirdametinib caused decreased ovarian organ weight and increased follicular cysts associated with decreases in the number of corpora lutea at doses ≥ 0.3 mg/kg/day (0.5 times the human exposure) as well as testicular hypocellularity and decreased weight of epididymides at 1 mg/kg/day (2.1 times the human exposure).
In preliminary embryo-foetal developmental toxicity studies in pregnant rats and rabbits, oral dosing of mirdametinib induced post-implantation loss (early and late resorptions) and decreased foetal body weights at exposures below the human exposures at the recommended dose. In the preliminary rat study, a single foetus had extremity malformations at doses 3.6-fold higher than the recommended human dose. Definitive embryo-foetal development and pre- and post-natal development studies were not conducted with mirdametinib.

Phototoxicity

Mirdametinib was equivocal in an *in vitro* mouse fibroblast phototoxicity assay at significantly higher concentrations than clinical exposures and was not retained in the skin or eyes of rats indicating that there is a low risk of phototoxicity in patients taking mirdametinib.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date marked as “EXP” on the pack.
Do not use this medicine six hours after dispersing tablet(s) in water.

Special precautions for storage

Do not store above 30°C.
Keep the container in the outer carton in order to protect the contents from light.
Keep out of reach of the children.

Instructions for handling

Preparation of the oral suspension

Patients should be instructed to fully disperse the prescribed number of dispersible tablet(s) in a small amount of drinking water (about 5 to 10 mL) in a dosing cup, if dosing as an oral suspension. The

liquid should be gently swirled until no lumps remain and administered orally. Alternatively, the liquid can be drawn into an oral syringe and administered.

Administration of oral suspension via dosing cup

After the suspension from the dosing cup or oral syringe is swallowed, the dosing cup (or syringe) should be rinsed with an additional small amount of drinking water (about 5 to 10 mL) and administered to ensure the full dose is taken. The dose should only be prepared using water.

Administration of oral suspension via enteral feeding tube

In case of administration using an enteral feeding tube, an appropriate commercially available gastric or nasogastric tube (8 French tube or larger) should be selected by the healthcare professional. Enteral feeding tubes made of polyvinylchloride (PVC) and polyurethane (PUR) have been shown to be compatible with the oral suspension. The oral suspension should be drawn into the syringe after dispersing in 5-10 mL of water as described above and injected into an enteral feeding tube with the syringe positioned horizontally. Following administration of the oral suspension, draw another 5-10 mL of water into the syringe and push that through the feeding tube to ensure any residual medication is administered to the patient.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

70392 (Swissmedic)

Packs

High-density polyethylene (HDPE) bottle, secured with child-resistant closure and aluminium foil induction seal. The bottles contain a cotton coil.
Each carton contains one bottle of 42 or 84 dispersible tablets. [A]
Not all pack sizes may be marketed.

Marketing authorisation holder

Merck (Schweiz) AG, Zug, an affiliate of Merck KGaA, Darmstadt, Germany

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March 2026