ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼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 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Ezmekly 1 mg hard capsules
Ezmekly 2 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ezmekly 1 mg hard capsules

Each hard capsule contains 1 mg of mirdametinib.

Ezmekly 2 mg hard capsules

Each hard capsule contains 2 mg of mirdametinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

Ezmekly 1 mg hard capsules

Size 3 (approximately 16 mm × 6 mm) capsule comprised of a light green opaque body and cap with ‘MIR 1 mg’ printed in white ink on the cap.

Ezmekly 2 mg hard capsules

Size 1 (approximately 19 mm × 7 mm) capsule comprised of a white opaque body and a blue-green opaque cap with ‘MIR 2 mg’ printed in white ink on the cap.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of 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).

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 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
Interruption and/or dose reduction or permanent discontinuation of Ezmekly may be required based on individual safety and tolerability (see sections 4.4 and 4.8). 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 reaction[a]	Recommended dose modification for Ezmekly
Ocular toxicity (see sections 4.4 and section 4.8)	
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.
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 4.4 and section 4.8)	
Asymptomatic, absolute decrease in LVEF less than 20% from baseline and is 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 4.4 and section 4.8)	
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 4.8)	
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 (see section 5.1).

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 5.2).

Hepatic impairment
No dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin > ULN to 1.5 x ULN or total bilirubin ≤ ULN and 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 5.2).

Paediatric population
The safety and efficacy of Ezmekly in children below 2 years of age have not been established. No data are available.

Method of administration

Ezmekly is for oral use.

The capsules can be taken with or without food (see section 5.2).

Ezmekly capsules should be swallowed whole with drinking water. The capsules should not be chewed, broken or opened to ensure the full dose is administered.

For paediatric patients 2 to <6 years of age and for patients who are unable to swallow whole capsules, Ezmekly is also available as a 1 mg dispersible tablet formulation that can be dispersed in water. Refer to the SmPC for Ezmekly dispersible tablets for method of administration.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 4.8).

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 4.2).

Decreased left ventricular ejection fraction (LVEF)

Asymptomatic decrease in LVEF ≥ 10% from baseline occurred in 17% 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 4.8).

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 4.2).

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 4.8).

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 4.2).

Carcinogenicity risk

A potential carcinogenicity risk in humans could not be excluded at the clinical exposure range (see section 5.3).

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 4.5 and 4.6). Both male and female patients (of reproductive potential) should be advised to use effective contraception.

Excipients with known effect

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

4.5 Interaction with other medicinal products and other forms of interaction

No clinical interaction studies have been performed (see section 5.2).

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 (UGTs inhibitors), rifampicin (UGT inducer) (see section 5.2).

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 4.6).

Effects of gastric acid reducing agents on mirdametinib

The combination of mirdametinib with proton-pump inhibitors, antacids, or H_2-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., H_2-receptor antagonists and proton pump inhibitors) without restrictions.

4.6 Fertility, pregnancy and 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 female and male patients (of reproductive potential) should be advised to use effective contraception during treatment and for 6 months and 3 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. Studies in animals have shown reproductive toxicity (see section 5.3). 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 5.3). There are no data on the effect of mirdametinib on human fertility. The potential risk for humans is unknown.

4.7 Effects on ability to drive and use machines

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 4.8). Patients who experience these symptoms should observe caution when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

In the 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 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 (3%)	-	Very Common (33%)	-
Nervous system disorders	Headache	Very common (16 %)	Common (1%)	Very common (36 %)	Common (2 %)
Eye disorders	Blurred vision	Common (9 %)	-	Common (7 %)	-
	Retinal vein occlusion	Common (3 %)	Common (1%)	-	-
	RPED (retinal pigment epithelial detachment)	Common (1 %)	-	-	-
Gastrointestinal disorders	Diarrhoea	Very common (55 %)	-	Very common (53 %)	Common (5 %)
	Nausea	Very common (55 %)	-	Very common (29 %)	-

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**
	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 (7 %)	-	-	-
	Stomatitis[b]	Common (5 %)	-	Very Common (1 9%)	-
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 %)	-
	Pruritus	Very common (13 %)	-	Very common (12 %)	-
	Eczema	Common (3 %)	-	Very common (14 %)	-
	Hair colour changes	Common (1 %)	-	Very common (12 %)	-
	Hair texture abnormal	Common (1 %)	-	Common (5 %)	-
Musculoskeletal and connective tissue disorders	Musculoskeletal pain [d]	Very common (41 %)	Common (7%)	Very common (41 %)	Common (2 %)

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**
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 %)
	AST increased	Very common (16 %)	-	Common (9 %)	-
	Blood alkaline phosphatase increased	Very common (14 %)	-	Very common (24 %)	-
	Ejection fraction decreased	Very common (12 %)	-	Very common (26 %)	Common (2 %)
	Neutrophil count decreased	Common (8 %)	Common (1%)	Very common (30 %)	Very common (11 %)
	Leukocyte count decreased	Common (7 %)	-	Very common (39 %)	-
	ALT increased	Common (7 %)	-	Very common (21 %)	-

[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 selected adverse reactions

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 4.2 and 4.4).

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 4.2 and 4.4).

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. Grade 3 dermatitis acneiform and non-acneiform rashes 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 4.2 and 4.4).

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 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 national reporting system listed in Appendix V.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents; Mitogen-activated protein kinase (MEK) inhibitors, ATC Code: L01EE05

Mechanism of action

Mirdametinib is a selective, non-competitive inhibitor of mitogen-activated protein kinase kinases 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.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies within one or more subsets of the paediatric population. See section 4.2 for information on paediatric use.

Conditional approval

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency (EMEA) will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetics of mirdametinib was studied in healthy subjects, NF1-PN patients and advanced cancer patients.

Absorption

Following multiple oral doses at 2 mg/m^2 twice daily, the geomean [geometric % coefficient of variation (CV)] C_{max} and 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 (AUCinf 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.

Biotransformation

Mirdametinib is highly metabolised via glucuronidation 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.

Interactions

Effect of mirdametinib on CYP450 enzymes
In vitro, mirdametinib is not an inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9 or CYP2C19. Mirdametinib is an inducer of CYP3A4 *in vitro*, however there is a low potential for CYP3A4 induction at clinically relevant concentrations.

Effect of mirdametinib on UDP glucuronosyltransferase (UGT)
In vitro, mirdametinib is not an inhibitor of the isoforms UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15 at clinically relevant concentrations.

Effect of mirdametinib on drug transporters
In vitro studies suggest that mirdametinib and its major metabolite do not inhibit the breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1 or MATE2K transporters.

Based on *in vitro* studies, mirdametinib is a substrate for BCRP and P-gp transporters and its major metabolite is a substrate for BCRP, but they are unlikely to be clinically relevant.

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.

Special populations

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 analysis 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.

5.3 Preclinical safety 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 GI 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 postimplantation 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 low risk for phototoxicity in patients taking mirdametinib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Microcrystalline cellulose (E460)
Croscarmellose sodium (E468)
Magnesium stearate (E572)

Capsule shell

Gelatin (E441)
Titanium dioxide (E171)
Yellow iron oxide (E172)
Brilliant blue (E133)

Printing ink

Potassium hydroxide (E525)
Propylene glycol (E1520)
Purified water
Shellac (E904)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

42 months.

6.4 Special precautions for storage

Store below 30°C.
Store in the original package to protect from light.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottle, secured with child-resistant closure and aluminium foil induction seal.

1 mg hard capsules are provided in a carton containing one bottle of 42 capsules.
2 mg hard capsules are provided in a carton containing one bottle of 42 or 84 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

SpringWorks Therapeutics Ireland Limited
Hamilton House, 28 Fitzwilliam Place
Dublin 2, D02 P283
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1950/003
EU/1/25/1950/004
EU/1/25/1950/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 July 2025

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼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 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Ezmekly 1 mg dispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains 1 mg of mirdametinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersible tablet.

Oval, white to off-white dispersible tablets (approximately 6 mm × 9 mm) debossed with 'S' on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of 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 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
Interruption and/or dose reduction or permanent discontinuation of Ezmekly may be required based on individual safety and tolerability (see sections 4.4 and 4.8). 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
$\geq$ 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 reaction[a]	Recommended dose modification for Ezmekly
Ocular toxicity (see sections 4.4 and section 4.8)	
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 4.4 and section 4.8)	
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 4.4 and section 4.8)	
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 4.8)	
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 (see section 5.1).

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 5.2).

Hepatic impairment
No dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin > ULN to 1.5x ULN or total bilirubin ≤ ULN and 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 5.2).

Paediatric population
The safety and efficacy of Ezmekly in children below 2 years of age have not been established. No data are available.

Method of administration

Ezmekly is for oral use.

The dispersible tablets can be taken with or without food (see section 5.2).

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 6.6 for instructions on preparation and administration of the oral suspension.

Ezmekly is also available as a 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 capsules.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 4.8).

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 4.2).

Decreased left ventricular ejection fraction (LVEF)

Asymptomatic decrease in LVEF ≥ 10% from baseline occurred in 17% 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 4.8).

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 4.2).

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 4.8).

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 4.2).

Carcinogenicity risk

A potential carcinogenicity risk in humans could not be excluded at the clinical exposure range (see section 5.3).

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 4.5 and 4.6). 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’.

4.5 Interaction with other medicinal products and other forms of interaction

No clinical interaction studies have been performed (see section 5.2).

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 5.2).

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 4.6).

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.

4.6 Fertility, pregnancy and 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 female and male patients (of reproductive potential) should be advised to use effective contraception during treatment and for 6 months and 3 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. Studies in animals have shown reproductive toxicity (see section 5.3). 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 5.3). There are no data on the effect of mirdametinib on human fertility. The potential risk for humans is unknown.

4.7 Effects on ability to drive and use machines

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 4.8). Patients who experience these symptoms should observe caution when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

In the 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 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 (3 %)	-	Very Common (33%)	-
Nervous system disorders	Headache	Very common (16 %)	Common (1%)	Very common (3 6%)	Common (2 %)
Eye disorders	Blurred vision	Common (9 %)	-	Common (7%)	-
	Retinal vein occlusion	Common (3 %)	Common (1%)	-	-
	RPED (retinal pigment epithelial detachment)	Common (1 %)	-	-	-
Gastrointestinal disorders	Diarrhoea	Very common (55 %)	-	Very common (5 3%)	Common (5 %)
	Nausea	Very common (55 %)	-	Very common (2 9%)	-
	Vomiting	Very common (37 %)	-	Very common (4 0%)	-

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**
	Abdominal pain[a]	Very common (20 %)	Common (4%)	Very common (4 0%)	Common (3 %)
	Constipation	Very common (19 %)	-	Very common (1 0%)	-
	Dry mouth	Common (7 %)	-	-	-
	Stomatitis[b]	Common (5 %)	-	Very Common (19%)	-
Skin and subcutaneous tissue disorders	Dermatitis acneiform	Very common (83 %)	Common (7%)	Very common (4 3%)	Common (2 %)
	Rash[c]	Very common (17 %)	Common (1%)	Very common (3 3%)	Common (2 %)
	Dry skin	Very common (13 %)	-	Very common (1 7%)	-
	Alopecia	Very common (12 %)	-	Very common (1 4%)	-
	Pruritus	Very common (13 %)	-	Very common (1 2%)	-
	Eczema	Common (3 %)	-	Very common (1 4%)	-
	Hair colour changes	Common (1 %)	-	Very common (1 2%)	-
	Hair texture abnormal	Common (1 %)	-	Common (5%)	-
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[d]	Very common (41 %)	Common (7%)	Very common (4 1%)	Common (2 %)
General disorders and administation site conditions	Fatigue	Very common (36 %)	Common (1%)	Very common (1 2%)	-
	Oedema peripheral[e]	Very common (12 %)	-	Common (5%)	-

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**
Investigations	Blood creatine phosphokinase increased	Very common (47 %)	Common (3%)	Very common (5 9%)	Common (5 %)
	AST increased	Very common (16 %)	-	Common (9%)	-
	Blood alkaline phosphatase increased	Very common (14 %)	-	Very common (2 4%)	-
	Ejection Fraction decreased	Very common (12 %)	-	Very common (2 6%)	Common (2 %)
	Neutrophil count decreased	Common (8 %)	Common (1%)	Very common (3 0%)	Very common (11 %)
	Leukocyte count decreased	Common (7 %)	-	Very common (3 9%)	-
	ALT increased	Common (7 %)	-	Very common (2 1%)	-

[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 selected adverse reactions

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 4.2 and 4.4).

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 4.2 and 4.4).

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. Grade 3 dermatitis acneiform and non-acneiform rashes 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 4.2 and 4.4).

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 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 national reporting system listed in Appendix V.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents; Mitogen-activated protein kinase (MEK) inhibitors, ATC Code: L01EE05

Mechanism of action

Mirdametinib is a selective, non-competitive inhibitor of mitogen-activated protein kinase kinases 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.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies within one or more subsets of the paediatric population. See section 4.2 for information on paediatric use.

Conditional approval

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency (EMEA) will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetics of mirdametinib was studied in healthy subjects, NF1-PN patients and advanced cancer patients.

Absorption

Following multiple oral doses at 2 mg/m^2 twice daily, the geomean [geometric % coefficient of variation (CV)] C_{max} and 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 (Tmax) 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 (AUCinf 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.

Biotransformation

Mirdametinib is highly metabolised via glucuronidation 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.

Interactions

Effect of mirdametinib on CYP450 enzymes
In vitro, mirdametinib is not an inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9 or CYP2C19. Mirdametinib is an inducer of CYP3A4 *in vitro*, however there is a low potential for CYP3A4 induction at clinically relevant concentrations.

Effect of mirdametinib on UDP glucuronosyltransferase (UGT)
In vitro, mirdametinib is not an inhibitor of the isoforms UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15 at clinically relevant concentrations.

Effect of mirdametinib on drug transporters
In vitro studies suggest that mirdametinib and its major metabolite do not inhibit the breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1 or MATE2K transporters.

Based on *in vitro* studies, mirdametinib is a substrate for BCRP and P-gp transporters and its major metabolite is a substrate for BCRP, but they are unlikely to be clinically relevant.

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.

Special populations

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 analysis 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.

5.3 Preclinical safety 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 GI 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 postimplantation 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 the eyes of rats indicating that there is a low risk of phototoxicity in patients taking mirdametinib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (E460)
Croscarmellose sodium (E468)
Sucralose (E955)
Magnesium stearate (E572)

Grape flavour
Dried glucose liquid
Natural flavour
Modified corn starch (E1422)
Triacetin (E1518)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years
Six hours after dispersing tablet(s) in water.

6.4 Special precautions for storage

Store below 30°C.
Store in the original package to protect from light.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottle, secured with child-resistant closure and aluminium foil induction seal. The bottles contain cotton coil.

One carton contains one bottle of 42 or 84 dispersible tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other 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.

7. MARKETING AUTHORISATION HOLDER

SpringWorks Therapeutics Ireland Limited
Hamilton House, 28 Fitzwilliam Place
Dublin 2, D02 P283
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1950/001
EU/1/25/1950/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 July 2025

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Mias Pharma Limited
Suite 1 First Floor, Stafford House
Strand Road, Portmarnock, D13 WC83
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex 1: Summary of Product Characteristics, section 4.2.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorization.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of mirdametinib in the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric and adult patients with neurofibromatosis type 1 (NF1) aged 2 years and above, the MAH should submit an updated analysis of the study MEK-NF-201 with a data cut-off of 22 December 2028 that will provide an additional 5 years of follow-up.	June 2029
Non-interventional post-authorisation safety study (PASS): In order to confirm the long-term safety of mirdametinib, in the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric and adult patients with neurofibromatosis type 1 (NF1) aged 2 years and above, the MAH should conduct and submit the results of a study conducted in patients with NF1 who have been prescribed at least one dose of mirdametinib and who are aged 2 and above at the start of mirdametinib.	August 2033

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CAPSULES 1 MG OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ezmekly 1 mg hard capsules
mirdametinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 1 mg mirdametinib

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule
42 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Do not break, crush or chew capsules.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.
Store in the original package to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SpringWorks Therapeutics Ireland Limited
Hamilton House, 28 Fitzwilliam Place
Dublin 2, D02 P283
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1950/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ezmekly 1 mg capsule

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

CAPSULES 1MG BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Ezmekly 1 mg capsules
mirdametinib

2. STATEMENT OF ACTIVE SUBSTANCE

Each capsule contains 1 mg mirdametinib

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Capsules
42 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Do not break, crush or chew capsules.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.
Store in the original package to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SpringWorks Therapeutics

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1950/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CAPSULES 2MG OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ezmekly 2 mg hard capsules
mirdametinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 2 mg mirdametinib

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule
42 hard capsules
84 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Do not break, crush or chew capsules.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.
Store in original package to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SpringWorks Therapeutics Ireland Limited
Hamilton House, 28 Fitzwilliam Place
Dublin 2, D02 P283
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1950/004 42 hard capsules
EU/1/25/1950/005 84 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ezmekly 2 mg capsule

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

CAPSULES 2MG BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Ezmekly 2 mg capsules
mirdametinib

2. STATEMENT OF ACTIVE SUBSTANCE

Each capsule contains 2 mg mirdametinib

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Capsules
42 capsules
84 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Do not break, crush or chew capsules.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.
Store in the original package to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SpringWorks Therapeutics

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1950/004 42 capsules
EU/1/25/1950/005 84 capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

DISPERSIBLE TABLETS 1MG OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ezmekly 1 mg dispersible tablets
mirdametinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dispersible tablet contains 1 mg mirdametinib

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersible tablet
42 dispersible tablets
84 dispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Swallow whole or disperse in water.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.
Store in the original package to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SpringWorks Therapeutics Ireland Limited
Hamilton House, 28 Fitzwilliam Place
Dublin 2, D02 P283
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1950/001 42 dispersible tablets
EU/1/25/1950/002 84 dispersible tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ezmekly 1 mg dispersible tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

DISPERSIBLE TABLETS 1MG BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Ezmekly 1 mg dispersible tablets
mirdametinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dispersible tablet contains 1 mg mirdametinib

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersible Tablet
42 dispersible tablets
84 dispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Swallow whole or disperse in water.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.
Store in the original package to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SpringWorks Therapeutics

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1950/001 42 dispersible tablets
EU/1/25/1950/002 84 dispersible tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Ezmekly 1 mg hard capsules
Ezmekly 2 mg hard capsules
mirdametinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you (or your child) start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ezmekly is and what it is used for

Ezmekly contains the active substance mirdametinib, and is a mitogen-activated protein kinase (MEK) inhibitor.

Ezmekly is used to treat plexiform neurofibromas in adults, adolescents, and children 2 years of age and older with a genetic condition called neurofibromatosis type 1 (NF1).

People with NF1 have a mutation (change) in the gene that encodes for the protein neurofibromin. This leads to a loss of this protein, which allows tumours to grow on the nerves in the body. Ezmekly works by blocking certain proteins involved in the growth of these tumour cells, which is expected to shrink them.

If you have any questions about how Ezmekly works or why this medicine has been prescribed for you, ask your doctor.

2. What you (or your child) need to know before you take Ezmekly

Do not take Ezmekly
- If you (or your child) are allergic to mirdametinib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Ezmekly, or if the following happen to you (or your child) while taking Ezmekly. Your doctor may decide to lower your dose, stop treatment temporarily or permanently:

- **Eye problems**
  Ezmekly can cause eye problems that can lead to blindness (see section 4 'Possible side effects'). A doctor (eye specialist) will have to check your vision (the vision of your child) before and regularly during treatment. Tell your doctor straight away if you get blurred vision, or any other changes to your vision during treatment.

- **Heart problems**
  Ezmekly can lower the amount of blood pumped by your heart (see section 4 'Possible side-effects'). In clinical studies of Ezmekly at the recommended dose, this did not cause any symptoms, however it can make you feel tired. Tell your doctor if you feel tired. Your doctor will check how well your heart works before and during your treatment with Ezmekly.

- **Skin rash**
  Skin rashes are very common with Ezmekly and can also become severe. Tell your doctor if you get a skin rash which may be bumpy or acne-like (see section 4 'Possible side effects'). Your doctor may provide guidance for managing your skin rash, including treatment (e.g., cream).

- **Pregnancy**
  Ezmekly is not recommended during pregnancy. Tell your doctor straight away if you or your partner becomes pregnant while taking this medicine. See 'Pregnancy, breast-feeding and fertility' section below.

Children younger than 2 years of age
Do not give Ezmekly to children younger than 2 years old. It has not been studied in this age group.

Other medicines and Ezmekly
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including herbal medicines while receiving Ezmekly.

Pregnancy, breast-feeding and fertility
Ezmekly is not recommended during pregnancy. It may cause harm to your unborn baby.

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Your doctor may ask you to take a pregnancy test before starting treatment.

You or your partner should not become pregnant while taking this medicine. If you are able to become pregnant, you must use effective contraception (birth control). See 'Contraception - information for women and men' below.
If you or your partner become pregnant during treatment, tell your doctor straight away.

Contraception – information for women and men
If you are a woman who could become pregnant, you should use effective contraception while you are taking this medicine and for 6 months after the last dose. If you are a man whose partner could become pregnant, you should use effective contraception while you are taking this medicine and for 3 months after the last dose. It is not known if Ezmekly reduces how well hormonal contraceptives work. Please tell your doctor if you or your partner are taking a hormonal contraceptive, as your doctor may recommend using a second form of birth control (e.g. condoms).

Breast-feeding
It is not known if Ezmekly passes into breast milk. A risk to the breast-fed child cannot be excluded. Do not breast-feed if you are taking Ezmekly and for one week after the last dose of Ezmekly.

Fertility (ability to have children)
Ezmekly may reduce fertility in men and women. You should discuss this with your doctor before starting treatment.

Driving and using machines
Ezmekly can cause side effects, including fatigue (feeling tired or weak) and blurred vision (see section 4 'Possible side-effects'), that may affect your ability to drive or use machines. Do not drive or use machines if you feel tired or if you have problems with your vision (such as blurred vision).

Ezmekly contains sodium
Each capsule contains less than 23 mg sodium (main component of cooking/table salt), that is to say it is essentially 'sodium-free'.

3. How to take Ezmekly

Always take this medicine exactly as your doctor or pharmacist told you. Check with your doctor or pharmacist if you are not sure.

How much to take
Your doctor will work out the correct dose for you (or your child) based on your height and weight. The maximum recommended dose is 8 mg a day (4 mg every 12 hours). The doctor will tell you how many capsules of Ezmekly to take.

How to take
- Take Ezmekly by mouth twice a day, about 12 hours apart. You should take this medicine every day for 21 days, and then stop taking it for 7 days. Each 28-day period is called a treatment cycle.
- Take Ezmekly with or without food.
- Swallow the capsules whole with water.
- Do not chew, break or open the capsules
- You can continue taking this medicine in treatment cycles until your disease gets worse or side effects become unacceptable. If you get side effects, your doctor may decide to lower your dose, stop treatment temporarily or permanently (see section 2 'Warnings and precautions').
- Ezmekly is also available as a dispersible tablet. Your doctor will determine the correct formulation for you.

If you (or your child) are sick after taking Ezmekly
If you are sick (vomit) at any time after taking Ezmekly, do not take an extra dose. Take the next dose at the normal time.

If you (or your child) take more Ezmekly than you should
If you have taken more Ezmekly than you should, contact your doctor or pharmacist immediately.

If you (or your child) forget to take Ezmekly
If you forget to take a dose of Ezmekly, skip the missed dose and then take the next dose at the normal time. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

If you (or your child) stop taking Ezmekly
Do not stop taking Ezmekly unless your doctor tells you as it may worsen your condition.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Contact your doctor if you experience any side effects. Your doctor may pause treatment with Ezmekly until your symptoms improve and/or they may reduce the dose you receive (see Section 3 “How to take”).

Serious side effects

Eye problems (common: may affect up to 1 in 10 people)
Ezmekly can cause eye problems in adults and children. Some of these eye problems may lead to a blockage of the vein draining to the eye (retinal vein occlusion or detachment of different layers of the eye (retinal pigment epithelial detachment)). Tell your doctor straight away if you get blurred vision or any other changes to your sight during treatment. Your doctor may ask you to stop taking this medicine or send you to a specialist, if you develop symptoms that include:

- blurred vision
- other changes to your vision (such as reduced vision, coloured dots in your vision)

Tell your doctor straight away if you notice any of the serious side effects above.

Other side effects
Talk to your doctor if you get any of the following side effects.

Adults

Very common (may affect more than 1 in 10 people):

- skin rash with a flat discoloured area or raised acne-like bumps (dermatitis acneiform)
- diarrhoea
- increased blood levels of creatine phosphokinase, an enzyme found mainly in heart, brain and skeletal muscle
- feeling sick (nausea)
- being sick (vomiting)
- pain in muscles or bone
- feeling tired, weak or lacking energy (fatigue)
- stomach (abdominal) pain
- constipation
- rash
- headache
- increased levels of liver enzymes, as shown in blood tests
- swelling of the hands or feet (oedema peripheral)
- a decrease in the amount of blood that the heart is pumping (decreased left ventricular ejection fraction)
- dry skin
- itching
- hair loss or thinning (alopecia)

Common (may affect up to 1 in 10 people):

- decreased blood levels of neutrophils and leukocytes (types of white blood cells that help fight infections)
- mouth sores (stomatitis)
- dry mouth
- infection around the nails (paronychia)
- dry or itchy skin rash (eczema)
- changes in hair color

- changes in hair texture

Paediatrics

Very common (may affect more than 1 in 10 people):
- increased blood levels of creatine phosphokinase, an enzyme found mainly in heart, brain, and skeletal muscle
- diarrhoea
- skin rash with a flat discoloured area or raised acne-like bumps (dermatitis acneiform)
- pain in muscles or bone
- stomach (abdominal) pain
- feeling sick (nausea)
- being sick (vomiting)
- a decrease in the amount of blood that the heart is pumping (decreased ejection fraction)
- headache
- rash
- infection around the nails (paronychia)
- decreased blood levels of neutrophils and leukocytes (types of white blood cells that help fight infections)
- mouth sores (stomatitis)
- increased levels of liver enzymes as shown in blood tests
- dry skin
- hair loss or thinning (alopecia)
- dry or itchy skin rash (eczema)
- itching
- changes in hair color
- feeling tired, weak or lacking energy (fatigue)
- constipation

Common (may affect up to 1 in 10 people):
- changes in hair texture
- swelling of the hands or feet (oedema peripheral)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Ezmekly

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.

Store below 30°C. Store in the original package to protect from light.

Do not throw away your medicine via wasterwater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ezmekly contains

The active substance is mirdametinib.

Ezmekly 1 mg hard capsules
Each hard capsule contains 1 mg of mirdametinib.

Ezmekly 2 mg hard capsules
Each hard capsule contains 2 mg mirdametinib.

The other ingredients are:

Capsule content
Microcrystalline cellulose (E460)
Croscarmellose sodium (E468) (see section 2 ‘Ezmekly contains sodium’)
Magnesium stearate (E572)

Capsule shell
Gelatin (E441)
Titanium dioxide (E171)
Yellow iron oxide (E172)
Brilliant blue (E133)

Printing ink
Potassium hydroxide (E525)
Propylene glycol (E1520)
Purified water
Shellac (E904)
Titanium dioxide (E171)

What Ezmekly looks like and contents of the pack

Ezmekly 1 mg hard capsules (capsules)
Capsule comprised of a light green opaque body and cap with ‘MIR 1 mg’ printed in white ink on the cap.

Ezmekly 2 mg hard capsules (capsules)
Capsule comprised of a white opaque body and a blue-green opaque cap with ‘MIR 2 mg’ printed in white ink on the cap.

Ezmekly is packaged in plastic bottles, secured with child-resistant closures and aluminium foil induction seals.

Ezmekly 1 mg hard capsules are provided in a carton box containing one bottle of 42 capsules.
Ezmekly 2 mg hard capsules are provided in a carton box containing one bottle of 42 or 84 capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

SpringWorks Therapeutics Ireland Limited
Hamilton House, 28 Fitzwilliam Place
Dublin 2, D02 P283
Ireland
Tel: +49 800 428 3289

Manufacturer

Mias Pharma Limited
Suite 1 First Floor, Stafford House
Strand Road, Portmarnock, D13 WC83
Ireland

This leaftlet was last revised in

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine. The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

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Package leaflet: Information for the patient

Ezmekly 1 mg dispersible tablets
mirdametinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you (or your child) start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you (or your child) only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ezmekly is and what it is used for

Ezmekly contains the active substance mirdametinib, and is a mitogen-activated protein kinase (MEK) inhibitor.

Ezmekly is used to treat plexiform neurofibromas in adults, adolescents, and children 2 years of age and older with a genetic condition called neurofibromatosis type 1 (NF1).

People with NF1 have a mutation (change) in the gene that encodes for the protein neurofibromin. This leads to the loss of this protein, which allows the tumours to grow on the nerves in the body. Ezmekly works by blocking certain proteins involved in the growth of these tumour cells, which is expected to shrink them.

If you have any questions about how Ezmekly works or why this medicine has been prescribed for you, ask your doctor.

2. What you (or your child) need to know before you take Ezmekly

Do not take Ezmekly
If you (or your child) are allergic to mirdametinib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Ezmekly, or if the following happen to you (or your child) while taking Ezmekly. Your doctor may decide to lower the dose, stop treatment temporarily or permanently:

Eye problems
Ezmekly can cause eye problems that can lead to blindness (see section 4 'Possible side effects'). A doctor (eye specialist) will have to check your vision (the vision of your child) before and regularly during treatment. Tell your doctor straight away if you get blurred vision, or any other changes to your vision during treatment.

Heart problems
Ezmekly can lower the amount of blood pumped by your heart (see section 4 'Possible side-effects'). In clinical studies of Ezmekly at the recommended dose, this did not cause any symptoms, however it can make you feel tired. Tell your doctor if you feel tired. Your doctor will check how well your heart works before and during your treatment with Ezmekly.

Skin rash
Skin rashes are very common with Ezmekly and can also become severe. Tell your doctor if you get a skin rash which may be bumpy or acne-like (see section 4 'Possible side effects'). Your doctor may provide guidance for managing your skin rash, including treatment (e.g. cream).

Pregnancy
Ezmekly is not recommended during pregnancy. Tell your doctor straight away if you or your partner becomes pregnant while taking this medicine. See 'Pregnancy, breast-feeding and fertility' section below.

Children younger than 2 years of age
Do not give Ezmekly to children younger than 2 years old. It has not been studied in this age group.

Other medicines and Ezmekly
Tell your doctor or pharmacist if you (or your child) are taking, have recently taken or might take any other medicines, including herbal medicines while receiving Ezmekly.

Pregnancy, breast-feeding and fertility
Ezmekly is not recommended during pregnancy. It may cause harm to your unborn baby.

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Your doctor may ask you to take a pregnancy test before starting treatment.

You or your partner should not become pregnant while taking this medicine. If you are able to become pregnant, you must use effective contraception (birth control). See 'Contraception - information for women and men' below.
If you or your partner become pregnant during treatment, tell your doctor straight away.

Contraception – information for women and men
If you are a woman who could become pregnant, you should use effective contraception while you are taking this medicine and for 6 months after the last dose. If you are a man whose partner could become pregnant, you should use effective contraception while you are taking this medicine and for 3 months after the last dose. It is not known if Ezmekly reduces how well hormonal contraceptives work. Please tell your doctor if you or your partner are taking a hormonal contraceptive, as your doctor may recommend using a second form of birth control (e.g. condoms).

Breast-feeding
It is not known if Ezmekly passes into breast milk. A risk to the breast-fed child cannot be excluded. Do not breast-feed if you are taking Ezmekly and for one week after the last dose of Ezmekly.

Fertility (ability to have children)
Ezmekly may reduce fertility in men and women. You should discuss this with your doctor before starting treatment.

Driving and using machines
Ezmekly can cause side effects, including fatigue (feeling tired or weak) and blurred vision (see section 4 'Possible side-effects'), that may affect your ability to drive or use machines. Do not drive or use machines if you feel tired or if you have problems with your vision (such as blurred vision).

Ezmekly contains sodium
Each dispersible tablet contains less than 23 mg sodium (main component of cooking/table salt), that is to say it is essentially 'sodium-free'.

3. How to take Ezmekly

Always take this medicine exactly as your doctor or pharmacist told you. Check with your doctor or pharmacist if you are not sure.

How much to take
Your doctor will work out the correct dose for you (or your child) based on your height and weight. The maximum recommended dose is 8 mg a day (4 mg every 12 hours). The doctor will tell you how many tablets of Ezmekly to take.

How to take
- Take Ezmekly by mouth twice a day, about 12 hours apart. You should take this medicine every day for 21 days, and then stop taking it for 7 days. Each 28-day period is called a treatment cycle.
- Take Ezmekly with or without food.
- You can continue taking this medicine in treatment cycles until your disease gets worse or side effects become unacceptable. If you get side effects, your doctor may decide to lower your dose, stop treatment temporarily or permanently (see section 2 'Warnings and precautions').

The dispersible tablets can be either:
1) Swallowed whole with drinking water. Do not split tablets.

OR

2) Dispersed in drinking water. Follow these instructions for dispersing the tablet:
   a) A dosing cup (and a 10 mL syringe if necessary), provided by your doctor or pharmacist can be used to prepare and administer the medicine.
   b) Disperse the prescribed number of dispersible tablets in a small amount (about 5-10 mL) of drinking water in the dosing cup.
   c) Swirl gently so that no lumps remain. Take care not to spill any medicine. The medicine will be white and cloudy.
   d) Administer the prepared medicine by mouth. Alternatively, the medicine can be drawn up from the dosing cup into a syringe and administered.
   e) After swallowing the suspension, there may be some medicine (residue) still inside the dosing cup or syringe that is difficult to see.
   f) Rinse the container with an additional small amount (about 5-10 mL) of drinking water and administer.
   g) Only water should be used to disperse the dispersible tablet.

OR

3) Administered via feeding tube
   a) Always talk to your doctor or pharmacist before administering Ezmkely suspension via a feeding tube. Your doctor, nurse or pharmacist should show you how to administer Ezmekly suspension via a feeding tube.
   b) Ezmekly suspension can be administered via a nasogastric (NG) or gastric (G) feeding tube of size French 8 or greater.
   c) Only use feeding tubes made of polyvinylchloride (PVC) or polyurethane (PUR).
   d) You may need an ENFIT adapter to connect the syringe to the feeding tube.

e) Follow steps above to disperse the tablet appropriately.
f) After dispersing the tablet in 5-10 mL of water, the oral suspension should be drawn up from the dosing cup into a syringe.
g) Slowly push the suspension into the feeding tube while holding the syringe in a horizontal position.
h) Use another 5-10 mL water to rinse the cup and draw the rinsate into the syringe and slowly push that through the feeding tube.
i) Flush the feeding tube according to the manufacturer's instructions immediately before and after administering Ezmekly suspension.

If you (or your child) are sick after taking Ezmekly
If you are sick (vomit) at any time after taking Ezmekly, do not take an extra dose. Take the next dose at the normal time.

If you (or your child) take more Ezmekly than you should
If you have taken more Ezmekly than you should, contact your doctor or pharmacist immediately.

If you (or your child) forget to take Ezmekly
If you forget to take a dose of Ezmekly, skip the missed dose and then take the next dose at the normal time. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

If you (or your child) stop taking Ezmekly
Do not stop taking Ezmekly unless your doctor tells you as it may worsen your condition

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Contact your doctor if you experience any side effects. Your doctor may pause treatment with Ezmekly until your symptoms improve and/or they may reduce the dose you receive (see Section 3 'How to take').

Serious side effects
Eye problems (common: may affect up to 1 in 10 people)

Ezmekly can cause eye problems in adults and children. Some of these eye problems may lead to a blockage of the vein draining to the eye (retinal vein occlusion) or detachment of different layers of the eye (retinal pigment epithelial detachment). Tell your doctor straight away if you get blurred vision or any other changes to your sight during treatment. Your doctor may ask you to stop taking this medicine or send you to a specialist, if you develop symptoms that include:
- blurred vision
- other changes to your vision (such as reduced vision, coloured dots in your vision)

Tell your doctor straight away if you notice any of the serious side effects above.

Other side effects
Talk to your doctor if you get any of the following side effects.

<u>Adults</u>
Very common (may affect more than 1 in 10 people):
- skin rash with a flat discoloured area or raised acne-like bumps (dermatitis acneiform)
- diarrhoea
- increased blood levels of creatine phosphokinase, an enzyme found mainly in heart, brain, and skeletal muscle

- feeling sick (nausea)
- being sick (vomiting)
- pain in the muscles or bone
- feeling tired, weak or lacking energy (fatigue)
- stomach (abdominal) pain
- constipation
- rash
- headache
- increased levels of liver enzymes, as shown in blood tests
- swelling of the hands or feet (oedema peripheral)
- a decrease in the amount of blood that the heart is pumping (decreased left ventricular ejection fraction)
- dry skin
- itching
- hair loss or thinning (alopecia)

Common (may affect up to 1 in 10 people):
- decreased blood levels of neutrophils and leukocytes (types of white blood cells that help fight infections)
- mouth sores (stomatitis)
- dry mouth
- infection around the nails (paronychia)
- dry or itchy skin rash (eczema)
- changes in hair color
- changes in hair texture

Paediatrics
Very common (may affect more than 1 in 10 people):
- increased blood levels of creatine phosphokinase, an enzyme found mainly in heart, brain, and skeletal muscle
- diarrhoea
- skin rash with a flat discoloured area or raised acne-like bumps (dermatitis acneiform)
- pain in muscles or bone
- stomach (abdominal) pain
- feeling sick (nausea)
- being sick (vomiting)
- a decrease in the amount of blood that the heart is pumping (decreased ejection fraction)
- headache
- rash
- infection around the nails (paronychia)
- decreased blood levels of neutrophils and leukocytes (types of white blood cells that help fight infections)
- mouth sores (stomatitis)
- increased levels of liver enzymes as shown in blood tests
- dry skin
- hair loss or thinning (alopecia)
- dry or itchy skin rash (eczema)
- itching
- changes in hair color
- feeling tired, weak or lacking energy (fatigue)
- constipation

Common (may affect up to 1 in 10 people):
- changes in hair texture
- swelling of the hands or feet (oedema peripheral)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Ezmekly

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.

Store below 30°C. Store in the original package to protect from light. After dispersing the tablet (s) in water, suspension is stable up to 6 hours.

Do not throw away your medicine via wasterwater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ezmekly contains
The active substance is mirdametinib.

Each dispersible tablet contains 1 mg mirdametinib.

The other ingredients are:

Microcrystalline cellulose (E460)
Croscarmellose sodium (E468) (see section 2 ‘Ezmekly contains sodium’)
Sucralose (E955)
Magnesium stearate (E572)

Grape flavour:
Dried glucose liquid
Natural flavour
Modified corn starch (E1422)
Triacetin (E1518)

What Ezmekly looks like and contents of the pack

Ezmekly 1 mg dispersible tablets
Oval, white to off-white dispersible tablets 6 × 9 mm, debossed with ‘S’ on one side.

Ezmekly is packaged in plastic bottles, secured with child-resistant closures and aluminium foil induction seals. The bottles include cotton coil.

Ezmekly 1 mg dispersible tablets are provided in a carton box containing one bottle of 42 or 84 dispersible tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
SpringWorks Therapeutics Ireland Limited
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Tel: +49 800 428 3289

Manufacturer
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Suite 1 First Floor, Stafford House
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Ireland.

This leaflet was last revised in

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine. The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

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ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.