# 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

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ezmekly 1 mg hard capsules

Each hard capsule contains 1 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.

## 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 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 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 4.8) | |
| Grade 1 or 2 dermatitis acneiform or non-acneiform rash | Continue treatment. |
| Intolerable Grade 2 or Grade 3 | Interrupt treatment until improvement. |

| **Severity of adverse reaction**[a] | **Recommended dose modification for Ezmekly** |
|---|---|
| dermatitis acneiform or non-acneiform rash | Resume at reduced dose (see Table 2). |
| Grade 3 or Grade 4 dermatitis acneiform or non-acneiform rash | Interrupt treatment until improvement.<br>Resume at reduced dose (see Table 2). |
| Other adverse reactions (see Section 4.8) | |
| Intolerable Grade 2 or Grade 3 | Interrupt treatment until improvement.<br>Resume at reduced dose (see Table 2). |
| Grade 4 | Interrupt treatment until improvement.<br>Resume at reduced dose (see Table 2).<br>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 $\geq$ 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%) | - |
| | 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 | - | Very Common | - |

| 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 |
| | | (5%) | | (19%) | |
| 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%) |
| General disorders and administation site conditions | Fatigue | Very common (36%) | Common (1%) | Very common (12%) | - |
| | 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 (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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search MHRA Yellow Card in the Google Play or Apple App Store.

### 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/m2 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%) |

| | Adult (N=58) | Paediatric (N=56) |
|---|---|---|
| **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 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 Agency 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/m2 twice daily, the geomean [geometric % coefficient of variation (CV)] Cmax and AUClast 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 Cmax, while the area under the concentration-time curve (AUC) was not significantly changed (AUCinf decreased by 7%). The time to reach maximum concentration (Tmax) was delayed by approximately 3 hours. The effect on Cmax is not considered clinically relevant due to the absence of effect on overall exposure.

Distribution

Following a single oral dose of 4 mg [14C] 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 Cmax and AUCtau, 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

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)

PL 59369/0004

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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## 10 DATE OF REVISION OF THE TEXT

11/12/2025