Report EZMEKLY® - Mirdametinib

Product & Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance: Mirdametinib **Brand Name:** Ezmekly **Originator/licensee:** Springworks Therapeutics Ireland Limited **Classification:** NCE **ATC code:** L01EE **Orphan Status:** **Eu:** Yes **Us:** Yes **Mechanism of action:** mirdametinib is a selective, non-competitive MEK 1/2 inhibitor. By inhibiting MEK, mirdametinib blocks the proliferation and survival of tumour cells, in which the rapidly accelerated fibrosarcoma -MEK-extracellular related kinase pathway is activated [1].	**Authorized Indication:** **EMA**: Mirdametinib as monotherapy is indicated for the treatment of symptomatic, inoperable PN in paediatric and adult pts. with NF1 aged ≥2 years [1]. **FDA:** Mirdametinib is indicated for the treatment of adult and paediatric pts. ≥2 years of age NF1 who have symptomatic PN not amenable to complete resection [2]. **Route of administration:** IV **Licensing status** **EU CHMP P.O. date:** 22/05/2025 **FDA M.A. date:** 11/02/2025 **EU Speed Approval Pathway:** No **FDA Speed Approval Pathway:** Yes ----- **ABBREVIATIONS:** **AE**: Adverse Event **BICR**: blinded independent central review **BID**: twice daily **CHMP**: Committee for Medicinal Products for Human Use **CI**: Confidential Interval **ECOG**: Eastern Cooperative Oncology Group **HR**: Hazard Ratio **IV**: Intravenously **M.A.:** Marketing Authorization **MEK**: mitogen-activated protein kinase **NA**: Not applicable **NF1**: neurofibromatosis type 1 **ORR:** overall response rate **PFS**: Progression-Free Survival **PN**: plexiform neurofibromas **P.O.**: Positive Opinion **PS**: Performance Status **Pts**: Patients **TRAE**: Treatment related AEs **WHO**: World Health Organization	**Summary of clinical EFFICACY:** **ReNeu (NCT NA)** is an open-label, multicentre, pivotal, phase II b trial of mirdametinib in adults and children with NF1-PN causing significant morbidities. Eligible pts. were ≥2 years of age with symptomatic, inoperable PN associated with NF1, which could not be completely surgically resected without a substantial risk of morbidity. Adults and children were enrolled in separate cohorts. Pts. (n=114, n=58 adults, n=56 children) received ≥1 dose of mirdametinib. Mirdametinib was administered as a capsule or tablet for oral suspension, at a dose of 2 mg/m2 (maximum dose, 4 mg) orally BID in 28-day cycles, on an intermittent dosing schedule of three weeks on, one week off, with no fasting requirement. The primary efficacy endpoint was ORR, defined as the percentage of pts. achieving either a complete response or a partial response (at least a 20% reduction in NP volume) assessed by BICR. End points were analysed separately for adults and children. Twenty-four adults (41%; 95% CI, 29 to 55) and twenty-nine children (52%;95%CI, 38 to 65) achieved a confirmed objective response by BICR, with a median best percentage change in target PN volume of -41% (range, –90 to 13) and –42% (range, –91 to 48), respectively [3]. **Summary of clinical SAFETY:** All adults reported ≥1 AE, and 98% experienced an AE that was deemed by investigators to be related to study treatment, with the majority being of grade 1 or 2. Treatment-related adverse events (TRAEs) reported in ≥20% of adults were dermatitis acneiform (78%), diarrhoea (48%), nausea (36%), vomiting (28%), and fatigue (21%). One serious TRAE occurred: a grade 3 retinal vein occlusion that resulted in treatment discontinuation. There was one non–treatment-related death because of COVID-19 disease. All children reported ≥1 AE, and 95% experienced an AE that was determined by an investigator to be related to study treatment, with the majority being of grade 1 or 2. TRAEs occurring in ≥20% of children were dermatitis acneiform (43%), diarrhoea (38%), paronychia (30%), nausea (21%), ejection fraction decreased (20%), and increased blood creatinine phosphokinase (20%) [3]. **Ongoing studies:** ● ***For the same indication:*** Yes ● ***For other indications:*** Yes **Discontinued studies (for the same indication):** No --- **References:** [1] https://www.ema.europa.eu/en/medicines/human/EPAR/ezmekly [2] https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219379Orig1s000lbl.pdf [3] https://ascopubs.org/doi/10.1200/JCO.24.01034 [4] https://pmc.ncbi.nlm.nih.gov/articles/PMC10500831/ [5] https://pmc.ncbi.nlm.nih.gov/articles/PMC10666383/ [6] https://pubmed.ncbi.nlm.nih.gov/35657359/	**Cost of therapy:** The price is not available yet. **Epidemiology:** NF1 is one of the most common autosomal dominant disorders, with an estimated minimum prevalence between 1 in 3,000 to 1 in 4,000 people and an incidence of 1 in 2,500 [4]. PN occur in 30–50% of pts with NF1 [5]. ---- **POSSIBLE PLACE IN THERAPY**: The standard treatment for NF1 -associated PN involves a multidisciplinary approach. Surgery represents the preferred option, when feasible. Recently, targeted therapies, such as MEK inhibitors (e.g., selumetinib), have demonstrated efficacy in reducing the tumour volume [6]. The addition of Mirdametinib to these regimens could represent a further opportunity for these pts. **OTHER INDICATIONS IN DEVELOPMENT:** Solid tumour (NCT05054374; NCT03905148) **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT**: - **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:** Tipifarnib (NCT00021541); Pirfenidone (NCT00076102); Cabozantinib (NCT02101736); Sorafenib (NCT00727233); FCN-159 (NCT05913037); *Service reorganization: No *Possible off label use: Yes

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