CLINUVEL

ASX ANNOUNCEMENT

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ASX: CUV | **Börse Frankfurt**: UR9 | **ADR Level 1**: CLVLY

SCENESSE® European Orphan Drug Designation for Xeroderma Pigmentosum (XP)

Summary

- European Medicines Agency grants orphan drug designation for afamelanotide in xeroderma pigmentosum
- Committee for Orphan Medicinal Products assessed four key criteria fulfilled by CLINUVEL:
    1. XP prevalence to be 1 per 450,000
    2. clinical data generated on reducing DNA skin damage
    3. high unmet need due to lack of any treatment to date
    4. life threatening nature
- ODD status provides financial, regulatory, and commercial incentives
- Fifth European ODD for afamelanotide

CLINUVEL's drug afamelanotide has received a positive opinion for an orphan drug designation (ODD) from the European Medicines Agency (EMA) for the treatment of xeroderma pigmentosum (XP).

The ODD acknowledges afamelanotide's potential to treat or prevent ultraviolet (UV) skin damage and enhance DNA repair in the genetic disorder XP. CLINUVEL submitted clinical data from its ongoing DNA Repair Program to support this ODD submission, marking the first time these data have been reviewed by a global regulator.

Orphan drug designation

The EMA's Committee for Orphan Medicinal Products (COMP) acknowledged that there is currently neither a cure for XP, nor are medicines authorised for the condition, while the submitted data indicated a new way to reduce UV skin damage.

In recent years, the EMA has evolved its approach to ODDs so that it can more rigorously assess the real-world plausibility for future use of medicinal products, insisting that sponsors submit clinical data to support any claims of efficacy. The COMP then assesses clinical data alongside other evidence to determine the eligibility of the product for ODD.

The ODD granted to afamelanotide for XP entitles CLINUVEL to receive incentives throughout the development program and, importantly, post-authorisation. This includes reduced fees for regulatory activities and ten years of market exclusivity post-approval. As SCENESSE® (afamelanotide 16mg) is already an approved

medication, marketing authorisation for XP would be added as a label extension (type II variation) for the drug, rather than through a completely new authorisation application process.

Generally, an ODD is granted for drugs which treat, prevent, or diagnose a life-threatening or chronically debilitating disorder affecting less than 5 in 10,000 individuals within the European Union. The designation also recognises that no satisfactory treatment, preventative or diagnostic exists or, if it does, that the designated intervention presents as a significant benefit to patients.

Afamelanotide to assist UV-provoked DNA skin damage

The proposed mechanism of action of afamelanotide – as a potent MC1R agonist – is to protect the genome against UV radiation (UVR) damage and repair UV-induced photodamage in the skin through five key mechanisms: elimination of photoproducts, optimisation of melanocyte signalling, antioxidative effects, enhancement of DNA repair via nucleotide excision repair (NER), and increased melanisation (pigmentation of the skin).

Commentary

“After two previous attempts in XP, I have seen the persistence of my regulatory team rewarded by an ODD for afamelanotide, opening the regulatory pathway for further interaction on final study design and expansion of our existing marketing label,” CLINUVEL’s Senior VP Regulatory Affairs, Dr Rose Quadbeck-Diel said.

“The EMA have now conducted their first review of evidence acknowledging that afamelanotide reduced photodamage provoked by ultraviolet (UV) radiation and activated relevant cellular DNA repair mechanisms in XPC and XPV patients, who are at highest risk of UV-induced skin cancers. The next step in 2024 is to analyse an additional set of clinical data before seeking an important meeting with the EMA to secure a path to market.”

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Background Xeroderma Pigmentosum (XP)

XP is a rare life-threatening inherited disorder (comprising seven complementation groups, XPA-XPG, and one variant, XPV) characterised by defects in the body’s own system to repair damage due to UV light. The median age at first melanoma is 22 years, versus 55 years in the general population. The risk for non-melanoma skin cancer, either basal cell or squamous cell carcinoma, is increased 10,000-fold, with a median age at first onset of nine years, in contrast to 67 years in the general population. Without photoprotection, XPC patients usually die before the age of 20 years due to metastatic skin cancer. UV damage to the eyes can result in loss of vision and ocular cancer. Rigorous photoprotective measures limit daytime activities and impact socio-psychological development. 25% of patients present with neurodegenerative symptoms, such as ataxia, sensorineural deafness, areflexia, microcephaly and intellectual deficiency. There are no current methods to prevent neurological symptoms.

A therapy providing systemic photoprotection, reducing photodamage, and assisting DNA skin repair – nucleotide excision repair (NER) and base excision repair (BER) – would be of high value to these patients. This therapeutic approach bears relevance for a wider population at higher risk of skin cancers.

XP is chronically debilitating due to rigorous photoprotective measures (complete body cover and isolation from outdoors) limit daytime activities and impact socio-psychological development, the need for surgical removal of precancerous lesions and skin cancer, and the appearance of neurologic abnormalities in some patients. The severe forms can present with short stature, gonadal hypoplasia, and neurodevelopmental disability. The condition is life-threating due to the increased risk of melanomas and non-melanoma skin cancers at a young age.

About CLINUVEL PHARMACEUTICALS LIMITED

CLINUVEL (ASX: CUV; ADR LEVEL 1: CLVLY; Börse Frankfurt: UR9) is a global specialty pharmaceutical group focused on developing and commercialising treatments for patients with genetic, metabolic, systemic, and life-threatening, acute disorders, as well as healthcare solutions for specialised populations. As pioneers in photomedicine and the family of melanocortin peptides, CLINUVEL’s research and development has led to innovative treatments for patient populations with a clinical need for systemic photoprotection, assisted DNA repair, repigmentation and acute or life-threatening conditions who lack alternatives.

CLINUVEL's lead therapy, SCENESSE® (afamelanotide 16mg), is approved for commercial distribution in Europe, the USA, Israel, and Australia as the world's first systemic photoprotective drug for the prevention of phototoxicity (anaphylactoid reactions and burns) in adult patients with erythropoietic protoporphyria (EPP). Headquartered in Melbourne, Australia, CLINUVEL has operations in Europe, Singapore, and the USA. For more information, please go to https://www.clinuvel.com.

Authorised for ASX release by the Board of Directors of CLINUVEL PHARMACEUTICALS LTD.

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Forward-Looking Statements

This release contains forward-looking statements, which reflect the current beliefs and expectations of CLINUVEL's management. Statements may involve a number of known and unknown risks that could cause our future results, performance, or achievements to differ significantly from those expressed or implied by such forward-looking statements. Important factors that could cause or contribute to such differences include risks relating to: our ability to develop and commercialise pharmaceutical products; the COVID-19 pandemic and/or other world, regional or national events affecting the supply chain for a protracted period of time, including our ability to develop, manufacture, market and sell biopharmaceutical products; competition for our products, especially SCENESSE® (afamelanotide 16mg), PRÉNUMBRA® or NEURACTHEL®; our ability to achieve expected safety and efficacy results in a timely manner through our innovative R&D efforts; the effectiveness of our patents and other protections for innovative products, particularly in view of national and regional variations in patent laws; our potential exposure to product liability claims to the extent not covered by insurance; increased government scrutiny in either Australia, the U.S., Europe, Israel, China and Japan of our agreements with third parties and suppliers; our exposure to currency fluctuations and restrictions as well as credit risks; the effects of reforms in healthcare regulation and pharmaceutical pricing and reimbursement; that the Company may incur unexpected delays in the outsourced manufacturing of SCENESSE®, PRÉNUMBRA® or NEURACTHEL® which may lead to it being unable to supply its commercial markets and/or clinical trial programs; any failures to comply with any government payment system (i.e. Medicare) reporting and payment obligations; uncertainties surrounding the legislative and regulatory pathways for the registration and approval of biotechnology and consumer based products; decisions by regulatory authorities regarding approval of our products as well as their decisions regarding label claims; our ability to retain or attract key personnel and managerial talent; the impact of broader change within the pharmaceutical industry and related industries; potential changes to tax liabilities or legislation; environmental risks; and other factors that have been discussed in our 2023 Annual Report. Forward-looking statements speak only as of the date on which they are made, and the Company undertakes no obligation, outside of those required under applicable laws or relevant listing rules of the Australian Securities Exchange, to update or revise any forward-looking statement, whether as a result of new information, future events or otherwise. More information on preliminary and uncertain forecasts and estimates is available on request, whereby it is stated that past performance is not an indicator of future performance.

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