PRESS RELEASE

Single-dose Kozenis (tafenoquine) approved for children with *Plasmodium vivax* malaria by Australian Therapeutic Goods Administration

- *P. vivax* malaria places a disproportionate burden on children, who are four times as likely to be affected as adults
- As a single dose, tafenoquine will support patient adherence
- TGA approval will support registrations in malaria-endemic countries where the medicine could support country malaria elimination goals

Geneva 14 March 2022. Medicines for Malaria Venture (MMV) today announces that the Australian Therapeutic Goods Administration (TGA) has approved the use of single-dose Kozenis (tafenoquine) in children aged 2 years and above in combination with chloroquine for the radical cure (prevention of relapse) of *Plasmodium vivax (P. vivax)* malaria.

The approval includes a novel, 50 mg dispersible tablet that can be dispersed in water and which was developed by GSK in partnership with MMV to facilitate use in children, who are disproportionately affected by the disease.

"We are proud to have worked with GSK to develop this child-friendly treatment and are thrilled by today's announcement. *P. vivax* malaria is particularly dangerous for young children for whom repeated relapses can lead to cumulative severe anaemia and, in some cases, be fatal. Today, we have a tool to put a stop to the relentless relapse both for adults and children – we are one step closer to defeating this disease." said Dr David Reddy, Chief Executive Officer, MMV.

Dr Thomas Breuer, Chief Global Health Officer, GSK, said: "We are delighted by this approval of Kozenis for paediatric populations. This achievement is testament to the dedication of GSK scientists and our partner MMV, who all worked tirelessly so the first relapse prevention treatment for *P. vivax* malaria in more than 60 years can be made available to the most vulnerable in society, our children."

The submission was supported by a Phase 2b clinical study (TEACH) that evaluated dosages of tafenoquine based on weight for children between the age of 2 years, and weighing at least 10 kg, and up to 15 years[1].

Kozenis is a single-dose treatment for the prevention of relapse of *P. vivax* and was approved for people aged 16 years and older by the TGA in 2018. It should be used with a course of chloroquine to treat the active blood stage infection, thereby achieving radical cure.

The current standard of care for prevention of *P. vivax* relapse requires a 7- or 14-day course of treatment with a drug called primaquine and at present there are no quality-assured, age-specific paediatric formulations marketed.

P. vivax malaria is estimated to cause between 4.1 and 5.1 million clinical infections every year, and poses a disproportionate burden for children aged 2 to 6 years who are four times as likely as adults

[1] Vélez ID, Hien TT, Green JA, et al. Tafenoquine exposure assessment, safety, and relapse prevention efficacy in children with Plasmodium vivax malaria: an open-label, single-arm, non-comparative, multicentre, pharmacokinetic bridging, phase 2 trial. Lancet Child Adolesc Health 2021; published online Dec 3. https://doi.org/10.1016/S2352-4642(21)00328-X

to be infected.[2] [3] The clinical features of *P. vivax* malaria include fever, chills, vomiting, malaise, headache and muscle pain, and in some cases, can lead to severe malaria and death.[4] *P. vivax* malaria infections also impact a child's development and educational progress with evidence showing that children who experience repeated *P. vivax* infections are likely to suffer from physical and cognitive impairment.[5,6,7]

Further regulatory submissions are planned in malaria-endemic countries for paediatric indications for tafenoquine.

About TEACH (TAF113577)
Tafenoquine Exposure Assessment in CHildren (TEACH) was an open-label, non-comparative, multi-centre Phase 2b study to assess the pharmacokinetics (PK), safety, and efficacy of single-dose tafenoquine in the treatment of paediatric subjects with *P. vivax* malaria.

The primary objective was to evaluate the pharmacokinetics of tafenoquine in children and adolescents aged ≥2 years to <16 years with *P. vivax* in order to identify appropriate doses that achieve a similar exposure to that of the approved tafenoquine adult dose of 300 mg. Secondary objectives were to assess the safety of tafenoquine when administered to paediatric subjects with *P. vivax* malaria; to assess the clinical and parasitological efficacy of tafenoquine as a radical cure for paediatric subjects with *P. vivax* malaria when co-administered with chloroquine. Another secondary objective was to assess the PK of tafenoquine in infants aged ≥6 months to <2 years (weighing ≥5kg) with *P. vivax* (if data permitted).

In total, 60 paediatric subjects with *P. vivax* malaria were recruited (median age 10 years [range 2 – 15 years]) and dosed at three sites in Vietnam and one site in Colombia. All subjects received a single dose of tafenoquine and a course of chloroquine administered per local or national treatment guidelines to treat the acute blood-stage of the illness. All subjects were screened for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to receiving tafenoquine and excluded from the study if they had <70% of the normal G6PD enzyme activity levels.

There were no unexpected safety findings. The overall percentage (62%) of subjects reporting adverse events was similar to previous studies with tafenoquine in adults and adolescents aged 16 years and older, with the highest-frequency adverse event being vomiting in 20% of subjects. No drug-related, serious adverse events were reported. The recurrence-free efficacy rate of 95 percent at four months was in line with studies of tafenoquine in adults and older adolescents.

About *P. vivax malaria*
P. vivax malaria has a significant public health and economic impact, primarily in South-Asia, South-East Asia, Latin America and the Horn of Africa. The *Plasmodium* parasite is a complex organism with a lifecycle spanning both humans and mosquitoes.[8] After an infected mosquito bite, the *P. vivax* parasite infects the blood and causes an acute malaria episode. It also has the ability to lie dormant in the liver (in a form known as hypnozoite), from where it periodically reactivates to cause relapses of *P. vivax* malaria. Hence, a single *P. vivax* infection can give rise to multiple episodes of malaria in the absence of a new mosquito bite. These relapses can occur weeks, months or even years after the initial infection. The dormant liver forms of the parasite cannot be treated with most antimalarial treatments active against the blood-stage parasite.

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[2] World Health Organization. World Malaria Report 2021 (2021)

3 Howes, R.E et al. Am J Trop Med Hyg 2016; 95(6 Suppl): 15-34

4 Price RN et al. Vivax malaria: neglected and not benign. Am J Trop Med Hyg 2007; 77:79–87.

[5] Fernando D et al. Cognitive performance at school entry of children living in malaria-endemic areas of Sri Lanka. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 97(2):161-5 (2003).

[6] Vorasan N et al. Long-term impact of childhood malaria infection on school performance among school children in a malaria endemic area along the Thai-Myanmar border. *Malaria Journal*. 14:401 (2015).

[7] Brasil LMBF et al. Cognitive performance of children living in endemic areas for Plasmodium vivax. *Malaria Journal*. 2017; 16: 370.

[8] Lima Jr JC, Pratt -Riccio LR. Major Histocompatibility Complex and Malaria: Focus on Plasmodium vivax Infection. Frontiers in Immunology 2016; 7(13): 1 -14

The co-administration of a blood-stage antimalarial such as chloroquine and a medicine that targets the dormant liver forms of the *P. vivax* parasite is known as radical cure.

About tafenoquine
Tafenoquine, developed by GSK and MMV, was first approved by the US Food and Drug Administration for the radical cure (prevention of relapse) of *P. vivax* malaria in July 2018 for use in adults and adolescents ≥16 years old. It was subsequently approved by regulators in Australia, Brazil, Thailand and Peru.

Regulatory applications are being progressed in other malaria-endemic countries. All approvals are based on efficacy and safety data from a comprehensive global clinical development programme for *P. vivax* radical cure, conducted in nine malaria-endemic countries, which supported an overall positive benefit–risk profile for the use of the product.

Tafenoquine should be co-administered with chloroquine to treat both the blood- and liver-stages of acute *P. vivax* malaria infections (known as radical cure). Before taking tafenoquine, patients must be tested for deficiency of a specific enzyme known as glucose-6-phosphate dehydrogenase (G6PD), which helps protect red blood cells. Patients with a G6PD enzyme deficiency could have severe adverse reactions, like haemolytic anaemia, during treatment with the 8 aminoquinoline class of drugs (such as tafenoquine and primaquine) and only patients with G6PD enzyme activity >70% of normal should receive tafenoquine.

About Medicines for Malaria Venture (MMV)
MMV is a leading product development partnership (PDP) in the field of antimalarial drug research and development. Its mission is to reduce the burden of malaria in disease-endemic countries by discovering, developing and facilitating delivery of new, effective and affordable antimalarial drugs.

MMV receives funding and support from government agencies, private foundations, international organizations, corporations, corporate foundations and private individuals. These funds are used to finance MMV's portfolio of R&D projects, as well as specific, targeted access & product management (APM) interventions that aim to facilitate increased access to malaria medicines by vulnerable populations in disease-endemic countries and support their appropriate use.

Since its foundation in 1999, MMV and partners have built the largest portfolio of antimalarial R&D and access projects ever assembled, have brought forward eleven new medicines and have assumed the access stewardship of a further two. An estimated 2.7 million lives have been saved by these MMV co-developed medicines. MMV's success is based on its extensive partnership network of around 150 active partners including from the pharmaceutical industry, academia and endemic countries.

MMV's vision is a world in which innovative medicines will cure and protect the vulnerable and under-served populations at risk of malaria, and help to ultimately eradicate this terrible disease.

For more information, visit http://www.mmv.org

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