PRESS RELEASE

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GSK, MMV filing for Kozenis (tafenoquine) in paediatric populations with *Plasmodium vivax* malaria accepted by Australian Therapeutic Goods Administration

GSK and Medicines for Malaria Venture (MMV) announced today that the Australian Therapeutic Goods Administration (TGA) accepted the submission of a Category 1 application to extend the indication of single-dose Kozenis (tafenoquine) to paediatric populations for the radical cure (prevention of relapse) of *Plasmodium vivax (P. vivax) malaria*.

The application includes data for a new, 50 mg tablet that can be dispersed in water and which was developed to facilitate use in children, who are disproportionately affected by the disease.

The submission is supported by a Phase 2b clinical study (TEACH) that evaluated dosages of tafenoquine based on weight for children between the age of 6 months and weighing at least 5 kg, up to 15 years.

Kozenis is a single-dose treatment for the radical cure (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.

The current standard of care for prevention of *P. vivax* relapse requires a 14-day course of treatment and at present there is no age-specific paediatric formulation.

P. vivax malaria is estimated to cause around 6.4 million clinical infections every year, and children are four times as likely as adults to be affected.[1] [2] 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.[3] The prevalence of *P. vivax* peaks in children aged 2-6 years old.[4]

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

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 PK 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 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).

1 World Health Organization. World Malaria Report 2020 (2020)

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

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

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

In all, 60 paediatric subjects were recruited (median age 10 years [range 2 – 15 years]) and dosed at three sites in Vietnam and one 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 of subjects reporting adverse events was similar to previous studies in adults and adolescents 16 years and older [37/60 (62%)], with the highest-frequency adverse event being vomiting in 12 (20%) subjects. No drug-related, serious adverse events were reported. The relapse-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.[5] 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.

The use of a medicine that targets the dormant liver forms of the *P. vivax* parasite, co-administered with currently available blood stage antimalarials such as chloroquine 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 of *P. vivax* malaria in July 2018 for use in adults and adolescents ≥16 years old who are receiving appropriate antimalarial therapy for acute *P. vivax* infection. It was subsequently approved by regulators in Australia, Brazil and Thailand.

Regulatory applications are being progressed in other malaria-endemic countries. All approvals were 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 needs to 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 or primaquine, 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 anemia, during treatment with radical cure drugs and only those with >70% G6PD enzyme activity should receive tafenoquine.

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

Important safety information

CONTRAINDICATIONS
Tafenoquine is contraindicated in the following:
• G6PD deficiency
• Pregnancy
• Breastfeeding an infant who is G6PD deficient or if the G6PD status of the infant is unknown
• Patients with known hypersensitivity to tafenoquine, other 8-aminoquinolines, or any component of the formulation

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Haemolytic anaemia and G6PD deficiency
Due to the risk of haemolytic anaemia in patients with G6PD deficiency, G6PD testing must be performed before prescribing tafenoquine. Withhold tafenoquine from patients with G6PD enzyme levels <70% of normal. Monitor patients for clinical signs or symptoms of haemolytic anaemia. Advise patients to seek medical attention if signs of haemolytic anaemia occur.

Methaemoglobinaemia
Asymptomatic elevations in methaemoglobin were observed in clinical studies (see section 4.8 Adverse effects). If signs or symptoms of methaemoglobinaemia occur, appropriate therapy should be instituted. Caution is advised in patients with nicotinamide adenine dinucleotide (NADH)-dependent methaemoglobin reductase deficiency.

Psychiatric Effects
Mild to moderate, self-limiting psychiatric adverse reactions (e.g. anxiety, abnormal dreams) have been reported in clinical trials of tafenoquine. While there were no reports of serious psychiatric adverse reactions in clinical trials following a single 300 mg dose, cases of depression and psychosis have occurred following higher single doses (350 to 600 mg) of tafenoquine, mostly in subjects with a previous history of psychiatric disorders. Serious psychiatric disorders such as psychosis and depression have been associated with some quinoline anti-malarials. Caution is advised when administering tafenoquine to patients with a current or past history of serious psychiatric disorders. Individual patient risk-benefit should be assessed. Due to the long half-life of tafenoquine (15 days), psychiatric effects and hypersensitivity reactionsmay be delayed in onset and/or duration.

INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS
Tafenoquine is an inhibitor of human transporters organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter (MATE) in vitro, potentially resulting in increased exposure to their substrates (e.g., dofetilide). There is a small risk of lactic acidosis due to increased metformin exposure secondary to blockade of these transporters. Therefore, use with caution with metformin. Drugs with a narrow therapeutic index that are substrates of the renal transporters OCT2 and MATE should not be co-administered (e.g. phenformin, buformin, dofetilide, procainamide, and pilsicainide).

ADVERSE EFFECTS (UNDESIRABLE EFFECTS)
Common adverse reactions (occurring in >1% of patients treated with tafenoquine) included blood creatinine increased, dizziness, elevated methaemoglobin, haemoglobin decreased, headache, insomnia, nausea, and vomiting

Reporting suspected adverse reactions after registration 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 at https://www.tga.gov.au/reporting-problems.

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About the partners

Medicines for Malaria Venture (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. 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 2.2 million lives have been saved by these medicines.

MMV's success is based on its extensive network of around 150 active partners from the pharmaceutical industry, academia, and research and malaria programmes in malaria-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 ultimately help to eradicate this terrible disease.
www.mmv.org

About GSK

GSK is a science-led global healthcare company with a special purpose: to help people do more, feel better, live longer. For further information please visit www.gsk.com/about-us.

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Cautionary statement regarding forward-looking statements

GSK cautions investors that any forward-looking statements or projections made by GSK, including those made in this announcement, are subject to risks and uncertainties that may cause actual results to differ materially from those projected. Such factors include, but are not limited to, those

described under Item 3.D "Risk Factors" in the company's Annual Report on Form 20-F for 2019 and as set out in GSK's "Principal risks and uncertainties" section of the Q3 Results and any impacts of the COVID-19 pandemic.

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