GLAXOSMITHKLINE PLC
Form 6-K
January 09, 2014

FORM 6-K

SECURITIES AND EXCHANGE COMMISSION
Washington D.C. 20549

Report of Foreign Issuer

Pursuant to Rule 13a-16 or 15d-16 of
the Securities Exchange Act of 1934

For period ending January 2014

GlaxoSmithKline plc
(Name of registrant)

980 Great West Road, Brentford, Middlesex, TW8 9GS
(Address of principal executive offices)

Indicate by check mark whether the registrant files or
will file annual reports under cover Form 20-F or Form 40-F

Form 20-F x Form 40-F

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Indicate by check mark whether the registrant by furnishing the
information contained in this Form is also thereby furnishing the
information to the Commission pursuant to Rule 12g3-2(b) under the
Securities Exchange Act of 1934.

Yes No x

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Issued: 09 January 2014, London UK - London Stock Exchange Announcement

GSK gains accelerated FDA approval for combination use of Mekinist® (trametinib) and Tafinlar®(dabrafenib)

- First approved combination of oral targeted therapies for unresectable or metastatic melanoma with BRAF V600E or V600K mutations1

GlaxoSmithKline plc [LSE/NYSE:GSK] announced today that the U.S. Food and Drug Administration (FDA) has approved Mekinist® (trametinib) for use in combination with Tafinlar® (dabrafenib) for the treatment of patients with unresectable melanoma (melanoma that cannot be removed by surgery) or metastatic melanoma (melanoma which has spread to other parts of the body) with BRAF V600E or V600K mutations. These mutations must be detected by an FDA-approved test.1 Tafinlar is not indicated for treatment of patients with wild-type BRAF melanoma.2

The approval of the combination is based on the demonstration of response rate and median duration of response in a Phase I/II study. Improvement in disease-related symptoms or overall survival has not been demonstrated for Mekinist in combination with Tafinlar.1 The combination was approved through the FDA's Accelerated Approval programme and reviewed under a Priority Review designation.3 This accelerated approval is contingent on the results of the ongoing Phase III trial (referred to as MEK115306 or Combi-D), which

"This approval marks another key moment in what continues to be a rapid evolution of the treatment landscape for metastatic melanoma patients. Combining agents that target different mechanisms regulating the growth of cancer cells is one of the promising areas in cancer research," said Dr. Paolo Paoletti, President of Oncology, GSK. "We are proud that the first approved combination of targeted therapies in metastatic melanoma is Mekinist and Tafinlar, and our hope is that it will become part of the new standard of care for appropriate patients with BRAF V600E or V600K mutation-positive metastatic melanoma."

The results from the randomised Phase II part of the Phase I/II open-label study, which evaluated the combination of trametinib and dabrafenib at the recommended dose (150/2mg) (N=54) and single-agent dabrafenib (150mg) (N=541, were as follows:

- The investigator-assessed overall response rate (ORR) (main efficacy endpoint) was 76% (95% CI, 62, 87) for patients treated with the combination, and 54% (95% CI, 40, 67) for patients treated with single-agent dabrafenib. The median duration of response was 10.5 months (95% CI, 7, 15) for patients treated with the combination, and 5.6 months (95% CI, 5, 7) for patients treated with single-agent dabrafenib.
- Data analyses of the blinded independent radiologic review committee (IRRC) supported the investigator results. The IRRC-assessed ORR was 57% (95% CI, 43, 71) for patients treated with the combination, and 46% (95% CI, 33, 60) for patients receiving single-agent dabrafenib. The median duration of response as assessed by the IRRC was 7.6 months (95% CI, 7, NR) for patients treated with the combination, and 7.6 months (95% CI, 6, NR) for patients treated with single-agent dabrafenib.

Trametinib in combination with dabrafenib can cause serious side effects, some of which can be life threatening, including: new primary cutaneous malignancies (new skin cancers); tumour promotion in wild-type BRAF melanoma; haemorrhagic events (symptomatic bleeding in a critical area or organ); venous thromboembolic events (blood clots); cardiomyopathy (heart problems, including heart failure); ocular (eye-related) toxicities; interstitial lung disease (ILD); serious febrile drug reactions (severe fevers); serious skin toxicity (rash); hyperglycaemia (blood sugar problems); haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency; and embryofoetal toxicity (potential harm to the unborn baby in pregnant women).1,2

The most frequently occurring adverse reactions at the recommended dose of trametinib 2mg once daily in combination with dabrafenib 150mg twice daily (all grades in more than 20% of patients) in the randomised part of Phase I/II study included: pyrexia (fever) (71%), chills (58%), fatigue (53%), rash (45%), nausea (44%), vomiting (40%), diarrhoea (36%), abdominal pain (33%), oedema peripheral (swelling of tissues, usually in the lower limbs) (31%), cough (29%), headache (29%), arthralgia (27%), night sweats (24%), decreased appetite (22%), constipation (22%) and myalgia (muscular pain) (22%). The most common (≥2%) Grade 3 or 4 adverse events observed in the combination group in this study were: renal failure (7%), pyrexia (5%), back pain (5%), haemorrhage (5%), fatigue (4%), chills (2%), nausea (2%), vomiting (2%), diarrhoea (2%), abdominal pain (2%), myalgia (2%) and urinary tract infection (2%).

Details Behind the Trametinib and Dabrafenib Combination Clinical Data
The safety of trametinib (2mg once daily) in combination with dabrafenib (150mg twice daily) was evaluated in 202 patients with BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma enrolled in a Phase I/II study. FDA approval of the combination therapy was based on the demonstration of response rate and median duration of response in a multicentre, open-label, randomised, active-controlled, dose-ranging part of the Phase I/II study enrolling patients with histologically-confirmed Stage IIIC or IV melanoma determined to be BRAF V600E or V600K mutation-positive. No more than one prior chemotherapy regimen and/or interleukin-2 were permitted. Patients with prior exposure to BRAF inhibitors or MEK inhibitors were ineligible. The main efficacy outcome measure was investigator-assessed overall response rate (ORR). Additional efficacy outcome measures were investigator-assessed duration of response, IRRC-assessed ORR, and IRRC-assessed duration of response.1

Trametinib was in-licensed by GSK in 2006. GSK holds the worldwide exclusive rights to develop, manufacture and commercialise Mekinist, while Japan Tobacco retains co-promotion rights in Japan.

The PDUFA date for the update to the Tafinlar label is 9 January 2014.

Important Safety Information for Mekinist in combination with Tafinlar

WARNINGS AND PRECAUTIONS: Mekinist and Tafinlar combination

New Primary Malignancies (cutaneous and non-cutaneous)1
When Tafinlar was used in combination with Mekinist at the recommended dose, the incidence of basal cell carcinoma was increased. The incidence of basal cell carcinoma was 9% (5/55) in patients receiving the combination compared to 2% (1/53) in patients receiving Tafinlar as a single agent. Tafinlar results in an increased incidence of cutaneous squamous cell carcinoma (cuSCC), keratoacanthoma and melanoma. Cutaneous squamous cell carcinoma, including keratoacanthoma, occurred in 7% of patients receiving the combination and 19% of patients receiving Tafinlar as a single agent.

Tumour Promotion in Wild-Type BRAF Melanoma2
In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in wild-type BRAF cells that are exposed to BRAF inhibitors.2

Haemorrhage1
Treatment with the combination resulted in an increased incidence and severity of haemorrhagic events: 16% (9/55) of patients treated with the combination compared with 2% (1/53) of patients treated with Tafinlar as a single agent. Intracranial haemorrhage was fatal in two (4%) patients receiving the combination.

Venous Thromboembolic Events1
Treatment with the combination resulted in an increased incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE): 7% (4/55) of patients treated with the combination compared with none of the 53 patients treated with

Tafinlar as a single agent. Pulmonary embolism was fatal in one (2%) patient receiving the combination.

Cardiomyopathy1
When Mekinist was used in combination with Tafinlar at the recommended dose, cardiomyopathy (defined as cardiac failure, left ventricular dysfunction, or decreased left ventricular ejection fraction [LVEF]) occurred in 9% (5/55) of patients treated with the combination and in none of patients treated with Tafinlar as a single agent.

Ocular Toxicities1
Retinal Vein Occlusion (RVO): across clinical trials of Mekinist the incidence of RVO was 0.2% (4/1,749). RVO may lead to macular oedema, decreased visual function, neovascularisation, and glaucoma.

Retinal Pigment Epithelial Detachment (RPED): in the randomised Phase II part of the Phase I/II open-label study 2% (1/55) of patients receiving Mekinist in combination with Tafinlar developed RPED.

Uveitis and Iritis: across clinical trials of the combination, uveitis occurred in 1% (2/202) of patients.

Interstitial lung disease (ILD)1
In clinical trials of Mekinist (N = 329) as a single agent, ILD or pneumonitis occurred in 2% of patients.1

Serious Febrile Drug Reactions1
Serious febrile reactions and fever of any severity accompanied by hypotension, rigors or chills, dehydration or renal failure, can occur when Mekinist is used in combination with Tafinlar. The incidence and severity of pyrexia are increased when Mekinist is given with Tafinlar compared with Tafinlar alone.

The incidence of fever (serious and non-serious) was 71% (39/55) in patients treated with the combination and 26% (14/53) in patients treated with Tafinlar as a single agent. Febrile reactions of any severity, accompanied by hypotension, rigors or chills, occurred in 25% (14/55) of patients treated with the combination compared with 2% (1/53) of patients treated with Tafinlar as a single agent.

Serious Skin Toxicity1
The incidence of any skin toxicity, the most common of which were rash, dermatitis acneiform rash, palmar-plantar erythrodysesthesia syndrome or erythema, was similar for patients receiving the combination (65% [36/55]) compared with patients receiving Tafinlar as a single agent (68% [36/53]). Across all clinical trials of the combination (N = 202), severe skin toxicity requiring hospitalisation occurred in 2.5% (5/202) of patients.

Hyperglycaemia1
Hyperglycaemia can occur when Mekinist is used in combination with Tafinlar. The incidence of Grade 3 hyperglycaemia based on laboratory values was 5% (3/55) in patients treated with the combination compared with 2% (1/53) in patients treated with Tafinlar as a single agent.

Glucose-6-Phosphate Dehydrogenase Deficiency2
Tafinlar, which contains a sulfonamide moiety, confers a potential risk of haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Embryofoetal Toxicity1,2
Tafinlar and Mekinist both can cause foetal harm when administered to a pregnant woman. Tafinlar can also render hormonal contraceptives ineffective.

Drug Interactions
Effects of Other Drugs on Dabrafenib2

Drugs that Inhibit or Induce Drug-Metabolising Enzymes: dabrafenib is primarily metabolised by CYP2C8 and CYP3A4. Strong inhibitors or inducers of CYP3A4 or CYP2C8 may increase or decrease, respectively, concentrations of dabrafenib.

Drugs that Affect Gastric pH: Drugs that alter the pH of the upper GI tract (e.g., proton pump inhibitors, H2-receptor antagonists, antacids) may alter the solubility of dabrafenib and reduce its bioavailability.

Effects of Dabrafenib on Other Drugs2
Dabrafenib induces CYP3A4 and CYP2C9. Dabrafenib decreased systemic exposures of midazolam (a CYP3A4 substrate), S-warfarin (a CYP2C9 substrate) and R-warfarin (a CYP3A4/CYP1A2 substrate). Coadministration of dabrafenib with other substrates of these enzymes, including dexamethasone, or hormonal contraceptives, can result in decreased concentrations and loss of efficacy.

Combination of trametinib with dabrafenib1
Co-administration of trametinib 2mg once daily and dabrafenib 150mg twice daily resulted in no clinically relevant pharmacokinetic drug interactions

Please see full Prescribing Information and Patient Information Leaflet for Mekinist:

The revised full U.S. Prescribing Information, including Patient Information Leaflet for Mekinist will be available soon at http://us.gsk.com/products/assets/us_mekinist.pdf. Prior to the revised label being posted online, a copy of the label may be requested from one of the GSK Media or Investor Relations contacts listed in the "GSK enquiries" section at the end of this document.

Please see full Prescribing Information and Medication Guide for Tafinlar:
http://us.gsk.com/products/assets/us_tafinlar.pdf

U.S. journalists, please click here for the U.S. electronic press kit:
http://us.gsk.com/html/media-news/tafmekpress-kit.html

B Kelly-Bisla
Corporate Secretariat
9 January 2014

About GSK Patient Assistance Programmes
GSK has a number of patient assistance programmes for eligible patients in the United States who need help affording their medicines and vaccines. Through our programmes, in 2012, more than 250,000 patients received GSK medicines and vaccines free of charge. Additionally, in 2012 we provided approximately 2.3 million prescriptions through our assistance programmes. GSK is committed to helping eligible patients who need Tafinlar and Mekinist receive therapy. Patients who qualify for the programmes may benefit from GSK's Commitment to Access programme for oncology and specialty medicines which offers services and programmes including co-pay assistance in addition to traditional patient assistance support. For more information, patients can call 1-8ONCOLOGY1 (1-866-265-6491).

GSK - one of the world's leading research-based pharmaceutical and healthcare companies - is committed to improving the quality of human life by enabling people to do more, feel better and live longer. For further information please visit www.gsk.com.

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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. Factors that may affect GSK' s operations are described under Item 3.D 'Risk factors' in the company's Annual Report on Form 20-F for 2012.

References

1 Glaxosmithkline. Mekinist Prescribing Information 2014.
2 GlaxoSmithKline. Tafinlar Prescribing Information 2013.
3 U.S. Food and Drug Administration. Fast Track, Breakthrough Therapy, Accelerated Approval and Priority Review. Accessed December 10, 2013. Available at: http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccesstoimportantnewtherapies/ucm128291.htm

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorised.

GlaxoSmithKline plc
(Registrant)

Date: January 09, 2014

By: SIMON BICKNELL

Simon Bicknell
Authorised Signatory for and on
behalf of GlaxoSmithKline plc