Taiwan Food and Drug Administration

Assessment Report

Trade Name：科舒洛膠囊 10 毫克/ Koselugo capsules 10 mg
科舒洛膠囊 25 毫克/ Koselugo capsules 10 mg

Active Ingredient：Selumetinib sulfate

License Number： MOHW-PI 028198
MOHW-PI 028199

Applicant：臺灣阿斯特捷利康股份有限公司

Approval Date： 2021. 12. 07

Indication：適用於治療 3 歲以上罹患第 1 型神經纖維瘤（NF1）合併有症狀且無法手術切除的叢狀神經纖維瘤之兒童病人。

KOSELUGO is indicated for the treatment of pediatric patients 3 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).

Background Information

<table>
<tr><td>Trade Name</td><td>科舒洛膠囊 10 毫克/ Koselugo capsules 10 mg
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<tr><td>Active Ingredient(s)</td><td>Selumetinib sulfate</td></tr>
<tr><td>Applicant</td><td>臺灣阿斯特捷利康股份有限公司</td></tr>
<tr><td>Dosage Form & Strengths</td><td>Capsules 10mg、25mg</td></tr>
<tr><td>Indication</td><td>適用於治療 3 歲以上罹患第 1 型神經纖維瘤（NF1）合併有症狀且無法手術切除的叢狀神經纖維瘤之兒童病人。
KOSELUGO is indicated for the treatment of pediatric patients 3 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).</td></tr>
<tr><td>Posology</td><td>KOSELUGO 的建議劑量依據體表面積 (BSA) 為 25 mg/m^2，每日口服兩次 (約每 12 小時一次)。劑量依據個別病人的體表面積 (mg/m^2) 計算，並以最接近 5 mg 或 10 mg 的劑量為給藥劑量 (單劑最高為 50 mg)。組合不同劑量的 KOSELUGO 膠囊，以達到所需劑量(表 1)。
表 1 每日兩次 selumetinib 25 mg/m^2 給藥方案
<table>
<tr><th>體表面積 (BSA)</th><th>建議劑量 [a]</th></tr>
<tr><td>0.55 – 0.69 m^2</td><td>早上 20 mg 及晚上 10 mg</td></tr>
<tr><td>0.70 – 0.89 m^2</td><td>20 mg 每天兩次</td></tr>
<tr><td>0.90 – 1.09 m^2</td><td>25 mg 每天兩次</td></tr>
<tr><td>1.10 – 1.29 m^2</td><td>30 mg 每天兩次</td></tr>
<tr><td>1.30 – 1.49 m^2</td><td>35 mg 每天兩次</td></tr>
<tr><td>1.50 – 1.69 m^2</td><td>40 mg 每天兩次</td></tr>
<tr><td>1.70 – 1.89 m^2</td><td>45 mg 每天兩次</td></tr>
<tr><td>≥1.90 m^2</td><td>50 mg 每天兩次</td></tr>
</table>
a.尚未確立體表面積低於 0.55 m^2 病人的建議劑量。
KOSELUGO 治療應持續至出現臨床效益，或是直到叢狀神經纖維瘤 (PN) 惡化</td></tr>
</table>

<table>
<tr><td></td><td>或無法耐受毒性為止。
The recommended dosage of KOSELUGO is 25 mg/m^2 orally twice daily (approximately every 12 hours) until disease progression or unacceptable toxicity.
The recommended dose of KOSELUGO based on body surface area (BSA) is shown in Table 1.
Table 1 Recommended Dosage Based on Body Surface Area
<table>
<tr><th>Body Surface Area*</th><th>Recommended Dosage</th></tr>
<tr><td>0.55 – 0.69 m^2</td><td>20 mg in the morning and 10 mg in the evening</td></tr>
<tr><td>0.70 – 0.89 m^2</td><td>20 mg twice daily</td></tr>
<tr><td>0.90 – 1.09 m^2</td><td>25 mg twice daily</td></tr>
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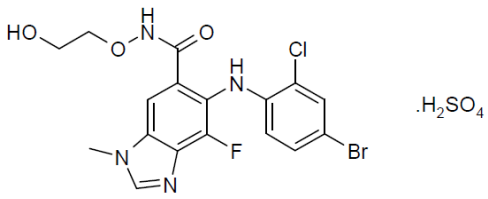
</table>
* The recommended dosage for patients with a BSA less than 0.55m^2 has not been established.</td></tr>
<tr><td>Pharmacological Category
ATC Code</td><td>L01EE04</td></tr>
</table>

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, selumetinib sulfate, is chemically designated as 5-[(4-bromo-2-chlorophenyl) amino]-4-fluoro-6-[(2-hydroxyethoxy) carbamoyl]-1- methyl-1*H*-benzimidazol-3-ium hydrogen sulfate. The molecular formula and the relative molecular mass for selumetinib sulfate are $C_{17}H_{17}BrClFN_4O_7S$ and 555.76 g/mol, respectively. The chemical structure of selumetinib sulfate is shown below:



It is a white to yellow powder. The structure of selumetinib sulfate is confirmed by IR spectrum, nuclear magnetic resonance (NMR) spectroscopy, ion chromatography (IC), single crystal X-ray diffraction (XRD) and mass spectrum. The specification for the drug substance includes tests for description, identity, assay, organic impurities, residual solvents, water content, residue on ignition and particle size.

2.1.2 Drug product

The drug product is supplied for oral use as capsules containing 10 mg and 25 mg selumetinib (equivalent to 12.1 mg selumetinib sulfate and 30.25 mg selumetinib sulfate, respectively). All excipients are well known ingredients and suitable for proposed formulation. The specification for the drug product includes description, identity, assay, degradation products, uniformity of dosage units and dissolution. Analytical methods are described well and validated. Stability studies of drug product under long term conditions (25°C/60% RH and 30°C/75% RH) and accelerated condition (40°C/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Selumetinib is a potent, selective, oral inhibitor of mitogen-activated protein kinase kinases 1 and 2 (MEK1/2) that is not competitive with respect to adenosine triphosphate (ATP). Pharmacology data demonstrated that selumetinib had shown activity in numerous in vitro and in vivo studies. In two mouse models of neurofibroma, selumetinib inhibits extracellular signal-related kinase (ERK) phosphorylation, reduces neurofibroma volume, proliferation, number, and growth. Core battery safety pharmacology studies indicated that selumetinib had no effects on the CNS, cardiovascular and respiratory systems. However, selumetinib induced dose-dependent gastric mucosal lesions and showed a mild increase in gastric motility in rats.

2.2.2 Toxicological Studies

The pivotal repeated-dose toxicity studies of selumetinib included a 3-month study in rats and 6-months studies in mice and monkeys. The main target organs identified were skin, bone, and GI. In rodents, soft tissue mineralization was noted in gastric mucosa, cornea, kidney, liver, myocardium, skeletal muscle, and stomach. All findings except soft tissue mineralization showed reversibility on cessation of dosing or following a recovery period. Selumetinib showed no evidence of mutagenicity or genotoxicity in vitro in bacteria or mammalian cells, respectively, but induced micronuclei in the bone marrow of mice in vivo, as a consequence of

aneugenicity, which is consistent with its pharmacology. Selumetinib showed no carcinogenicity in a 6-month study in CByB6F1/Tg rasH2 mice and a 2-year bioassay in Han Wistar rats. Reproductive and developmental studies indicated that selumetinib had no effect on fertility in male or female mice but resulted in embryo-fetal toxicity and fetal abnormalities. Women of childbearing potential are advised to use effective contraceptive methods.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Koselugo 10 mg and 25 mg capsules contained selumetinib, which is an inhibitor of mitogen-activated protein kinase kinases 1 and 2 (MEK1/2). The posology was 25 mg/m^2 of body surface area (BSA), taken orally twice daily (approximately every 12 hours). The detailed recommended dosage is described labeling. After oral selumetinib, the T_{max} was achieved at 1 hour. Absolute oral bioavailability was 62.1%. The PK characteristics was similar between adult healthy subjects and adult patients, and between pediatric patients and adult patients. Over the dose range of 20 mg/m2 to 30 mg/m2 in pediatric patients, selumetinib showed dose proportionality. Food (high-fat meal or low-fat meal) decreased the AUC and C_{max} of selumetinib by 16% ~ 38% and 50% ~ 62%; thus, selumetinib should be taken on an empty stomach with no food or drink other than water. The in vitro human plasma protein binding of selumetinib was high (98.4%), and preferred to distribute to human serum albumin (HAS). Both CYP (56%) and UGT (29%) participated the metabolism of selumetinib. The main CYP enzyme was CYP3A4 (88.5%), and then CYP3A5, CYP2C19 and CYP2C9. Additionally, UGT1A1 and UGT1A3 were responsible of the glucuronidation. Based on Mass balance study, the total recovery was 92.8%, 58.5% from feces (parent: 19.3% of the dose) and 33.0% from urine (parent: 0.8% of the dose). In pediatric patients after single dosing of selumetinib, mean half-life was 6.2 ~ 9.4 hours across the 20 to 30 mg/m^2 dose range.

2.3.2 Interaction Studies

Avoid coadministration of strong or moderate CYP3A4 inhibitors, strong or moderate CYP2C19 inhibitors or fluconazole with selumetinib. If coadministration with strong or moderate CYP3A4 inhibitors or fluconazole cannot be avoided, reduce the dose of KOSELUGO. Besides, avoid concomitant use of strong and moderate CYP3A4 inducers.

2.3.3 Special Populations

No dose adjustment is recommended based on gender. No dose adjustment is recommended in patients with renal impairment or those with end stage renal disease. Based on dedicated hepatic impairment study, no dose adjustment is needed in mild hepatic impairment population. However, moderate hepatic impairment population need to reduce the dose of 20 mg/m^2, and selumetinib is not recommended for use in severe hepatic impairment population.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

There is only one pivotal study, D1532C00057 (single-arm), to support the efficacy and safety. Fifty subjects with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN) were enrolled to receive oral selumetinib 25 mg/m^2 twice daily, doses were rounded to the nearest 5 to 10 mg and was capped at 50 mg when BSA was ≥1.9 m^2. Dose reduction was required according to toxicities.; two dose levels of reduction were provided. Mean age of enrolled subjects was 10.2 y/o (range: 3.5-17.4).

The primary endpoint, ORR, was 66% (95% CI: 51.2, 78.8) by NCI POB (National Cancer Institute Pediatric Oncology Branch) central analysis; the lower bound was greater than the pre-specified margin of null hypothesis 15%. Median duration of response was not reached, and 100% of subjects with response remaining in response at Week 48 was noted. Sensitivity analysis by ICR (independent central review) revealed ORR of 44% (95% CI: 30.0, 58.7).

Improvement trends were found in pain intensity, strength of muscle / ROM of joints, FEV1 and bowel/bladder functions.

2.4.2 Safety Results

The most important safety items affecting benefit risk evaluation are cardiomyopathy, ocular toxicities (retinal vein occlusion and retinal pigment epithelial detachment), diarrhea, and severe skin rash.
Physeal dysplasia and the effects of growth and development is a signal of serious risk.
Post-marketing safety studies for the above important risks and signal are required.

2.5 Bridging Study Evaluation

Japanese and Chinese healthy subjects had higher drug exposure (Dose normalized AUC) than Western healthy subjects about 65% and 40%, respectively. Based on population PK model, the simulated exposure ($AUC_{ss,0-24}$) of East Asian population treated at 20 mg/m^2 was highly close to that of Western population treated at 25 mg/m^2. Because the efficacy evidences have been based on the 25 mg/m^2 until now, no specific adjustment to the starting dose is recommended for pediatric Asian patients. However, these patients should be closely monitored for adverse events. Besides, the optimal dosing regimen for pediatric Asian patients may be revaluated under two new clinical studies (Study D1346C00011, Study D1346C00013) completed.

Due to rarity of disease, the clinical ethnic difference will be evaluated in post-marketing setting.

2.6 Conclusion

The benefit of Koselugo was demonstrated by tumor response in limited number of subjects; other beneficial clinical outcomes such as pain intensity, strength of muscle / ROM of joints, FEV1 and bowel/bladder functions would be expected. Important risks include cardiomyopathy, ocular toxicities, severe skin rash and physeal dysplasia.

Higher AUC and C_{max} were found in East Asians as compared to Caucasians even if these data was adjusted by BW or BSA; close monitor for adverse events and adjustment of dose is essential for patients in this country.

Due to rarity of disease and unmet clinical need, approval of Koselugo is recommended.

3. Post-Marketing Requirements

(1) Post-marketing safety studies for the important risks and physeal dysplasia
(2) Submit the following study reports for further evaluation of ethnic difference.
    1) Study D1346C00011 (32 subjects)
    2) Study D1346C00013 (12 subjects)
(3) Pediatric study of food effects