Taiwan Food and Drug Administration

Assessment Report

Trade Name：
舒停復膜衣錠 6 毫克 / SOTYKTU film-coated tablets 6 mg

Active Ingredient：Deucravacitinib

License Number：MOHW-PI-028554

Applicant：台灣必治妥施貴寶股份有限公司

Approval Date： 2023.10.26

Indication：
適用於治療適合全身性療法或光照療法的中度至重度成人斑塊型乾癬。

SOTYKTU is indicated for the treatment of adults with moderate-to-severe plaque psoriasis and who are candidates for systemic therapy or phototherapy.

1. Background Information

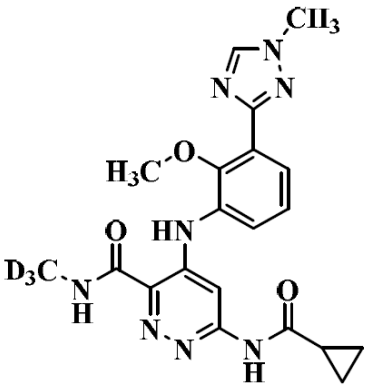
Trade Name	舒停復膜衣錠 6 毫克 / SOTYKTU film-coated tablets 6 mg
Active Ingredient(s)	Deucravacitinib
Applicant	台灣必治妥施貴寶股份有限公司
Dosage Form & Strengths	膜衣錠 6 mg
Indication	適用於治療適合全身性療法或光照療法的中度至重度成人斑塊型乾癬。 SOTYKTU is indicated for the treatment of adults with moderate-to-severe plaque psoriasis and who are candidates for systemic therapy or phototherapy.
Posology	詳見仿單 / Please refer to the approved package insert
Pharmacological Category **ATC Code**	L04AA56

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, deucravacitinib, is chemically designated as 6-(cyclopropanecarbonylamido)-4-[2-methoxy-3-(1-methyl-1,2,4-triazol-3-yl)anilino]-*N*-(trideuteriomethyl)pyridazine-3-carboxamide and has the following structure:



It is a white to yellow powder. The molecular formula and the molecular weight are $C_{20}H_{19}D_3N_8O_3$ and 425.47 g/mol, respectively.

Adequate information of characterization of the drug substance has been provided. The molecular structure of deucravacitinib has been confirmed by UV spectrum, IR spectrum, nuclear magnetic resonance (NMR) spectroscopy, single-crystal X-ray diffraction and mass spectrometry. Adequate specification has been presented for the drug substance and the test items include description, identity, assay, impurities, isotopologues, residual solvents and inorganic impurities. Batch analysis data from commercial scale batches of the drug substance are provided and the test results are within the specifications.

2.1.2 Drug product

The drug product is supplied for oral use as film-coated tablets containing 6 mg of deucravacitinib. The deucravacitinib, with "BMS 895 6mg" printed on one side in two lines with no content on the other side. The specifications for excipients used in the drug product formulation are adequate.

Adequate specification has been presented for the drug product and the test items includes appearance, identity, assay, degradation products, content uniformity, dissolution and microbial limits. Batch analysis data from commercial scale batches of the drug product are provided and the test results are within the specifications. Analytical methods are described well and validated.

Stability studies of drug product under long-term condition (5°C, 25°C/60% RH and 30°C/75% RH) and accelerated condition (40°C/75% RH) have been carried out. Up to 36 months of long-term and 6 months of accelerated stability data are submitted. No significant

chemical or physical changes are observed for the drug product, the shelf life and storage condition of drug product can be granted for 36 months under the storage condition of 30°C.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Deucravacitinib inhibited multiple TYK2-dependent cellular functions, including Type I IFNs and IL-23 signaling, and transcriptional activities like IL-12-induced IFNγ expression and IFNα-stimulated interferon-inducible protein 10 production. Deucravacitinib showed a preference for TYK2 over JAK1, JAK2, and JAK3. Deucravacitinib inhibited IFNα-stimulated CD86 expression on B cells, monocyte differentiation, STAT5 phosphorylation, and IL-12-stimulated IFNγ production. Besides, deucravacitinib reduced Type I IFN-dependent gene expression in lupus patients' whole blood. In NZB/W lupus-prone mice, oral deucravacitinib inhibited Type I IFN-dependent gene expression in blood and kidney, ameliorated severe proteinuria, and prevented kidney inflammation. Deucravacitinib inhibited the IL-12-driven wasting disease and IL-23-driven colitis in SCID mice in a dose-dependent manner. Deucravacitinib was more effective than the anti-IL-23 adnectin in inhibiting IL-23-induced epidermal hyperplasia and inflammatory cellular infiltration. In safety pharmacology, *in vitro* hERG inhibition and the QT prolongation, reduced BP, and increased HR in anesthetized rabbits were noted. However, no electrophysiologic cardiovascular effects were seen in telemetered monkeys.

2.2.2 Toxicological Studies

In a 6-month rat repeated-dose toxicity study, most findings were consistent with deucravacitinib-mediated pharmacologic immunosuppression, and most deucravacitinib-related changes were reversible. In the high-dose recovery group, a higher number of unexplained deaths and increased incidences of alveolar macrophage aggregation in the lungs were associated with deucravacitinib. In the 9-month monkey toxicity study, the major findings were likely infectious in etiology and secondary to deucravacitinib-mediated pharmacologic immunosuppression. Additional findings included transient GI effects, decreased RBC parameters, decreased activity, hunched posture, pale gums, and increased body temperature, with decreased platelets and occult blood in urine in the high-dose group. Following the 2-month recovery, all deucravacitinib-related findings were partially or fully reversible. Deucravacitinib did not affect the reproductive parameters or early embryonic development in rats, and there was no evidence of teratogenicity or development effects in embryo-fetal development toxicity studies. Deucravacitinib administered to pregnant/lactating dams was well tolerated with no maternal toxicity; however, it was associated with adverse effects on pup body weight in the preweaning period, which recovered in the postweaning period. In juvenile rats, deucravacitinib decreased spleen weights, and this finding persisted after recovery in female rats. No evidence of excess treatment-related tumors was observed. Besides,

deucravacitinib was not genotoxic, phototoxic, and not a sensitizer in a mouse local lymph node assay.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

SOTYKTU is an oral Tablets with 6 mg deucravacitinib as the active ingredient. Deucravacitinib (DEUC) is an inhibitor of tyrosine kinase 2 (TYK2) and is used for treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. The recommended dosage of SOTYKTU is 6 mg taken orally once daily, with or without food.

The absolute oral bioavailability of deucravacitinib was 98.9%. The pharmacokinetics of single doses of deucravacitinib administered as tablets was linear across 3 mg to 36 mg dose range. Following a single dose of 6 mg deucravacitinib Tablets, the median T_{max} was reached at 2 - 3 hours, and $T_{1/2}$ was around 10 -11 hours in healthy subjects. The predicted geo-metric mean $C_{max,ss}$, $C_{min,ss}$ and $C_{avg,ss}$ of deucravacitinib at 6 mg once daily in psoriasis (PsO) subjects were 45.1, 7.33 and 19.7 ng/ml, respectively. The PK of deucravacitinib and its active metabolite, BMT-153261 (M13), were comparable between healthy subjects and subjects with psoriasis. In plasma, the most abundant compound was deucravacitinib (43% of the total plasma exposure), and its metabolites were BMT-158170 (M7; 24%), BMT-153261 (M13; 11%) and BMT-334616 (M6; 7%) in turn.

Food did not significantly affect the PK of deucravacitinib (C_{max}:↓24%, AUC:↓11%) and M13. Thus, SOTYKTU Tablets can administered regardless of food. Besides, pH modifying agents (famotidine and rabeprazole) also did not have impact on the PK of deucravacitinib and M13.

Deucravacitinib is widely distributed in rats, especially in the endocrine and thyroid gland, metabolic/excretory systems and the gastrointestinal tract. Based on population PK (pop-PK) analysis, the Vc (central volume of distribution) and Vp in subjects with PsO was 108 L and 46.1 L, respectively. Deucravacitinib was metabolized via four primary biotransformation pathways and several enzymes included: N-demethylation to form M13 (by CYP 1A2), Cyclopropyl carboxamide hydrolysis to form M7 (by CES2), N-glucuronidation to form M6 (by UGT1A9) and Mono-oxidation to form M11 (by CYP 2B6 and 2D6).

The model predicted half-half ($T_{1/2}$) and clearance (CL) of deucravacitinib in subjects with PsO was 16.2 hours and 10 L/h, respectively. After a single dose of radiolabeled deucravacitinib, the total amount of deucravacitinib and metabolites in urine and feces were 50.2% (DEUC: 12.9% + metabolites: 37.3%) and 48.0% (DEUC: 25.9% + metabolites: 22.0%) of the dose, respectively. This indicated that 59.3% of orally administered [^{14}C]-deucravacitinib dose eliminated as metabolites. The unchanged parent drug in feces maybe due to biliary and intestinal excretion.

2.3.2 Interaction Studies

According to *in vitro* and *in vivo* DDI evaluation, no dose adjustment for deucravacitinib Tablets is required when coadministered with strong CYP1A2 inhibitors, CYP1A2 inducers, UGT1A9 inhibitors, OCT1 inhibitors and Pgp/BCRP inhibitor. Deucravacitinib Tablets can be co-administered with oral contraceptives (norethindrone (NET); ethinyl estradiol (EE)), rosuvastatin (substrate of BCRP and OATP), methotrexate (substrate of BCRP and other transporters), and MMF (substrate of CES1 and 2).

2.3.3 Special Populations

Body weight (57-125 kg), gender, and age (22-67 years) did not have a clinically meaningful effect on deucravacitinib exposure. Based on two dedicated organ impairment (renal and hepatic) studies, no dose adjustment of deucravacitinib Tablets is recommended in patients with mild, moderate, or severe renal impairment or in patients with end stage renal disease (ESRD) on dialysis, and in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. However, deucravacitinib Tablets is not recommended in patients with severe hepatic impairment (Child-Pugh C).

Overall, the pharmacokinetic studies met the minimum requirements to support the marketing authorization of SOTYKTU Tablets. It is recommended to approve the NDA of SOTYKTU Tablets from the PK/PD perspective.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Two Phase III, randomized, double-blind, multi-national, multi-center pivotal studies ([IM011046] and [IM011047]) have been provided to support the efficacy of Sotyktu 6 mg QD for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

The co-primary endpoints for both studies were sPGA 0/1 response rate at Week 16 and PASI 75 response rate at Week 16. A statistically significantly greater proportion of subjects on Sotyktu 6 mg QD compared with placebo achieving sPGA 0/1 response and PASI 75 response at Week 16 for both Study [IM011046] and Study [IM011047] (Table 2.4.1-1).

Table 2.4.1-1 Co-primary efficacy endpoints: sPGA 0/1 and PASI 75 responses at Week 16 (FAS)

Co-primary endpoints	Study [IM011046]			Study [IM011047]		
	Sotyktu (N = 332)	Placebo (N = 166)	p-value	Sotyktu (N = 511)	Placebo (N = 255)	p-value
sPGA 0/1	178 (53.6%)	12 (7.2%)	< 0.0001	253 (49.5%)	22 (8.6%)	< 0.0001
PASI 75	194 (58.4%)	21 (12.7%)	< 0.0001	271 (53.0%)	24 (9.4%)	< 0.0001

In addition, Sotyktu 6 mg QD achieved statistical significance in all of the ranked key secondary efficacy endpoints versus placebo and versus Apremilast, except for the last endpoint in each of the respective hierarchical testing branches for each pivotal study (Table 2.4.1-2).

Table 2.4.1-2 Results of key secondary efficacy endpoints (FAS)

Study [IM011046]					Study [IM011047]				
Sotyktu vs. Placebo at Week 16 (2-sided alpha = 0.025)					Sotyktu vs. Placebo (2-sided alpha = 0.025)				
Rank	Endpoint	Sotyktu (N = 332)	Placebo (N = 166)	p-value	Rank	Endpoint	Sotyktu (N = 511)	Placebo (N = 255)	p-value
1	PASI 90	35.5%	4.2%	< 0.0001	1	PASI 90 at W16	27.0%	2.7%	< 0.0001
2	ss-PAG 0/1	70.3%	17.4%	< 0.0001	2	ss-PAG 0/1 at W16	59.7%	17.3%	< 0.0001
3	sPAG 0	17.5%	0.6%	< 0.0001	3	sPAG 0 at W16	15.7%	1.2%	< 0.0001
4	PASI 100	14.2%	0.6%	< 0.0001	4	PASI 100 at W16	10.2%	1.2%	< 0.0001
5	PSSD Symptom Score 0	7.9%	0.7%	0.0013	5	PSSD Symptom Score 0 at W16	7.5%	1.3%	0.0005
6*	DLQI 0/1	41.0%	10.6%	< 0.0001	6*	DLQI 0/1 at W16	37.6%	9.8%	< 0.0001
7	PGA-F 0/1	20.9%	8.8%	0.1049	7*	Time to Relapse until W52 in Wk 24 PASI 75 Responders	—[a]	—[a]	< 0.0001
					8	PGA-F 0/1	20.3%	7.9%	0.0621
Sotyktu vs. Apremilast (2-sided alpha = 0.025)					Sotyktu vs. Apremilast (2-sided alpha = 0.025)				
Rank	Endpoint	Sotyktu (N = 332)	Apremilast (N =168)	p-value	Rank	Endpoint	Sotyktu (N = 511)	Apremilast (N = 254)	p-value
1	sPGA 0/1 at W16	53.6%	32.1%	< 0.0001	1	sPAG 0 at W16	49.5%	33.9%	< 0.0001
2	PASI 75 at W16	58.4%	35.1%	< 0.0001	2	PASI 75 at W16	53.0%	39.8%	0.0004
3	PASI 90 at W16	35.5%	19.6%	0.0002	3	PASI 90 at W16	27.0%	18.1%	0.0046
4	sPGA 0/1 at W24	58.7%	31.0%	< 0.0001	4	sPGA 0/1 at W24	49.8%	29.5%	< 0.0001
5	PASI 75 at W24	69.3%	38.1%	< 0.0001	5	PASI 75 at W24	58.7%	37.8%	< 0.0001
6	PASI 90 at W24	42.2%	22.0%	< 0.0001	6	PASI 90 at W24	32.5%	19.7%	0.0001
7	CFB in PSSD Symptom Score at W16	-26.7	-17.8	< 0.0001	7	CFB in PSSD Symptom Score at W16	-28.3	-21.1	< 0.0001
8	ss-PGA 0/1 at W16	70.3%	39.1%	< 0.0001	8	ss-PGA 0/1 at W16	59.7%	36.7%	< 0.0001
9	sPGA 0/1 at W24 and W52	45.5%	22.2%	< 0.0001	9	sPGA 0 at W16	15.7%	6.3%	0.0002
10	PASI75 at W52 and W24	56.3%	30.5%	< 0.0001	10	PSSD Symptom Score 0 at W16	7.5%	4.3%	0.0928
11	PASI90 at W52 and W24	31.0%	15.6%	0.0002					
12	sPGA 0 at W16	17.5%	4.8%	< 0.0001					
13	PSSD Symptom Score 0 at W16	7.9%	4.4%	0.1702					

* Endpoint in the EX-US hierarchy only

[a] Median times are not estimable since less than 50% had relapse in each treatment group. P-value is for Kaplan-Meier comparison of time to relapse.

As a result, two adequately-designed and well-controlled pivotal studies have provided sufficient evidence to support the efficacy of Sotyktu 6 mg QD for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

2.4.2 Safety Results

The safety of Sotyktu was primarily assessed from data of studies IM011046, IM011047, and long-term extension study IM011075. The most common adverse reactions were upper respiratory tract infections, blood creatine phosphokinase increased, herpes simplex, mouth ulcers, and folliculitis. The most common SAEs were COVID-19 and pneumonia. Increased triglyceride and reduced GFR had been reported in more deucravacitinib treated subjects. The safety issues should be adequately described in the

labeling. In addition, post-marketing assessment will be required to further characterize the potential risk of MACE, malignancy, and opportunistic infections after prolonged exposure of deucravacitinib based on the clinical information from JAK inhibitor pharmacologic class.

2.5 Bridging Study Evaluation

The exposure of East Asian healthy volunteers was higher than that in non-East Asian healthy volunteers according the results from clinical trials. But the difference between East Asian psoriasis patients and non-East Asian psoriasis patients decreased to <30 % based on the simulated exposure. Considering the PK characteristics of deucravacitinib, PK performance in East Asian and non-East Asian population, and the flat exposure-response relationship for efficacy and safety. The bridging study can be waived, and ethnic difference was negligible, from PK point of view.

The subgroup analyses of pivotal study IM011046, and cross-study comparison between Asia study IM011065 and Global studies IM011046 & IM011047 demonstrated that the efficacy and safety profile of Sotyktu were generally consistent with that of the overall population. The ethnic difference of clinical efficacy and safety was minimal, thus the bridging study could be waived.

2.6 Conclusion

In conclusion, Sotyktu as the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy demonstrates a favorable risk benefit profile to recommend regular approval.

3. Post-Marketing Requirements

A post-marketing randomized, active-controlled trial (PMR 4336-6) was required to characterize the long-term safety of Sotyktu regarding cardiovascular events, malignancy, and opportunistic infections.