1. NAME OF THE MEDICINAL PRODUCT

SOTYKTU 6 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 6 mg of deucravacitinib.

Excipient with known effect

Each film-coated tablet contains 44 mg of lactose (see section 4.4).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Pink, round, biconvex, film-coated tablet laser printed with “BMS 895”, and “6 mg” on one side in two lines with no content on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SOTYKTU is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

4.2 Posology and method of administration

Treatment should be initiated under the guidance and supervision of a physician experienced in the diagnosis and treatment of psoriasis.

Posology

The recommended dose is 6 mg taken orally once daily.

If a patient shows no evidence of therapeutic benefit after 24 weeks, treatment discontinuation should be considered. The patient's response to treatment should be evaluated on a regular basis.

Special populations

Elderly
No dose adjustment is required in elderly patients aged 65 years and older (see section 5.2). Clinical experience in patients ≥ 75 years is very limited and deucravacitinib should be used with caution in this group of patients.

Renal impairment
No dose adjustment is required in patients with renal impairment, including end stage renal disease (ESRD) patients on dialysis (see section 5.2).

Hepatic impairment
No dose adjustment is required in patients with mild or moderate hepatic impairment. Deucravacitinib is not recommended to be used in patients with severe hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of deucravacitinib in children and adolescents below the age of 18 years have not yet been established. No data are available.

Method of administration

For oral use.

Tablets can be taken with or without food. Tablets should be swallowed whole and should not be crushed, cut, or chewed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Clinically important active infections (e.g. active tuberculosis, see section 4.4).

4.4 Special warnings and precautions for use

Infections

Deucravacitinib may increase the risk of infections (see section 4.8).

Treatment with deucravacitinib should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated (see section 4.3). Caution should be exercised when considering the use of deucravacitinib in patients with a chronic infection or a history of recurrent infection.

Patients treated with deucravacitinib should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a clinically important infection or is not responding to standard therapy, the patient should be monitored carefully and deucravacitinib should not be given until the infection resolves.

Pre-treatment evaluation for tuberculosis

Prior to initiating treatment with deucravacitinib, patients should be evaluated for tuberculosis (TB) infection. Deucravacitinib should not be given to patients with active TB (see section 4.3). Treatment of latent TB should be initiated prior to administering deucravacitinib. Anti-TB therapy should be considered prior to initiation of deucravacitinib in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients receiving deucravacitinib should be monitored for signs and symptoms of active TB.

Malignancies

Malignancies, including lymphomas and non-melanoma skin cancer (NMSC), were observed in clinical studies with deucravacitinib.

It is not known whether tyrosine kinase 2 (TYK2) inhibition may be associated with the adverse reactions of Janus Kinase (JAK) inhibition. In a large randomised active controlled study of a JAK inhibitor in rheumatoid arthritis (RA) patients 50 years and older with at least one additional cardiovascular risk factor, a higher rate of malignancies, particularly lung cancer, lymphoma and NMSC, was observed with a JAK inhibitor compared to tumour necrosis factor (TNF) inhibitors.

Limited clinical data are available to assess the potential relationship of exposure to deucravacitinib and the development of malignancies. Long-term safety evaluations are ongoing. The risks and benefits of deucravacitinib treatment should be considered prior to initiating patients.

Major adverse cardiovascular events (MACE), deep venous thrombosis (DVT) and pulmonary embolism (PE)

It is not known whether TYK2 inhibition may be associated with the adverse reactions of JAK inhibition. In a large randomised active-controlled study of a JAK inhibitor in RA patients 50 years and older with at least one additional cardiovascular risk factor, a higher rate of MACE, defined as cardiovascular death, non-fatal myocardial infarction and non-fatal stroke, and a dose dependent higher rate of venous thromboembolism including DVT and PE were observed with a JAK inhibitor compared to TNF inhibitors.

An increased risk of MACE, DVT and PE was not observed in clinical trials with deucravacitinib. Long-term safety evaluations for deucravacitinib are ongoing. The risks and benefits of deucravacitinib treatment should be considered prior to initiating patients.

Immunisations

Prior to initiating therapy with deucravacitinib, consider completion of all age-appropriate immunisations according to current immunisation guidelines. Use of live vaccines in patients being treated with deucravacitinib should be avoided. The response to live or non-live vaccines has not been evaluated.

Excipients

Lactose
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Clinical studies indicate that deucravacitinib does not have clinically relevant drug interactions upon coadministration with the following other medicinal products and therefore no dose adjustments are needed.

Effect of deucravacitinib on other medicinal products

Deucravacitinib does not meaningfully impact plasma exposures of rosuvastatin (BCRP and OATP substrate), methotrexate (substrate of BCRP and renal transporters), mycophenolate mofetil (MMF) (CES1 and CES2 substrate), or oral contraceptives (norethindrone acetate and ethinyl estradiol).

Effect of other medicinal products on deucravacitinib

Medicinal products that are inhibitors or inducers of CYP enzymes or transporters such as cyclosporine (dual P-gp/breast cancer resistance protein [BCRP] inhibitor), fluvoxamine (strong CYP 1A2 inhibitor), ritonavir (moderate CYP 1A2 inducer), diflunisal (UGT 1A9 inhibitor), pyrimethamine (OCT1 inhibitor), famotidine (H2 receptor antagonist) or rabeprazole (proton pump inhibitor) do not meaningfully affect plasma deucravacitinib exposures (see section 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data on the use of deucravacitinib in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of deucravacitinib during pregnancy.

Breast-feeding

It is unknown whether deucravacitinib/metabolites are excreted in human milk.
Available data in animals have shown excretion of deucravacitinib in milk (see section 5.3).

A risk to the newborns/infants by breast-feeding cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from deucravacitinib therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

The effect of deucravacitinib on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Deucravacitinib has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reaction is upper respiratory infections (18.9%), most frequently nasopharyngitis. The longer-term safety profile of deucravacitinib was similar and consistent with previous experience.

Tabulated list of adverse reactions

The following list of adverse reactions for deucravacitinib is from clinical trials in plaque psoriasis (Table 1). These reactions are presented by MedDRA System Organ Class and by frequency.

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10);
uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Table 1: List of adverse reactions

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Very common	Upper respiratory infections[a]
	Common	Herpes simplex infections[b]
	Uncommon	Herpes zoster
Gastrointestinal disorders	Common	Oral ulcers[c]
Skin and subcutaneous tissue disorders	Common	Acneiform rash[d] Folliculitis
Investigations	Common	Blood creatine phosphokinase increased

[a] Upper respiratory infections include nasopharyngitis, upper respiratory tract infection, viral upper respiratory tract infection, pharyngitis, sinusitis, acute sinusitis, rhinitis, tonsillitis, peritonsillar abscess, laryngitis, tracheitis, and rhinotracheitis.
[b] Herpes simplex infections include oral herpes, herpes simplex, genital herpes, and herpes viral infection.
[c] Oral ulcers include aphthous ulcer, mouth ulceration, tongue ulceration, and stomatitis.
[d] Acneiform rash includes acne, dermatitis acneiform, rash, rosacea, pustule, rash pustular, and papule.

Description of selected adverse reactions

Infections
In POETYK PSO-1 and POETYK PSO-2 (see section 5.1), infections occurred in 29.1% of patients in the deucravacitinib group (116.0 events per 100 person-years) compared to 21.5% of patients in the placebo group (83.7 events per 100 person-years) during the first 16 weeks. The majority of infections were non-serious and mild to moderate in severity and did not lead to discontinuation of deucravacitinib. The incidence of serious infections in the deucravacitinib group was 0.6% (2.0 events per 100 person-years) and in the placebo group was 0.5% (1.6 events per 100 person-years).

The rate of infections in the deucravacitinib group did not increase through week 52 (95.4 events per 100 person-years). The rate of serious infections in the deucravacitinib group did not increase through week 52 (1.7 events per 100 person-years).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse event should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/.

4.9 Overdose

Deucravacitinib has been administered in healthy subjects as single doses up to 40 mg (>6 times the recommended human dose of 6 mg/day) and in multiple doses up to 24 mg/day (12 mg twice daily) for 14 days without dose-limiting toxicity.

In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted immediately. Dialysis does not substantially clear deucravacitinib from systemic circulation (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, ATC code: L04AF07

Mechanism of action

Deucravacitinib selectively inhibits the TYK2 enzyme (TYK2 belongs to the JAK family). Deucravacitinib binds to the regulatory domain of TYK2, stabilizing an inhibitory interaction between the regulatory and the catalytic domains of the enzyme. This results in allosteric inhibition of receptor-mediated activation of TYK2 and its downstream functions in cells. TYK2 mediates signalling of interleukin-23 (IL-23), interleukin-12 (IL-12), and type I interferons (IFN), which are naturally occurring cytokines involved in inflammatory and immune responses. Deucravacitinib inhibits the release of proinflammatory cytokines and chemokines.

Pharmacodynamic effects

In patients with psoriasis, deucravacitinib reduced psoriasis associated gene expression in psoriatic skin including reductions in IL-23-pathway and type I IFN pathway regulated genes. Deucravacitinib reduced IL-17A, IL-19 and β-defensin by 47-50%, 72% and 81-84%, respectively following 16 weeks of once daily treatment.

Clinical efficacy and safety

The efficacy and safety of deucravacitinib were assessed in two multicentre, randomised, double-blind, placebo- and apremilast-controlled clinical studies (POETYK PSO-1 and POETYK PSO-2) in patients who were 18 years of age and older with moderate-to-severe plaque psoriasis and were eligible for systemic therapy or phototherapy. Patients had body surface area (BSA) involvement of ≥ 10%, a Psoriasis Area and Severity Index (PASI) score ≥ 12, and a static Physician's Global Assessment (sPGA) ≥ 3 (moderate or severe) on a 5-point scale of overall disease severity.

POETYK PSO-1 and POETYK PSO-2 evaluated a total of 1686 patients with 843 randomised to deucravacitinib 6 mg once daily, 422 to apremilast 30 mg twice daily, and 421 to placebo.

In both studies, patients receiving placebo switched to deucravacitinib at week 16, which continued up to week 52. Patients randomised to apremilast who did not achieve a PASI 50 (POETYK PSO-1) or PASI 75 (POETYK PSO-2) response at week 24 switched to deucravacitinib, and continued up to week 52. In POETYK PSO-1 patients who were randomised to deucravacitinib continued treatment up to week 52. In POETYK PSO-2, deucravacitinib treated patients who achieved PASI 75 at week 24 were re-randomised 1:1 to continue deucravacitinib (maintenance) or were switched to placebo (withdrawal).

Baseline disease characteristics were consistent for the study population in both studies: the majority of patients were male (67%), mean age was approximately 47 years old with the majority of patients between 40 and 64 years of age. 10% of patients were ≥ 65 years of age. The overall median PASI score was 18.7, and median BSA was 20%. Baseline sPGA score was 3 (moderate) in 79.8% of patients and 4 (severe) in 20.2%. Median Dermatology Life Quality Index (DLQI) score was 11. A total of 18.4% of study patients had a history of psoriatic arthritis.

Across both studies, 40% of patients had received prior phototherapy, 42.4% were naive to any systemic therapy (including biologic and/or non-biologic treatment), 41% received prior non-biologic systemic treatment, and 34.8% had received prior biologic therapy (16.1% TNF, 4.9% IL-12/23, 16.6% IL-17 and 4.4% IL-23 inhibitors).

The co-primary endpoints in the two studies were the proportions of patients who achieved 1) at least a 75% improvement in PASI scores (PASI 75) from baseline and 2) a sPGA score of clear or almost clear (0 or 1) at week 16 versus placebo.

In study POETYK PSO-1, PASI 75 was achieved with deucravacitinib in 58.4%, with apremilast in 35.1% and with placebo in 12.7% of the patients at week 16. Static Physician's Global Assessment (sPGA) of clear or almost clear at week 16 was achieved in 53.6%, 32.1% and 7.2% of the patients in the deucravacitinib, apremilast and placebo groups respectively. For these co-primary endpoints

superiority of deucravacitinib to placebo was demonstrated. Consistent results were seen in study POETYK PSO-2.

Table 2 presents the main efficacy results for the co-primary and other endpoints.

Table 2: Main efficacy results in adults with plaque psoriasis

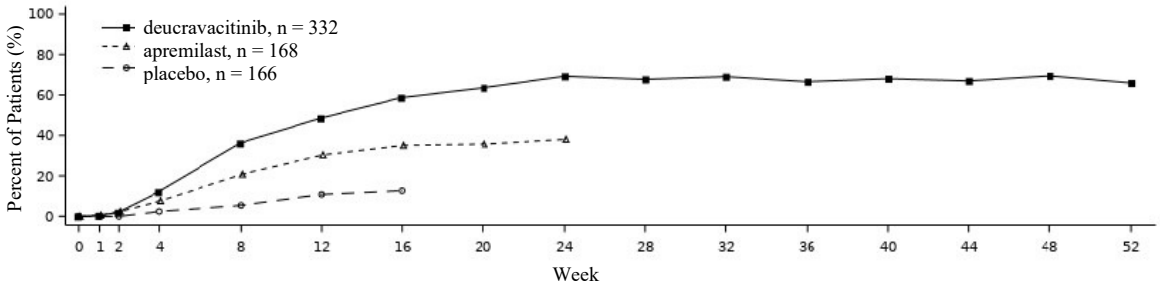
	POETYK PSO-1			POETYK PSO-2		
Endpoint	**Deucravacitinib (N = 332) n (%)**	**Apremilast (N = 168) n (%)**	**Placebo (N = 166) n (%)**	**Deucravacitinib (N = 511) n (%)**	**Apremilast (N = 254) n (%)**	**Placebo (N = 255) n (%)**
sPGA 0/1						
Week 16	178 (53.6)	54 (32.1)[d]	12 (7.2)[a,d]	253 (49.5)	86 (33.9)[d]	22 (8.6)[a,d]
Week 24	195 (58.7)	52 (31.0)[d]	-	251 (49.8)[b]	75 (29.5)[d]	-
sPGA 0						
Week 16	58 (17.5)	8 (4.8)[d]	1 (0.6)[d]	80 (15.7)	16 (6.3)[e]	3 (1.2)[d]
PASI 75						
Week 16	194(58.4)	59 (35.1)[d]	21 (12.7)[a,d]	271 (53.0)	101 (39.8)[e]	24 (9.4)[a,d]
Week 24	230 (69.3)	64 (38.1)[d]	-	296 (58.7)[b]	96 (37.8)[d]	-
PASI 90						
Week 16	118 (35.5)	33 (19.6)[e]	7 (4.2)[d]	138 (27.0)	46 (18.1)[f]	7 (2.7)[d]
Week 24	140 (42.2)	37 (22.0)[d]	-	164 (32.5)[b]	50 (19.7)[d]	-
PASI 100						
Week 16	47 (14.2)	5 (3.0)[d]	1 (0.6)[d]	52 (10.2)	11 (4.3)[f]	3 (1.2)[d]
Scalp Specific PGA 0/1[c]	**(N = 209)**	**(N = 110)**	**(N = 121)**	**(N = 305)**	**(N = 166)**	**(N = 173)**
Week 16	147 (70.3)	43 (39.1)[d]	21 (17.4)[d]	182 (59.7)	61 (36.7)[d]	30 (17.3)[d]

Non-responder imputation (NRI) was used; patients who discontinued treatment or the study prior to the endpoint or had missing data were counted as non-responders.
[a] Co-primary endpoint comparing deucravacitinib with placebo
[b] N = 504 accounting for missed assessments due to COVID-19 pandemic
[c] Includes patients with baseline Scalp Specific PGA score of ≥ 3
[d] $p \leq 0.0001$ for comparison between deucravacitinib and placebo or deucravacitinib and apremilast
[e] $p < 0.001$ for comparison between deucravacitinib and apremilast
[f] $p < 0.01$ for comparison between deucravacitinib and apremilast

Examination of age, gender, race, body weight, duration of disease, baseline disease severity, and previous treatment with biologic or non-biologic agents did not identify differences in response to deucravacitinib among these subgroups.

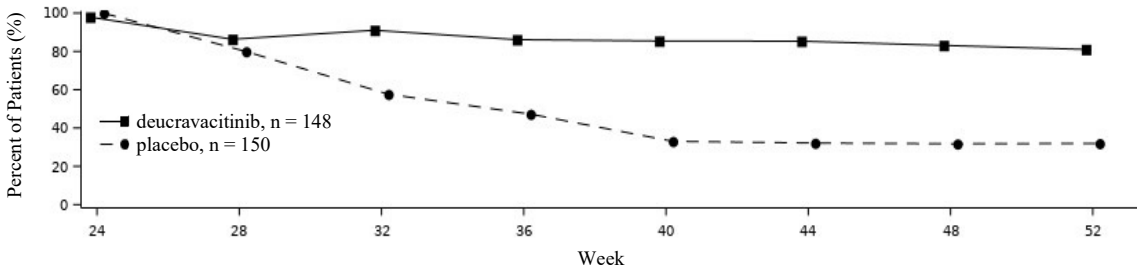
Response over time
Deucravacitinib showed rapid onset of efficacy with maximum PASI 75 response achieved by week 24 (POETYK PSO-1 and PSO-2) and maintained through week 52 (POETYK PSO-1) (see Figure 1).

Figure 1: PASI 75 response (NRI) through week 52 by visit in POETYK PSO-1



Maintenance and durability of response
In POETYK PSO-2, to evaluate maintenance and durability of response, patients who were originally randomised to deucravacitinib and achieved PASI 75 response at week 24, were re-randomised to either continue treatment on deucravacitinib or receive placebo. For responders at week 24 who were re-randomised to placebo, the median time to loss of PASI 75 response was approximately 12 weeks. Figure 2 shows the PASI 75 responses in the two arms from week 24-52.

Figure 2: PASI 75 response (NRI) after re-randomisation at week-24 in POETYK PSO-2



Patient reported outcomes
Significantly greater improvements in health-related quality of life as measured by Dermatology Life Quality Index (DLQI) and in patient reported psoriasis symptoms (itch, pain, burning, stinging, and skin tightness) and signs (skin dryness, cracking, scaling, shedding or flaking, redness, and bleeding) as measured by the Psoriasis Symptoms and Signs Diary (PSSD) were observed in deucravacitinib-treated patients compared to placebo at week 16 and to apremilast at week 16 and week 24. Improvement of these responses in patients receiving continuous deucravacitinib treatment were maintained through week 52 in POETYK PSO-1.

Table 3: Patient reported outcomes in POETYK PSO-1 and POETYK PSO-2

	POETYK PSO-1			POETYK PSO-2		
	Deucravacitinib	Apremilast	Placebo	Deucravacitinib	Apremilast	Placebo
DLQI Patients achieving 0 or 1 (NRI)*	N = 322	N = 161	N = 160	N = 495	N = 247	N = 246
Week 16, n (%)	132 (41.0)	46 (28.6)[a]	17 (10.6)[b]	186 (37.6)	57 (23.1)[b]	24 (9.8)[b]
Week 24, n (%)	155 (48.1)	39 (24.2)[b]	-	205 (41.4)	53 (21.5)[b]	-
PSSD symptom score Change from baseline (mBOCF)**	N = 306	N = 158	N = 151	N = 466	N = 233	N = 239
Week 16, mean (SE)	-26.7 (1.8)	-17.8 (2.2)[b]	-3.6 (2.1)[b]	-28.3 (1.1)	-21.1 (1.4)[b]	-4.7 (1.4)[b]
Week 24, mean (SE)	-31.9 (2.0)	-20.7 (2.4)[b]	-	-29.1 (1.1)	-21.4 (1.5)[b]	-
PSSD sign score Change from baseline (mBOCF)*	N = 306	N = 158	N = 151	N = 466	N = 233	N = 239
Week 16, mean (SE)	-28.9 (1.8)	-20.0 (2.2)[b]	-5.3 (2.1)[a]	-31.9 (1)	-23.8 (1.4)[b]	-7.1 (1.4)[b]
Week 24, mean (SE)	-33.8 (2.0)	-22.5 (2.4)[b]	-	-32.4 (1.1)	-24.2 (1.5)[b]	-

* Patients with baseline score ≥ 2
** Adjusted mean change; mBOCF – modified baseline observation carried forward; standard error (SE)
[a] $p < 0.01$ for comparison between deucravacitinib and placebo or deucravacitinib and apremilast
[b] $p < 0.0001$ for comparison between deucravacitinib and placebo or deucravacitinib and apremilast

Elderly population

Of the 1519 patients with plaque psoriasis treated with deucravacitinib in clinical studies, 152 patients were 65 years or older, including 21 patients who were 75 years or older (see section 4.2). No overall differences in exposure, safety or effectiveness were observed between older and younger patients who received deucravacitinib.

5.2 Pharmacokinetic properties

Deucravacitinib exhibited near complete oral absorption, dose-related increase in exposure, and no evident time-dependent pharmacokinetics.

Absorption

Following oral administration of tablets, deucravacitinib exhibited rapid and near complete absorption. The median T_{max} ranged from 2 to 3 hours and absolute oral bioavailability was 99% in healthy volunteers. Modest accumulation (<1.4-fold at steady state) was observed following once daily dosing.

Food
Deucravacitinib can be administered without consideration for food or gastric pH modulators (H2 receptor blockers and proton pump inhibitors). Co-administration of food or gastric pH modulators did not affect total exposure ($AUC_{[INF]}$) of deucravacitinib.

Distribution

The volume of distribution at steady state (Vss), is 140 L, which is greater than total body water [42 L] indicating extravascular distribution. Deucravacitinib is 81.6% bound to human plasma proteins, primarily to human serum albumin.

Deucravacitinib distributes similarly between plasma and red blood cell components with blood-to-plasma concentration ratio of 1.26.

Biotransformation

In humans, deucravacitinib is metabolised via four primary biotransformation pathways, which include N-demethylation at the triazole moiety by cytochrome P-450 (CYP) 1A2 to form major metabolite BMT-153261, cyclopropyl carboxamide hydrolysis by carboxylesterase 2 (CES2) to form major metabolite BMT-158170, N-glucuronidation by uridine glucuronyl transferase (UGT) to form BMT-334616, and mono-oxidation by CYP 2B6/2D6 at the deuterated methyl group to form M11.

At steady state, deucravacitinib is the major circulating species constituting 49% of measured compound related components. Two major circulating metabolites, BMT-153261 and BMT-158170, were identified, both of which have half-lives comparable to the parent deucravacitinib. BMT-153261 has comparable potency to the parent compound and BMT-158170 is not pharmacologically active. The circulating exposure of BMT-153261 is much lower than the parent compound and therefore, the predominant pharmacological activity is attributed to the parent compound deucravacitinib.

Additionally, no unique to human metabolites and no long-lived circulatory metabolites were identified.

Elimination

Deucravacitinib is eliminated via multiple pathways, including Phase I and II metabolism, along with direct renal and faecal elimination. Additionally, no single enzyme contributed more than 26% of total clearance. Deucravacitinib is extensively metabolised, with 59% of orally administered [^{14}C]-deucravacitinib dose eliminated as metabolites in urine (37% of the dose) and faeces (22% of the dose). Unchanged deucravacitinib in urine and faeces represented 13% and 26% of the dose, respectively.

The terminal elimination half-life of deucravacitinib 6 mg in healthy human adults is 10 hours, with a total clearance of 15.3 L/h (CV 27%). Deucravacitinib is a substrate of efflux transporters, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) and uptake transporter OCT1. Due to high passive permeability, high oral bioavailability and low affinity for these transporters, contribution of these transporters to deucravacitinib pharmacokinetics is minimal.

Deucravacitinib is not a substrate of transporters OATP, NTCP, OAT1, OAT3, OCT2, MATE1, or MATE2K.

Linearity/non-linearity

The pharmacokinetics of single doses of deucravacitinib administered as tablets was linear across 3 mg to 36 mg dose range.

Interactions

Effect of deucravacitinib on other medicinal products
In vitro studies have shown no evidence that deucravacitinib and its major circulating metabolites, at clinically relevant exposures, inhibit major CYPs (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4), UGTs (1A1, 1A4, 1A6, 1A9, 2B7), CES2 and drug transporters (P-gp, BCRP, OATP1B1, OATP1B3, BSEP, MRP2, OAT1, OAT3, OCT1, OCT2, MATE1, and MATE2K). Additionally, deucravacitinib does not induce CYP 1A2, 2B6, and 3A4 (see section 4.5).

Special populations

Elderly
Based on the population pharmacokinetic analysis, deucravacitinib mean steady state exposure ($C_{avg,ss}$) was higher, 31% in patients aged 65-74 years [n = 87 of 1387 (6.3%)] and 53% in patients aged 75-84 years [n = 13 of 1387 (0.94%)]. Exposures in patients aged ≥ 85 years old are not available.

Patients with renal impairment
Renal impairment has no clinically meaningful effect on deucravacitinib exposures (see section 4.2) based on a dedicated study where estimated glomerular filtration rate (eGFR) was determined using a modification of diet in renal disease (MDRD) equation. Compared to normal renal function group, deucravacitinib C_{max} was altered by up to 15% and AUC[$_{INF}$] increased by up to 48% across renal impairment groups (mild (eGFR: ≥ 60 to < 90 mL/min), moderate (eGFR: ≥ 30 to < 60 mL/min), severe (eGFR: < 30 mL/min), and ESRD (eGFR: < 15 mL/min)). Compared to the normal renal function group, BMT-153261 C_{max} increased by up to 34% and AUC[$_{INF}$] increased up to 84% across renal impairment groups.

Dialysis does not substantially clear deucravacitinib from systemic circulation (5.4% of dose cleared per dialysis).

Patients with hepatic impairment
Mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment has no clinically meaningful effect on deucravacitinib exposures (see section 4.2). Compared to normal hepatic function group, total deucravacitinib C_{max} and AUC[$_{INF}$] in mild and moderate hepatic impairment group increased by up to 10% and 40%, respectively while the unbound deucravacitinib C_{max} and AUC($_{INF}$) increased by up to 26% and 60%, respectively. In severe (Child-Pugh Class C) hepatic impaired adults, total deucravacitinib C_{max} was comparable and total AUC was 43% higher relative to matched healthy adults. In these adults, unbound C_{max} and AUC($_{INF}$) increased by 62% and 131%, respectively. Deucravacitinib is not recommended for use in patients with severe hepatic impairment (see section 4.2).

The AUC($_{0-T}$) of BMT-153261 decreased by 19%, 53% and 76% in subjects with mild, moderate, and severe hepatic impairment, respectively, compared to subjects with normal hepatic function, while C_{max} of BMT-153261, decreased by 25%, 59%, and 79% in subjects with mild, moderate, and severe hepatic impairment, respectively.

Gender
Based on population pharmacokinetic modelling and simulation, females are expected to have an about 30% higher deucravacitinib mean steady-state exposure ($C_{max,ss}$ and $C_{avg,ss}$) compared to male.

Body weight
Based on population pharmacokinetic modelling and simulation, patients with lower body weight (< 60 kg) are expected to have a higher geometric mean steady-state exposure of deucravacitinib of 37.4% (C_{maxss}) and 24.8% (C_{avgss}). Patients with a higher body weight (> 90 kg) are expected to have a lower geometric mean steady-state deucravacitinib exposure of 24.8% (C_{maxss}) and 19.6% (C_{avgss}) (compared to patients with body weight 60-90 kg).

Intrinsic factors
Race, and ethnicity did not have a clinically meaningful effect on deucravacitinib exposure.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development.

Repeated dose toxicity

In the chronic toxicity study in rats, decreases in lymphocyte counts, bone marrow cellularity and lymphoid cellularity in tissues of the immune system were observed at exposure (AUC) at lowest-observed-effect-level (LOEL) approximately 9 times the recommended human dose (RHD). These effects were not associated with clinical signs of immunosuppression (e.g., infections). Decreases in platelet counts and red blood cell (RBC) mass parameters were observed at exposure (AUC) at the LOEL approximately 42 times the RHD. In the chronic toxicity study in monkeys, clinical and microscopic skin changes and decreased RBC mass parameters were observed at exposure (AUC) at LOEL approximately 7 times the RHD.

Developmental and reproductive toxicity

Deucravacitinib had no effects on fertility or early embryonic development in male and female rats at exposures (AUC) up to approximately 247 and 171 times the RHD, respectively.
Deucravacitinib was neither embryo-lethal nor teratogenic at maternal exposures (AUC) up to approximately 266 times the RHD in rats or 91/20 (total/free) times the RHD in rabbits.

In a pre- and post-natal development study in rats, transiently lower pup body weights were noted during the pre-weaning period at maternal exposure (AUC) approximately 110 times the RHD. This effect fully recovered during the post-weaning period.

Following administration of radiolabelled deucravacitinib to lactating rats, deucravacitinib and/or its metabolites were present in the milk with milk-to-plasma concentration ratios of 2.7 to 30.9.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose (PH-102)
Anhydrous lactose
Hypromellose acetate succinate
Croscarmellose sodium
Silica, colloidal hydrated
Magnesium stearate

Film-coating

Polyvinyl alcohol
Titanium dioxide
Macrogol
Talc
Iron oxide red
Iron oxide yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

Polyvinyl chloride/polychlorotrifluoroethylene (PVC/PCTFE) clear blister with push through aluminium foil containing 7 or 14 film-coated tablets per blister (calendar blisters).

Pack sizes: 28 film-coated tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. REGISTRATION HOLDER

Bristol-Myers Squibb (Israel) Ltd,
18 Aharon Bart st., POB 3361, Kiryat Arye, Petach Tikva 4951448

8. REGISTRATION NUMBERS

175-38-37671-99

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