Deucravacitinib (Sotyktu™) New Drug Update

September 2022

Nonproprietary Name	deucravacitinib
Brand Name	Sotyktu
Manufacturer	Bristol-Myers Squibb
Form	Tablet
Strength	6 mg
FDA Approval	September 9, 2022
Market Availability	September 2022
FDA Approval Classification	Standard Review
FDB Classification- Specific Therapeutic Class (HIC3)	Antipsoriatic Agents, Systemic (L1A)

INDICATION[1]

Deucravacitinib (Sotyktu) is a tyrosine kinase 2 (TYK2) inhibitor indicated for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. It is not recommended for use in combination with other potent immunosuppressants.

PHARMACOKINETICS

Deucravacitinib is 99% bioavailable after oral dosing. The median time to maximum plasma concentration (Tmax) is 2 to 3 hours. Food does not appear to significantly affect the pharmacokinetics, including a high-fat, high-calorie meals. Deucravacitinib is 82% to 90% protein bound with a blood-to-plasma concentration ratio of 1.26. The primary metabolite, BMT153261, is formed by cytochrome P-450 (CYP) 1A2 metabolism. It has comparable potency to the parent compound and accounts for 20% of the systemic exposure of the drug. Deucravacitinib is also metabolized by CYP2B6, CYP2D6, carboxylesterase (CES) 2, and uridine glucuronyl transferase (UGT) 1A9. The terminal half-life of deucravacitinib is 10 hours. Approximately 13% and 6% of the parent compound and BMT153261, respectively, are eliminated in the urine and approximately 26% and 12%, respectively, are eliminated in the feces.

CONTRAINDICATIONS/WARNINGS

Deucravacitinib is contraindicated in patients with a history of hypersensitivity to any component of the product. Hypersensitivity reactions may include angioedema.

Deucravacitinib may increase the risk of infection, such as pneumonia, coronavirus disease 2019 (COVID-19), and herpes virus reactivation. Deucravacitinib is not recommended in patients with active hepatitis

B or C or active tuberculosis (TB). Screening and monitoring for viral hepatitis and latent and active TB are recommended before starting and during deucravacitinib therapy; if positive for TB, treat TB prior to starting deucravacitinib. If a serious infection of any kind develops during deucravacitinib therapy, interrupt deucravacitinib until the infection resolves or is properly treated.

In clinical trials, malignancies, including lymphoma, were reported with deucravacitinib. Benefits and risks should be considered prior to starting therapy.

Rhabdomyolysis was reported in patients treated with deucravacitinib leading to treatment interruption or discontinuation. Asymptomatic elevations in creatine phosphokinase (CPK) were also reported. If significant CPK increases occur, discontinue deucravacitinib.

Deucravacitinib has been associated with increased triglyceride levels and serum liver transaminase levels. Evaluate liver enzymes prior to starting therapy and evaluate both triglycerides and liver enzymes periodically during therapy in patients with known or suspected liver disease.

All age-appropriate immunizations should be completed prior to starting therapy. Avoid live vaccines.

Increased mortality (e.g., all-cause mortality, major adverse cardiovascular events, thrombosis, malignancies) has been reported with Janus kinase (JAK) inhibitors in patients 50 years of age and older with rheumatoid arthritis and cardiovascular risks. It is unknown if this risk is associated with other members of the JAK family, such as TYK2 inhibitors, like deucravacitinib.

DRUG INTERACTIONS

No drug-drug interactions were reported for deucravacitinib.

COMMON ADVERSE EFFECTS

The most common adverse effects (≥ 1%) reported with deucravacitinib relative to placebo, respectively, in clinical trials, were upper respiratory infections (19.2% versus 14.8%), blood CPK increases (2.7% versus 1.2%), herpes simplex (2% versus 0.2%), mouth ulcers (1.9% versus 0%), folliculitis (1.7% versus 0%), and acne (1.4% versus 0.2%).

In 2 clinical trials (exposure, 986 patient-years), malignancies, such as breast cancer, hepatocellular carcinoma, and lymphoma, were reported among 3 patients treated with deucravacitinib during the 52-week treatment period. Pooled data from these trials plus an open-label extension trial reported lymphoma in 3 deucravacitinib-treated patients.

SPECIAL POPULATIONS

Pregnancy

Data for deucravacitinib in pregnancy are inadequate to advise of maternal or fetal risk. No effect on embryo-fetal development were seen in animal reproductive studies.

Pediatrics

Safety and efficacy of deucravacitinib have not been established in pediatric patients (< 18 years of age).

Geriatrics

In clinical trials, no difference in effectiveness of deucravacitinib were reported between patients ≥ 65 years of age and younger populations. However, serious adverse reactions were reported at a higher rate overall the in the older population.

Hepatic Impairment

No dosage adjustment is required in patients with mild or moderate hepatic impairment. Deucravacitinib is not recommended in patients with severe hepatic impairment (Child-Pugh C).

Renal Impairment

No dosage adjustment is required in patients with any level of renal impairment, including end stage renal disease (ESRD).

DOSAGES

The recommended dosage of deucravacitinib is 6 mg orally once daily, with or without food. Tablets should not be crushed, chewed, or cut.

CLINICAL TRIALS[2,3]

A literature search was performed using "deucravacitinib" and "psoriasis."

The efficacy and safety of deucravacitinib were assessed in two double-blind, placebo-controlled, and active-controlled clinical trials, PSO-1 (NCT03624127) and PSO-2 (NCT03611751). They included a total of 1,684 adults with moderate to severe plaque psoriasis who were eligible for systemic therapy or phototherapy.[4] Enrolled patients had psoriasis body surface area (BSA) involvement of ≥ 10% of (median at baseline, 20%), Psoriasis Area and Severity Index (PASI) score ≥ 12, and a static Physician's Global Assessment (sPGA) ≥ 3. Across both trials, 40% of patients received prior phototherapy, 41% received prior non-biologic systemic treatment, 35% had received prior biologic therapy, and 42% had received no prior systemic therapy. Both trials randomized patients 2:1:1 to deucravacitinib 6 mg orally once daily, placebo, or apremilast 30 mg orally twice daily. At week 16, all patients randomized to placebo were switched to deucravacitinib. The **co-primary endpoints** in both trials were the proportion of patients who achieved **sPGA score** of 0 (clear) or 1 (almost clear) with ≥ 2-grade improvement from baseline and the proportion of patients who achieved ≥ 75% improvement from baseline in the **PASI score (PASI 75)** at week 16, each compared to placebo. Comparison of these measures to apremilast at week 16 were secondary endpoints.

In **PSO-1** at week 16, a **sPGA score** of 0/1 was achieved by 54% of patients in the deucravacitinib group, 7% in the placebo group, and 32% in the apremilast group ($p<0.0001$ versus placebo and apremilast). **PASI 75** was achieved by 58%, 13%, and 35% of patients in each group, respectively ($p<0.0001$ versus placebo and apremilast). Regarding additional secondary endpoints, among deucravacitinib-treated patients with an sPGA 0/1 response at week 24, 78% maintained sPGA 0/1 at week 52 and among this group who had PASI 75 at week 24, 82% maintained a PASI 75 at week 52.

Similarly, in **PSO-2** at week 16, a **sPGA** score of 0/1 was achieved by 50% of patients in the deucravacitinib group, 9% in the placebo group, and 34% in the apremilast group ($p<0.0001$ versus placebo and apremilast). **PASI 75** was achieved by 53%, 9%, and 40% of patients in each group, respectively, versus

placebo (p<0.001)and apremilast (p=0.003). Patients in the deucravacitinib group who had achieved PASI 75 at week 24 were re-randomized to continue deucravacitinib or switch to placebo. Secondary endpoints showed that among these patients who also had an sPGA score of 0/1 at week 24, 70% who continued deucravacitinib maintained sPGA 0/1 at week 52 compared to 24% who were switched to placebo. Also, PASI 75 was maintained at week 52 in 80% of patients who continued deucravacitinib versus 31% who were switched to placebo. Among patients who were switched to placebo, the median time to loss of a sPGA score of 0/1 was 8 weeks and PASI 75 and 12 weeks.

In both trials, other secondary endpoints, including PASI 90 at weeks 16 and 24 and scalp sPGA (ssPGA) of 0/1 (ssPGA reported only in patients with baseline ss-PGA ≥ 3) at week 16, favored deucravacitinib over placebo and apremilast, respectively (PASI 90 at week 16: PSO-1, 36%, 4%, and 20%; PSO-2, 27%, 3%, and 18%; PASI 90 at week 25: PSO-1, 42%, not reported, and 22%; PSO-2, 32%, not reported, and 20%; ssPGA 0/1 at week 16: PSO-1, 70%, 17%, and 39%; PSO-2, 60%, 17%, and 37%).

Across both studies, at week 16, 1.8% of patients in the deucravacitinib group compared to 2.9% and 1.2% of patients in the placebo and apremilast groups experienced a serious adverse event. In addition, 2.4%, 3.8%, and 5.2% of patients in the deucravacitinib, placebo, and apremilast groups, respectively, discontinued therapy due to adverse events.

OTHER DRUGS USED FOR CONDITION[5,6,7,8,9,10,11,12,13,14,15,16,17,18]

Other non-biologic agents approved to treat moderate to severe plaque psoriasis include the oral phosphodiesterase 4 (PDE4) inhibitor apremilast (Otezla®; adults only) as well as methotrexate (MTX), cyclosporine, acitretin, and methoxsalen. Non-steroidal topical options for psoriasis of any severity include the aryl hydrocarbon receptor agonist tapinarof (Vtama®), approved for use in adults, and the PDE4 inhibitor roflumilast (Zoryve™) for plaque psoriasis, including intertriginous areas, in patients as young as 12 years. Injectable biologic immunotherapy agents for this indication include tumor necrosis factor alfa (TNFα) inhibitors (e.g., adalimumab [Humira®], certolizumab pegol [Cimzia®], etanercept [Enbrel®], infliximab [Remicade® and its biosimilars) and inhibitors of various interleukins (IL) including IL-12, IL-17, IL-17A, and IL-23 (e.g., brodalumab [Siliq®], guselkumab [Tremfya®], ixekizumab [Taltz®], risankizumab-rzaa [Skyrizi®], secukinumab [Cosentyx®], tildrakizumab-asmn [Ilumya®], ustekinumab [Stelara®]) – ixekizumab, secukinumab, and ustekinumab are approved for use in pediatric patients ≥ 6 years of age and etanercept may be used in those as young as 4 years.

PLACE IN THERAPY[19,20,21,22]

Psoriasis is a chronic, multisystem, immune-mediated, inflammatory disease involving the skin and joints and is characterized by hyperproliferation of epidermal keratinocytes. It affects an estimated 8 million people in the United States (US). Psoriasis can present at any age, but onset is highest between 20 to 30 years and 50 to 60 years. Approximately 60% of people with psoriasis report that the condition negatively impacts their daily life. Nearly 25% of people with psoriasis have moderate to severe cases.

Treatment is based on the severity of the condition. Systemic agents are usually reserved for treatment of patients with moderate to severe plaque psoriasis. Candidates for systemic therapy include those with a BSA involvement > 10% and/or disease affecting special areas of the body (e.g., hands, feet, head and neck, genitalia). The American Academy of Dermatology (AAD) in collaboration with the National Psoriatic Foundation (NPF) recommends systemic therapy with non-biologic agents (e.g., apremilast,

methotrexate, cyclosporine, acitretin). If an adequate response is not achieved with a non-biologic agent, the group recommends either switching to another non-biologic agent or to a different treatment modality, including topical therapy, phototherapy, or biologic immunotherapy.

Deucravacitinib (Sotyktu) is a first-in-class, oral, selective TYK2 inhibitor. It inhibits IL-12, IL-23, and type 1 interferon signaling. While it is a member of the Janus kinase (JAK) inhibitor family, it does not inhibit JAK 1, 2, or 3 to a meaningful extent and does not carry the Boxed warnings regarding increased risk of serious infections, mortality, malignancy, major adverse cardiovascular events, and thrombosis. Deucravacitinib could compete with twice-daily, oral apremilast (Otezla) for the treatment of moderate to severe plaque psoriasis in patients who are candidates for phototherapy or systemic therapy. In clinical trials, deucravacitinib demonstrated a favorable safety profile and significant improvement in skin clearance and symptom burden compared to apremilast. This, along with its convenient once-daily oral dosing schedule, could make deucravacitinib a desirable oral option for patients with moderate to severe plaque psoriasis.

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	Cytokine and CAM Antagonists
Clinical Edit	**Initial Approval Criteria** ▪ Patient is ≥ 18 years of age; **AND** ▪ Patient has moderate to severe plaque psoriasis as assessed utilizing an objective measure/tool; **AND** ▪ Patient has documented plaque psoriasis diagnosis for ≥ 6 months; **AND** ▪ Patient has moderate to severe disease with at least ONE of the following: – Involvement of ≥ 3% of body surface area (BSA); **OR** – Psoriasis Area and Severity Index (PASI) score ≥ 10; **OR** – Incapacitation or serious emotional consequences due to plaque location (e.g., hands, feet, head and neck, genitalia) or with intractable pruritis; **AND** ▪ Patient did NOT respond adequately (or is not a candidate) to a 4-week minimum trial of topical agents (e.g., anthralin, coal tar preparations, corticosteroids, emollients, immunosuppressives, keratolytics, retinoic acid derivatives), vitamin D analogues); **AND** ▪ Patient did NOT respond adequately (or is not a candidate) to a 3-month minimum trial of at least 1 non-biologic systemic agent (e.g., immunosuppressives, retinoic acid derivatives, and/or methotrexate); **AND** ▪ Patient did not respond adequately (or is not a candidate*) to a 3-month minimum trial of phototherapy (e.g., psoralens with UVA light (PUVA) or UVB with coal tar or dithranol); **AND** ▪ Patient does NOT have severe hepatic impairment (Child-Pugh C); **AND** ▪ Patient does NOT have an active infection, including clinically important localized infections; **AND**

Suggested Utilization Management (continued)

Clinical Edit (continued)	▪ Patient is negative for active and latent tuberculosis (TB) and will receive ongoing monitoring for presence of TB during therapy; **AND** ▪ Patient is NOT on concurrent treatment with tumor necrosis factor [TNF] inhibitor, biologic response modifier, or other non-biologic immunomodulator (tofacitinib [Xeljanz®, Xeljanz XR®], baricitinib [Olumiant®], upadacitinib [Rinvoq™]); **AND** ▪ Deucravacitinib will not be used in combination with other potent immunosuppressants (e.g., cyclosporine, mycophenolate mofetil, sirolimus, tacrolimus); **AND** ▪ Prescriber has counseled patient on the importance of completing all age-appropriate immunizations according to current guidelines prior to initiating therapy; **AND** ▪ Patient will not receive a live vaccine during therapy. **Contraindications to phototherapy include:* – *Xeroderma pigmentosum* – *Pregnancy or lactation (PUVA only)* – *Lupus Erythematosus* – *History of one of the following: photosensitivity diseases (e.g., chronic actinic dermatitis, solar urticaria), melanoma, non-melanoma skin cancer, extensive solar damage (PUVA only), or treatment with arsenic or ionizing radiation* – *Immunosuppression in an organ transplant patient (UVB only)* – *Photosensitizing medications (PUVA only)* – *Severe liver, renal, or cardiac disease (PUVA only)* **Renewal Criteria** ▪ Patient must continue to meet the above criteria; **AND** ▪ Patient must have disease improvement compared to baseline in signs and symptoms, such as redness, thickness, scaliness, and/or body surface area (BSA) involvement and/or improvement on a disease activity scoring tool (e.g., Psoriasis Area and Severity Index [PASI] score, a Physician's Global Assessment [sPGA], Dermatology Life Quality Index [DLQI]); **AND** ▪ Patient has NOT experienced any treatment-restricting adverse effects (e.g., hypersensitivity reaction, TB reactivation, severe infection, malignancy, severe elevation of creatinine kinase [CPK], severe hepatotoxicity, rhabdomyolysis, major adverse cardiovascular event [MACE], thrombosis [pulmonary embolism, deep vein thrombosis]).
Quantity Limit	30 tablets per 30 days
Duration of Approval	Initial: 6 months Renewal: 6 months
Drug to Disease Hard Edit	Any active serious infection (TB, hepatitis, etc.) Severe hepatic impairment (Child-Pugh C)

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