Mallinckrodt Announces UVADEX® (Methoxsalen) Approved in Australia for use with the THERAKOS® CELLEX® Photopheresis System for Treatment of Chronic Graft Versus Host Disease (cGvHD) and Skin Manifestations of Cutaneous T-Cell Lymphoma (CTCL) in Adults

October 31, 2019

-Approval marks first combined indication label and first regulatory approval in the world for UVADEX in conjunction with the THERAKOS Extracorporeal Photopheresis (ECP) System for the treatment of chronic GvHD in adults-

STAINES-UPON-THAMES, United Kingdom, Oct. 31, 2019 /PRNewswire/ -- Mallinckrodt plc (NYSE: MNK), a global biopharmaceutical company, today announced that UVADEX® (methoxsalen) has received regulatory approval in Australia by the Therapeutic Goods Administration (TGA) for extracorporeal administration with the THERAKOS® CELLEX® Photopheresis System. The treatment is indicated for steroid-refractory and steroid-intolerant chronic graft versus host disease (cGvHD) in adults following allogeneic hematopoietic stem cell (HSC) transplantation. The TGA also approved Uvadex in conjunction with the THERAKOS CELLEX Photopheresis System for the palliative treatment of skin manifestations of cutaneous T-cell lymphoma (CTCL) that is unresponsive to other forms of treatment.

The TGA approval marks the first combined indication label and the first regulatory approval in the world for UVADEX in conjunction with the THERAKOS Photopheresis System for the treatment of chronic graft versus host disease in adults.

"The TGA approval of UVADEX with the Therakos ECP platform opens up new treatment options for patients with these challenging conditions," said **Steven Romano, M.D., Executive Vice President and Chief Scientific Officer, Mallinckrodt**. "The cGvHD indication is also an important milestone for Mallinckrodt, confirming the potential benefit of this therapeutic option for patients who are refractory to or intolerant of steroid treatments."

About Chronic Graft Versus Host Disease (cGvHD)

Graft-versus-host-disease is a common complication of hematopoietic stem cell (HSC) transplantation resulting in significant morbidity and mortality.[1] It can be classified as acute or chronic based on the clinical presentation and the time of occurrence after the transplantation. Signs and symptoms of cGvHD nearly always occur within the first year post transplantation but can occasionally happen several years later.[2] In cGvHD, the skin is the most frequently affected organ with manifestations of itchy rash, hyper or hypopigmentation and changes in texture. However, the disease can affect multiple sites, which may have a major impact upon a patient's quality of life.[2,3] Chronic GvHD can lead to debilitating consequences, such as joint contractures, loss of sight, end-stage lung disease, or mortality resulting from profound chronic immune suppression leading to recurrent or life-threatening infections.[1]

About Cutaneous T-Cell Lymphoma (CTCL)

Cutaneous T-cell lymphoma (CTCL) is an umbrella term for a group of non-Hodgkin lymphomas involving T lymphocytes that localize in the skin. It is a relatively rare cancer, with 2,500 to 3,000 new cases per year in the United States.[4] The age of onset of the condition is typically greater than 50 years, with the incidence rising significantly in the later decades of life.[5] CTCL causes visible skin symptoms ranging from a small rash to extensive redness, peeling, burning, soreness, and itchiness all over the body.[6,7] CTCL falls into different categories based on the severity of the disease and symptoms.[8]

Minimum Product Information: UVADEX® (methoxsalen) Concentrated Injection for extracorporeal circulation via photopheresis (ECP)

This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

Indications in Australia: UVADEX (methoxsalen) is indicated for extracorporeal administration with the THERAKOS CELLEX Photopheresis System for the:

- treatment of steroid-refractory and steroid-intolerant chronic graft versus host disease (cGVHD) in adults following allogeneic HSC transplantation.
- palliative treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL) that is unresponsive to other forms of treatment.

Contraindications: History of idiosyncratic or hypersensitivity reaction to methoxsalen, psoralen compounds or any excipients of UVADEX; co-existing melanoma, basal cell or squamous cell skin carcinoma; lactation; aphakia. ECP procedure contra-indications: Photosensitive disease; inability to tolerate extracorporeal volume loss; WBC count > 25,000 mm^3; previous splenectomy; coagulation disorders. **Special warnings and precautions:** Only physicians who have special competence in the

diagnosis and treatment of cGVHD and CTCL who have special training and experience with the THERAKOS CELLEX Photopheresis System should use UVADEX. Men and women being treated with UVADEX should take adequate contraceptive precautions both during and after completion of photopheresis treatment. Exposure to large doses of UVA causes cataracts in animals, an effect enhanced by the administration of oral methoxsalen. The patient's eyes should be protected from UVA light by wearing wrap-around, UVA-opaque sunglasses during the treatment cycle and during the following 24 hours. Exposure to sunlight or ultraviolet radiation (even through window glass) may result in serious burns and, in the long-term, "premature aging" of the skin therefore patients should avoid exposure to sunlight during the 24 hours following photopheresis treatment. Thromboembolic events, such as pulmonary embolism and deep vein thrombosis, have been reported with UVADEX administration through photopheresis systems for treatment of patients with graft versus host disease. This product contains 4.1% w/v ethanol and each 1 mL of UVADEX contains 40.55 mg of ethanol. Caution is advised in patients with liver disease, alcoholism, epilepsy, brain injury or disease. No specific information is available for use in renal or hepatic impairment and there is no evidence for dose adjustment in the elderly. The safety and efficacy of UVADEX have not been established in children. **Use in pregnancy**: Category D. **Use in Lactation**: UVADEX is contra-indicated. **Interactions with other medicines:** Effects on P450 system metabolism may affect clearance / activation of other drugs (caffeine, paracetamol) or may extend the methoxsalen half-life leading to prolonged photosensitivity in patients. Methoxsalen binding to albumin may be displaced by dicoumarol, warfarin, promethazine and tolbutamide with potential for enhanced photosensitivity. Caution when treating with concomitant photosensitising agents. **Adverse effects:** In the clinical trials, published information and postmarketing surveillance of UVADEX/ECP, adverse events were usually mild and transient and in most cases, related to the underlying pathology. *Very common*: diarrhoea, anaemia, nausea, headache, hypertension, sinusitis, upper respiratory tract infection, fatigue, pain in extremity, pyrexia, cough, dyspnoea, cushingoid, dry eye, photophobia, toothache, anorexia. *Common*: depression, lacrimation increased, abdominal pain, hypokalaemia, paraesthesia oral, pharyngolaryngeal pain, tachycardia, conjunctivitis, eye pain, visual acuity reduced, dysphagia, chills, mucosal inflammation, nasopharyngitis, contusion, blood pressure diastolic decreased, haemoglobin decreased, hyperglycaemia, hypocalcaemia, neuropathy peripheral, tremor, rash, hypotension. Additional adverse effects seen in clinical trials include vomiting, infections. Adverse events related to the ECP/CELLEX procedure – thromboembolism and severe allergic reactions, vascular access complication, vasovagal spasm, hickman catheter infection/thrombosis, headache, hypercoagulability, haemolysis. Additional adverse events identified post-marketing: anaphylactic reaction, allergic reaction, dysgeusia, exacerbation of congestive heart failure, sepsis, endocarditis, and vomiting. **Dosage and Administration**: Chronic Graft versus Host Disease: Three ECP treatments in the first week then two ECP treatments per week for at least 12 weeks, or as clinically indicated. Cutaneous T-cell Lymphoma: ECP treatment on two successive days each month for six months. Patients who show an increase in skin scores after eight treatment sessions may have their treatment schedule increased to two successive days every two weeks for the next three months. Refer to full Product Information and THERAKOS CELLEX Operator's Manual for information regarding administration.

Store below 25°C. Date of first approval: 16 September 2019. Date of revision: 11 October 2019.

Indications and Prescribing Information for Uvadex vary globally. Please refer to the individual country product label for complete information.

Before prescribing Uvadex, please refer to the full Product Information also available by calling + 1 800.778.7898.

ABOUT THERAKOS
Mallinckrodt is the world's only provider of approved, fully-integrated systems for administering immunomodulatory therapy through ECP. Its Therakos ECP platforms, including the latest generation THERAKOS ™ CELLEX ™ Photopheresis System, are used by academic medical centres, hospitals, and treatment centres in nearly 40 countries and have delivered more than 1 million treatments globally. For more information, please visit www.therakos.co.uk.

Terumo BCT is the exclusive distributor of the Therakos ECP platform in Australia, as well as Latin America and select countries in Europe. To learn more about Terumo BCT, visit www.terumobct.com.

UVADEX (methoxsalen) and THERAKOS CELLEX Photopheresis Systems are separately approved in a number of global markets. Please refer to your local approved labelling for Uvadex and the Operator's Manual for CELLEX for more information on approved uses for specific indications.

Before administering therapy using the THERAKOS CELLEX Photopheresis System, please refer to the Operator's Manual available at +61 2 9429 3600 or +1 (800)778-7898.

ABOUT MALLINCKRODT
Mallinckrodt is a global business consisting of multiple wholly owned subsidiaries that develop, manufacture, market and distribute specialty pharmaceutical products and therapies. The company's Specialty Brands reportable segment's areas of focus include autoimmune and rare diseases in specialty areas like neurology, rheumatology, nephrology, pulmonology and ophthalmology; immunotherapy and neonatal respiratory critical care therapies; analgesics and gastrointestinal products. Its Specialty Generics reportable segment includes specialty generic drugs and active pharmaceutical ingredients. To learn more about Mallinckrodt, visit www.mallinckrodt.com.

Mallinckrodt uses its website as a channel of distribution of important company information, such as press releases, investor presentations and other financial information. It also uses its website to expedite public access to time-critical information regarding the company in advance of or in lieu of distributing a press release or a filing with the U.S. Securities and Exchange Commission (SEC) disclosing the same information. Therefore, investors should look to the Investor Relations page of the website

for important and time-critical information. Visitors to the website can also register to receive automatic e-mail and other notifications alerting them when new information is made available on the Investor Relations page of the website.

CAUTIONARY STATEMENTS RELATED TO FORWARD-LOOKING STATEMENTS

This release includes forward-looking statements for Mallinckrodt concerning THERAKOS Photopheresis including potential benefits associated with its use. The statements are based on assumptions about many important factors, including the following, which could cause actual results to differ materially from those in the forward-looking statements: satisfaction of regulatory and other requirements; actions of regulatory bodies and other governmental authorities; changes in laws and regulations; issues with product quality, manufacturing or supply, or patient safety issues; and other risks identified and described in more detail in the "Risk Factors" section of Mallinckrodt's most recent Annual Report on Form 10-K and other filings with the SEC, all of which are available on its website. The forward-looking statements made herein speak only as of the date hereof and Mallinckrodt does not assume any obligation to update or revise any forward-looking statement, whether as a result of new information, future events and developments or otherwise, except as required by law.

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1Filipovich, Biol Blood Marrow Transplant 2005; 11:945-956
2Jagasia 2015. Biol Blood Marrow Transplant. 2015; 21(3): 389–401.
3Pavletic et al. Biol Blood Marrow Transplant. 2006;12:252–66.
4Agar NS, Wedgeworth E, Crichton S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. *JCO*. 2010;28:4730–4739
5Kim YH, Liu HL, Mraz-Gernhard S, et al. Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome: clinical prognostic factors and risk for disease progression. *Arch Dermatol*. 2003;139:857–866.
6Knobler R, et al. J Eur Acad Dermatol Venereol. 2014;28 Suppl 1:1-37.
7Sokołowska-Wojdyło M, et al. Postepy Dermatol Alergol. 2015;32(5):368-383.
8Trautinger F, et al. Eur J Cancer. 2006;42(8):1014-1030

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