# About Otsuka

## Otsuka–people creating new products for better health worldwide.

**Otsuka's roots date back to 1921, when the original Otsuka Factory was founded in Tokushima, Japan.**

In 1964, Otsuka Pharmaceutical Co, Ltd. (OPC) was established to enhance Otsuka's pharmaceutical product development and commercialization. The company has since grown and diversified, investing in local enterprises and establishing corporations in 18 countries and regions around the world. These comprise the Otsuka Pharmaceutical Group, a collection of 106 companies employing more than 33,000 people worldwide.

In the U.S., Otsuka America, Inc. has three pharmaceutical subsidiaries: Otsuka America Pharmaceutical, Inc. (OAPI),* Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC)* and Otsuka Maryland Medicinal Laboratories, Inc. (OMML).*

OAPI is a successful, innovative, fast-growing healthcare company that commercializes Otsuka-discovered and other product opportunities in North America, with a strong focus on and commitment to oncology, neuroscience, cardiology, and gastroenterology. Since its establishment in 1989, OAPI has a solid reputation for providing quality products, engaging well-trained professionals, and contributing to an industry that is undergoing significant and rapid changes.

OPDC develops drug candidates following initial discovery of a compound through life cycle management, developing a strategy and preparing a plan that will lead to ultimate global registration and marketing of the product. The Company is dedicated to the improvement of the quality of human life and health of patients around the world with a strong commitment to research and development in the areas of cardiovascular, gastrointestinal, respiratory, renal and neuroscience systems, and to treat cancer and ophthalmic disorders.

OMML is focused on basic and applied research, conducting innovative basic research to support global clinical studies and engaging in drug discovery in conjunction with Otsuka Pharmaceutical Co., Ltd. in Japan.

Otsuka is comprised of a vast, global network of employees who share a commitment to enhance the health and quality of human life around the world. Otsuka's employees embrace the corporate spirit and vision for which the company is known around the world, leveraging the advantages of its global presence, scientific resources and long-term commitment to research to fulfill its mission of improving people's health and quality of human life.

*OAPI, OPDC and OMML are subsidiaries of Otsuka America, Inc. (OAI), a holding company established in the U.S. in 1989. OAI is wholly owned by Otsuka Pharmaceutical Co., Ltd.

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# IVBusulfex®
(busulfan) Injection

# Otsuka and IV Busulfex®

**Otsuka is a health care company dedicated to improving the quality of human life, with an unwavering passion for treating patients with serious illnesses and unmet medical needs.**

The Company is focused on global opportunities to contribute to the health of patients and dedicated to providing effective and safe cancer therapies that significantly improve patients' prognosis and quality of life.

In 2008, Otsuka acquired IV Busulfex® (busulfan), a first-in-class drug therapy for conditioning prior to allogeneic hematopoietic progenitor cell transplantation (HSCT). We invite you to take a closer look at IV Busulfex and learn how Otsuka is working to help bone marrow transplant patients and the health care professionals that treat them.

## About IV Busulfex

### Indication

IV Busulfex is approved for use in combination with cyclophosphamide as a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia (CML). IV Busulfex is the only drug that is FDA-approved as a conditioning agent for allogeneic hematopoietic stem cell transplantation.

IV Busulfex is an intravenous form of busulfan, an oral drug with an almost 50-year history in cancer treatment. IV Busulfex for intravenous injection was created to minimize problems associated with first-pass metabolism and drug absorption. It is a unique formulation of busulfan, which is well established with proven benefits for patients in the HSCT field.

### Mechanism of Action

IV Busulfex is a bifunctional alkylating agent. The alkyl groups irreversibly bind to the DNA of rapidly dividing cells, leading to apoptosis. The net effect is profound reduction of myeloid cells combined with immuno-suppression. As a result, the patient is prepared for stem cell transplantation, which following high-dose chemotherapy, is the only treatment that has shown a consistent cure rate in CML.

### Benefits of Intravenous Administration

IV Busulfex® allows consistent patient systemic drug exposure because intravenous administration means:

- Predictable linear intra- and inter-patient pharmacokinetics
- Therapeutic drug monitoring is possible with all patients
- Therapy can be individualized to target optimal therapeutic exposure to balance efficacy and toxicity
- Ease of administration

### Efficacy

Data from a clinical trial of 61 patients receiving an allogeneic transplant demonstrate that IV Busulfex has consistent linear pharmacokinetics, has efficacy as evidenced by sustained engraftment, has a low incidence of hepatic veno-occlusive disease, and has no unexpected toxicities. Further, it has clinical utility in patients over 50 years of age.

Engraftment was successful in all evaluable patients. Sixty-two percent of patients were free from disease with a median follow-up of 269 days post-treatment and 70% of patients were alive with a median follow-up of 288 days post-treatment.

**Important Safety Information** At the recommended dosage, IV Busulfex produced profound myelosuppression in all patients (ie, severe granulocytopenia, thrombocytopenia, anemia, or a combination thereof). Frequent complete blood counts should be monitored during treatment and until recovery. Hepatic veno-occlusive disease was diagnosed in 5/61 patients and was fatal in 2/5 cases. Anticonvulsant prophylactic therapy should be administered prior to treatment. Caution should be exercised in patients with a history of seizure disorder or head trauma or who are receiving other potentially epileptogenic drugs. Bronchopulmonary dysplasia with pulmonary fibrosis is a rare but serious condition following chronic busulfan therapy. Women of childbearing potential should be advised to avoid becoming pregnant as busulfan may cause fetal harm.

The most common nonhematologic adverse events were nausea (92% mild/moderate, 7% severe), stomatitis (71% grade 1–2, 26% grade 3–4), vomiting (95% mild/moderate) anorexia (64% mild/moderate, 21% severe), diarrhea (75% mild/moderate, 5% grade 3-4) insomnia (83% mild/moderate, 1% severe), and fever (78% mild/moderate, 3% life-threatening).

Please see accompanying Full Prescribing Information.

**WARNING:** BUSULFEX® (busulfan) Injection is a potent cytotoxic drug that causes profound myelosuppression at the recommended dosage. It should be administered under the supervision of a qualified physician who is experienced in allogeneic hematopoietic stem cell transplantation, the use of cancer chemotherapeutic drugs and the management of patients with severe pancytopenia. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available. SEE "WARNINGS" SECTION OF FULL PRESCRIBING INFORMATION FOR INFORMATION REGARDING BUSULFAN-INDUCED PANCYTOPENIA IN HUMANS.

For information about Busulfex clinical trials, please visit www.clinicaltrials.gov.