Erlotinib (Tarceva)

**Manufacturer:** Genentech, Inc./OSI Pharmaceuticals, Inc.

**Indication:** Erlotinib (Tarceva), in combination with gemcitabine (Gemzar, Eli Lilly), is indicated for the first-line treatment of patients with locally advanced, unrespectable or metastatic pancreatic cancer.

**Drug Class:** Erlotinib is a human epidermal growth factor receptor type-1/epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor. Its chemical name is \( N-(3\text{-ethynylphenyl})-6,7\text{-bis}(2\text{-methoxyethoxy})-4\text{-quinazolinamine}. \)

**Uniqueness of Drug:** Erlotinib inhibits the intracellular phosphorylation of tyrosine kinase associated with the epidermal growth factor receptor (EGFR). Its specificity of inhibition of other tyrosine kinase receptors has not been fully characterized. EGFR is expressed on the cell surfaces of normal cells and cancer cells.

**Warnings:**

**Pulmonary Toxicity.** There have been infrequent reports of serious interstitial lung disease (ILD)-like events, including fatalities, in patients receiving erlotinib for the treatment of NSCLC, pancreatic cancer, or other advanced solid tumors. In the pancreatic cancer study, the incidence of these events was 2.5% with erlotinib/gemcitabine and 0.4% with placebo/gemcitabine.

Reported diagnoses in patients thought to have ILD-like events included pneumonitis, radiation and hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, acute respiratory distress syndrome, and lung infiltration. Symptoms began from five days to more than nine months (median, 39 days) after erlotinib therapy was initiated.

**Myocardial Infarction and Ischemia.** In the pancreatic carcinoma trial, myocardial infarction (MI)/ischemia developed in six patients receiving erlotinib/gemcitabine (with an incidence of 2.3%). One of these patients died because of an MI. In comparison, three patients receiving placebo/gemcitabine developed MIs (incidence, 1.2%); MI was the cause of death in one of these patients.

**Cerebrovascular Accident.** In the same trial, six patients who were given erlotinib/gemcitabine experienced cerebrovascular accidents (CVAs) (incidence, 2.3%). One of the CVAs was hemorrhagic, and this was the only fatal event. In comparison, the placebo/gemcitabine patients had no CVAs.

**Microangiopathic Hemolytic Anemia with Thrombocytopenia.** In the trial, two patients receiving erlotinib and gemcitabine concurrently developed microangiopathic hemolytic anemia with thrombocytopenia (incidence, 0.8%). This event did not occur with any patients in the placebo/gemcitabine arm.

**Pregnancy Category D.** Erlotinib has been shown to cause maternal toxicity with associated embryo and fetal lethality and abortion in rabbits when it was given at doses that result in plasma drug concentrations of approximately three times those in humans (i.e., an area-under-the-curve [AUC] concentration at a 150-mg daily dose).

**Precautions:** Co-treatment with the potent cytochrome CYP3A4 inhibitor ketoconazole increases the AUC of erlotinib by two thirds. Caution should be used when administering erlotinib with ketoconazole and other strong CYP3A4 inhibitors.

Asymptomatic increases in liver transaminase levels have been observed with erlotinib; therefore, periodic liver function testing of transaminase, bilirubin, and alkaline phosphatase levels should be considered.

The erlotinib dose should be reduced or therapy interrupted if changes in liver function are severe. In vitro and in vivo evidence suggest that erlotinib is cleared primarily by the liver. Therefore, erlotinib exposure may be increased in patients with hepatic dysfunction.

**Dosage and Administration:** The recommended daily dose of erlotinib is 100 mg, taken at least one hour before or two hours after the ingestion of food, in combination with gemcitabine. Treatment should continue until disease progression or unacceptable toxicity occurs.

**Commentary:** Pancreatic cancer is the fourth leading cause of cancer deaths in the U.S. Erlotinib’s new use focuses on pancreatic cancer patients who have not undergone chemotheraphy and whose disease is locally advanced or has spread to other parts of the body.

Erlotinib was originally used to treat non–small cell lung cancer. The Food and Drug Administration (FDA) approved erlotinib for pancreatic cancer based on a phase 3 clinical trial of 569 patients. In a blinded study, 50% of the patients took erlotinib and gemcitabine; the others took gemcitabine and placebo. A year later, 24% of the erlotinib group was still alive, compared with 19% of those who did not take erlotinib.

Pancreatic cancer is a major health problem because there are no effective ways to treat it. It is difficult to diagnose at an early stage, when it is most treatable, and this cancer can be aggressive. Because of the lack of effective systemic therapies, only 1% to 4% of patients are living five years after diagnosis.

Radiation therapy is commonly used as adjuvant therapy with surgery and may improve survival in some patients. 5-Fluorouracil (5-FU) is the mainstay of chemotherapy for pancreatic cancer, and it is frequently used as a radiation enhancer. When used as a single agent in the treatment of pancreatic cancer, 5-FU can be given in a variety of schedules. Responses last between three and six months.

Gemcitabine represents an important advance in the treatment of pancreatic cancer. It was the first chemotherapy agent approved on the basis of clinical response instead of the
and neutropenia, including febrile neutropenia, have been
associated with nelarabine therapy. Complete blood counts,
including platelets, should be monitored regularly.

General: Patients receiving nelarabine should receive IV
hydration according to standard medical practice for the
management of hyperuricemia in patients at risk for tumor lysis
syndrome. The use of allopurinol should be considered for
patients at risk of hyperuricemia. Administration of live
vaccines to immunocompromised patients should be avoided.

Dosage and Administration: The recommended adult
dose of nelarabine is 1,500 mg/m² administered intravenously
and undiluted over two hours on the first, third, and fifth days
and repeated every 21 days. The recommended pediatric dose
is 650 mg/m² administered intravenously and undiluted over
one hour daily for five consecutive days repeated every 21
days.

Commentary: Each year, T-ALL or T-LBL is diagnosed in
approximately 1,600 adults and children in the U.S. A subset
of these patients experience relapse or develop disease that is
refractory to treatment. There is no standard of treatment for
these patients, and their prognosis is poor.

The FDA’s accelerated approval of nelarabine was granted
on the basis of complete response rates shown in two phase 2
trials in patients who had exhausted standard treatment
options. Postmarketing evaluation to verify and describe the
product’s clinical benefit is planned through a randomized,
multicenter phase 3 trial. Nelarabine represents new hope for
adults and children with these rare and deadly cancers.

Sources: www.pharmacyonesource.com; www.fda.gov/
bbs/topics/NEWS; www.fda.gov/cder/foi/label/2005
Nelarabine (Arranon) Injection
Manufacturer: GlaxoSmithKline, Inc., Research Triangle
Park, NC

Indication: Nelarabine is indicated for the treatment of
adults and children with T-cell acute lymphoblastic leukemia
(T-ALL) and T-cell lymphoblastic lymphoma (T-LBL). It is
used when the disease has not responded to or has returned
after at least two chemotherapy regimens.

Biological Class: Nelarabine is a water-soluble pro-drug of
the cytotoxic deoxyguanosine analogue, 9-β-D-arabinofuranosylguanine (ara-G) with T-cell selectivity. Nelarabine is
demethylated by adenosine deaminase (ADA) to ara-G, mono-
phosphorylated by deoxyguanosine kinase and deoxycytidine
kinase, and subsequently converted to the active 5′-triphos-
phate, ara-GTP. Accumulation of ara-GTP in leukemic blasts
allows for incorporation into DNA, leading to inhibition of
DNA synthesis and cell death.

Uniqueness of Product: Nelarabine is a cancer chemother-
apy drug that kills cancer cells by blocking the cell’s ability
to reproduce. Rapidly dividing cancer cells are more sensitive
to cancer chemotherapy drugs than the more slowly dividing
normal cells.

Nelarabine was approved under the FDA’s accelerated
approval program, which allows FDA to approve products for
cancer and other serious or life-threatening diseases based on
early evidence of a product’s effectiveness. In this case, this
evidence consisted of the complete disappearance of cancer
cells in some patients. In most cases, however, the cancer
later returned. For patients who responded to nelarabine, the
disappearance of cancer cells was sometimes accompanied by
a return of normal blood cell counts.

Warnings: Nelarabine Injection should be administered
under the supervision of a physician experienced in the use of
cancer chemotherapeutic agents. This product is intended for
intravenous (IV) use only.

Neurological Events: Severe neurological events have
included altered mental states such as severe somnolence;
central nervous system (CNS) effects (e.g., convulsions); and
peripheral neuropathy ranging from numbness and pares-
thesias to motor weakness and paralysis. There have also been
reports of events associated with demyelination, and ascend-
ning peripheral neuropathies similar in appearance to Guillain-
Barré syndrome. Full recovery from these events has not
always occurred with cessation of therapy with nelarabine.
Close monitoring for neurological events is strongly recom-
ended. Nelarabine should be discontinued for neurological
events that have the National Cancer Institute’s Common
Toxicity Criteria of grade 2 or greater.

Precautions:

Hematological: Leukopenia, thrombocytopenia, anemia,
and neutropenia, including febrile neutropenia, have been

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death. For people who were using GHB for recreational purposes, the circumstances surrounding the ADEs have not always been clear. For example, the dose of GHB taken, the nature and amount of alcohol imbibed, or any concomitant drugs ingested could not always be determined.

Under the Xyrem Success Program, this agent is made available to prescribers through a single centralized pharmacy and with the following procedures:

1. The prescriber contacts the centralized pharmacy, which provides educational materials that explain the drug’s risks and proper use as well as details of the program.
2. After the prescriber reads the materials and returns the necessary form, the pharmacy ships educational materials to the patient.
3. After it has been documented that the patient has read the materials, the drug is shipped to the patient.

The program also provides for detailed surveillance. Patients are to be seen no less frequently than every three months, and physicians are expected to report all serious ADEs to the manufacturer and to disseminate information to help minimize the risks of inadvertent use.

**Precautions:**

**Incontinence.** During clinical trials, 9% of narcoleptic patients receiving sodium oxybate experienced either a single episode of sporadic nocturnal urinary incontinence; fewer than 1% experienced a single episode of nocturnal fecal incontinence. Fewer than 1% of patients discontinued taking the drug as a result of incontinence. Incontinence was reported for all doses tested.

If a patient experiences urinary or fecal incontinence during therapy, the prescriber should attempt to rule out underlying causes, such as worsening sleep apnea and nocturnal seizures. However, there is no evidence to suggest that incontinence has been associated with seizures in patients treated with this agent.

**Sleepwalking.** The term “sleepwalking” refers to confused behavior occurring at night and, at times, behavior that is associated with wandering. It is unclear whether these episodes correspond to true somnambulism, which is a parasomnia occurring during non–rapid-eye movement sleep, or to any other specific medical disorder.

Sleepwalking was reported in 7% of 448 treated patients in clinical trials. Fewer than 1% of these patients discontinued therapy because of sleepwalking. In controlled trials of up to four weeks’ duration, the incidence of sleepwalking was 1% with both placebo and sodium oxybate. In one independent uncontrolled trial, sleepwalking was reported by 32% of treated patients for periods up to 16 years. Fewer than 1% of these patients stopped taking sodium oxybate because of sleepwalking.

Several instances of significant or potential injury were associated with sleepwalking during one trial. These included a patient falling down, clothing being set on fire while the patient attempted to smoke, the attempted ingestion of nail polish remover, and an overdose of oxybate. Episodes of sleepwalking should be fully evaluated, and appropriate interventions should be considered.

**Sodium Intake.** Daily sodium intake in patients taking sodium oxybate ranges from 0.5 g for a 3-g dose to 1.6 g for a 9-g dose. The dosage should be increased in patients with heart failure, hypertension, or compromised renal function.

**Hepatic Insufficiency.** Patients with compromised liver function have an increased elimination half-life and systemic exposure to sodium oxybate. The starting dose should therefore be decreased by one-half in such patients, and patient responses to dose increments should be monitored closely.

**Renal Insufficiency.** No studies have been conducted in patients with renal failure. Because less than 5% of sodium oxybate is excreted via the kidneys, no dose adjustment should be necessary in patients with renal impairment. The sodium load associated with the administration of sodium oxybate should be considered in patients with renal insufficiency.

**Dosage and Administration.** The dose varies among patients. The usual initial dose is 1.5 g at bedtime and three to four hours later. The usual maximal dose is 4.5 g at bedtime and three to four hours later. Carefully monitored higher doses may sometimes be required.

**Commentary:** GHB is a natural substance, found in cells throughout the body. Approximately 150,000 Americans are afflicted with narcolepsy. Research shows that GHB is an excellent treatment against narcolepsy and is definitely beneficial for such patients. Given at bedtime, GHB reduces the number of daytime sleep attacks, cataplexy, hypnogogic hallucinations, and sleep paralysis.

GHB is also effective in reducing nocturnal sleep disruptions and consolidating nocturnal sleep. It is associated with an “alerting effect” during the day; that is, patients seem to be able to cope with a lower dose of stimulant medication and are able to stay aware during the day.

Because sodium oxybate is a Schedule III drug under the Controlled Substances Act and is available only through a restricted distribution system, there is adequate protection against abuse. The expanded indication for use in treating excessive daytime sleepiness is a positive therapeutic achievement for patients with narcolepsy.