

Recommendations and Reasons

Committee to Evaluate Drugs (CED)

Fludarabine (oral) for first-line treatment of chronic lymphocytic leukemia (CLL)

Product:

FLUDARABINE (Fludara®) 10 mg tablets

Class of drugs:

anti-cancer agent; antineoplastic

Indication:

Chronic lymphocytic leukemia (CLL)

Manufacturer:

Genzyme Canada Inc.

Date of CED Review:

April 2011

CED Recommendation

The CED recommended that oral fludarabine (Fludara®) be funded when used in combination with rituximab for the first-line treatment of chronic lymphocytic leukemia (CLL), on the basis that this drug has been shown to provide efficacy and value for money in this clinical setting.

Executive Officer Decision

Based on the CED's recommendation, the Executive Officer decided to fund oral fludarabine (Fludara®) when used in combination with rituximab for the first-line treatment of chronic lymphocytic leukemia (CLL).

Status

Funded as a Limited Use Benefit on the Ontario Drug Benefit Formulary.

Highlights of Recommendation:

- ◆ Fludarabine is an anti-cancer drug that can be used to treat different types of cancers. The drug is available in both an oral tablet form and an intravenous form. This review examined the use of oral fludarabine for the treatment of CLL in patients who have not undergone previous treatment (i.e. in the first-line setting).
- ◆ The use of oral fludarabine in the first-line treatment of CLL is supported by:
 - ◇ A key clinical study which demonstrated that intravenous fludarabine, when used in combination with another anti-cancer agent called rituximab, prolongs survival, and
 - ◇ Data from various studies that showed oral fludarabine to be similar to intravenous fludarabine in efficacy and safety.
- ◆ A clinical study conducted in CLL patients who had not undergone previous treatment showed that patients who received a regimen containing rituximab, fludarabine and cyclophosphamide had higher survival rates than patients who were treated with a regimen containing only fludarabine and cyclophosphamide. Because of this study, the combination use of rituximab and fludarabine (with or without cyclophosphamide) has become a standard first-line treatment for CLL.
- ◆ Although this study used the intravenous fludarabine rather than the oral formulation, evidence from several studies support that intravenous and oral fludarabine have similar efficacy and safety when appropriate relative doses are used.
- ◆ Oral fludarabine costs approximately \$5,000 per treatment course. When administration and other health care expense are factored in, the costs for oral and intravenous fludarabine are comparable.
- ◆ Overall, the CED noted that oral fludarabine, when used in combination with rituximab, has been shown to provide efficacy and value for money in the first-line treatment of CLL.

Background:

Chronic lymphocytic leukemia (CLL) is a blood cancer that causes an increase in abnormal B lymphocytes (a type of white blood cells). The cancer cells spread from the bone marrow to the blood, replacing healthy blood cells and platelets. CLL eventually causes the bone marrow to fail, leading to infection, anemia and bleeding. Enlargement of lymph nodes, liver and spleen can also occur.

Treatment for CLL is typically focused on controlling the disease and extending life. Treatment options include chemotherapy drugs. Radiation may sometimes be used for locally enlarged lymph nodes. Blood transfusions or platelet transfusions may be required if blood counts are low. Bone marrow or stem cell transplantation may be considered in younger patients with advanced or high-risk CLL.

Fludarabine belongs to a class of anti-cancer drugs called purine analogues.

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Detailed Discussion:

- ◆ A randomized controlled study in 817 previously untreated patients with CLL (*Hallek et al. Lancet 2010*) compared the use of two regimens, one consisting of rituximab in combination with fludarabine and cyclophosphamide, and the other consisting of only fludarabine and cyclophosphamide. The study found that patients who were treated with rituximab in combination with fludarabine and cyclophosphamide had significant improvements in progression-free survival, overall survival and disease response rates.
- ◆ Data from several phase 2 clinical studies, pharmacokinetic studies, and real-world use support that oral and intravenous fludarabine are comparable in efficacy and safety when appropriate relative doses are used (25mg/m² intravenously versus 40mg/m² orally). In addition, retrospective reviews have found the side effect profiles of each fludarabine formulation to be similar, although there is a slightly higher risk of gastrointestinal side effects from the oral formulation.
- ◆ A treatment course of oral fludarabine costs approximately \$5,000. Relative to intravenous fludarabine, oral fludarabine may be more convenient for patients. It also has the added advantage of freeing up hospital resources needed for intravenous administration. An economic analysis showed that oral and intravenous fludarabine are likely comparable in total health system cost (including drug, administration and hospital expenses, etc.).
- ◆ **Overall, the committee agreed that fludarabine, when used in combination with rituximab, has been shown to improve survival in the first-line treatment of CLL, and that oral fludarabine is a cost-effective option in this setting.**

The CED worked jointly with a subcommittee involving cancer experts to review this cancer drug, as it does for all cancer drug treatments.

Limited Use Criteria:

Oral fludarabine (Fluarda®) is funded by the Ontario Public Drug Programs as a Limited Use Benefit on the Ontario Drug Benefit Formulary according to the following criterion:

For the first-line treatment of chronic lymphocytic leukemia (CLL) in combination with rituximab (with or without cyclophosphamide).



Ministry of
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Ontario Public Drug Programs

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