HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

10 May 2006

Zavedos 5 mg, capsules
Bottle of 1 capsule (CIP code: 365 749-1)

Zavedos 10 mg, capsules
Bottle of 1 capsule (CIP code: 365 751-6)

Zavedos 25 mg, capsules
Bottle of 1 capsule (CIP code: 365 748-5)

Applicant: Pfizer Holding France

idarubicin hydrochloride

List I

Date of Marketing Authorisation: 28/10/1998

Reason for request: inclusion on the list of drugs reimbursed by National Health Insurance (no longer exclusively for hospital use).

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

idarubicin hydrochloride

1.2. Indications

Acute myeloblastic leukaemia without hyperleukocytosis, identifiable under the FAB classification, AML3 excepted, in patients over 60 years old, in the following circumstances:

- contraindication to intravenous chemotherapy and/or long stay in hospital,
- risks related to prolonged aplasia considered greater than potential benefits.

1.3. Dosage and administration route

Two dosage schedules are proposed:

- **weekly schedule:**
  induction and consolidation therapy: the recommended dose is 20 mg/m²/week for 4 weeks;

  salvage therapy: in nonresponding patients the dose can be increased to 40 mg/m²/week for 4 weeks.
- **daily schedule:**
  recommended dose 30 mg/m²/day for 3 consecutive days, as monochemotherapy, or 15–30 mg/m²/day for 3 consecutive days, in combination with other cytostatics.

These dosage schedules should take into account the patient's haematological status and doses of other cytotoxic drugs used concomitantly.

In patients with liver failure the dose should be reduced (see SPC, "Special warnings and precautions for use").

Method and route of administration

To avoid all skin contact, capsules should be taken straight from the bottle.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

L	: ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS
L01	: ANTINEOPLASTIC AGENTS
L01D	: CYTOTOXIC ANTIBIOTICS AND RELATED SUBSTANCES
L01DB	: ANTHRACYCLINES AND RELATED SUBSTANCES
L01DB06	: Idarubicin

2.2. Medicines in the same therapeutic category

Comparator medicines

Zavedos is the only oral medicine containing an anthracycline that is indicated in acute myeloid leukaemia in patients over 60 years old who are not suitable for IV chemotherapy.

2.3. Medicines in the same therapeutic area

Medicines indicated in treating acute myeloid leukaemia, based on daunorubicin, cytarabine, etoposide, amsacrine, cladribine, thioguanine or methotrexate.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The applicant submitted 3 clinical trials:

- one to assess the efficacy of oral idarubicin monotherapy (pivotal trial No. 96 OIDA 90[1])
- two to assess the efficacy of idarubicin in combined therapy (Jackson G.H. *et al*., 2004[2] and Ruutu T. *et al*. 1997[3]).

Trial 96 OIDA 90

The Marketing Authorisation for Zavedos capsules is based on this phase II, noncomparative trial, which was submitted in the dossier requesting inclusion on the list of medicines approved for hospital use (Transparency Committee Opinion of 3 February 1999).

Trial objective: The main objective was to assess the efficacy of oral idarubicin in treating AML without hyperleukocytosis in patients over 60 years old with contraindication to IV chemotherapy or a long stay in hospital, in whom the risks of prolonged aplasia were considered to outweigh the potential benefits.

Patients included: 51 patients over 60 years old, diagnosed with *de novo* AML (excluding AML3) or in first relapse in the 12 months following therapy, with a life expectancy of more than 3 months and at least one contraindication to chemotherapy.

Treatment: The protocol consisted of 4 phases.

1. Induction therapy

Idarubicin 20 mg/m^2/week for 4 weeks on day 1, day 8, day 15 and day 22.
Response to the induction therapy (primary endpoint) was assessed on day 28.
After this assessment:

- if complete remission (CR), consolidation therapy started on day 45
- if partial remission (PR), consolidation therapy started on day 28
- if treatment failure, salvage therapy started on day 28
- if cytopenia at day 28 but bone marrow blasts < 5%, further assessment on day 45 using the same criteria.

[1] Bouabdallah R *et al*.: A phase II trial of induction and consolidation therapy of acute myeloid leukemia with weekly oral idarubicin alone in poor risk elderly patients. Leukemia 1999;13:1491-6.
[2] Jackson GH *et al*.: The use of an all oral chemotherapy (idarubicin and etoposide) in the treatment of acute myeloid leukaemia in the elderly: a report of toxicity and efficacy. Leukemia. 1997;11:1193-6.
[3] Ruutu T *et al*.: Oral treatment of acute myeloid leukaemia with etoposide, thioguanine, and idarubicin (ETI) in elderly patients: a prospective randomised comparison with intravenous cytarabine, idarubicin, and thioguanine in the second and third treatment cycle. Eur J Haematol 2004;72:38-44.

2. Consolidation therapy
Idarubicin 20 mg/m^2/week for 4 weeks.

3. Salvage therapy
Idarubicin 40 mg/m^2/week for 4 weeks.

4. Maintenance therapy
Patients in PR or CR at 3 months were given six 3-month courses of maintenance therapy comprising:

- 6-mercaptopurine 2 mg/kg/day 4 days/week for 2 months by the oral route
- aracytine 1 mg/kg/week in one injection/week for 2 months
- idarubicin 20 mg/m^2 on day 1 and day 8 of the 3rd month.

Primary endpoint: complete remission (CR) defined according to the Cancer and Leukemia Group B criteria:

- bone marrow cell count: blasts < 5%
- complete blood count normal: neutrophils ≥ 1.0x10^9/L, platelets ≥ 100x10^9/L, no blood transfusion.

Secondary endpoint: partial remission (PR) defined according to the Cancer and Leukemia Group B criteria:

- bone marrow cell count: 5% ≤ blasts < 30%
- complete blood count normal: neutrophils ≥ 1.0x10^9/L, platelets ≥ 100x10^9/L, no blood transfusion.

Results

All patients included (n = 51) received induction therapy. Of these, 37 patients then received:

- salvage therapy (n = 30)
- or consolidation therapy (n = 7)
- or salvage therapy followed by consolidation therapy (n = 6).

Maintenance therapy was given to 11 patients.

Results were analysed by ITT.

At day 75, of the 51 patients enrolled in the trial:

- 12/51 (23.5%) were in complete remission (primary endpoint)
- 2/51 (4.0%) were in partial remission
- 15/51 (29.5%) were in treatment failure
- 19/51 (37.2%) had died.

Of 12 patients in complete remission, 7 were given salvage therapy.

G.H. Jackson trial

This noncomparative trial assessed the safety and efficacy of idarubicin and etoposide combined oral therapy in 28 patients aged 55 years with AML, whose state of health ruled out intensive IV therapy.

Patients were given 1–4 courses of oral chemotherapy comprising idarubicin 30 mg/m^2 and etoposide 80 mg/m^2 once daily for 3 consecutive days, with 3 weeks between courses of treatment. Patients in remission were given 2 further courses of consolidation therapy, on the decision of the doctor in charge.

Twenty-five patients were actually treated (11 patients received 1 course, 8 had 2 courses and 6 had 3–4 courses of chemotherapy). Nine of the 28 patients included (32%) achieved complete remission.

Comment: This noncomparative trial studied the efficacy of idarubicin in combination therapy. It is therefore not possible to assess the contribution of idarubicin.

T. Ruutu trial

This randomised, open-label trial compared the efficacy of a combination of idarubicin, cytarabine and thioguanine, by the oral and IV routes, in 2nd and 3rd courses of chemotherapy in 92 patients over 65 years old with *de novo* AML, whose state of health ruled out intensive IV therapy.

All patients were given an initial 6-day course of combined idarubicin and cytarabine by the IV route. Patients were then randomised to receive 2 courses of combined oral therapy comprising etoposide, thioguanine and idarubicin (ETI, n = 36) or combined IV therapy comprising thioguanine, cytarabine and idarubicin (TAI, n = 32). After the consolidation phase, patients were given maintenance therapy until relapse or progression, or up to 3 years.

After the second course of consolidation therapy, 22/36 patients were in remission in the ETI group and 19/32 in the TAI group. Remission was defined as absence of clinical signs of leukaemia, normal bone marrow cells with < 5% blast cells, peripheral neutrophils > $1x10^9$/L and platelets > $100x10^9$/L.

Median survival was 12 months in both groups. There was no significant difference in cumulative risk of relapse at 2 years between the ETI group (67%) and the TAI group (72%).

Comment: it is not possible to compare oral and IV idarubicin in this trial, which compared oral and IV protocols combining idarubicin with different active ingredients.

3.2. Safety/undesirable effects

Therapeutic doses of idarubicin always cause substantial myelosuppression, which can cause serious or sometimes fatal infections. Haemotological monitoring of the blood and bone marrow is therefore necessary.

As with other anticancer agents that modify DNA, myelodysplastic syndromes and acute myeloid leukaemia have been seen after combined therapy that includes an anthracycline.

With topoisomerase II inhibitors, an unexpectedly high incidence of secondary leukaemia has been reported, presenting as *de novo* AML2, AML3, or AML4. These forms can have a short latency period (1–3 years). These forms are curable and need early diagnosis and appropriate curative therapy.

The main nonhaematological undesirable effects are gastrointestinal, with diarrhoea, vomiting, nausea and mucositis. In the pivotal trial, 10% of patients had gastrointestinal toxicity > grade 3 in the induction phase and 23% in the salvage phase.

Like other anthracyclines, idarubicin exposes patients to a risk of immediate or delayed cardiovascular toxicity. Because cardiovascular disorders can occur during therapy or several weeks after the end of therapy, prior assessment and regular cardiac monitoring are necessary (clinical, functional and ECGs).

The pharmacovigilance report for the period 1 June 1997 to 31 August 2002 showed no new undesirable effects not already mentioned in the SPC.

3.3. Conclusion

The efficacy of oral idarubicin monotherapy was assessed in a single noncomparative trial in 51 patients over 60 years old with AML whose state of health ruled out intensive IV chemotherapy. At the end of the consolidation phase (3 months of therapy), the complete remission rate was 23% and partial remission 4%.

Two other trials submitted in the dossier assessed the efficacy of oral idarubicin in combination with other cytotoxics. One was noncomparative, the other compared oral idarubicin with an IV protocol that combined idarubicin with other cytotoxics than those used in the oral protocol. On the basis of these trials, it is difficult to assess the value of idarubicin within these combinations, or the benefit of using the oral route.

There are no data available comparing oral idarubicin with low-dose cytarabine by subcutaneous injection.

The haematological toxicity of idarubicin is substantial because of its potent myelosuppressant effect (bone marrow aplasia, myelodysplasia, acute myeloid leukaemia), requiring haematological monitoring. Other undesirable effects are mainly gastrointestinal (almost all grade 1–2). As with other anthracyclines, idarubicin can lead to immediate or delayed cardiac toxicity, requiring cardiac monitoring of patients during and after treatment.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Reassessment of actual benefit

Acute myeloid leukaemia is a malignant proliferation of haematopoietic stem cells with blocked maturation, leading to:

- a tumoral syndrome with accumulation of blast cells in the bone marrow and blood, and sometimes the infiltration of other organs,
- haematopoietic failure or regeneration of blood tumoral cells leading to anaemia, spontaneous haemorrhage, or spontaneous or severe aggravated infections.

Acute myeloblastic leukaemia mainly affects adults, and is always fatal. Median survival time without treatment is around 2 months.

Acute myeloblastic leukaemia in patients over 60 years old is difficult to treat and often requires less aggressive therapy than in younger patients.

This medicine is curative therapy.

Public health benefit

- Acute myeloblastic leukaemia without hyperleukocytosis, the indication for Zavedos, is a serious disease. However, its rarity makes it a low public health burden.
- In view of the current prognosis for acute myeloblastic leukaemia, there is an unmet therapeutic need. In the subpopulation of patients concerned, Zavedos should offer a partial response to this need.
- Zavedos is expected to have a low impact at population level on morbidity and mortality and quality of life.
- Zavedos is therefore expected to benefit public health. This benefit is low.

The efficacy/safety ratio is substantial.

There are few alternative therapies.

Zavedos is first line therapy for acute myeloblastic leukaemia in patients over 60 in the following situations:

- contraindication to intravenous chemotherapy and/or long stay in hospital,
- risks related to prolonged aplasia considered greater than potential benefits.

The actual benefit of Zavedos capsules is substantial.

4.2. Improvement in actual benefit

Zavedos offers a moderate Improvement in Actual Benefit (IAB level III) in the treatment of AML in patients over 60 years old unsuitable for intensive chemotherapy.

4.3. Therapeutic use

The usual schedule for treating AML is:

- Induction therapy: the aim is complete remission, and therapy is based on a combination of an anthracycline (idarubicin or daunorubicin) and cytarabine. Other drugs such as etoposide and mitoxantrone may be added to this standard combination. If response is partial, the patient is given salvage therapy.
- Post-induction therapy: this is started when complete remission has been achieved. The aim is to eliminate the residual blast population completely. After therapy to consolidate the complete response, still based on the anthracycline-cytarabine combination, several options are possible, depending on initial prognostic factors, patient age, cytogenetic abnormalities, response to induction therapy, and whether an HLA-compatible donor can be found:
    - maintenance therapy with continuous oral chemotherapy based on methotrexate and 6-mercaptopurine is preferred in patients over 60 years old (12–18 months of therapy);
    - intensification therapy, using the same drugs as for induction therapy, in combination with high-dose cytarabine;
    - allogenic (HLA-compatible donor) or autologous bone marrow transplant may be considered in patients under 50 years old.

A mixed schedule may be proposed, combining continuous chemotherapy with reinduction. Bone marrow transplantation may also be combined with intensive chemotherapy.

Patients over 60 unsuitable for intensive chemotherapy are given symptomatic treatment or, if the patient's health permits, palliative care at home, aimed at improving the patient's quality of life. Oral idarubicin monotherapy is currently the palliative therapy of choice; low-dose cytarabine by subcutaneous injection may be an alternative.

4.4. Target population

The target population is defined as patients over 60 years old with acute myeloblastic leukaemia, with a contraindication to IV chemotherapy.

Of patients with acute leukaemia, around 1350 are over 60[1].

Incidence peaks for ALL and AML indicate that 80% of acute leukaemia patients over 60 have AML, i.e. around 1080 patients.

Of these 1080 patients:

- 20% cannot be given any anticancer therapy because of their precarious state of health. In such cases only palliative care should be given (expert opinion).
- 40% are well enough to be given intravenous anticancer chemotherapy (expert opinion).
- 40% are in a state of health between these two 2 options, i.e. suitable for oral anticancer chemotherapy.

The target population for Zavedos capsules should therefore be 400–500 patients per year.

[1] *Evolution de l'incidence et de la mortalité par cancer en France de 1978 à 2000;* InVS, October 2003

4.5. Transparency Committee Recommendations

The Committee recommended inclusion on the list of medicines reimbursed by National Health Insurance for the indications and at the dosages given in the Marketing Authorisation.

4.5.1. **Packaging**: Suitable for conditions of prescription

4.5.2. **Reimbursement**:**rate**: 100%