HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION
15 March 2006

FLISINT 20 mg, capsule
B/42 capsules: Code CIP 567 665-3

Applicant : Sanofi Aventis France

fumagillin

list I
Medicinal product for hospital prescription only
Medicinal product requiring careful monitoring during treatment

Fumagillin has been granted orphan drug status.

Date of Marketing Authorisation: 17/11/2005

Reason for request : Inclusion on the list of medicines approved for use by hospitals
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Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Fumagillin

1.2. Indications

Treatment of severe diarrhoea caused by intestinal microsporidiosis caused by *Enterocytozoon bieneusi* in severely immunocompromised HIV-infected adult patients, following unsuccessful immune restoration by antiretroviral therapy.

The efficacy of fumagillin was established by a double-blind placebo-controlled trial (EFC4918/ ANRS090) in 12 male immunocompromised patients, 10 of whom were HIV-infected and 2 organ transplant recipients.

1.3. Dosage

Oral route.
The recommended dosage is 3 x 20 mg capsules i.e. 60 mg of fumagillin per day for 14 days.
There are no available data on repeated treatment cycles.
There have been no trials in children or patients over the age of 65.
There have been no trials in patients with renal or liver failure.
There are no available data on interactions with food. In the clinical trials it was recommended that fumagillin should not be taken at mealtimes.
Keep frozen (-20℃).
After opening the bottle, Flisint may be kept for up to 14 days in the refrigerator (2-8℃).
Store in the original outer packaging and protect from light.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

P : ANTIPARASITICS, INSECTICIDES AND REPELLENTS
P01 : ANTIPROTOZOALS
P01A : MEDICINAL PRODUCTS FOR THE TREATMENT OF AMOEBIASIS AND OTHER PROTOZOOAL DISEASES
P01AX : OTHER MEDICINAL PRODUCTS FOR THE TREATMENT OF AMOEBIASIS AND OTHER PROTOZOOAL DISEASES

2.2. Medicinal products in the same therapeutic category

None of the medicinal products in the same therapeutic drug category has this indication.

2.3. Medicinal products with a similar therapeutic aim

No other medicinal product has this indication.

3 ANALYSIS OF AVAILABLE DATA

Three trials to assess the efficacy and safety of fumagillin have been conducted in 60 patients:

- A non-comparative, multicentre pilot trial (ACT 4916/ANRS 034[1]) to assess the potential of several drugs to clear *Enterocytozoon bieneusi* from the stools of HIV-infected patients with chronic diarrhoea.
- An open-label dose-escalation trial (DRI 4917/ANRS 054[2]) to determine the most effective and safest dose to treat intestinal microsporidiosis in HIV-infected patients.
- A pivotal randomised double-blind placebo-controlled phase II/III trial (EFC 4918/ANRS 090) to establish the efficacy and safety profile of a 60 mg daily dose of fumagillin (20 mg x 3/day) in immunocompromised patients.

3.1. Efficacy

Trial ACT4916/ANRS 034

In this pilot trial in 5 HIV-infected patients, Flisint at 60 mg/day in 3 x 20 mg doses for 21 days achieved clearance of *Enterocytozoon bieneusi* from the stools of all 5 patients (absence of spores from stools in 2 consecutive tests at the end of treatment). A duodenal biopsy at the end of treatment (day 23), to confirm the absence of spores, was performed in only 2 patients. In one case parasites were detected; in the other, the parasite test was negative, but so was the pre-treatment examination.

Trial DRI 4917/ANRS 054

In this dose-escalation trial in 43 HIV-infected patients, 60 mg/day of Flisint given as 20 mg 3 times daily for 14 days (n = 11) was identified as the effective dose having an acceptable associated risk of thrombocytopenia.

Pivotal trial EFC4918/ ANRS 090

A randomised double-blind placebo-controlled phase II/III trial in 12 severely immunocompromised patients, to assess the efficacy and safety of fumagillin in the treatment of chronic *Enterocytozoon bieneusi* infections. The trial was followed by an open-label evaluation phase for the patients initially given the placebo.

The patients were followed up for 12 months to assess the parasitological relapse rate.

Trial characteristics

This trial began before the advent of antiproteases. Oral Fumagillin was given at a dosage of 20 mg three times daily for 14 days, avoiding mealtimes.

[1] Molina JM, Goguel J, Sarfati C, Chastang C, Desportes-Livage I, Michiels JF, et al, for the French Microsporidiosis Study Group. Potential efficacy of fumagillin in intestinal microsporidiosis due to *Enterocytozoon bieneusi* in patients with HIV infection: results of a drug screening study. AIDS 1997;11:1603-10.

[2] Molina JM, Goguel J, Sarfati C, Michiels JF, Desportes-Livage I, Balkan S et al, for the ANRS054 study group. Trial of oral fumagillin for the treatment of intestinal microsporidiosis in patients with HIV infection. AIDS 2000; 14:1341-48.

Concomitant therapies permitted during the trial were:

- symptomatic treatment of diarrhoea
- primary or secondary preventive treatment of opportunistic infections
- antiretroviral therapy started or modified more than two months before inclusion (no modification of antiretroviral therapy was allowed during the trial).

Excluded therapies were: aspirin, albendazole, metronidazole and other nitroimidazoles, fluconazole, ketoconazole, itraconazole, rifampicin, rifabutin, phenobarbital, cimetidine, phenytoin, antiarrhythmics, antacids and cytotoxics.

Inclusion criteria

Patients over 18 infected with HIV or immunocompromised for any other reason (e.g. organ transplant patients).

Presence of microsporidia in stools on two occasions at least 4 days apart in the 14 days before starting treatment.

Primary endpoint

Eradication of the parasite from the stools.

Clearance of the parasite was defined as absence of *Enterocytozoon bieneusi* spores from the stools in 2 out of 3 examinations on D15, D17 and D19 after two weeks of treatment.

The diagnosis of intestinal microsporidiosis was made by parasitological examination of the stools and species diagnosis was confirmed by PCR.

Secondary endpoints

- change in body weight, change in stools (weight, consistency, frequency), and use of symptomatic treatment for diarrhoea,
- blood xylose level measured by the D-xylose absorption test,
- relapse time after parasite clearance,
- level of parasite clearance at the end of the open-label treatment phase that followed the double-blind treatment phase,
- safety of fumagillin.

Results

The primary analysis by intent to treat (ITT) covered all the randomised patients.

Patient characteristics at inclusion:

Twelve male patients between 26 and 71 with a median CD4 count of 19 cells/mm^3 (4–99) were enrolled in the trial (10 HIV-infected patients and 2 organ transplant patients).

Results for the primary endpoint:

Efficacy results for the double-blind phase of the trial are shown in the table on the next page:

Elimination of parasites – Double-blind phase (trial EFC 4918/ANRS 090)

		Placebo (N = 6)			Fumagillin (N = 6)		
		Day 15	Day 17	Day 19	Day 15	Day 17	Day 19
Presence of spores							
- Negative	N				6	6	3
- Positive	N	6	5	4			
- Test done (result not known)	N						1
- Test not done	N		1	2			2
Quantity of spores*							
2 (spores)	N	3	2	1			
3 (numerous spores)	N	2	2	2			
Data missing	N	1	1	1			
Eradication							
- Yes	N (%)					6 (100)	
- No	N (%)		6 (100)				
Fisher's Exact Test	P			0.001			

* Semiquantitative scale: 0 (absence of spores); 1 (few spores); 2 (spores); 3 (numerous spores). In the fumagillin group the scale scores were all 0.

Parasite clearance (absence of spores from the stools on D15 and D17, or on D15 and D19, or on D17 and D19) was achieved in all 6 patients in the fumagillin group and none of the patients in the placebo group (p = 0.001) during the double-blind phase.

Results for secondary endpoints at 4 weeks:
D-xylose absorption (p = 0.02) was increased in the group treated with fumagillin compared with the placebo group. The patients' Karnofsky scores (p = 0.054) and body weight were not significantly different in the two groups.
No patients in the fumagillin group took loperamide (2 mg capsules), while in the placebo group 3 patients were given 1–8 capsules of loperamide per day. The number of stools was reduced by 47.7% in the fumagillin group versus 40% in the placebo group (NS) and stool weight was reduced by 45.2% in the fumagillin group versus 35.4% in the placebo group (NS).

Open-label phase
The 6 patients in the placebo group were treated with fumagillin at 60mg/day for 14 days in an open-label phase. All 6 patients were clear of parasites at the end of this phase.

1-year follow-up phase
With their stools clear of spores, the 12 patients were then monitored (stool examination) every month for a maximum of 12 months.
Two HIV-infected patients suffered a relapse of parasitic infection during the follow-up phase.

3.2. Undesirable effects/Safety

Safety data were analysed for the 69 patients who had taken the drug in these 4 trials.

The main undesirable events reported for the 69 patients in the 4 studies (three clinical trials and one pharmacokinetic trial) were haematological and gastrointestinal.

23/69 were treated with fumagillin at the recommended dose (60 mg/day for 14 days). No deaths were reported. In 9 cases (7 being thrombocytopenia), the undesirable event led to discontinuation of treatment.

Clinical and laboratory expression of haematological disorders

Thrombocytopenia was reported in 22/69 patients who had taken fumagillin, including 13 patients with fewer than 50 000 platelets/mm^3. Eleven were asymptomatic and 2 had bleeding (nosebleeds/rectal bleeding and nosebleeds/purpura), requiring platelet transfusion.

The thrombocytopenia was observed after at least one week of treatment, and resolved satisfactorily within 2–4 weeks of the last dose.

Granulocytopenia occurred in 41/69 patients including 2 with a PMN count < 500/mm^3. No associated clinical symptoms were reported. Twenty-seven patients had a pre-existing abnormality.

Finally, in 8/69 patients, haemoglobin fell from 2 to 6.5 g/dL, including 6 cases of anaemia with haemoglobin < 9.5 g/dL.

Other laboratory abnormalities were observed, notably 15 cases of asymptomatic raised ALT (10 pre-existing abnormalities), 8 cases of asymptomatic raised AST (4 pre-existing abnormalities), 22 cases of raised lipase (20 pre-existing abnormalities and 21 occurring during the trial ANRS 054), and 11 cases of asymptomatic raised alkaline phosphatase (10 pre-existing abnormalities).

Gastrointestinal disorders

Gastrointestinal disorders reported were pain (29/69 patients), diarrhoea, nausea and vomiting. The majority were not serious, except for one case of abdominal pain.

3.3. Conclusion

The efficacy of fumagillin in the treatment of intestinal infections caused by *Enterocytozoon bieneusi* has been studied in a small number of patients (12 patients). All the results suggest that fumagillin is rapidly effective in clearing parasites from stools, compared with placebo. However, the digestive signs and associated clinical parameters (notably number and weight of stools) were not significantly reduced over the assessment period.

Haematotoxicity of fumagillin was common and substantial in the clinical trials. In particular, severe thrombopenia was common but appeared to be reversible within 2–4 weeks of end of treatment.

In view of the small number of patients enrolled in the pivotal trial and the heterogeneity of the population (10 HIV-infected and 2 organ transplant recipients, naïve or pre-treated with antiretroviral therapy), it is difficult to extrapolate the results of this trial to all severely immunocompromised HIV-infected patients with intestinal microsporidiosis caused by *Enterocytozoon bieneusi*.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

- Intestinal microsporidiosis caused by *Enterocytozoon bieneusi* is a serious opportunistic disease. The host becomes infected with this protozoal disease by ingesting spores. In severely immunocompromised patients, the parasites cause chronic diarrhoea, resulting in a gradual but constant deterioration in the patient's general health (malnutrition and dehydration can lead to wasting syndrome). This may be life-threatening.
- This is a curative drug for symptomatic adults (severe diarrhoea).

- The efficacy/safety ratio for fumagillin is high.
- Flisint is a first-line therapy in the indication specified in the Marketing Authorisation.
- There are no alternative therapies.
- Public Health benefit
  - Severe diarrhoea caused by intestinal microsporidiosis caused by *Enterocytozoon bieneusi* in adult HIV-infected patients is a light burden on public health.
  - Improvement in the management of HIV-positive patients is a public health need. By clearing *Enterocytozoon bieneusi* infection causing severe diarrhoea and abdominal pain, Flisint could partially meet this need since there is no currently available treatment for this indication.
  - Flisint is expected to produce a rapid clinical improvement in these patients, but no impact on quality of life or morbidity is anticipated at population level
  - In view of the possible contribution to public health needs, it is therefore expected that Flisint will benefit public health. The public health benefit is minor.

The actual benefit of this medicinal product is substantial.

4.2. Improvement in actual benefit

In view of
- the very reliable efficacy of the treatment in eradicating parasites in 2 weeks,
- the serious but reversible nature of the undesirable events observed,
- the absence of any alternative therapy in this indication,

Flisint offers a substantial improvement in actual benefit (IAB II) in the management of severe diarrhoea caused by intestinal microsporidiosis due to *Enterocytozoon bieneusi* in severely immunocompromised HIV-infected adult patients, following unsuccessful immune restoration by antiretroviral therapy.

4.3. Therapeutic use [3]

The treatment strategy for intestinal infection caused by intestinal microsporidiosis depends on the species involved.

- In infection with *Enterocytozoon bieneusi*, a dose of 20 mg of fumagillin given 3 times/day for 14 days has been shown to be effective in clearing parasites from the stools and is the only therapy available at present. However, the treatment causes haemototoxicity (thrombopenia, neutropenia) which, although reversible, must be carefully monitored.
- In infection with *Encephalitozoon*, albendazole is effective at a dosage of 400 mg twice daily for 3 weeks. No maintenance therapy appears to be necessary.

4.4. Target population

The target population is HIV-infected adult patients who are severely immunocompromised after unsuccessful immune restoration by antiretroviral therapy and who have severe diarrhoea caused by intestinal microsporidiosis due to *Enterocytozoon bieneusi*.

[3] *Prise en charge thérapeutique des personnes infectées par le VIH, Report, 2004 - Recommandations du groupe d'experts sous la direction du Professeur Jean-François Delfraissy, June 2004, Médecine Sciences Flammarion*]

Since antiretroviral therapy was introduced, there are few patients in this situation, in contrast to the early years of HIV disease. It is therefore difficult to estimate the target population for Flisint in the indication in the Marketing Authorisation, in view of the scarcity and lack of precision of published data. In France, it is thought that a maximum of 100 patients a year would be concerned (expert opinion).

4.5. Transparency Committee recommendations

The Transparency Committee recommended inclusion on the list of medicines approved for use by hospitals and various public services in the marketing authorisation.