HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

July 18, 2007

ZELITREX 500 mg coated tablet
Packs of 10 tablets (CIP: 341 708-3)

ZELITREX 500 mg coated tablet:
Pack of 42 tablets (CIP: 338 444-9)

ZELITREX 500 mg coated tablet:
Pack of 112 tablets (CIP: 352 242-0)

Applicant: GLAXOSMITHKLINE

Valaciclovir

List I

Date of Marketing Authorisation: February 8, 1995; MA variations of May 15, 2006 and February 6, 2007 *(*extensions of indications).

Reason for request: inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the extension of the following 4 indications to immunocompromised subjects:

- Treatment of the first episode of genital *Herpes simplex* infections and any subsequent recurrences.
- Prevention of recurrent genital *Herpes simplex* virus infections in subjects with at least 6 recurrences per year.
- Prevention of recurrent orofacial *Herpes simplex* virus infections in subjects with at least 6 recurrences per year.
- Prevention of chemotherapy- or radiotherapy-induced oral *Herpes simplex* virus infections (mucositis)

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Valaciclovir
Valaciclovir is a precursor of aciclovir.

1.2. Background

This is an extension of indication in immunocompromised subjects in the treatment and prevention of certain *Herpes simplex* virus infections.

1.3. Indications

Varicella-zoster virus infections:

- Prevention of pain caused by herpes zoster (reduction of its duration and incidence), in immunocompetent subjects aged over 50 years.
- Prevention of the ocular complications of ophthalmic zoster in immunocompetent adult subjects.

Treatment must be administered early and no later than 72 hours after the onset of the first skin manifestations.

Herpes simplex virus infections:

Immunocompetent subject

- Treatment of the first episode of genital *Herpes simplex* infection and any subsequent recurrences.
- Prevention of recurrent genital *Herpes simplex* virus infections in subjects with at least 6 recurrences per year.
- Prevention of recurrent orofacial *Herpes simplex* virus infections in subjects with at least 6 recurrences per year.
- Prophylaxis of recurrent ocular *Herpes simplex* virus infections during:
  - Epithelial keratitis after 3 recurrences per year or in the event of a known activation factor,
  - Stromal keratitis and kerato-uveitis after 2 recurrences per year,
  - Infections related to eye surgery.
- Treatment of keratitis and *Herpes simplex* virus kerato-uveitis, other than severe lesions.

Immunocompromised subject *(new indications: MA Variations of May 15, 2006 and February 6, 2007)*

- Treatment of the first episode of genital *Herpes simplex* infections and any subsequent recurrences.
  In immunocompromised subjects, oral treatment is possible when the seriousness of the clinical picture and the degree of immune deficiency do not justify use of parenteral aciclovir.
  Treatment should be started as early as possible to improve efficacy.
  Rigorous monitoring of the outcome of the lesions is recommended: The patient should be re-examined within 48 hours and preferably in a specialised department.
- Prevention of recurrent genital *Herpes simplex* virus infections in subjects with at least 6 recurrences per year.
- Prevention of recurrent orofacial *Herpes simplex* virus infections in subjects with at least 6 recurrences per year.
- Prevention of chemotherapy- or radiotherapy-induced oral Herpes simplex virus infections (mucositis).

Cytomegalovirus Infections:

- Prophylaxis of cytomegalovirus (CMV) infection and disease, following organ transplantation except lung transplantation, and in particular renal transplantation.

Because of its mechanism of action, valaciclovir does not eradicate latent viruses. After treatment, the patient will therefore remain exposed to the same incidence of recurrences as before.

1.4. Dosage

In adults:

Varicella-zoster virus infections:

- Prevention of zoster-associated pain and prevention of ocular complications of ophthalmic zoster: 1,000 mg of valaciclovir, i.e. two 500-mg tablets, 3 times daily for 7 days.

Treatment must be initiated as soon as possible after the onset of the infection within 72 hours of the first skin manifestations.

Herpes simplex virus Infections:

Immunocompetent subjects

- Treatment of genital *Herpes simplex* virus infections: one 500-mg tablet, two times daily for 10 days during the first episode; two 500-mg tablets per day in one or two doses for 5 days during recurrences.
- Prevention of recurrent genital *Herpes simplex* virus infections: 500 mg per day in one or two doses (in the case of failure after administration of a single 500-mg dose per day or in the case of frequent or very symptomatic recurrences, administration in two divided doses (250 mg x 2/day) may give better results).
  In this indication, the value of treatment must be re-evaluated after 6 to 12 months of treatment.
- Prevention of recurrent orofacial *Herpes simplex* virus infections: 500 mg per day in a single dose.
  In this indication, treatment must be re-evaluated after 6 to 12 months.

Immunocompromised subject *(new indications*: *MA Variations of May 15, 2006 and February 6, 2007)*

- Treatment of genital *Herpes simplex* virus infections: 2 g per day, i.e. two 500-mg tablets, 2 times daily for at least 5 days.
  Treatment must be initiated as early as possible.
- Prevention of recurrent genital *Herpes simplex* virus infections: 1 g per day, i.e. one 500-mg tablet, 2 times daily.
  In this indication, treatment should be re-evaluated after 6 to 12 months.
- Prevention of recurrent orofacial *Herpes simplex* virus infections: 1 g per day, i.e. one 500-mg tablet, 2 times daily.
  In this indication, treatment should be re-evaluated after 6 to 12 months.
- Prevention of chemotherapy- or radiotherapy-induced oral Herpes simplex virus infections (mucositis): 1 g per day in two doses for the duration of neutropenia, i.e. one 500-mg tablet, 2 times daily.

In adults and adolescents from 12 years of age:

Herpes simplex virus infections:

- Prophylaxis of recurrent ocular *Herpes simplex* virus infections in immunocompetent subjects:
  - Epithelial keratitis after 3 recurrences per year, stromal keratitis and keratouveitis after 2 recurrences per year: One 500-mg tablet per day. Treatment should be re-evaluated every 6 to 12 months to evaluate any change related to the natural course of the disease.
  - In the case of eye surgery: One 500-mg tablet per day.
- Treatment of *Herpes simplex* virus keratitis and keratouveitis: Two 500-mg tablets, in 1 or 2 doses per day.

Cytomegalovirus Infections:

- Prevention of cytomegalovirus (CMV) infections and disease: 2,000 mg of valaciclovir, i.e. four 500-mg tablets, 4 times daily.

Treatment must be administered as soon as possible after organ transplantation.
The dosage should be adjusted according to creatinine clearance (cf. SPC).
The treatment duration is usually 90 days.

Elderly patients:
The dosage must be adjusted in the case of renal impairment (cf. SPC).
Adequate hydratation should be maintained.

In patients with renal impairment:
The dosage must be adjusted according to creatinine clearance (cf. SPC).

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2007)

J : Antiinfectives for systemic use
J05 : Antivirals for systemic use
J05A : Direct acting antivirals
J05AB : Nucleosides
J05AB11 : Valaciclovir

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

ZOVIRAX 200 mg and its generics - aciclovir 200 mg tablet.
ZOVIRAX 200 mg/5mL oral suspension – aciclovir 200 mg/5mL.
In herpes in immunocompromised subjects, ZOVIRAX is only indicated for prophylaxis of Herpes simplex virus (HSV) infections.

ZOVIRAX 500 mg and 250 mg, powder for solution for injection (IV)
Indicated in HSV infections in immunocompromised subjects

3 ANALYSIS OF AVAILABLE DATA

The laboratory submitted 5 studies in immunocompromised patients:

- 3 studies conducted in HIV-infected patients:
  - 1 study *versus* placebo in the prophylaxis of recurrent genital herpes (HSV_2),
  - 1 study *versus* aciclovir in the prophylaxis of recurrent genital herpes,
  - 1 study *versus* aciclovir in the treatment of episodes of genital herpes infection.

- 2 open-label studies, presented only in the form of publications, in patients with mucositis after bone marrow transplantation.

3.1. Clinical study *versus* placebo in the prophylaxis of recurrent genital herpes in HIV-infected patients

This randomised, double-blind, multicentre, parallel-group study[1] was conducted on 293 HIV-infected patients, with documented HSV_2 infection who had presented with at least 4 recurrent episodes of genital herpes during the 12 months prior to enrolment.

The study compared a group of 194 patients treated by valaciclovir at a dosage of 500 mg twice daily with a group of 99 patients receiving a placebo twice daily. Treatment duration was 6 months.

The primary endpoint was the percentage of subjects without a recurrence of genital herpes during the 6 months of the study.

Enrolled patients were men in 88% of the cases, with a median age of 41 years. The median CD4 lymphocyte counts in enrolled patients were 336 cells/mm^3 in the valaciclovir-treated group and 313 cells/mm^3 in the placebo group; 70% of patients were asymptomatic and 30% were symptomatic.

Two hundred and thirty-one of the 293 enrolled patients completed the study (21% of premature trial discontinuations), 8% of patients in the valaciclovir group and 9% in the placebo group were lost to follow-up and 2% of patients in each group stopped treatment because of adverse effects.

Results after 6 months of treatment in the ITT population (table 1), showed that 65% (126/194) of patients treated by valaciclovir had no recurrence *versus* 26% (26/99) of the patients receiving placebo (p<0.001).

Table 1: Primary endpoint data for the ITT population

Endpoints	Placebo n=99	Valaciclovir n=194	p
Recurrent genital herpes after 6 months:			
- No recurrence	26 (26%)	126 (65%)	<0.001
- Documented recurrences	56 (57%)	33 (17%)	
- Withdrawal from trial without documented recurrence	12 (12%)	29 (15%)	
- Withdrawal from trial, with documented recurrence	5 (5%)	6 (3%)	

[1] Study HS230018; DeJesus A. Valaciclovir for the suppression of recurrent genital Herpes in Human Immunodeficiency Virus-Infected subjects. J Infect Dis 2003; 188: 1009-1016

To conclude, this study showed the efficacy of valaciclovir for a period of 6 months in the prophylaxis of recurrent genital herpes in a population of HIV-infected patients.

3.2. Clinical study *versus* aciclovir in the prophylaxis of recurrent genital herpes in HIV-infected patients

The purpose of this controlled, randomised, double blind, parallel-group, multicentre study[2] was to show the superiority of valaciclovir compared to aciclovir in terms of efficacy in the prophylaxis of recurrent genital herpes.

The study was carried out on 1,062 HIV-infected patients presenting at least 1 recurrence of genital herpes during the 12 months prior to enrolment.

The dosage of valaciclovir was 500 mg twice daily (355 patients) or 1,000 mg once daily (358 patients), and that of aciclovir 400 mg twice daily (349 patients). Treatment duration was 48 weeks. The CD4 lymphocyte count had to be at least 100 cells/mm^3.

The primary endpoint was the time to onset of the first recurrence of genital herpes calculated in the ITT population.

Ninetu-one % of enrolled patients were men and their median age was 36 years. The median CD4 lymphocyte count in enrolled patients was 320 cells/mm^3; 70% of patients were asymptomatic and 30% were symptomatic.

Six hundred and three of the 1,062 enrolled patients completed the study and 459 (43%) dropped out including 84 (8%) for adverse events and 137 (13%) lost to follow-up.

Results: No result was provided for the primary endpoint.
Only the following results were provided for the number of recurrence-free patients at 48 weeks which was a secondary endpoint determined *a posteriori*.

Table 2: Results for the number of patients without recurrence at 48 weeks

	Valaciclovir 500 mg BID N = 355	Valaciclovir 1,000 mg QD N =358	Aciclovir 400 mg BID N =349
Number of recurrence-free patients at 48 weeks	305 (86%)	277 (77%)	287 (82%)
p	p = 0.10 vs. aciclovir p = 0.001 vs. valaciclovir 1,000 mg x 1	p = 0.11 vs. aciclovir	

To conclude, this superiority study failed to demonstrate any difference in efficacy assessed from the time to onset of the first recurrence between aciclovir and valaciclovir, in the prophylaxis of recurrent genital herpes in HIV-infected patients.

3.3. Clinical study *versus* aciclovir in the treatment of recurrent genital herpes in HIV-infected patients,

The purpose of this controlled, randomised, double blind, multicentre study[3] was to show the superiority of valaciclovir compared to aciclovir.

[2] Study 123-007; Conant MA, Valaciclovir versus acyclovir for herpes simplex virus infection in HIV-infected individuals: two randomised trials. International Journal of STD & AIDS 2002; 13: 12-21.
[3] Study 123-008; Conant MA, Valaciclovir versus acyclovir for herpes simplex virus infection in HIV-infected individuals: two randomised trials. International Journal of STD & AIDS 2002; 13: 12-21.

The study was carried out on 639 HIV-infected patients: 314 in the valaciclovir group and 325 in the aciclovir group. The patients had to have a history of genital herpes and at least two exacerbations during the 6 months prior to enrolment.

The dosage of valaciclovir was 1 g twice daily, and that of aciclovir was 200 mg five times daily. Treatment duration was 5 months.

The primary endpoint was the duration of symptoms.

Enrolled patients were men in 91% of the cases, with a median age of 36 years. They were asymptomatic in 55% of cases and symptomatic in 45% of the cases.
Four hundred and sixty-seven (73%) of the 639 patients enrolled with a clinical diagnosis of recurrent genital herpes had an HSV recurrence that was confirmed in the laboratory by a positive culture or positive Western Blot and were included in the ITT analysis.

Forty-three patients prematurely discontinued the study including 7 for adverse effects (3 on valaciclovir and 4 on aciclovir).

Results: No difference between valaciclovir and aciclovir could be demonstrated for the duration of symptoms. The median duration of symptoms was of 5 days.

To conclude, this superiority study in the treatment of recurrent genital herpes failed to demonstrate any difference between aciclovir and valaciclovir on the duration of symptoms in HIV-infected patients.

3.4. Eisen Study in the prevention of herpes mucositis:

The objective of this non-controlled, open-label, study[4] was to evaluate the efficacy of valaciclovir in the prevention of herpes mucositis. This study enrolled 60 bone marrow transplant recipients with a history of HSV infection.

The dosage was 500 mg valaciclovir twice daily. Treatment was begun 3 days before transplantation and was continued until the end of the neutropenia period. Patients unable to tolerate oral administration received aciclovir IV: 125 mg/m^2 every 6 hours until they could take oral treatment.

The primary endpoint was the onset of clinical signs of orofacial herpes confirmed by laboratory tests.

Results: all the patients finished the study. No infectious episode of oral or oropharyngeal herpes was reported, and there was no HSV1 or HSV2-positive culture.

To conclude, this open-label study does not make it possible to assert that valaciclovir is effective for the prophylaxis of chemotherapy- or radiotherapy-induced reactivation of oral herpes infections in the case of mucositis.

3.5. Dignani[5] study in the prevention of mucositis

The objective of this non-controlled, open-label study was to evaluate the efficacy of valaciclovir in the prevention of herpes mucositis. This study enrolled 108 bone marrow transplant recipients with a history of HSV infection.

[4] Eisen D, Essell J, Broun ER et al. Post transplant complications. Clinical utility of oral valacyclovir compared with oral acyclovir for the prevention of herpes simplex virus mucositis following autologous bone marrow transplantation or stem cell rescue therapy. Bone Marrow Transplantation 2003; 31: 51-55

[5] Dignani M. Infections post transplant. Valacyclovir prophylaxis for the prevention of Herpes simplex virus reactivation in recipients of progenitor cells transplantation. Bone Marrow Transplantation 2002; 29: 263-267

The dosage was 500 mg of valaciclovir twice daily. Treatment was begun 3 days before transplantation and was continued until the end of the neutropenia period and for no more than 30 days after transplantation. Patients unable to tolerate oral administration received aciclovir IV: 125 mg/m^2 every 6 hours until they could take an oral treatment.

The primary endpoint was the onset of clinical signs of herpes infection.

Results: The median duration of treatment was 14 days. HSV reactivation was observed in 3 patients out of 108 (2.7%). This involved genital localisation. No HSV reactivation at an oral site was observed.

To conclude, this open-label study does not make it possible to assert that valaciclovir is effective for the prophylaxis of chemotherapy- or radiotherapy-induced reactivation of oral herpes infections in the case of mucositis.

3.6. Resistance to aciclovir and to valaciclovir

The risks of resistance to valaciclovir may be related to the risks of resistance to aciclovir as valaciclovir is a pro-drug of aciclovir.
In France[6], a national survey of aciclovir resistance gave a mean value of 3.5 % for the level of resistance of HSV strains to aciclovir in immunocompromised patients. During this study, the prevalence rate of aciclovir resistance did not increase between 1987 and 1999. The risk of resistance increased with the severity of the immune deficiency and the duration of exposure to the medicinal product.
This data is relatively old and only concerns aciclovir. The risk of an increase in valaciclovir resistance in immunocompromised patients cannot be ruled out and should be monitored over time.

3.7. Adverse effects

Safety results obtained during these new studies in immunocompromised subjects did not detect any specific differences in the safety profile in this population compared to that observed in immunocompetent subjects.

No addition has been made to the “Undesirable effects” section of the SPC for 5 years. The main adverse effects are gastrointestinal, neurological, skin and psychiatric disorders.

In practice, and according to current recommendations, ZELITREX is already prescribed in immunocompromised patients. PSUR data therefore concern immunocompromised patients as well as immunocompetent subjects. These data did not show any difference in terms of safety between immunocompetent and immunocompromised patients.

To conclude, the safety data for ZELITREX in immunocompromised subjects show an identical safety profile to that observed in immunocompetent subjects.

3.8. Conclusion

For prophylaxis of herpes infections in immunocompromised subjects:
- The efficacy of valaciclovir has been shown primarily by comparison with a placebo, in a study on the prophylaxis of recurrent genital herpes in HIV-infected patients.
- No difference in terms of efficacy could be demonstrated between valaciclovir and aciclovir during a superiority study in the prophylaxis of recurrent genital herpes in HIV-infected patients.
- In the prevention of radiotherapy- or chemotherapy-induced mucositis, the methodological quality of the studies submitted (open-label) was insufficient to show the efficacy of valaciclovir.

[6] Danve-Szatanek C, Aymard M, Thouvenot D et al. Surveillance Network for Herpes Simplex Virus Resistance to Antiviral Drugs: 3-Year Follow-up. J Clin Microbiol 2004; 42: 242-249.

- No study was submitted concerning the prophylaxis of recurrent orofacial herpes in immunocompromised subjects.

In the treatment of genital herpes, no difference in terms of efficacy *versus* aciclovir was observed during a superiority study.

Proof of the efficacy of ZELITREX in immunocompromised patients, in the treatment and prophylaxis of recurrent herpes infections, is therefore mainly based on data from immunocompetent subjects.

The available data show a satisfactory safety profile in immunocompromised subjects.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual Benefit

4.1.1. Actual benefit in the treatment of the first episode of genital *Herpes simplex* virus infections and subsequent recurrences in immunocompromised patients.

The first episode of genital *Herpes simplex* infections and possible subsequent recurrences may cause a marked deterioration in quality of life. In immunocompromised patients, these infections are generally more severe and are more frequently likely to cause complications.

ZELITREX is intended to provide curative treatment.

The efficacy/safety ratio of ZELITREX is modest.

ZELITREX is used for first-line therapy.

There is an alternative for use by parenteral route or orally in immunocompromised subjects.

Public health benefit:
Recurrent genital *Herpes simplex* virus infections in immunocompromised subjects are a small public health burden.
The need for an improvement in their management comes within the scope of an identified public health priority (law of public health, GTNDO). The need for a curative treatment of these infections is already largely covered by aciclovir.
According to available data, ZELITREX is not expected to have an impact on the reduction in morbidity due to these infections in immunocompromised subjects compared to aciclovir. Nevertheless, the marketing of an oral treatment, in particular by ZELITREX, is useful as it allows immunocompromised patients to be managed on an outpatient basis.
Overall, ZELITREX is not expected to benefit public health.

The actual benefit of ZELITREX is substantial in this indication.

4.1.2. Actual benefit in the prophylaxis of recurrent genital *Herpes simplex* virus infections in immunocompromised subjects suffering from at least 6 recurrences per year.

The repeated occurrence of recurrent genital Herpes simplex virus infections 6 or more times a year causes a marked deterioration in quality of life. In immunocompromised patients, these infections are generally more severe and more frequently lead to complications.

ZELITREX is intended for prophylaxis.

The efficacy/safety ratio of ZELITREX is high.

There is an alternative for use by the oral route in immunocompromised subjects.

Public health benefit:
Recurrent genital *Herpes simplex* virus infections in immunocompromised subjects are a small public health burden.
The need for an improvement in their management comes within the scope of an identified public health priority (public health law, GTNDO). The need for a prophylactic treatment of these infections is already largely covered by aciclovir.
According to available data, ZELITREX is not expected to have an impact on the reduction in morbidity due to these infections in immunocompromised subjects compared to aciclovir ZELITREX does not therefore provide an additional response to the identified need.
Consequently, ZELITREX is not expected to benefit public health in this indication.

The actual benefit of ZELITREX is substantial in this indication.

4.1.3. Actual benefit in the prophylaxis of recurrent orofacial *Herpes simplex* virus infections in immunocompromised subjects suffering from at least 6 recurrences per year.

The repeated occurrence of recurrent orofacial *Herpes simplex* virus infections 6 or more times per year causes a marked deterioration in quality of life. These infections are generally more severe in immunocompromised patients and more frequently lead to complications.

ZELITREX is intended to be used for prophylaxis.

The efficacy/safety ratio of ZELITREX is modest.

ZELITREX is used for first-line therapy.

There is an alternative for use by the oral route in immunocompromised subjects.

Public health benefit
The public health burden of recurrent orofacial Herpes simplex virus infections in immunocompromised subjects is difficult to quantify.
The need for their prevention is not an established public health priority.
As no data were submitted, ZELITREX is not expected to have an impact on the reduction in morbidity due to these infections compared to aciclovir.
Consequently, ZELITREX is not expected to benefit public health in this indication.

The actual benefit of ZELITREX is substantial in this indication.

4.1.4. Actual benefit in the prophylaxis of chemotherapy- or radiotherapy-induced oral Herpes simplex virus infections (mucositis).

Herpes virus reactivation during chemotherapy- or radiotherapy-induced mucositis causes a worsening of the mucositis and may lead to serious complications such as the spread of the herpes infection.

ZELITREX is intended to be used for prophylaxis.

The efficacy/safety ratio of ZELITREX is modest.

ZELITREX is used for first-line therapy.

There is an alternative for use by the oral or parenteral routes in immunocompromised subjects.

Public health benefit:
The public health burden of Herpes virus mucositis in immunocompromised subjects is difficult to quantify.
The need for their improved management lies within the scope of an identified public health priority (Law of public health). The need for a preventive treatment of these infections is already largely covered by aciclovir.
There are insufficient available data to evaluate if ZELITREX will have an impact on the reduction in morbidity due to these infections compared to aciclovir. It cannot therefore be assumed that ZELITREX will provide another solution to meet the identified need.
Consequently, ZELITREX is not expected to benefit public health in this indication.

The actual benefit of ZELITREX is substantial in this indication.

4.2. Improvement in actual benefit

ZELITREX does not improve the actual benefit (IAB V) in the management of herpes in immunocompromised subjects compared to aciclovir, in all indications.
The dosing regimen of ZELITREX is simpler than that of aciclovir because of its increased bioavailability.

4.3. Therapeutic use

In the population of HIV-infected patients, current guidelines are as follows[7]:

Curative treatment:
When the CD4 count is above 200/mm^3, valaciclovir is recommended (500 mg twice daily), or, in particularly severe forms, aciclovir IV (5 to 10 mg/kg every 8 hours) for 8 days.
When the CD4 count is less than 200/mm^3, aciclovir IV is preferred; valaciclovir may be used in mild mucocutaneous forms detected early after onset. In the case of aciclovir-resistant HSV (cross-resistance with ganciclovir), treatment comprises foscarnet (Foscavir®) IV at a dosage of 90 mg/kg every 12 hours (with hyperhydration and dosage adjustment according to renal function) for at least 10 to 14 days.

Secondary prophylaxis:
The prevention of recurrences is indicated in the case of severe (extensive and invalidating lesions and a CD4 count < 100/mm^3) or frequently recurring (> 4 to 6 episodes per year) or chronic herpes lesions. Secondary prophylaxis is achieved with oral valaciclovir (500 mg twice daily). This prophylaxis may be continued for prolonged periods if it is beneficial. The risk of selecting aciclovir-resistant strains of HSV (estimated however to be less than 5 %) must be taken into account in the decision to initiate this secondary prophylaxis.

Radiotherapy- or chemotherapy-induced herpes mucositis[8]:
Mucositis is a frequent and potentially severe complication of anti-cancer treatments by radiotherapy and chemotherapy. It is one of the side effects most difficult to tolerate by patients receiving intensive treatment followed by bone marrow transplantation. Herpes reactivation (or herpes mucositis) frequently occurs in those patients who are seropositive for HSV.

During bone marrow transplantation, the commonly accepted strategy for the prevention of radiotherapy or chemotherapy-induced oral herpes reactivation is the use of an antiviral

[7] Prise en charge des personnes infectées par le VIH. (Management of HIV-infected persons). Report of Professor Patrick YENI. 2006.
[8] Rubenstein EB, Peterson DE, Schubert M et al. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. Cancer 2004;100(9 suppl):2026-2046.

agent in HSV-seropositive patients, which may either be oral valaciclovir or oral or IV aciclovir. The choice of antiviral agent is based on the severity of the mucositis and whether or not the patient may take an oral treatment.

4.4. Target population

The extension of indications of ZELITREX as defined by the new wording of the Marketing Authorisation corresponds to the recognition of established practices.

These extensions of indications should not cause a notable increase in the number of patients currently treated by ZELITREX for all indications together. In 2006, the total number of ZELITREX prescriptions was 481,000.

However, in indications in immunocompromised subjects, the target population may be estimated as follows:

- Treatment of the first episode of genital *Herpes simplex* infections and any subsequent recurrences in immunocompromised patients.

The prevalence of immunocompromised patients in France may be estimated to be 335,000 from:

- The prevalence of HIV-infected subjects with a low CD4 count (CD4< 285): 46,000 cases in 2004 [6],
- The number of new cases of cancer diagnosed per year: 280,000 in 2000[9],
- The number of organ transplantations[10]: 4,500 organ transplantations in 2006,
- The number of bone marrow transplantations[9]: 4,300 haematopoietic stem cell transplantations in 2005.

The other causes of immune deficiency are uncommon and were not taken into account in the calculation of the target population.
In the general population, the prevalence of genital herpes is estimated to be 2%[11] or 2.5%[12] depending on the source. In the absence of specific data, this percentage may be extrapolated to the immunocompromised population.
According to these assumptions, the target population for the treatment of a first episode of genital *Herpes simplex* virus infection and any subsequent recurrences in immunocompromised patients may be estimated to be between 6,500 and 8,500 persons per year.

- Prevention of recurrent genital *Herpes simplex* virus infections in the immunocompromised subject with at least 6 recurrences per year.

The prevalence of immunocompromised patients in France may be estimated to be 335,000[6,8 9]:
In the general population, the prevalence of genital herpes is estimated to be 2%[8] or 2.5%[9] depending on the source. In the absence of specific data, this percentage may be extrapolated to the immunocompromised population.

[9] Remontet L, Buemi A, Velten M, Jougla E, Esteve J. Evolution de l'incidence et de la mortalité par cancer en France de 1978 à 2000. August 2003 BEH: n°41-42/2003 a vailable at: http://www.invs.sante.fr
[10] http://www.agence-biomedecine.fr/fr/chiffres-principaux.aspx
[11] Dréno B. L'Herpès vu par les Français: résultat d'une enquête portant sur 10 000 personnes. Pathologie Biologie 50 (2002) 436-439
[12] Bossi P. Consensus conference: Herpès génital: épidémiologie, modes de transmission, clinique, excrétion virale asymptomatique, conséquences sur les autres maladies sexuellement transmissibles, traitement et prévention. Ann Dermatol Venerol 2002; 129: 477-493.

The number of subjects who suffer more than 6 genital herpes recurrences per year may be estimated to be approximately 1/3 of patients[13].
According to these assumptions, the population liable to receive preventive treatment for recurrent genital *Herpes simplex* virus infections among immunocompromised subjects with at least 6 recurrences per year is approximately 2,000 to 3,000 patients per year.

- Prevention of recurrent orofacial Herpes simplex virus infections in immunocompromised subjects with at least 6 recurrences per year.

The prevalence of immunocompromised patients in France may be estimated to be 335,000[6,8 9].
The prevalence of orofacial herpes in the general population may be estimated to be 14.8% (INSTANT study[14]). It may be estimated that approximately 13%[13] of these subjects suffer more than 6 recurrences of orofacial herpes per year. In the absence of specific data, this percentage may be extrapolated to the immunocompromised population.

4.4.1. According to these assumptions, the population of immunocompromised subjects suffering from at least 6 recurrences per year and liable to receive preventive treatment for recurrent orofacial *Herpes simplex* virus infections is approximately 6,500 patients per year.

- Prevention of chemotherapy- or radiotherapy-induced oral Herpes simplex virus infections (mucositis).

In 2005, 4,000 bone marrow transplantations were performed[9].
The number of persons with cancer of the upper airways and gastrointestinal tract[8] was estimated to be 25,500 in 2000. Approximately 2/3 of these patients may be considered to be at high-risk of mucositis, in particular because of radiotherapy.
Other types of cancer management, in particular certain intensive chemotherapy protocols, also have a high risk of mucositis. However, these situations are uncommon in comparison with ENT cancer and bone marrow transplantation and were not taken into account in the calculation of the target population.
The seroprevalence of HSV1 infections (orolabial transmission) is 65% in the general population[12].
According to these assumptions, the target population for prophylaxis of recurrences of chemotherapy- or radiotherapy-induced oral herpes infections may be estimated to be about 14,000 cases per year.

4.5. Transparency Committee Recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indications and dosages of the MA.

4.5.1. Packaging:

There are specific packs for each indication of ZELITREX.
In the new indications in immunocompromised subjects, the pack of 10 is particularly appropriate for the treatment of herpes. Packaging should be devised that is better suited to the indication of prophylaxis of herpes in immunocompromised subjects.

4.5.2. Reimbursement rate : 65 %

[13] Boelle PY, Fagnani F, Valleron PJ, Detournay B, El Hasnaoui A, Halioua B, Nicolas JC. Un modèle épidémiologique de l'herpès génital pour l'évaluation des interventions thérapeutiques et prophylactiques: application à la France. Ann Dermatol Venereol 2004; 131:17-26.
[14] Lorette G, Crochard A, Mimaud V, Wolkenstein P, Stalder Jf, El Hasnaoui A. A survey on the prevalence of orofacial herpes in France. The instant study. Journal of American Academy of Dermatology. (in press, Accepted October 2005).