HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

28 March 2007

CHAMPIX 0.5 mg and 1 mg, film-coated tablets
Box of 11 0.5 mg + 14 1 mg film-coated tablets in a case
CIP: 377180-9

CHAMPIX 0.5 mg film-coated tablets
Box of 28 film-coated tablets in a case, CIP: 377182-1
Box of 56 film-coated tablets in a bottle, CIP: 377184-4
Box of 56 film-coated tablets in a case, CIP: 377183-8

CHAMPIX 1 mg film-coated tablets
Box of 28 film-coated tablets in a case, CIP: 377185-0
Box of 56 film-coated tablets in a bottle, CIP: 377190-4
Box of 56 film-coated tablets in a case, CIP: 377186-7

Applicant: PFIZER Laboratories

Varenicline

List I

Marketing Authorisation (MA) date: 26 September 2006

Reason for request: Inclusion on the list of medicines approved for use by hospitals

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Varenicline

1.2. Background

Varenicline is a partial agonist of nicotinic acetylcholine receptors. It is a new treatment for cessation of smoking.

1.3. Indication

CHAMPIX is indicated for smoking cessation in adults.

1.4. Dosage

The probability of success for smoking cessation treatment is higher in patients who are motivated to stop smoking and who receive additional advice and supervision.

The recommended dose is 1 mg varenicline two times daily after a week of dose escalation as follows:

Days 1-3	0.5 mg 1 times daily
Days 4-7	0.5 mg 2 times daily
Day 8-end of treatment	1 mg 2 times daily

The patient must fix a date on which to stop smoking. Administration of CHAMPIX should start 1 to 2 weeks before this date.

The dose may be reduced to 0.5 mg 2 times daily temporarily or permanently in patients who cannot tolerate the adverse effects of CHAMPIX.

CHAMPIX tablets should be swallowed whole with water. They may be taken with or without food.

Patients should be treated for 12 weeks.

In the case of patients who succeed in stopping smoking after 12 weeks, a further treatment of 12 weeks at 1 mg 2 times per day may be envisaged.

In the case of patients who do not achieve smoking cessation during the initial treatment or who relapse after treatment, there are no data available on the efficacy of further 12 week treatments.

In treatment for smoking cessation, the risk of returning to smoking is increased in the period immediately following the completion of treatment. In the case of patients at high risk of relapse, a progressive cessation may be planned (see section 4.4).

Patients with renal impairment:

No dose adjustment is required with mild (estimated creatinine clearance > 50 ml/min to ≤ 80 ml/min) to moderate (estimated creatinine clearance ≥ 30 ml to ≤ 50 ml/min) renal impairment.

However, in the case of moderate renal impairment with poorly tolerated adverse events, the dosage may be reduced to 1 mg once daily.

In the case of severe renal impairment (estimated creatinine clearance < 30 ml/min), administration should start with 0.5 mg once daily for the first 3 days, and then increase to 1 mg 1 once daily. Due to the limited clinical experience with CHAMPIX in patients with end-stage renal failure, this treatment is not recommended for this patient population.

Patients with hepatic impairment:

No dose adjustment is required in cases of hepatic impairment.

Use in the elderly:

No dose adjustment is necessary for elderly patients.

Paediatric population:

CHAMPIX should not be used in children and adolescents aged less than 18 years due to the lack of data on safety and efficiency.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2006)

N: Nervous system

07: Other medicines for the nervous system

B: Medicines used for dependency phenomena

A: Medicines used for nicotine dependency

03: Varenicline

2.2. Medicines with a similar therapeutic aim

- Nicotine substitution treatments take different forms: chewing gums, transdermal systems, pastilles for sublingual use or sucking, inhaler, buccal spray. They are approved for hospital use.
- Zyban LP[®] tablets are not approved for hospital use.

All these products are available in pharmacies and are not reimbursed by national health insurance.

3 ANALYSIS OF AVAILABLE DATA

Four phase III studies have assessed the efficacy and safety of varenicline:

- two studies of smoking cessation;
- one study of maintenance of abstinence;
- one study to assess the tolerability of the product.

The three studies assessing the efficacy of varenicline were randomised, parallel group studies with bupropion and placebo controls (studies on smoking cessation) or solely with placebo (study of maintenance of abstinence).

1. Studies of smoking cessation:

Purpose

The objective of the two studies, with the same experimental design, was to show the superiority of varenicline over bupropion and placebo for smoking cessation.

These were double-blind studies.

Treatments

Subjects received one treatment (varenicline, bupropion or placebo) for 12 weeks. After that, the subjects did not receive any treatment for 40 weeks.

In addition, all subjects received individual support during these studies.

During the first week, a titration is performed:

- varenicline
0.5 mg per day from D1 to D3
then 0.5 mg twice daily from D4 to D7
then 1 mg twice daily until the 12th week.
- bupropion
150 mg per day from D1 to D3
then 150 mg twice daily until the 12th week.

It should be noted that the bupropion (Zyban) dosage recommended in the MA is 150mg per day for the first 6 days, then 150 mg twice daily. The recommended duration of treatment is 7 to 9 weeks.

Inclusion criteria and characteristics of the subjects

These two studies included subjects aged 18 to 75 who smoked at least 10 cigarettes per day and who were motivated to stop smoking.

The subjects should not have stopped smoking for more than 3 months in the year prior to inclusion.

Subjects with the following conditions were excluded from these studies: type 2 diabetes, uncontrolled hypertension, severe COPD, psychosis, bipolar disorders, antidepressant treatment in the previous 12 months, aged 75 years or older and pregnant women.

The exclusion criteria were namely based on the contraindications for bupropion. These resulted in a different population being recruited from that eligible for treatment with varenicline.

Table 1: Data on the smoking habits of the subjects included and their distribution by group

Study 1028	Study 1036
Varenicline	Bupropion	Placebo	Varenicline	Bupropion	Placebo
Population	N=352	N=329	N=344	N=344	N=342	N=341
Mean number of years of smoking (SD)	24.3 (11.5)	24.1 (11.5)	24.7 (12.1)	27.1 (11.5)	25.4 (12.0)	24.4 (12.0)
Mean number of cigarettes smoked per day during the previous month (SD)	21.1 (9.5)	21.0 (8.5)	21.5 (9.5)	22.5 (9.5)	21.8 (8.7)	21.5 (8.7)

These studies included more men than women (56% versus 44%).
The mean age of the subjects included was approximately 42 years.

Endpoints

The primary endpoint was the rate of continuous abstinence for 4 weeks (RCA-4W), from week 9 to week 12, confirmed by measurement of expiratory carbon monoxide (CO).

One of the secondary endpoints was the rate of continuous abstinence at week 52 (RCA 9-52).

The percentage of continuous abstinence was defined as the proportion of subjects who had not smoked (not even one drag) between week 9 and week 52, with an expiratory CO measured at < 10 ppm.

Results

The results are presented in the following table (with the primary endpoint data in bold type):

The results were compared between the groups for the ITT population, namely the population of patients who had received at least one dose of the treatment.

Table 2: Comparison of the rate of continuous abstinence for 4 weeks from week 9 to week 12, confirmed by measurement of expiratory CO

Study 1028	Study 1036
Study arms: Population	Varenicline N = 349	Bupropion N = 329	Placebo N = 344	Varenicline N = 343	Bupropion N = 340	Placebo N = 340
Rate of continuous abstinence between W9 and W12	44.4 % (155/349)	29.5 % (97/239)	17.7 % (61/344)	44 % (151/343)	30 % (102/340)	17.7 % (60/340)
OR (IC 95 %,p)
Vs placebo	3.91 (2.74-5.59) <0.0001	2.00(1.38-2.89) 0.0002	3.85 (2.69-5.50) <0.0001	2.03 (1.41-2.94) 0.0001
Vs bupropion	1.96 (1.42-2.72) <0.0001	1.89 (1.37-2.61) <0.0001
RR (IC 95 %,p)
Vs placebo	2.50 (1.94-3.24) <0.0001	1.66 (1.25-2.21) 0.0003	2.49 (1.93-3.23) <0.0001	1.70 (1.28-2.25) 0.0002
Vs bupropion	1.51 (1.23-1.85) 0.0001	1.47 (1.20-1.80) 0.0001

OR: odds ratio
RR: relative risk
IC: confidence interval

In the 2 studies, after 12 weeks of treatment, varenicline was superior to placebo and to bupropion with respect to the primary endpoint (rate of continuous abstinence for 4 weeks : week 9 to week 12).

Table 3: Results for the rate of continuous abstinence between the 9th and 52nd weeks (secondary endpoint)

Study 1028	Study 1036
Study arms:	Varenicline N = 349	Bupropion N = 329	Placebo N = 344	Varenicline N = 343	Bupropion N = 340	Placebo N = 340
Rate of continuous abstinence between W9 and W52	22.1 % (77/349)	16.4 % (54/329)	8.4 % (29/344)	23 % (79/343)	15 % (51/340)	10.3 % (35/340)
OR (CI 95 %,p)
Vs placebo	3.13 (1.97-4.97) <0.0001	2.16 (1.33-3.51) 0.0014	2.66 (1.72-4.11) <0.0001	1.54 (0.97-2.45) 0.0634
Vs bupropion	1.45 (0.98-2.14) <0.0640	1.72 (1.16-2.55) <0.0062
RR (CI 95 %,p)
Vs placebo	2.62 (1.75-3.91) <0.0001	1.94 (1.27-2.98) 0.0016	2.24 (1.55-3.23) <0.0001	1.46 (0.97-2.18) 0.065
Vs bupropion	1.34 (0.98-1.84) 0.063	8.0 (3.1-12.9) 0.0016	1.54 (1.12-2.11) 0.008

OR: odds ratio
RR: relative risk
CI: confidence interval.

➤ Comparison with placebo:

In both studies, the rate of continuous abstinence between the 9th and the 52nd weeks was significantly higher with varenicline than with placebo.

➤ Comparison with bupropion:

In study 1028, the rate of continuous abstinence between the 9th and the 52nd weeks was significantly higher with varenicline than with bupropion.

In study 1036, the rate of continuous abstinence between the 9th and the 52nd weeks was not significantly different with varenicline than with bupropion.

2. Study of maintenance of abstinence

Purpose

The literature and clinical trials with varenicline indicate that relapses occur most frequently during the first weeks following cessation of treatment. Study 1035 assessed whether a further 12 weeks of treatment with varenicline increased the rate of continuous abstinence in subjects who had stopped smoking by the 12th week.

Design

This study, assessing the efficacy of varenicline in the maintenance of abstinence was a randomised, parallel group, placebo-controlled study.

During the first 12-week phase of treatment with varenicline, the study was an open one. After this, subjects who had stopped smoking were randomised to receive varenicline or placebo in a double-blind manner.

The inclusion criteria were similar to those of the two studies presented above.

Treatments

- Initial open phase of treatment with varenicline at a dosage of 1 mg twice daily (1928 patients recruited) for 12 weeks.
On completion of the first phase, subjects who had stopped smoking were eligible for the second phase.
- Second double-blind phase for 12 weeks only in subjects who had stopped smoking during the 1st phase:
Varenicline (1 mg twice daily): n = 603 randomised subjects (602 received at least one dose)
Placebo: n = 607 randomised subjects (604 received at least one dose).
- Third phase: follow-up of subjects without treatment (for 28 weeks) until the 52nd week
Varenicline: n= 494 completed the study
Placebo: n= 463 completed the study

Endpoints

The principal endpoint was the rate of continuous abstinence from week 13 to week 24 confirmed by measurement of expiratory carbon monoxide (CO).

One of the secondary endpoints was the rate of continuous abstinence at week 52.

Results

The results were compared between the 2 groups in the intention to treat (ITT) population, namely patients who had received at least one dose of treatment.

Table 4 : results for the two endpoints

Varenicline N=602	Placebo N=604	Odds ratio (CI 95%)	P
Primary endpoint: Rate of continuous abstinence between W13 and W24	70.6 % (425/602)	49.8 % (301/604)	2.47 (1.95-3.15)	<0.0001
Secondary endpoint: Rate of continuous abstinence between W13 and W52	44.0 % (288/602)	37.1 % (224/604)	1.35 (1.07-1.70)	0.0126

In the ITT population, the rates of continuous abstinence between weeks 13 and 24 and between weeks 13 and 54 were significantly higher in subjects treated with varenicline than in patients on placebo.

For patients who had stopped smoking after a first treatment with varenicline, this study shows the benefit of a further 12 weeks on varenicline for maintenance of abstinence.

3. Adverse effects

Smoking cessation, with or without treatment, is associated with various symptoms, such as insomnia, irritability, anxiety, depressive mood. Within the studies was not planned to differentiate between adverse events associated with treatment and events that could be associated with smoking cessation.

Tolerability study

One double-blind, placebo-controlled study was conducted in order to evaluate the tolerability of varenicline.

Subjects received the treatment for 52 weeks.

Adverse events were analysed in 251 subjects in the varenicline group and in 125 subjects in the placebo group.

The most frequent adverse events were similar in nature to those observed in other clinical trials with varenicline of shorter duration, but their frequency was higher. Nausea was observed in 40.2% subjects on varenicline and insomnia in 19.1%.

Adverse effects

The studies included approximately 4,000 subjects treated with varenicline for a maximum of 1 year. The mean exposure period was 84 days.

In subjects treated with the dose recommended in the MA, nausea was the most frequent adverse event (28.6%). This generally appeared at the start of treatment and was mild to moderate in severity.

After nausea, the most frequent adverse events (>10%) were insomnia, abnormal dreams, headache. These are the main symptoms which were responsible for treatment being stopped on account of an adverse effect.

Serious adverse effects

Cases of serious adverse effects and death observed during treatment or in the 30 days following the last dose during the clinical trials are presented in table 5.

Table 5: Serious adverse effects

Varenicline (N = 3,940)	Bupropion (N = 795)	Placebo (N = 1,209)
Death	3	1	1
Serious adverse effects (SAE)	86	15	19
SAE associated with treatment	16	8	1

No death was considered to be treatment-related.

Risk Management Plan (RMP)

The European RMP, which complements routine pharmacovigilance, includes a programme of intensified post-marketing surveillance including the establishment of several studies of efficacy and safety in the following populations, which were not studied initially:

- subjects aged less than 18 years, patients with cardiovascular disease, COPD or psychosis,
- a cohort study in pregnant women conducted on the basis of data from the Danish and Swedish registers.

In addition, Afssaps has set up intensified pharmacovigilance surveillance with national pharmacovigilance monitoring.

4. Conclusion

Two studies have shown the efficacy of varenicline to be superior to those of bupropion and placebo in smoking cessation over the short term (12 weeks).

The rates of continuous abstinence between the 9th and 12th weeks following 12 weeks of treatment were higher with varenicline (44.4 %) than with bupropion (29.5 %) or placebo (17.7 %).

In both studies, the rate of continuous abstinence from the 9th to the 52nd weeks was higher with varenicline (22.1% and 23%) than with placebo (8.4% and 10.3%). Only one of the two studies showed a significant difference in favour of varenicline as compared to bupropion (15 % and 16.4 %).

One placebo-controlled study showed the benefit of supplementary treatment with varenicline for 12 weeks in order to maintain abstinence from smoking.

After 24 weeks (24 weeks on varenicline or 12 weeks on varenicline followed by 12 weeks on placebo), the rate of continuous abstinence between the 13th and 24th weeks was 70.6 % with varenicline and 49.8 % with placebo.

After 1 year, a significant difference in the rate of continuous abstinence between the 13th and the 52nd weeks was demonstrated in favour of varenicline (44.0 %) compared to placebo (37.1 %).

Table 6: Summary table of rates of continuous abstinence:

At 3 months	Rate of continuous abstinence	Varenicline	Bupropion	placebo
Smoking cessation studies	Between W9 and W12	44%	30%	18%
Study of maintenance	Between W13 and W24	71%	-	50%

At 1 year	Rate of continuous abstinence	Varenicline	Bupropion	placebo
Smoking cessation studies	Between W9 and W52	22% - 23 %	15% - 16%*	8% - 10%
Study of maintenance	Between W13 and W52	44%	-	37%

* The difference between varenicline and bupropion was not significant in one of the 2 studies.

The other differences between varenicline and bupropion and between varenicline and placebo are statistically significant.

Nausea was the most frequent adverse event (almost one third of the subjects). Insomnia, abnormal dreams and headache were also observed frequently (>10%).

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Mortality

Smoking is the major cause of avoidable mortality in France: 66,000 people die each year as a consequence of tobacco¹. One out of two regular smokers dies due of the damaging effects of smoking and half of the deaths occur before the age of 69 years. Passive smoking is responsible for 3,000 to 5,000 deaths per year.

Smoking is responsible for premature mortality: half of the deaths due to tobacco occur in the population aged from 35 to 69 years, leading to a decrease in life expectancy of 20 to 25 years compared to that of a non-smoker.²

Comorbidities

Smoking is responsible for 25% of all cancers, primarily bronchopulmonary and ENT cancers³. Tobacco is implicated in almost 90% of lung cancers⁴.

Smoking is a risk factor for cardiovascular disease such as coronary disease, peripheral occlusive arterial disease of the lower limbs and cerebrovascular accidents.

In men, more than one death in 7 due to cardiovascular disease can be attributed to smoking².

Chronic obstructive pulmonary disease (COPD) is the principal respiratory complication of smoking. Tobacco is implicated in more than 90% of deaths due to COPD⁴. Smoking also leads to a doubling in the risk of infections such as pneumococcal pneumonia, legionellosis and pulmonary tuberculosis⁵.

Benefits of stopping smoking

Stopping smoking reduces overall mortality and particularly that linked to cardiovascular diseases and lung cancer. Thus, the mortality rate for lung cancer in all age groups combined is estimated to be 15.9 in 1,000 for smokers compared to 2.0 to 7.5 in 1,000 for ex-smokers⁶.

Data in the literature has demonstrated a reduction in the risk of death due to myocardial infarction following cessation of smoking. A systematic review, which included 20 cohort studies (n= 12,603) published between 1996 and 2003, has demonstrated a reduction of 36% in the relative risk of death in patients with coronary disease, who have stopped smoking, compared to those who continued to smoke (RR 0.64 – CI95% [0.58-0.71])⁷.

As well as causing a reduction in mortality, stopping smoking also decreases the risks of appearance or exacerbation of smoking-related pathologies.

¹ Bulletin Epidémiologique Hebdomadaire n°21/22, 31 mai 2005 ; 94-108

² Bulletin Epidémiologique Hebdomadaire, n°22-23, 20 03, 27 mai 2003 ; 97-108

³ Les stratégies thérapeutiques médicamenteuses et non médicamenteuses de l'arrêt du tabac, Recommandations de bonne pratique, Afssaps, mai 2003

⁴ Le Faou A-L, Scemama O, Epidémiologie du tabac, Rev Mal Resp 2005 ; 22 :8S27-8S32

⁵ Bulletin Epidémiologique Hebdomadaire, n°21-22, 20 06, 30 mai 2006 ; 141-152

⁶ Doll R, Peto R, Boreham J, Sutherland I, Mortality in relation to smoking: 50's years observations on male British doctors. BMJ 2004; 328 (7455):1519

⁷ Crichtley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: a systematic review. JAMA 2003;290(1):86-97

Dependency

Smoking involves a double dependency:

- a psychological and behavioural dependency
- a pharmacological dependency associated with inhaled nicotine.

In the event of hospitalisation, especially in an emergency, the sudden discontinuation of tobacco administration, and thus of nicotine, can manifest as a true deprivation syndrome.

Discontinuation of tobacco generally provokes a withdrawal syndrome. It is observed in regular smokers who suddenly decrease their consumption. This syndrome includes mood disturbances with: mood instability, insomnia, problems with concentration, feelings of frustration and anxiety. The withdrawal syndrome starts within several hours and is most intense during the 24/48 hours following discontinuation. Most of the symptoms last for approximately 4 weeks. This syndrome is mainly due to lack of nicotine.

Efficacy / adverse effects

CHAMPIX has proven efficacy as an aid in smoking cessation. At 12 weeks, its efficacy is superior to that of placebo and bupropion. This efficacy in the maintenance of abstinence from smoking is maintained at 52 weeks in comparison to placebo. After one year, the results for smoking cessation with varenicline compared to results with bupropion are inconsistent.

CHAMPIX is a supplementary method to enable cessation of smoking. The alternatives are nicotine substitution treatments and bupropion.

No comparison with nicotine substitution of treatments is currently available.

The actual benefit of CHAMPIX is substantial.

4.2. Therapeutic use⁸

The objective of smoking cessation treatment is total abstinence over the long term.

The management of a smoker who is motivated to stop smoking is based on an initial clinical assessment which enables the degree of nicotine dependency to be assessed (by means of the Fagerström test), problems with anxiety and depression to be identified and screening for a co-dependency (alcohol, cannabis...) to be performed. Prolonged follow-up of patients who have stopped smoking is always necessary. In the event of relapse, prolonged psychological support combined with cognitive behavioural therapy is recommended.

Specific strategies to assist in cessation of smoking should be considered, in addition, for the following populations:

- pregnant and breastfeeding women;
- patients with associated psychiatric problems;
- adolescents.

Nicotine substitutes:

Regardless of their pharmaceutical form, their dosage should be adjusted to the Fagerström score and with respect to signs of overdosage (diarrhoea, palpitations, insomnia) or underdosage (appearance of a marked withdrawal syndrome).

⁸ Les stratégies thérapeutiques médicamenteuses et non médicamenteuses de l'arrêt du tabac, Recommandations de bonne pratique, Afssaps, mai 2003

After one year, the benefit of treatment with nicotine substitutes is almost double that observed with placebo. After one year, 18% of smokers treated with nicotine substitutes were abstinent compared with 10% in the placebo group⁹.

They are generally well tolerated. Administration of nicotine is not associated with a significant risk of induction of cardiovascular accidents.

It may be useful to combine two nicotine substitutes in patients who are very strongly dependent or who are underdosed with a single type of substitute.

Several studies have shown a good tolerance and sometimes an increased efficacy when two nicotine substitutes are combined in order to obtain the optimum dosage.

This strategy may be recommended for patients who are very strongly dependent or who are underdosed with a single type of substitute (grade B).

The recommended duration of administration of nicotine substitutes during the initial phase of smoking cessation ranges from a minimum of 6 weeks to a maximum of 6 months.

Bupropion (Zyban LP)

This should be used with due attention to its contraindications and following systemic investigation in all patients with risk factors for convulsions. Bupropion lowers the convulsive threshold; patients on bupropion have a risk of convulsion (estimated to be 0.1%). These attacks are primarily generalised tonic-clonic seizures. Insomnia is the most frequent adverse effect.

The usual duration of bupropion treatment is 7 to 9 weeks.

Combination of bupropion and nicotine substitutes has not demonstrated a superior efficacy to that of each of these treatments used alone.

Cognitive behavioural therapies (CBT):

These may be offered as individual or group consultations.

They are recommended techniques to assist smoking cessation (grade A). They are means to enable the cessation of smoking and the prevention of relapses.

The process involved in these techniques is a long one and requires several in-depth consultations.

The efficacy of varenicline as an aid to smoking cessation has been demonstrated in three clinical trials in smokers of 10 cigarettes or more per day.

This product is a supplementary therapeutic agent in the management of smoking cessation.

4.3. Target population

CHAMPIX is intended for adult smokers who are motivated to stop smoking, according to their degree of dependency.

⁹ Silagy et al, Cochrane Tobacco Addiction Group. Nicotine replacement therapy for smoking cessation. Cochrane Database of Systematic Reviews. Issue 1,2001.

In France, the number of smokers aged 15 years and older is estimated to be 14 million, of whom 12.6 million are regular smokers.¹⁰ The number of smoking minors, (excluded from population for whom treatment with this product is justified) is not known.

Adults aged from 26 to 75 years who smoke on average 15 cigarettes per day on a regular basis, with signs of dependency, represent approximately 6.3 million persons (source: Inpes).

It is difficult to know the number of adult smokers who are dependent and are motivated to stop smoking. Given that smokers often make several attempts before succeeding in stopping smoking.

As a result, the number of these smokers who could benefit from this proprietary product in a hospital environment cannot be defined.

It is however estimated that each year 750,000 persons stop smoking for at least one year.

4.4. Transparency Committee recommendations

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

¹⁰ Bulletin Epidémiologique Hebdomadaire n°21/22, 31 mai 2005 ; 94-108