Assessment of dossier of product included for a limited period, in compliance with the decree of 27 October 1999 (Official Journal 30 October 1999) and the order of 15 December 2004 (Official Journal 24 December 2004)

**FONLIPOL 400 mg, tablets**  
B/50 (CIP: 313 202-1)  
B/360 (CIP: 371 795-1)

**Applicant: SERP**

Tiadenol  
List II  
ATC Code: C10AX03  
Date of Marketing Authorisation: 11 June 1987

**Reason for request:** Renewal of inclusion on the list of reimbursed medicinal products.

Medical, Economic and Public Health Assessment Division
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active substance
Tiadenol

1.2. Indications

"Hypercholesterolaemia:
- when a suitable and closely-followed diet has proved insufficient.
- when blood cholesterol following diet has remained high and/or there are associated risk factors.

- In children: indications are limited to essential hypercholesterolaemia that is life-threatening in the short term.

Comment: efficacy in primary or secondary prevention of the complications of atherosclerosis has not been demonstrated"

1.3. Posology (see SPC)

"Initial treatment: 6 tablets per 24 h in 2 doses.
Maintenance treatment: 4 tablets per 24 h in 2 doses."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification
C: Cardiovascular system
C10: Lipid modifying agents
C10AX: Other lipid modifying agents
C10AX03: Tiadenol

2.2. Medicines in the same therapeutic category
Not applicable.

2.3. Medicines with a similar therapeutic aim
All other lipid modifying agents:
- statins: TAHOR (atorvastatin), FRACTAL, LESCOL (fluvastatin), ELISOR, VASTEN and generics (pravastatin), CRESTOR (rosuvastatin), LODALES, ZOCOR and generics (simvastatin)
- fibrates: BEFIZAL (bezafibrate), LIPANOR (ciprofibrate), FEGENOR, LIPANTHYL and generics (fenofibrate), LIPUR (gemfibrozil).

and other medicinal products indicated in the treatment of dyslipidaemia that is not controlled by statins or if statins are not well tolerated:
- cholestyramine: QUESTRAN
- nicotinic acid: NIASPAN
- ezetimibe: EZETROL
3. SUMMARY OF PREVIOUS TRANSPARENCY COMMITTEE OPINIONS

Committee Opinion dated 24 November 1999 - Re-evaluation
Actual clinical benefit: low

Opinion of the Committee, dated 1 March and 18 October 2006 - Inclusion of Box of 360
Actual clinical benefit: low
Improvement in clinical benefit: No improvement in actual clinical benefit (IACB V)

4. UPDATE ON DATA MADE AVAILABLE SINCE PREVIOUS OPINION

In support of its application, the applicant has submitted 10 bibliographical references: 5 published studies, 2 unpublished studies and 3 conference abstracts. Only the published studies are presented below; unpublished studies and conference abstracts will not be addressed in this opinion.

4.1. Efficacy

The open-label non-comparative study by Rouffy (1975)\(^1\) evaluated the efficacy and safety of tiadenol in 30 patients with type IIa or IIb essential hyperlipoproteinaemia (17 vs 13) for over 22 months (23-55 months).

In comparison with baseline, after 11 months of treatment, there were mean reductions of:
- 11% in total cholesterol (TC); this reduction was maintained until 43 months;
- 19% in triglycerides (TG). This reduction in triglycerides was 31% at 23 months, 27% at 35 months and 46% at 43 months.

The study by Gennes 1976\(^2\) evaluated the efficacy and safety of tiadenol after 3 months of treatment in 14 patients with essential hyperlipoproteinaemia type IIa, who had previously been treated with placebo for 3 months. Only 11 of the 14 patients completed the study.

After 3 months of treatment, a reduction in TC levels was observed in the tiadenol arm in comparison with the placebo arm: 2.91 g/L versus 3.51 g/L.

The study by Crepaldi 1979\(^3\), which was open-label and non-comparative, evaluated the efficacy and safety of tiadenol in 8 patients with familial hypercholesterolaemia who were followed up for 5 months. The authors state that a significant reduction in TC and levels of LDL-c from baseline was observed, but no precise data were available.

The study by Sirtori 1983\(^4\) evaluated the efficacy and safety of tiadenol and clofibrate in 27 patients with hypercholesterolaemia (type IIa, IIb and IV) in two sequential (cross-over) periods of 4 weeks.

Patients with type IIa hypercholesterolaemia: a reduction in TC levels was observed for tiadenol vs clofibrate: -15.4% versus -13%, p<0.01.

Patients with type IIb hypercholesterolaemia: a significant reduction in TG levels was observed for clofibrate vs tiadenol: -38% versus -12.5%, p<0.01.

The study by Sabe 1980\(^5\), which was open-label and non-comparative, evaluated the efficacy and safety of tiadenol in 21 patients with hypercholesterolaemia who were followed up for 4

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months. After 4 months of treatment, a significant reduction in LDL-c levels and TG was observed in comparison with baseline. Precise data are not available.

4.2. **Adverse effects**
In the studies mentioned above, safety was described as "good" by the authors, but no more precise data are available.

According to the SPC, the most frequently observed adverse effects are rare allergic reactions in the form of urticaria or Quincke’s oedema.

4.3. **Conclusion**
Given the methodological inadequacies of the available studies (e.g. low patient numbers, lack of statistical power, absence of comparator, lack of precise data, lack of endpoint in terms of morbidity and mortality), it is difficult to assess the clinical relevance of these results. The efficacy of FONLIPOL in terms of reduction in lipid levels, morbidity and mortality cannot therefore be clearly established.

### 5. DATA RELATING TO USE OF MEDICINAL PRODUCT

According to DOREMA data (IMS-EPPM, mobile cumulative total August 2008), FONLIPOL has been prescribed 3000 times. This small number of prescriptions means that qualitative data analysis is not possible.

### 6. TRANSPARENCY COMMITTEE CONCLUSIONS

6.1. **Re-assessment of actual benefit**
The cardiovascular conditions that can arise in the presence of hypercholesterolaemia can be life-threatening.

Because the available data are limited, and because of the methodological inadequacies of the studies provided by the applicant, and the limited nature of the effect observed, the efficacy/adverse effects ratio of FONLIPOL has not been established.

This product is intended to provide preventative treatment.

For the majority of patients with hypercholesterolaemia, therapeutic needs are for the most part met by the use of statins. For others, there are numerous treatment alternatives: fibrates, nicotinic acid, cholestyramine, ezetimibe.

**Public health benefit:**
The burden represented by the cardiovascular conditions to which hypercholesterolaemia predisposes patients is major. For the majority of patients with hypercholesterolaemia, therapeutic needs are for the most part met by the use of other available lipid modifying agents. FONLIPOL has not been shown to have an impact on morbidity or mortality. The extent of the effect of the product has not been well established and the clinical relevance of the results is arguable. Given the current knowledge of the subject, FONLIPOL has not been shown to benefit public health.

Considering the methodological inadequacies of the studies provided by the applicant, which mean that the effect of this product and the numerous available alternatives cannot be
assessed, the Committee considers that the actual benefit provided by FONLIPOL is inadequate to justify its reimbursement by the National Insurance.

6.2. Therapeutic use

Gold-standard treatment strategy
Management of hypercholesterolaemia aims to prevent ischaemic cardiovascular diseases. Management must start with diet and lifestyle measures (reduction in fat consumption, physical exercise) and by management of other cardiovascular risk factors (e.g. smoking, hypertension, diabetes, obesity, sedentary lifestyle). If these measures prove inadequate, lipid-lowering agents may be offered.

According to the current guidelines (Afssaps, 2005), therapeutic management should be guided by the patient's overall cardiovascular risk, with several levels of LDL-c proposed as aims of treatment:
- In patients receiving secondary prevention or who are considered as high-risk, the aim of treatment is to reduce LDL-c to below the 1 g/L threshold. In such cases, treatment with minimal-dose statins can be started, preferably with those that have been proven to be effective. If this dose proves inadequate, it will be necessary to increase it in order to achieve this aim.
- When the agent is given as primary prevention, the aim will depend on the number of risk factors (see Afssaps guidelines) and patient characteristics (e.g. hypertension, diabetes). The patient can receive a dose of 10 mg/day when treatment is started. If this dose proves inadequate, it will be necessary to increase it in order to achieve the therapeutic aim.

In dyslipidaemic patients whose condition is not controlled by statins alone, continuation and reinforcement of diet and lifestyle measures (reduction in fat consumption, physical exercise) and management of other risk factors, particularly smoking, are the first things that should be implemented.
If statin treatment is taken regularly at an appropriate dose and the dyslipidaemia is still uncontrolled, the prescriber can prescribe the statin in combination with other lipid modifying agents, the choice of which will depend on the nature of the residual lipid abnormality on monotherapy:
- if LDL-c needs to be lowered, statin+ezetimibe and statin+cholestyramine are possible choices;
- in order to lower triglycerides or HDL-c, a combination of a statin and nicotinic acid is possible.

For dyslipidaemic patients who do not tolerate statin treatment well, the prescriber currently has a choice between three types of agent: fibrates, cholestyramine and ezetimibe. Fibrates are the treatment of choice in mixed dyslipidaemias with raised LDL-c and triglyceride levels, while cholestyramine and ezetimibe are the treatments of choice in pure hypercholesterolaemia.

Role of FONLIPOL
Given the methodological inadequacies of the studies provided by the applicant, the effect of FONLIPOL is difficult to assess. For this reason, the previously cited Afssaps guidelines state that "the currently available data are insufficient and do not meet current methodological requirements".

6.3. Transparency Committee recommendations
The Transparency Committee does not recommend renewal of inclusion on the list of medicines reimbursed by National Insurance.

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