TRANSPARENCY COMMITTEE 

OPINION 

16 February 2011 

FONZYLANE 150 mg, film-coated tablet 
B/20 (CIP code: 346 595-2) 

Applicant: CEPHALON FRANCE 

Buflomedil (hydrochloride) 
ATC code: C04AX20 

List I 

Date of Marketing Authorisation: FONZYLANE 150 mg 05/12/1988 

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Buflomedil (hydrochloride)

1.2. Reimbursable indication
“Symptomatic treatment of intermittent claudication due to chronic obliterating arteriopathies of the lower limbs (stage II)”

1.3. Dosage

**Due to the narrow therapeutic margin, the patient’s renal function must be assessed and the following dosages must be observed**

“Normal renal function:
300 mg to 600 mg per day in at least two divided doses. The recommended maximum dosage must not exceed 600 mg per day.

Mild to moderate renal failure (creatinine clearance between 30 and 80 ml/min"): The maximum daily dosage must be reduced by half: one 150-mg tablet morning and evening. The maximum daily dosage for these patients must not exceed 300 mg.

**Determination of renal function:**
- systematic determination of serum creatinine before starting treatment,
- creatinine clearance must be calculated using Cockcroft’s formula*, especially in the case of patients aged over 65 and those weighing less than 50 kg (see section 4.4 of the SPC).

(*) creatinine clearance calculated on the basis of creatininaemia and adjusted for age, weight and gender, according to Cockcroft’s formula for example, accurately reflects renal function in this type of patient:

| In men: Crcl = \( \frac{(140 - \text{age}) \times \text{weight}}{0.814 \times \text{serum creatinine}} \) |
| In women: Crcl = \( \frac{(140 - \text{age}) \times \text{weight}}{0.814 \times \text{serum creatinine}} \times 0.85 \) |

(\( \text{Cr}_{\text{cl}} \) is expressed in ml/min, age in years, weight in kg and serum creatinine in \( \mu \text{mol} \))."
2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification
C : cardiovascular system
C04 : peripheral vasodilators
C04A : peripheral vasodilators
C04AX : other peripheral vasodilators
C04AX20 : buflomedil

2.2. Medicines in the same therapeutic category
Peripheral vasodilators (minor AB): PRAXILENE (naftidrofuryl) and generic equivalents. Plus proprietary medicinal products based on: gingko biloba, ifenprofil, nicergoline, pentoxifylline, piribedil (inadequate AB).

2.3. Medicines with a similar therapeutic aim
Other drugs indicated for patients with claudication, in particular platelet antiaggregants:
- PLAVIX (clopidogrel)
- TICLID (ticlopidine)
- PLETAL (cilostazol), not refundable

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy
The pharmaceutical company considered that “there was no need to submit a dossier for the reassessment of the AB” of buflomedil, particularly since no new data had become available since the last renewal of its registration on 4 October 2006.

3.1.1. Reminder of the data available when the Transparency Committee reevaluated vasodilators on 7 June 2006
The Committee reached the following conclusions with regard to the indication “type II arteriopathy of the lower limbs”:

Buflomedil has been investigated in several placebo-controlled trials over short durations. The total number of patients taking part in trials was around 2,300, which is a small number given the frequency of the condition and the fact that buflomedil has been on the market for 30 years.

The Trübstein\(^1\), Diamantopoulos\(^2\), Fonseca\(^3\) and LIMB Treadmill studies showed that buflomedil had a symptomatic effect on the distance that patients could walk without pain during treadmill tests conducted under standard conditions. Some aspects of methodology, such as the definition of inclusion criteria and the results of ITT analyses, are unknown. The

comparisons conducted were “before and after” comparisons. The Transparency Committee was unable to take the two studies written in German (Bisler\textsuperscript{4} and Zinnag\textsuperscript{5}) into account.

In these studies, carried out under standardised conditions, the following improvements were observed (the exact figure varied according to the study):

- pain-free walking distance in patients treated with buflomedil compared to those treated with placebo: 35 to 80 metres;
- maximum walking distance in patients treated with buflomedil compared to those treated with placebo: 60 to 170 metres.

The results observed are too heterogeneous to allow the efficacy of buflomedil in this indication to be accurately quantified with any relevance.

The data presented does not allow the percentage of responders among patients with a sufficiently severe handicap to be assessed in such a way for the response to be accepted as clinically relevant (percentage of patients who were severely handicapped in their everyday lives before treatment and who experience a clinically significant improvement). The data shows at best a modest effect.

The LIMB study assessed morbidity and mortality on the basis of a combined criterion. A significant improvement in this criterion was observed in patients treated with buflomedil compared to those treated with placebo after a median treatment period of three years. These results need to be interpreted with caution given the methodological shortcomings of this study.

No other data is available which would allow the symptomatic effect of buflomedil to be compared directly to that of other vasoactive drugs or analgesics.

Sporadic data is available for patients receiving optimum treatment in other respects (help in stopping smoking, walking exercise programmes, antiaggregant treatment and statins).

In order to assess the therapeutic benefit of these results, it is first of all essential to take account of the extent of the difference observed compared to placebo (the CHMP regards a difference of over 30% as clinically significant), but also the severity of the initial handicap.

The quantitative effect of the drug is poorly established, and is of dubious clinical relevance.

3.1.2. New available data

A Cochrane update produced in 2001\textsuperscript{6} described in the Transparency Committee’s opinion of 7 July 2006 was published in 2009\textsuperscript{7}.

The authors conclude that “the risk-benefit ratio of buflomedil in the treatment of intermittent claudication is unfavourable”.

It is interesting to note that the authors of this meta-analysis did not take the LIMB study into consideration because of its methodological shortcomings.


3.2. Adverse effects

Neurological and cardiac toxicity: reminder of the three reassessments of the risk/benefit ratio for buflomedil (tablet and injectable forms) and of the action taken by AFSSAPS

1) First reassessment of the risk/benefit ratio: 1997

A. First pharmacovigilance survey: Limoges and Lille regional pharmacovigilance centres
This survey revealed potentially fatal neurological toxicity (convulsions, attacks of myoclonia, tremor, vertigo, balance disorders) and cardiac toxicity (slowing of ventricular conduction). Toxicity occurred in the context of acute accidental or deliberate intoxication or therapeutic overdose.

The following action was taken after the results were presented to the National Pharmacovigilance Committee on 2 October 1997:
- buflomedil was transferred from list II to list I,
- a letter was sent to emergency physicians reminding them of the nature and the severity of buflomedil acute intoxication syndrome,
- the SPC was revised to add warnings (for patients with renal and hepatic failure) and a contraindication (for patients with epilepsy),
- the pack size of buflomedil 150 mg was reduced from 30 to 20 tablets.

B. First reassessment of the risk/benefit ratio by AFSSAPS
In its opinion dated 6 February 1998, the marketing authorisation committee stated that buflomedil (tablet and injectable forms) still had a favourable risk/benefit ratio, but asked for a “programme of studies to be carried out in order to obtain more information on the risk/benefit ratio”.

2) Second reassessment of the risk/benefit ratio: 2005-2006

A. Second pharmacovigilance survey: Lyon regional pharmacovigilance centre
This second survey, submitted to the National Pharmacovigilance Committee on 5 July 2005, revealed significant misuse of buflomedil despite the measures taken during the first survey. This misuse took the form of administration of the drug for indications not covered by the marketing authorisation (especially in the case of the injectable form, which accounted for 63% of cases) and administration of the drug at excessively high doses or at doses which were inappropriate given the patient’s renal function status (definite misuse in 22% of cases and possible misuse in 8% of cases), accompanied by serious neurological and/or cardiovascular adverse effects.

In view of the significant risks associated with the product, which were still largely unknown to healthcare professionals, and the fact that the benefit was regarded as insufficient, the members of the National Pharmacovigilance Committee unanimously voted for a reassessment of the risk/benefit ratio of buflomedil by a joint committee (the National Pharmacovigilance Committee and the marketing authorisation committee).

B. Second reassessment of the risk/benefit ratio by AFSSAPS
The results of the second pharmacovigilance survey and of the LIMB study (submitted by the pharmaceutical company) were examined by the Cardiology Working Group in December 2005 and again in May 2006, submitted to the National Pharmacovigilance Committee on 20 June 2006 and finally to the marketing authorisation committee on 29 June 2006.

In its opinion dated 29 June 2006, the marketing authorisation committee which met on 29 June 2006 recommended:
- withdrawal of marketing authorisation for the 300 mg dose of buflomedil (28/11/2006),
- maintenance of marketing authorisation for the 150 mg dose of buflomedil subject to the SPC being amended to:
  - delete the indication “improvement of Raynaud’s phenomenon”,

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add references to **narrow therapeutic range**, the need to measure renal function before starting treatment and at regular intervals throughout treatment (calculation of creatinine clearance in patients over 65 by means of Cockcroft's formula), contraindication for patients with renal failure and CrCl < 30 ml/min, dosage adjustment for patients with renal failure and CrCl of 30 to 80 ml/min, reminder of neurological and cardiac adverse effects associated with overdose contrary to the dosage instructions or if the dosage is not adjusted for patients with moderate renal failure.

- maintenance of marketing authorisation for injectable forms provided that the pharmaceutical company undertook to conduct an efficacy and adverse effects of use study, which would be a condition for maintaining marketing authorisation for these forms.
- sending an information letter to healthcare professionals: generalists, cardiologists, angiologists, emergency doctors, hospital and community-based pharmacists,
- the creation of a risk reduction plan examining the impact of the action taken.

3) Third reassessment of the risk/benefit ratio: 2010

**A Third pharmacovigilance survey: Lyon regional pharmacovigilance centre**

This survey examined the findings of pharmacovigilance and toxicovigilance monitoring between 2007 and 2009. An increase in avoidable cases due to non-compliance with contraindications or dosage instructions was observed during the cases reported in this period (40% of cases reported vs. 23%, p = 0.067). The AE profile was the same as in the previous survey (expected AEs in 50% of cases).

The results of this new pharmacovigilance survey and of the Thalès study show no improvement in the adverse effects profile of buflomedil despite the aforementioned fall in the number of spontaneous reports.

In view of the persistent misuse, non-compliance with dosage instructions, failure to monitor renal function and mortality caused by accidental or deliberate drug intoxication, which was similar in 2008 to the figure observed the previous year, the National Pharmacovigilance Committee concluded that the risk profile of buflomedil is unacceptable under current conditions as defined in the marketing authorisation, and asked for a risk/benefit reassessment of buflomedil to be conducted as a matter of urgency.

**B Third reassessment of the risk/benefit ratio by AFSSAPS**

The Cardiothrombosis working group met on 2 December 2010 and examined the issues mentioned above and concluded that the **risk/benefit ratio of buflomedil** in the treatment of intermittent claudication was **unfavourable** in view of:

- its minor and poorly demonstrated efficacy,
- the persistence of the risk of serious neurological and cardiac adverse effects despite the action taken by AFSSAPS; this persistence being due mainly to misuse (non-compliance with the indication and contraindications), non-compliance with dosage instructions, insufficient monitoring of renal function, as the product has a narrow therapeutic range.
- the existence of alternative therapies.

This unfavourable opinion was upheld by the marketing authorisation committee which met on 27 January 2011. Given the urgent need to withdraw these products from the market (FONZYLANE 150 mg and FONZYLANE 50mg/5 ml and 400mg/120ml solution for injection, FONZYLANE 400 mg lyophilisate for infusion and LOFTYL 50mg/5 ml and their generic equivalents) the procedure described in article 31 of Directive 2001/83 has to be launched.

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8 The main aim of which was to describe prescribing modalities for the oral form of buflomedil before and after the publication of the AFSSAPS communication in order to assess the impact of the action taken by AFSSAPS in respect of the oral form of buflomedil.

9 Injectable forms of these proprietary medicinal products were withdrawn from the market in 2008.
4.1. Reassessment of actual benefit

Intermittent claudication is a manifestation of atheromatous disease which can have severe functional consequences (handicap, amputation, loss of independence) and impair quality of life.

This proprietary medicinal product provides symptomatic treatment.

As the quantitative effect and clinical relevance of the medicinal product are poorly established, and in view of the risks of serious adverse events associated with the use of buflomedil [neurological manifestations (convulsions which can lead to epilepsy) and serious cardiac disorders (rhythm and conduction disorders, cardiogenic shock) which could develop into coma and/or cardiocirculatory arrest], the efficacy/adverse effects ratio of this proprietary medicinal product is unfavourable.

Alternative medicinal products exist: some platelet antiaggregants and other vasodilators.

The actual benefit of FONZYLANE 150 mg (buflomedil) and its generic equivalents is insufficient to justify it being paid for public funds, given the poorly established quantitative effect, the dubious clinical relevance of the effect, and the risk of serious (neurological and cardiac) events associated with its use.

4.2. Therapeutic use

Patients with claudication are at greater cardiovascular risk.

Management of intermittent claudication has two aims:
- to identify and treat associated cardiovascular risk factors in order to prevent the occurrence of cardiovascular events,
- functional improvement of claudication and the resulting improvement in quality of life.

Management of cardiovascular risk factors:

Patients with arteritis need overall management incorporating:

10 Article 31 states that the Member States, the Commission or the applicant or the marketing authorisation holder shall, in specific cases where the interests of the Community are involved, refer the matter to the Committee for application of the procedure laid down in Articles 32, 33 and 34 before any decision is reached on a request for a marketing authorisation or on the suspension or revocation of an authorisation, or on any other variation to the terms of a marketing authorisation which appears necessary, in particular to take account of pharmacovigilance information which has been collected.
13 Guidelines for management of patients with peripheral arterial disease. ACC/AHA, 2006.
14 NHG Practice Guideline: Peripheral arterial disease. The Dutch college of general Practitioners, December 1999
16 Clagett et al. Antithrombotic therapy in peripheral arterial occlusive disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004 Sep; 126(3 Suppl): 609S-26S.
17 Prise en charge de l’artériopathie chronique athéroscléreuse des membres inférieurs [Management of chronic atherosclerotic arteriopathy of the lower limbs], HAS 2006.
20 Recommandations de la société française de cardiologie concernant la pratique de la réadaptation cardiovasculaire chez l’adulte [Guidelines of the French Cardiology Association on cardiovascular rehabilitation in adults], Archives des maladies du cœur et des vaisseaux [Archives of heart and blood vessel disease], Volume 95, no10, October 2002.
1/ Management of associated cardiovascular risk factors:
- smoking (giving up),
- obesity (target BMI < 25 kg/m2),
- diabetes (target HbA1C < 6.5%),
- dyslipidaemia,
- hypertension.

2/ Prevention of cardiovascular complications:
Patients suffering from obstructed arteriopathies of the lower limbs are at high cardiovascular risk and require long-term management involving the three following types of treatment:
- an antiaggregant: low-dose aspirin (75 to 160 mg/day) or clopidogrel (75 mg/day),
- a statin,
- an ACE inhibitor, with the dose gradually increasing while the patient's blood pressure and creatininaemia are monitored, or a beta-blocker.

Symptom management
1/ Physical exercise:
As a general rule, the first step in symptomatic treatment of intermittent claudication of arterial origin is a supervised walking exercise (grade B). Vascular rehabilitation under supervision is an effective way of treating intermittent claudication, better than simply advising the patient to walk, and should be offered as a first-line therapy (grade B). It is carried out at a clinic or on an out-patient basis, after assessment of the patient's coronary tolerance of exertion, and is based on a tailor-made programme under supervision and with regular assessment by means of walking tests. The programme comprises at least three one-hour sessions a week for at least three months.

2/ Pharmaceutical treatments:
The purpose of pharmaceutical treatment for intermittent claudication is to reduce functional impairment and consequently improve the patient's quality of life, in particular by increasing the distance he or she is able to walk.

According to the HAS guidelines\textsuperscript{17}, no studies have found vasodilators to have a positive impact on the systemic complications of the disease or on long-term prevention of arterial degradation of the lower limbs and the risk of amputation.

4.3. Transparency Committee recommendations
The Transparency Committee does not recommend maintaining FONZYLANE (buflomedil) 150 mg and its generic equivalents on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the therapeutic indication and at the dosage in the marketing authorisation.

The Transparency Committee recommends removal of FONZYLANE (buflomedil) 150 mg and its generic equivalents from the list of medicines refundable by National Health Insurance and from the list of medicines approved for hospital use and various public services.