TRANSPARENCY COMMITTEE

OPINION

1 December 2010

TRONOTHANE 1% gel for local application
B/10(CIP code: 553 563-9)

Applicant: LISA-PHARM

Pramocaine hydrochloride
Propylene glycol
Hypromellose
ATC code: C05AD07

Date of (validated) Marketing Authorisation: 2 July 1996

Reason for request: Inclusion on the list of medicines approved for hospital use.

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

1.1. Active ingredients

Pramocaine hydrochloride
Propylene glycol
Hypromellose

1.2. Indications

“Symptomatic treatment of anal itching and pain, particularly in haemorrhoidal crisis.
Second-line treatment in certain endoscopic examinations”.

1.3. Dosage

“For rectal use.
Applied directly or with a compress.
Haemorrhoidal crisis: 1 application to the painful area morning and evening.
Endoscopic examination: applied before the examination.”

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

C: Cardiovascular system
C05: Vasoprotectives
C05A: Agents for treatment of haemorrhoids and anal fissures for topical use
C05AD: Local anaesthetics
C05AD07: Pramocaine

2.2. Medicines in the same therapeutic category

These are the other proprietary medicinal products indicated in anal itching and pain, particularly in haemorrhoidal crisis, containing a local anaesthetic:
- TITANOREINE with lidocaine (cream): insufficient actual benefit (deleted in 2006),
- SEDORRHOIDE (cream and suppositories) with benzocaine: not reimbursable,
- ULTRAPROCT (ointment and suppositories) with cinchocaine: not reimbursable.

2.3. Medicines with a similar therapeutic aim

These are the other medicines indicated in the treatment of anal pain and as second-line treatment in endoscopic examinations: venotonics, analgesics, antiinflammatories, etc.
3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The company submitted 7 literature references:

- An open clinical study (Grove 2004\(^1\)) carried out in 24 women, the aim of which was to evaluate the efficacy of TRONOTHANE against itching of the skin.
- A comparative clinical study (Young 2009\(^2\)) of pramoxine versus a control lotion carried out in 28 haemodialysis patients, the aim of which was to evaluate the efficacy of TRONOTHANE against itching of the skin.
- An expert opinion reporting on the way he used TRONOTHANE in his clinical practice\(^3\).
- An interim report\(^4\) on the efficacy of TRONOTHANE in various clinical situations. As regards proctology, the data available in this report relate to postoperative use of TRONOTHANE after haemorrhoidectomy.
- A study\(^5\) comparing the pharmacological properties of pramocaine hydrochloride with those of cocaine hydrochloride.
- An excerpt from the “Medical Letter on drugs and therapeutics 1981”, going over author opinions on the “strength” of pramoxine.
- An expert opinion\(^6\) on non-surgical treatments of haemorrhoids.

The clinical studies cited by the company did not evaluate TRONOTHANE in any of the indications validated by the Marketing Authorisation; they thus cannot be taken into account in this opinion. The expert opinions and the pharmacological data provided do not prove the clinical efficacy of TRONOTHANE in its indications.

Thus none of the data submitted by the company prove the clinical efficacy of TRONOTHANE in its indications: anal pain and itching, particularly in haemorrhoidal crisis, and second-line treatment in certain endoscopic examinations; the use of local anaesthetics in this kind of disease is not justified in the absence of an effect on the mucosa of the lower rectum on account of the absence of sensitivity in this area.

3.2. Adverse effects

According to the SPC, the most frequent adverse events are allergies and irritation.

3.3. Conclusion

None of the data (clinical studies submitted by the company, pharmacological data, and three experts’ opinions) prove the clinical efficacy of TRONOTHANE in its indications: anal pain and itching, particularly in haemorrhoidal crisis, and as second-line treatment in certain endoscopic examinations.

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4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

**Haemorrhoidal crisis pain:**
External haemorrhoid disease is a chronic disease that progresses through episodic flare-ups. When the disease is at a not very advanced stage, haemorrhoid episodes do not show the usual severity and regress spontaneously within a few days (including in regard to bleeding and pain). Nevertheless, the symptoms and their repeated occurrence can impair patients' quality of life.
This proprietary medicinal product is intended as a symptomatic therapy.
No clinical study relevant to the assessment of the efficacy and tolerance of this proprietary medicinal product was presented by the company. The Committee has thus been unable to assess the efficacy of this proprietary medicinal product in this indication and, in particular, the size of its effect.
Its efficacy/adverse effects ratio has not been clearly established.
Alternative medicinal products exist.

**Public health benefit:**
Haemorrhoid disease is a common, but non-serious disorder, though its symptoms can impair patients' quality of life. The public health burden which it represents is small.
Treatment of haemorrhoid disease does not constitute a public health need.
Given that the available data are insufficient, the likely effect of the proprietary product TRONOTHANE on morbidity and quality of life cannot be evaluated.
It is not certain that the data can be carried over into clinical practice.
Consequently, it is not expected that the proprietary product TRONOTHANE will benefit public health in this indication.

The available data do not prove the clinical efficacy of TRONOTHANE in this indication. Consequently, the actual benefit of TRONOTHANE in haemorrhoidal crisis pain is insufficient.

**Second-line treatment in certain endoscopic examinations**
Certain endoscopic examinations can be associated with anal pain.
This proprietary product is intended as a preventive therapy.
No clinical study relevant to the assessment of the efficacy of this proprietary product in this indication was presented by the company. The Committee has thus been unable to assess the efficacy or tolerance of this proprietary product in this indication and, in particular, the size of its effect.
The efficacy/adverse effects ratio for this proprietary medicinal product has not been clearly established.
Endoscopic examinations are usually painless and do not call for any anaesthetic preparation.

**Public health benefit:**
The discomfort caused by an endoscopic examination represents a small public health burden.
Second-line treatment for endoscopic examinations does not constitute a public health need.
In view of the absence of data and according to the opinion of the experts, it is not expected that the proprietary product TRONOTHANE will benefit public health in this indication.

On the basis of the available data, it is not possible to assess the clinical efficacy of TRONOTHANE in this indication. Consequently, the actual benefit of TRONOTHANE as a second-line treatment in certain endoscopic examinations is insufficient.
4.2. Improvement in actual benefit (IAB)

Not applicable

4.3. Therapeutic use

**Symptomatic treatment in haemorrhoid episodes**\(^7\)

Haemorrhoid disease may be treated with a combination of two types of therapy: medical and surgical, which can be combined, but are often used in succession. However, the occurrence of haemorrhoids and their complications (thrombosed prolapsed haemorrhoids can cause iron-deficiency anaemia) is encouraged by disturbances of intestinal transit; treating or stopping the latter is often enough to cure the patient. In addition, non-excessive local hygiene and physical activities to combat sedentariness are recommended.

Medical treatment for haemorrhoids is aimed at eliminating or reducing the symptoms (in terms of intensity, duration, and/or frequency). It may be decided, in agreement with the patient, not to treat symptoms that he considers trivial.

It must be offered as the first-line treatment for patients with internal haemorrhoids whose symptoms are isolated rectal bleeding.

No recommendation can be formulated for the following local treatments: use of cold, sitz baths, local anaesthetics, topical agents containing a prokinetic or a venotonic. It does not seem appropriate to use local laxatives in symptomatic periods of haemorrhoid disease (level C). Their long-term and preventive effect has not been documented; the same applies to the benefit of combining them (level C).

There are no literature data validating the use of local topical agents in external or internal haemorrhoid disease.

Systemic therapy must be of short duration. If the symptoms do not quickly recede, a proctological examination should be carried out and the treatment should be re-evaluated.

- Peripheral analgesics are effective against pain caused by external and internal haemorrhoidal thrombosis (opinion of experts).
- Non-steroidal antiinflammatories are effective against pain caused by internal and external haemorrhoidal thrombosis. They can be prescribed in combination with laxatives (mucilages, osmotic laxatives, lubricant laxatives).

**Adjuvant therapy in certain endoscopic examinations by the rectal route**

No guideline recommends the use of the proprietary product TRONOTHANE in endoscopic examinations. No clinical study on the basis of which this proprietary product could be concluded as being effective in endoscopic examinations is available.

4.4. Transparency Committee recommendations

The Transparency Committee does not recommend inclusion on the list of medicines approved for hospital use and various public services in the indications and at the dosages in the Marketing Authorisation.

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\(^7\) Cf. Recommandations pour la pratique clinique sur le traitement des hémorroïdes [Clinical practice guidelines on the treatment of haemorrhoids]. Société Nationale Française de Colo-Proctologie [French National Society of Coloproctology], 2001. These clinical practice guidelines were given the ANAES [National Health Accreditation and Assessment Agency] method quality mark.