HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

9 May 2007

RECTOGESIC 4 mg/g, rectal ointment
B/1 (CIP 376 537-0)

Applicant : PROSTRAKAN PHARMA SAS

Glyceryl trinitrate

List II

Marketing authorisation (MA) date: September 19, 2006
MA revision: 8 December 2006

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals.

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

glyceryl trinitrate (GTN)

1.2. Indications

Rectogesic 4 mg/g rectal ointment is indicated for the relief of pain associated with chronic anal fissure.

1.3. Dosage

Route of administration:

Rectal.

Adults and the elderly:

In order to apply the ointment, the finger should be covered with a stall or plastic film. Finger stalls may be purchased in pharmacies or medical appliance outlets, while plastic film is found in shops with products for domestic use. The covered finger is placed along the 2.5 cm dosage line printed on the external packaging of Rectogesic. A quantity of ointment corresponding to the length of the line is placed onto the finger tip by pressing lightly on the tube. The quantity of ointment extracted is approximately 375 mg (1.5 mg GTN). The finger is then gently inserted into the anal passage, up to the distal phalangeal joint; the anal passage and its outline is then covered with the ointment.

A dose of 4 mg/g ointment delivers 1.5 mg of glyceryl trinitrate. The dose should be applied every twelve hours. Treatment may be continued until the pain resolves, up to a maximum of 8 weeks.

Children and adolescents:

Rectogesic rectal ointment should not be used in children and adolescents due to the lack of data concerning the safety and efficacy of the product in individuals under the age of 18.

1.4. Pharmacodynamic properties

The principal pharmacological activity of glyceryl trinitrate is induced by the liberation of nitric oxide. Relaxation of the internal anal sphincter is observed following application of GTN ointment by the intra-anal route.

Hypertonia of the internal anal sphincter, not of the external anal sphincter, is a factor favouring the formation of anal fissures. The blood circulates towards the anoderm through the internal anal sphincter (IAS). Hypertonia of the IAS can therefore result in a decreased blood flow and cause ischaemia in this region.

Distension of the rectum involves an anorectal inhibitor reflex and the relaxation of the internal anal sphincter. The nerves responsible for mediating this reflex are found in the intestinal wall. Liberation of the neurotransmitter NO by these nerves plays an important part in the physiology of the internal anal sphincter. In particular, NO is the mediator of the anorectal inhibitor reflex in humans, which involves the relaxation of the IAS.

The relationship between IAS hypertonia, spasms and the presence of an anal fissure has been established. Patients with chronic anal fissure have a maximal mean anal pressure at rest, which is significantly higher than of controls, and the blood flow through the anoderm of patients with chronic anal fissure is significantly lower than that of controls. In patients in whom the fissures are scarified following sphincterectomy, a decrease in the anal pressure and an improvement in blood flow through the anoderm have been observed, which is supplementary evidence for the ischaemic nature of an anal fissure. Local application of an NO donor (glyceryl trinitrate) causes the anal sphincter to relax, which leads to a decrease in anal pressure and an improvement in blood flow through the anoderm.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification (in the course of validation)

C05A : Agents for topical use for the treatment of haemorrhoids and anal fissures
C05AE : Muscle relaxants
C05AE01 : Glyceryl trinitrate

2.2. Medicines in the same therapeutic category

No other proprietary product based on nitrate derivatives exists for this indication.

2.3. Medicines with a similar therapeutic aim

None.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

Three randomised, double-blind, parallel-group, placebo-controlled phase III studies have assessed the efficacy and tolerability of Rectogesic® rectal ointment, applied twice daily, in 726 patients with pain associated with chronic anal fissures.

Study NTG-98-03-01

Phase III placebo-controlled, randomised, double-blind study in 304 patients with chronic anal fissure observed on physical examination and with pain for a period of at least 30 days prior to inclusion.

The study included 8 groups:

- one arm with Rectogesic 0.1% (n= 39), twice daily
- one arm with Rectogesic 0.1% (n= 37), three times daily

- one arm with Rectogesic 0.2% (n= 39), twice daily
- one arm with Rectogesic 0.2% (n= 39), three times daily

- one arm with Rectogesic 0.4% (n= 38), twice daily
- one arm with Rectogesic 0.4% (n= 42), three times daily

- one arm with placebo (n= 34), twice daily
- one arm with placebo (n= 36), three times daily

The primary endpoint was complete scarification of the fissure (complete re-epithelialisation).

Treatment duration: 56 days or until scarification.

The administration of concomitant treatments (fibre-rich dietary supplements, laxatives, sitz baths) was permitted.

Results (ITT population = 289 patients):

The scarification of anal fissures in patients treated with Rectogesic rectal ointment 4 mg/g did not differ statistically from that obtained with placebo (p=0.62) regardless of the frequency of administration.

Study NTG-00-03-01

Phase III placebo-controlled, randomised, double-blind study in 229 patients with chronic anal fissure observed on physical examination and with pain felt during at least 50% of bowel movements during one week over a period of at least 30 days prior to inclusion.

The study included 3 groups:

- one arm with Rectogesic 0.2% (n= 73),
- one arm with Rectogesic 0.4% (n= 78),
- one arm with placebo (n= 78).

The treatment was administered twice daily.

The primary endpoint was assessment of the mean daily intensity of pain using a visual analogue scale (VAS) scale[1] for 56 days (mean pain felt, the most acute pain and pain on defecation).
One of the secondary endpoints was the time to scarification.

Treatment duration: 56 days, not taking into account the state of scarification.
The use of concomitant treatments (laxatives every 12 hours, sitz baths daily if required) was permitted.

Results: ITT population = 219 patients (Rectogesic 0.4% arm = 74 patients, placebo arm = 75 patients).
A decrease of 17.2 mm in the mean intensity of pain was observed in the Rectogesic 0.4% group (baseline value 33.4/100) *versus* 13.8 mm in the placebo group (baseline value 34/100). Despite the statistically significant difference ($p<0.0039$), a difference of 3.4 mm on a scale of 100 mm is of disputable clinical relevance.
No statistically significant difference was observed for:

- intensity of the most acute pain,
- intensity of pain on defecation,
- scarification.

Study CP125-03-02-01

Phase III placebo-controlled, randomised, double-blind study in 193 patients with chronic anal fissure observed on physical examination and with pain felt during at least 50% of bowel movements during one week over a period of at least 30 days prior to inclusion.
The study included 2 groups:

- one arm with Rectogesic 0.4% (n= 93),
- one arm with placebo (n= 100).

The treatment was administered twice daily.

The primary endpoint was assessment of the variation in the daily mean intensity of pain (on the VAS scale) during 21 days of treatment.

Duration of study follow-up: 56 days.
The administration of concomitant treatments (fibre-rich dietary supplements, laxatives) was permitted as prior to inclusion. In addition, a daily sitz bath was permitted. The patients were also able to take paracetamol (650 to 1000 mg) in the event of headache (maximum of 8 doses during the first 21 days).

Results: ITT population = 187 patients (Rectogesic arm = 89 patients, placebo arm = 75 patients).
The use of paracetamol was greater in the treatment group (40.4%) than in the placebo group (26.5%) due to the more frequent occurrence of adverse events such as headache.

Over the 21 days of treatment, a decrease of 28.1 mm in the mean intensity of pain was observed in the Rectogesic 0.4% group (baseline value 55/100) *versus* 24.9 mm in the placebo group (baseline value 54.1/100). Despite the statistically significant difference ($p<0.0489$), a difference of 3.2 mm on a scale of 100 mm is of disputable clinical relevance.

[1] The intensity of the pain was measured daily on a visual analogue scale 100 mm in length with "no pain" being 0 and "the most severe pain imaginable" being 100 mm.

No statistically significant difference was observed in the intensity of pain on defecation over 21 days of treatment ($p<0.072$). In contrast, this difference was statistically significant over 56 days of treatment ($p<0,031$).
No statistically significant difference was observed between the two groups with respect to scarification ($p=0.42$).

3.2. Adverse events

In patients treated with Rectogesic, the most frequent treatment-associated adverse event was headache, observed in 57 % of cases.

In the Phase III clinical trials with Rectogesic 4 mg/g rectal ointment, the frequency of headaches was 18 % with mild symptoms, 25 % with moderate symptoms and 20 % with severe symptoms. These headaches resulted in 7.8% of subjects treated with Rectogesic withdrawing prematurely from the studies compared with 0.8% of subjects in the placebo group.

Patients with a history of migraine or chronic headaches had an increased risk of developing headaches during treatment. The headaches were observed after each daily dose, especially at higher concentrations. They could be treated with non-opioid analgesics such as paracetamol and generally disappeared following completion of the treatment.

Transient episodes of vertigo, sometimes associated with variations in arterial pressure could also occur. Hypotension was not very frequent but, in certain patients, could be sufficiently severe to justify withdrawal of treatment. Fainting, exacerbation of angina and rebound hypertension were reported, but were not very frequent. Allergic reactions to glyceryl trinitrate were not very frequent and most of those reported were cases of contact eczema or drug-induced rash occurring in patients who received glyceryl trinitrate in the form of an ointment or patches. Several cases of true anaphylactoid reactions have been reported, and it is probable that these reactions appear in patients receiving glyceryl trinitrate via other routes of administration. In very rare cases, normal doses of organic nitrates have caused methaemoglobinaemia in patients without any evident pathology. In rare cases, hot flashes have been observed as an adverse reaction to other products containing glyceryl trinitrate.

3.3. Conclusion

The results obtained with Rectogesic 4 mg/g have shown a statistically significant decrease, in comparison to placebo, in the daily mean intensity of pain associated with chronic anal fissure (reduction of 3 to 4 mm more than with placebo on a VAS of 0 to 100 mm). However, this difference is of disputable clinical relevance.
In contrast, the scarification of anal fissures in patients treated with Rectogesic 4 mg/g did not differ statistically from that obtained with placebo.

In terms of tolerability, the occurrence of headache was significantly more frequent than with placebo causing an increase in treatment interruptions. These are known dose-dependent adverse effects for products based on nitrate derivatives and resolve when treatment is stopped. The SPC states that, on account of the predictable adverse effects, a careful assessment of the benefit/risk ratio should be performed on a case-by-case basis.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Chronic anal fissure is a condition that is not usually serious, but it involves intense pain which can be incapacitating and cause a marked deterioration in the quality of life.
This proprietary product is part of treatment addressing the symptoms.
The efficacy/adverse effects ratio of this product in this indication is moderate.
This is a second-line treatment following hygienic and dietary measures.
There is one non-pharmaceutical alternative, surgery.

Public health benefit:

The epidemiology of chronic anal fissure has not been thoroughly documented, therefore the public health burden of this condition is difficult to quantify.
Improvement of the management of pain associated with chronic anal fissure in adults is a therapeutic need; however it does not constitute a public health priority.
The available data do not permit an assessment of the impact of RECTOGESIC on recurrences following surgery and on the use of surgery.
Taking into account the difficulty of assessing the clinical relevance of the reduction in the mean daily pain associated with chronic anal fissure, which was observed in comparison to placebo in the clinical trials, the expected impact of RECTOGESIC on improving the quality of life is difficult to estimate.
Consequently, RECTOGESIC is not expected to have an impact on public health.

The actual benefit of this medicinal product is moderate.

4.2. Improvement in actual benefit

Taking into account the extremely limited effect compared with placebo, RECTOGESIC does not provide an improvement in actual benefit (IAB V) in the management of patients with chronic anal fissures.

4.3. Therapeutic use

Conservative treatment
The symptomatic treatment of pain associated with chronic anal fissures is based on regularising transit and softening the stools by means of hygienic and dietary measures (abundant fluid consumption, fibre-rich diet). Hot sitz baths can be offered to give relief to patients. Where this approach fails, a locally applied topical treatment (nitrate derivatives, diltiazem, botulism toxin) may be offered to reduce the intensity of the pain[2]. However, in France, only glyceryl trinitrate has obtained a MA. It shows a minimal efficacy on pain intensity but has no effect on scarification.

Surgical treatment
Surgery may be proposed as a last resort. The standard surgical treatment for chronic anal fissure is lateral internal sphincterectomy, the objective of which is to reduce the hypertonia of the sphincter. In enables scarification to take place in 90% of patients within 5 weeks.

However, complications affecting anal continence (emission of gas and/or seepage), of variable severity, are observed in about one third of patients[3].

[2] Jonas M, Scholefield J. Anal fissure (chronic), Clin Evid 2005 ;13 :458-465
[3] American Gastroenterological Association, AGA technical review on the diagnosis and care of patients with anal fissure, Gastroenterology 2003 ;124 :235-245

4.4. Target Population

The target population corresponds to adult patients with a chronic anal fissure which is defined by the macroscopic appearance of the fissure (erosive, exposing the fibres of the internal sphincter, whitish in colour and existence of fibrosis around the fissure), or by the duration of development (more than 6 weeks of suggestive symptoms).
Anal fissures are the 2nd most frequent reason for proctological consultations (15%) among adults (after haemorrhoids). There is a peak in frequency towards 40 years. The prevalence and incidence of chronic anal fissure in France are not known.

The company carried out an audit on the diagnosis and treatment of anal fissures among prescribers in the USA between October 2005 and September 2006. 500,000 patients underwent consultation for anal fissure. The proportion of acute to chronic anal fissures is not known. The prevalence of anal fissure was 0.2%.

Applying this figure to the French adult population would mean that approximately 93,000 adult patients would be affected by anal fissures.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the new indication and at the posology in the Marketing Authorisation.

4.5.1. Packaging: Appropriate for the prescription conditions
4.5.2. Reimbursement rate: 35%