



HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

20 February 2008

GRANUDOXY Gé 100 mg film-coated scored tablet

Pack of 15 (CIP: 344 334-7)

Pack of 28 (CIP: 344 335-3)

Applicant : PIERRE FABRE DERMATOLOGIE

doxycycline monohydrate

List I

Date of initial Marketing Authorisation (MA): 24 July 1997 (national procedure), revision of MA on 8 January 2007

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the extension of indication to **“aggressive periodontitis, as an adjunct to local mechanical treatment”**.

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active substance

doxycycline

1.2. Indication

- “Therapeutic indications deriving from both the antibacterial action and the pharmacokinetic properties of doxycycline. They take account of both the role of this antibiotic within the range of currently available antibacterials and up-to-date information on bacterial resistance.
 - brucellosis
 - pasteurellosis
 - pulmonary, genito-urinary and ophthalmic infections due to *Chlamydia* spp.
 - pulmonary and genito-urinary infections due to *Mycoplasma* spp.
 - rickettsioses
 - *Coxiella burnetii* (Q fever)
 - gonorrhoea
 - ENT and broncho-pulmonary infections due to *Haemophilus influenzae*, particularly acute exacerbations of chronic bronchitis
 - *Treponema* infections (tetracyclines are only indicated for syphilis in cases of beta-lactam allergy)
 - spirochaete diseases (Lyme disease, leptospirosis)
 - cholera
 - moderate and severe inflammatory acne and inflammatory components of mixed forms of acne
 - **aggressive periodontitis, as an adjunct to local mechanical treatment.**
- Rosacea in its cutaneous and ocular manifestations.
- Malaria prophylaxis for travellers to endemic regions in cases of resistance, contraindication or intolerance to mefloquine.
- **Specific situations**
Post-exposure prophylaxis and curative treatment for anthrax.

NB: The official guidelines on the appropriate use of microbicides must be taken into consideration.”

1.3. Dosage (Extension of indication)

- Aggressive periodontitis, as an adjunct to local mechanical treatment.

Adults: 200 mg daily in a single dose, preferably in the morning with breakfast, for 14 days.

The duration of treatment and dosage may be adapted for paediatric use.

Method of administration

Administer during a meal with a glass of water (100 ml) and at least one hour before going to bed.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

J	:	Antiinfectives for systemic use
J01	:	Antibacterials for systemic use
J01A	:	Tetracyclines
J01AA	:	Tetracyclines
J01AA02	:	doxycycline

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

GRANUDOXY Gé (doxycycline) is the only medicinal product in the tetracycline class with the indication “**aggressive periodontitis, as an adjunct to local mechanical treatment**”

The other antibiotics for systemic use indicated for the treatment of mouth infections are:

- tetracycline antibiotics (methylenecycline – LYSOCLIN), which is indicated for “treatment of odontostomatological and periodontological infections”
- beta-lactam antibiotics (amoxicillin), with the indication of “mouth infections”
- beta-lactam antibiotics (amoxicillin + clavulanic acid), with the indication of “severe mouth infections: abscesses, phlegmons and cellulitis”
- macrolide antibiotics (azithromycine) and nitro-5-imidazole antibiotics (metronidazole), with the indication of “mouth infections”
- macrolide antibiotics (spiramycin) and nitro-5-imidazole antibiotics (metronidazole), with the indication of “curative treatment of subacute, chronic or recurrent mouth infections, including periodontitis”.

2.3. Medicines with a similar therapeutic aim

Other medicines indicated for the treatment of periodontitis.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

Documentation of the clinical efficacy of GRANUDOXY Gé (doxycycline) in the treatment of aggressive periodontitis¹ is based on a placebo-controlled study², the principal objective of which was to demonstrate the therapeutic benefit of doxycycline as an adjunct to mechanical treatments (scaling and root planing).

Population:

The study was open to subjects aged between 20 and 35 years (or 40 if their history of the disease was well documented) with rapidly progressive (early-onset) periodontitis who had at least one periodontal pocket ≥ 5 mm depth in each quadrant and bleeding on probing for at least 50% of sites tested.

Patients with refractory periodontitis (periodontitis that had not responded to previous treatment) and those who had had scaling/root planing or periodontal surgery during the three months prior to inclusion could not be included in this study.

Treatments:

Of the included patients (n=97), 92 were randomised and were treated for 14 days with:

- either 100 mg doxycycline monohydrate twice daily (n=46)
- or placebo (n=46).

Mechanical treatment (scaling and root planing) was performed during treatment (2-4 sessions).

Endpoints and assumptions

The primary endpoint was pocket depth after 3 months (Day 84).

The secondary endpoints were:

- pocket depth after 6 months (Day 168): difference compared with baseline
- bleeding on probing at Day 84 and Day 168: % of sites
- recession and attachment level (mm) at Day 84 and Day 168: difference compared with baseline and attachment gain/loss
- gingival and plaque measurements at Day 84 and Day 168: difference compared with prior to baseline
- detection of certain pathogens with DNA probe at Day 84 and Day 168
- clinical safety.

The number of subjects necessary was calculated on the basis of a change of -1.2 mm in the placebo group and -2.2 mm in the doxycycline group, i.e. a difference of 1 mm.

Statistical analysis:

Two approaches were used for pocket depth:

- mean for sites considered diseased (≥ 5 mm):³ the statistical unit was each site
- patient mean for all sites tested: the statistical unit was the patient.

For the other endpoints, a patient mean across all sites was applied.

¹ Aggressive periodontitis covers the conditions formerly known as early-onset, prepubertal, juvenile, rapidly progressive and refractory periodontitis, whether localised or generalised.

² Unpublished study.

³ Given the disease in question and since approximately 75% of sites were disease free at baseline, the diseased site approach was considered more appropriate by AFSSAPS when it assessed the file.

Efficacy results:

- Evaluation of the primary endpoint between baseline and Day 84 (mITT: population that has received at least one dose of the treatment): ANCOVA analysis (adjusted to baseline)

Table 1: Evolution of the primary endpoint between D0 and D84

Change in pocket depth at Day 84				
	Doxycycline	Placebo	Difference	p
<i>Mean for diseased sites^a (mm)</i>				
	n= 1479 sites	n= 1876 sites		
Pocket depth at baseline (mm)	6.11 ± 1.32	6.32 ± 1.38		
Change	-2.20±1.52	-1.76±1.69		
Change adjusted to baseline [95% CI]	-2.24±0.04	-1.72±0.04	- 0.52 [-0.65 ; -0.42]	<0.001
<i>Patient mean for all sites tested (mm)</i>				
	N=43 patients	N=41 patients		
Pocket depth at baseline (mm)	3.42 ± 0.70	3.79 ± 0.81		
Change	-0.79±0.47	-0.71±0.61		
Change adjusted to baseline [95% CI]	-0.86±0.07	-0.64±0.07	- 0.22 [-0.43 ; -0.02]	0.03

^a A site is considered diseased when the periodontal pocket depth is > 5 mm.

At the request of AFSSAPS, an additional analysis on diseased pocket depth averaged by patient was performed on the mITT population between baseline and Day 84: a reduction of -2.21±0.81 mm in periodontal pocket depth was observed in the doxycycline group against -1.73±0.79 mm in the placebo group. The difference between the two groups was -0.50 mm (adjusted difference; 95% CI [-0.84 – 0.16], p=0.005).

- Evaluation of the secondary endpoints between baseline and Days 84 and 168 (patient mean across all sites) (mITT)
 - Pocket depth at Day 168 (adjusted to baseline): a reduction of -0.92±0.07 mm in periodontal pocket depth was observed in the doxycycline group against -0.70±0.07 mm in the placebo group (p=0.027).
 - Bleeding on probing and gingival measurement was significantly improved with antibiotic treatment compared with placebo after 3 months.
 - For changes in recession, attachment level and plaque measurement, no difference was noted between antibiotic treatment and placebo at either comparison time.
 - For the microbiological analysis (pathogen detection), no significant difference was observed between the doxycycline group and the placebo group at Days 84 and 168 for *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Campylobacter rectus* and *Fusobacterium nucleatum*. A significant difference was observed for *Eikenella corrodens* at Day 168 (p=0.049).
 - The appearance of new diseased sites (≥ 5 mm) was less frequent in the doxycycline group (1.74% against 4.40%, p < 0.001).
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3.2. Safety

The safety analysis involved 92 patients, 36 of whom (39.10%) had at least one adverse event. A total of 54 adverse events were observed, 13 of them reported in connection with GRANUDOXY Gé.

Most adverse events were of moderate intensity and essentially of a digestive nature: mild to moderate vomiting, low-intensity abdominal cramps, diarrhoea, moderate to severe nausea, moderate to severe dental abscesses, moderate to severe tooth sensitivity, toothache and dental problems. In most cases they can be attributed to the doxycycline, which is known to have these side effects.

One patient in the doxycycline group stopped treatment after 2 days because of an episode of nausea, which regressed spontaneously.

3.3. Conclusion

A placebo-controlled study⁴ assessed the efficacy of oral doxycycline (GRANUDOXY Gé) at a dose of 200 mg daily for 14 days in the treatment of aggressive periodontitis as an adjunct to local mechanical treatment in subjects aged 19-42 years (mean 34 years) with rapidly progressive (early-onset) periodontitis who had at least one periodontal pocket \geq 5 mm depth in each quadrant and bleeding on probing for at least 50% of sites tested.

After 3 months of post-treatment monitoring, periodontal pocket depth was improved by the antibiotic treatment, particularly in sites considered diseased (depth > 5 mm). However, the effect size was modest (difference *versus* placebo of -0.22 mm for all periodontal sites, and -0.52 mm for diseased sites).

The safety profile of doxycycline observed in this study is in conformity with the effects expected and described in the summary of product characteristics.

In the absence of any comparison with an active treatment, the data presented are insufficient for any conclusions to be drawn regarding the efficacy of this product compared with that of other antibiotics recommended in the current management of periodontitis.

⁴ Unpublished study.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Periodontitis is an infectious disease that can lead to marked deterioration in quality of life and disability, particularly when it restricts the ability to chew and swallow food. In rare cases, it may be life threatening as a result of infectious complications (endocarditis, neuro-meningeal disease or necrotising cellulitis).

This medicinal product is intended for curative and preventive therapy. This is a second-line treatment for use as an adjunct to mechanical treatment. The efficacy/safety ratio of this product in this indication is modest.

There are non-medicinal or medicinal alternatives to this product.

Public health benefit

Despite the shortage of epidemiological data on aggressive periodontitis, the public health burden caused by this condition may be regarded as low.

The need to prevent and improve the management of periodontal disease falls within the scope of an established public health priority. There are effective medicinal and non-medicinal means that address this need.

In light of the available data, GRANUDOXY Gé is not expected to have any additional impact in terms of improving quality of life or reducing morbidity compared with currently recommended treatments in the management of aggressive periodontitis. This medicinal product is therefore unlikely to make any improvement to meeting the identified need.

Accordingly, GRANUDOXY Gé is not expected to benefit public health.

The actual benefit is low.

4.2. Improvement in actual benefit

In light of the available data, the Committee believes that GRANUDOXY Gé does not provide an improvement in actual benefit (IAB V) in the current management of aggressive periodontitis as an adjunct to local mechanical treatment.

4.3. Therapeutic use

In 2001 AFSSAPS issued guidelines⁵ specifying the appropriate indications for antibiotics in the curative treatment of periodontitis.

Antibiotics should be reserved solely for clinical situations in which their efficacy has been demonstrated so as to limit the onset of adverse effects and the increasingly frequent emergence of resistant strains of bacteria.

Antibiotic therapy is indicated in periodontal disease to treat aggressive periodontitis and necrotising ulcerative gingivitis. Antibiotic therapy is not justified in subjects not recognised to be at risk of infection to treat chronic gingivitis and periodontal abscesses. It has not been determined whether antibiotic therapy is of value in treating chronic periodontitis.

The choice of antibiotic should be based on the pathogenic bacteria assumed to be present in a given disease, the product's antibacterial activity spectrum, and its pharmacokinetics. The severity of the disease and the patient's history should also be taken into account. Routine microbiological sampling is not justified in the majority of cases.

⁵ AFSSAPS, 2001: Prescription des antibiotiques en odontologie et stomatologie. Recommandation et argumentaire (Prescription of antibiotics in dentistry and stomatology. Guideline and rationale). <http://agmed.sante.gouv.fr/pdf/5/rbp/stomcomp.pdf>

For moderate infections, the antibiotics recommended for first-line treatment include penicillin A (amoxicillin), 5-nitro-imidazoles either alone or combined with macrolides and, (especially in cases of allergy to beta-lactams) macrolides, streptogramins (pristinamycin) and lincosamides.

The amoxicillin/clavulanic acid combination is recommended as second-line treatment.

Cyclines should be reserved only for the treatment of localised juvenile periodontitis, even if other antibiotics may be used.

Use of cephalosporins is not recommended.

For severe infections, in a specialist environment, the same families of antibiotics are recommended intravenously, the dosage being adapted according to the focus of infection and the patient's functional state. Glycopeptides should be prescribed in cases of beta-lactam allergy and/or resistance. Cephalosporins may be used as second-line treatment once the microorganism has been documented and after a bacterial sensitivity test.

Therapeutic use of GRANUDOXY Gé

In line with the marketing authorisation, GRANUDOXY Gé should only be prescribed for aggressive periodontitis as an adjunct to local mechanical treatment.

It is difficult to specify the value of GRANUDOXY Gé in the management of aggressive periodontitis since there is a lack of data comparing it with other recommended antibiotics. On the basis of the data presented, moreover, the therapeutic benefit provided by GRANUDOXY as an adjunct to mechanical treatments (scaling and root planing) is minimal.

4.4. Target population

The target population comprises patients with aggressive periodontitis who need adjuvant systemic antibiotic treatment as an adjunct to mechanical treatment (scaling and root planing).

Periodontal disease has been the subject of few epidemiological research projects on the French population. The target population for GRANUDOXY Gé cannot be estimated from the existing partial data.⁶

As a rough guide, periodontal conditions affect about 80% of the adult population to varying degrees (ANAES, 2002).⁷ Just 15% of these individuals have severe forms of periodontitis (attachment loss of more than 5 mm, with associated signs).⁸ Among children and adolescents, periodontal disease generally affects only a minority of the population.⁷

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicinal products approved for use by hospitals and various public services in the extension of indication and at the dosage of the Marketing Authorisation.

4.5.1. Packaging: Appropriate to the prescription requirements.

4.5.2. Reimbursement rate: 35 %

⁶ DGS/GTND0, 2003: Affections Bucco-dentaires (Bucco-dental conditions). According to a study conducted in 1993 on a sample (selected by the quota method) of the French adult population aged 35-44 years and 65-74 years. <http://www.sante.gouv.fr/htm/dossiers/losp/64buccodentaire.pdf>

⁷ ANAES, 2002. Parodontopathies : diagnostic et traitement (Periodontal diseases : diagnosis and treatment).

⁸ INSERM Panel of Experts, 1999: Maladies parodontales - Thérapeutique et prévention. Rapport établi à la demande de la MGEN. Les Editions INSERM, 1999. Paris.