HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

13 December 2006

GUTRON 2.5 mg, tablet
B/30 (CIP: 348 257-8)
B/90 (CIP: 348 255-4)

Applicant: NYCOMED

Midodrine (hydrochloride)

ATC code: C01CA17

List II

Date of Marketing Authorisation: 16 June 1992
Date of last revisions to Marketing Authorisation: 5 May 2004

Removal from hospital-only listing: 15 June 2004

Medicinal product included on the list of medicines approved for use by hospitals since 17 March 1993 (JO of 28 August 1993).

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance following removal from the hospital-only listing of 11 December 1997.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Midodrine (hydrochloride)

1.2. Indication

Treatment of **severe orthostatic hypotension,** particularly in the context of degenerative neurological diseases (Parkinson's disease, Shy-Drager disease, olivo-ponto-cerebellar atrophy, etc.).

1.3. Dosage

Oral administration. The medicine should preferably be taken in the morning and should not be taken before bed. Dosage must be adapted according to patient sensitivity and benefit/risk ratio.

For optimal individual dosage the treatment should be started at 2.5 mg per administration, with 2 or 3 administrations daily. If necessary, dosage may be adjusted on a weekly basis in 2.5 mg increments until the optimal clinical response is obtained.

Most patients respond to a dose of less than 30 mg/day, with 3 to 4 administrations daily. For optimal patient tolerance and acceptability, the lowest effective dose possible should be used.

Dosage should not exceed 40 mg/day. Treatment should be combined with traditional, mechanical, non-pharmacological methods (compression stocking, high-sodium diet, etc.).

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

C Cardiovascular system
01 Cardiac therapy
C Cardiac stimulant
A Adrenergic and dopaminergic agent
17 Midodrine

2.2. Medicines in the same therapeutic category

These consist of sympathomimetic-induced hypertensive medicines:

- PRAXINOR: theodrenaline, cafedrine (insufficient AB, opinion of 10 May, 2006).
- EFFORTIL: ethylephrine (non-reimbursed, insufficient AB)
- HEPT-A-MYL: heptaminol (non-reimbursed, insufficient AB)

2.3. Medicines with a similar therapeutic aim

- Dihydroergotamine; SEGLOR, IKARAN, TAMIK and generic formulations (insufficient AB for this indication at the AB reassessment in 2001).
- Fludrocortisone: available under hospital magistral formulation, without Marketing Authorisation (MA) in France and cited in European recommendations as a potential treatment for managing arterial hypotension.

3 ANALYSIS OF AVAILABLE DATA

The company has submitted 16 studies, 10 of which were randomised, previously analysed and summarised in the opinion of 20 November 1998:
- 6 studies *versus* placebo,
- 4 studies *versus* active substances.

New clinical data has not been submitted by the company.

3.1. Placebo-controlled studies

Of the 6 randomised, placebo-controlled studies, two (studies IVB3 and IVB16) were conducted on populations of less than 20 patients and will not be detailed in this opinion.
In the absence of available statistic tests, study IVB11 will also not be described here.

- *Study IVB6 (Gilden et al.):*

This placebo-controlled, randomised, double-blind study evaluated the efficacy and safety of midodrine 10mg for one day in 70 patients with idiopathic, moderate to severe orthostatic hypotension.

Efficacy:
Primary endpoints were:
- Increase in systolic blood pressure (SBP), in standing position after 1 to 3 minutes after standing up,
- Improvement of hypotension clinical symptoms.

All the randomised patients were treated with midodrine for 1 day and only those responsive patients were evaluated (n=53), which constitutes a selection bias.
Clinical symptom evaluation criteria are not detailed.

Results:
- *SBP after standing up:*

At 1 minute, SBP increased under midodrine compared to placebo [72.6±3.8mmHg to 104.2±8.5mmHg, (47%) *versus* 75.2±4.6mmHg to 89.2±6.3mmHg, (21%)], $p<0.05$.
Statistical comparison of results at 3 minutes was not performed.
- *Clinical hypotension symptoms* (vertigo, shivering, lipothymia, etc.): in the absence of available data on the methods used to evaluate symptoms, the results are not taken into consideration.

Tolerance*:*
15.6% of patients under midodrine presented adverse events.
Common adverse events included tingling, pruritus, and piloerection (9.4%). Data for the placebo treatment is not available.

- *Study IVB7 (Low et al. 1997)[1]:*

This placebo-controlled, randomised, double-blind study evaluated the efficacy and safety of midodrine 10mg, 3 times daily, in 171 patients with neurogenic orthostatic hypotension treated for 6 weeks (1st week in simple-blind under placebo, weeks 2, 3, and 4 in double-blind midodrine or placebo, weeks 5 and 6 wash-out under placebo).
Note: Included patients represent a specific and infrequent population: young patients without a cardiovascular history.

Efficacy*:*

[1] Low et al. "Efficacy of midodrine vs. placebo in neurogenic orthostatic hypotension", JAMA April 2, 1997-vol244 n°13: 1046-51.

Primary endpoints were:

- Increase of SBP and diastolic blood pressure (DBP) after standing up,
- Improvement of clinical hypotension symptoms.

Results:

After 3 weeks, midodrine, compared to placebo, significantly increased:

- *SBP after standing up* (19.5 to 22.4 mmHg versus 3.5 to 6 mmHg, p<0.01),
- *DBP after standing up* (11.1 to 13.3 mmHg *versus* 1.3 to 4.3 mmHg, p<0.01).

Clinical hypotension symptoms (vertigo, tremors, lipothymia, etc.): in the absence of available data on the methods used to evaluate these symptoms, the results are not taken into consideration.

Tolerance:

Adverse events were more frequently observed in the midodrine group than in the placebo group (p=0.001). Common adverse events included pruritus (12% *versus* 2%), piloerection (13% *versus* 0%), urine retention (6% *versus* 0%), paraesthesia (17% *versus* 5%) and arterial hypertension in supine position (6% *versus* 0%).

- *Study IVB15 (Jankovic et al. 1993)*[2]*:*

This placebo-controlled, randomised, double-blind, parallel group study evaluated the efficacy and safety of midodrine 2.5, 5 and 10mg and of placebo, 3 times daily in 94 patients with orthostatic hypotension treated over 2 periods of 4 weeks, with a wash-out period of one week between the two periods.

Efficacy:

Primary endpoints were:

- Increase of SBP after standing up,
- Improvement of clinical hypotension symptoms (vertigo, lipothymia, syncope, etc.).

Results:

One hour after administration, *SBP after standing up* was significantly increased under midodrine 10mg compared to placebo [22mmHg (28% ± 6) *versus* 3mmHg (4% ± 4), p<0.001].

Clinical hypotension symptoms (vertigo, shivering, lipothymia, etc.): in the absence of available data on the methods used to evaluate these symptoms, the results are not taken into consideration.

Safety:

27% (20/74) of patients under midodrine and 22% (5/23) of patients under placebo experienced adverse events. The most frequently observed undesirable effects were pruritus (13.5% *versus* 2%) and arterial hypertension in supine position (8% *versus* 1%).

[2] Jankovic et al. « Neurogenic orthostatic hypotension: a double-blind, placebo-controlled study with midodrine » The American Journal of Medicine 1993,;95: 38-48.

3.2. Studies *versus* an active substance

The company submitted 4 studies *versus* an active substance:

- 2 studies *versus* ephedrine 6mg (IVB1 Tarazi et al; and IVB12 Conolly *et al*.),
- 1 study *versus* dihydroergotamine (DHE) 5 to 20mg (IVB5 Vinik *et al*.),
- 1 study *versus* fludrocortisone 0.1mg (IVB2 Yahr *et al*.).

These studies, considering the low level of methodological quality and the very small population, do not permit conclusion on the efficacy of midodrine compared to the comparator products.

Summary tables are attached to the opinion.

3.3. Adverse effects

The Transparency Committee regrets the insufficiency of the data presented for the adverse events of midodrine in the context of these clinical studies.

According to the SPC, the most frequently observed adverse events are of adrenergic type: cold sensation, tingling, compelling urination, exanthaema.

Supine position hypertension is frequent during long-term treatment of severe orthostatic hypotension.

Bradycardia and conduction disorders have been reported with the use of midodrine in association with digitalis glycosides.

3.4. Conclusion

The seven studies described in this opinion evaluated the efficacy and safety of GUTRON compared to placebo and to three active reference substances (ephedrine, DHE and fludrocortisone) in patients with orthostatic hypotension.

In the three placebo-controlled studies, significant statistical improvement of SBP after standing up was observed under midodrine with different effects according to the studies (from 19.5 to 31.6mmHg under midodrine *versus* 3 to 14mmHg under placebo) but the populations studied are not precisely described in terms of severity.

In light of the methodological weaknesses of the studies *versus* active reference substances, a formal conclusion on the compared efficacy of midodrine *versus* these comparator products cannot be drawn.

Furthermore, the pertinence of the comparators chosen in the studies *versus* active substances is debatable. Indeed, the ephedrine-based products available on the market are restricted to hospital usage and are limited to injectable formulations whose efficacy has not been evaluated in the above-mentioned studies.

The Transparency Committee regrets the absence of a study evaluating the impact of GUTRON treatment on cardiovascular mortality or on orthostatic hypotension complications (specifically hospitalisations).

4 DATA ON MEDICINAL PRODUCT USAGE

According to the data provided by the laboratory, approximately 57,000 boxes of GUTRON 2.5mg, box of 30 tablets and 74,000 boxes of GUTRON 2.5mg, box of 90 tablets, were used in a hospital setting in 2005.
The mean dosage is 10mg/day, i.e., 4 tablets.

5 TRANSPARENCY COMMITTEE CONCLUSIONS

5.1. Actual benefit

Severe orthostatic hypotension is a serious and debilitating disease which, due to the risk of fall, can led to complications and may compromise quality of life.

This medicinal product is intended as symptomatic therapy.

The efficacy/adverse effects ratio in these indications is high.

> *Public health benefit:*
> The burden on public health imposed by severe symptomatic orthostatic hypotension in the context of degenerative neurological diseases cannot be quantified.
> Reducing the number of fall in the elderly, specifically those related to orthostatic hypotension, is a necessity falling within the scope of an identified public health priority (GTNDO priority), the response for which is not necessarily a pharmacological treatment.
> There is no data available that allows the impact of GUTRON on reducing morbidity/mortality rates related to severe orthostatic hypotension or on improving quality of life to be quantified. Inappropriate prescription of GUTRON related to the removal from hospital-only listing and exposing certain patients to a heightened risk for strokes cannot be discarded, particularly in the very elderly, in patients with high vascular risk or in diabetic patients, who have not been the subject of GUTRON studies.
> Therefore, it is not expected that GUTRON will benefit public health.

The actual benefit of this medicinal product is substantial in patients with severe orthostatic hypotension in the context of degenerative neurological diseases (Parkinson's disease, Shy-Drager disease, olivopontocerebellar atrophy, etc.).

5.2. Improvement in actual benefit

In the context of the request for inclusion on the list of medicines reimbursed by National Insurance, the Committee considers that the improvement in actual benefit provided by GUTRON in the treatment of patients with severe orthostatic hypotension in the context of degenerative neurological diseases (Parkinson's disease, Shy-Drager disease, olivopontocerebellar atrophy, etc.) remains substantial.

5.3. Therapeutic use

Orthostatic hypotension is characterised by a decrease in systolic arterial pressure of at least 20 mmHg and/or diastolic arterial pressure of at least 10 mmHg, accompanied or not by symptoms, when standing up from a supine position.

The causes of orthostatic hypotension are many: medicinal products, endocrine diseases, hypovolaemia, aging, bacterial infections, neurological disease, heart diseases.

Thus, prior to initiating treatment, the causes of orthostatic hypotension must be identified.
Iatrogenic orthostatic hypotension (mainly due to anti-hypertensive, psychotropic and anti-Parkinsonian drugs) is usually reversible upon discontinuing or adjusting the treatment.
According to European recommendations (European Cardiology Association 2004 and European Federation of Neurological Societies 2006), the treatment strategy for managing orthostatic hypotension is based, initially, on eliminating sedative medicinal products or those inducing orthostatic hypotension, and alcohol.

Other than a iatrogenic cause, the main methods employed to manage orthostatic hypotension consist of lifestyle, and postural changes, such as:

- Avoiding prolonged standing position, improving leg mobility and raising the head of the bed,
- Adopting a high-sodium and high-water diet, fragmentation of low-carbohydrate meals.

Compression socks or stockings may also be used.

In rare cases these measures are insufficient and further treatment is then based on the use of fludrocortisone. An additional effect may be obtained using products to increase peripheral resistance. Midodrine (GUTRON) offers a particular benefit in light of the generally positive data resulting from clinical studies conducted on this molecule (level B).

In practice GUTRON and fludrocortisone are very rarely prescribed for the treatment of simple orthostatic hypotension but much more so for neurogenic orthostatic hypotension. The selection of one or the other molecule rests largely on their respective contraindications.

Thus, in light of its potent vasoconstrictor effect, the use of midodrine is specifically contraindicated in cases of arterial hypertension or high vascular risk. Fludrocortisone is contraindicated in cases of cardiac insufficiency (Pathak 2005).

Furthermore, as the effect of midodrine has been insufficiently documented in diabetic patients, the use of fludrocortisone is preferred, as there are studies demonstrating its efficacy in this type of patient.

5.4. Target population

The target population is composed of patients with orthostatic hypotension requiring a pharmacological treatment, particularly in the context of degenerative neurological diseases.

The majority of patients are affected with Parkinsonian syndromes.

According to the 2001 CNAM report, the prevalence of treated Parkinson's disease was 241 for every 100,000 patients, i.e., 143,000 individuals.

Approximately 15 to 20% of Parkinson's disease patients could present orthostatic hypotension requiring pharmacological treatment (expert opinion).

The target population of GUTRON is therefore estimated at 21,000 to 29,000 patients.

5.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance for patients with severe orthostatic hypotension in the context of degenerative neurological diseases (Parkinson's disease, Shy-Drager disease, olivo-ponto-cerebellar atrophy, etc.) at the posology in the Marketing Authorisation.

The Transparency Committee recommends that the initial prescription for GUTRON be undertaken in a hospital setting.

Packaging: Appropriate for prescription conditions.

Reimbursement rate: 65%

Study	Methodology	Number of patients and BP at baseline	Primary endpoints	Efficacy results	p	Safety	Methodology limitations
IVB1	Ephedrine 6mg and placebo-controlled, randomised, double-blind, cross-over study to evaluate the efficacy and safety of midodrine in patients with severe idiopathic orthostatic hypotension over two periods of 3 to 5 days with a wash-out period of 4 days	N=8 Standing BP: 89.2/63.5mmHg	Increase in standing position SBP after 1 minute	Standing BP: increased by +16.4/5mmHg under midodrine *versus* +1.2/-0,4mmHg under ephedrine	p<0.05	The most frequently observed adverse event was hypertension (2/8 patients in each group)	Very low number of patients Cross-over experimental design
IVB12	Ephedrine 6mg and placebo-controlled, randomised, double-blind, cross-over study to evaluate the efficacy and safety of midodrine in patients with severe orthostatic hypotension over two periods of 3 to 5 days with a wash-out period of 2 days.	N=22 randomised N=8 analysed patients Standing BP: 95.5/59mmHg Sitting BP: 95,5/59mmHg Supine BP: 131.3/76.4mmHg,	Increase in standing, sitting, and supine BP	Standing BP: no increase was observed. Sitting BP: increased by 7.1/7.1mmHg under midodrine compared to baseline *versus* placebo. No results *versus* ephedrine. Supine BP: no significant increase under midodrine compared to: - baseline, - placebo, - ephedrine.	 p=0.02 p=0.05 ND NS NS NS	Adverse events - 2 patients under midodrine - 4 patients under ephedrine, - 2 under placebo Hypertension in one patient under midodrine	Very low number of patients Exclusion of 14 patients prior to analysis Cross-over experimental design

Study	Methodology	Number of patients and BP at baseline	Primary endpoints	Efficacy results	p	Safety	Methodology limitations
IVB5	DHE 5 at 20mg and placebo-controlled, double-blind, cross-over study to evaluate the efficacy and safety of midodrine 2.5 to 10mg in patients with severe orthostatic hypotension over two periods of 3 to 5 days with a wash-out period of 2 days	N=11 randomised N=9 analysed BP at baseline not available	Increase in standing and supine BP Improvement in ability to maintain standing position	Standing BP: no improvement was observed Supine SBP: increased *128 ± 13mmHg under midodrine *120 ± 19mmHg under placebo Increased by 122 ± 15mmHg under DHE but Ability to maintain position: improvement in - 3 of the 5 patients evaluated for this criterion under midodrine (60%) - 40 to 60% of patients under DHE, - and in 40% of patients under placebo	 p<0.05 ND ND ND	Hypertension: 3/9 patients under midodrine and DHE.	Very low number of patients Cross-over experimental design Absence of statistical tests *versus* DHE Absence of data on pressure levels at baseline

Study	Methodology	Number of patients and BP at baseline	Primary endpoints	Efficacy results	p	Safety	Methodology limitations
IVB2	Fludrocortisone 0.1mg and placebo-controlled, randomised, double-blind, cross-over study to evaluate the efficacy and safety of midodrine in patients with orthostatic hypotension and disorders of the autonomous nervous system over 6 periods: 1/ wash-out (4 to 8 days), 2/ investigation of optimal midodrine dosage (6 to 16 days), 3/ constant midodrine dosage (4 to 6 days), 4/ midodrine + fludrocortisone or placebo + fludrocortisone (5 to 8 days), 5/ placebo + fludrocortisone (2 days), 6/ placebo + fludrocortisone or midodrine + fludrocortisone (6 to 12 days). The randomised, double-blind study consisted of phases 4 and 6.	N=7 BP at baseline not available	Increase in standing SBP after 2 minutes	Standing SBP: +11.4mmHg under midodrine + fludrocortisone sub-group but no difference versus fludrocortisone + placebo.	NS	Temporary pruritus: 2 under midodrine	Very low number of patients Cross-over experimental design Absence of data on pressure levels at baseline