HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

21 October 2009

TEMERIT DUO 5 mg/12.5 mg, film-coated tablets
Pack of 30 (CIP: 393 976-9)
Pack of 90 (CIP: 393 977-5)

TEMERIT DUO 5 mg/25 mg, film-coated tablets
Pack of 30 (CIP: 393 978-1)
Pack of 90 (CIP: 393 979-8)

Applicant: A.MENARINI FARMACEUTICA INTERNAZIONALE Srl

Nebivolol /hydrochlorothiazide

ATC code: C07BB

List I

Date of Marketing Authorisation: 27/05/2009

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

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredients
Nebivolol hydrochloride
Hydrochlorothiazide

1.2. Indication
“Treatment of essential hypertension.

TEMERIT DUO 5 mg/12.5 mg is a fixed-dose combination indicated in patients whose blood pressure is controlled by the concomitant administration of 5 mg of nebivolol and 12.5 mg of hydrochlorothiazide

TEMERIT DUO 5 mg/25 mg is a fixed-dose combination indicated in patients whose blood pressure is controlled by the concomitant administration of 5 mg of nebivolol and 25 mg of hydrochlorothiazide

1.3. Dosage
“Adults:
TEMERIT DUO 5 mg/12.5 mg is indicated in patients whose blood pressure is controlled by concomitant administration of 5 mg of nebivolol and 12.5 mg of hydrochlorothiazide

TEMERIT DUO 5 mg/25 mg is indicated in patients whose blood pressure is controlled by concomitant administration of 5 mg of nebivolol and 25 mg of hydrochlorothiazide

The dosage is one tablet per day, preferably at the same time of the day. Tablets may be taken with meals.

Patients with renal insufficiency: TEMERIT DUO should not be used in patients with severe renal failure.

Patients with hepatic insufficiency: Data in patients with hepatic insufficiency or impaired liver function are limited, The use of TEMERIT DUO is contra-indicated in these patients.

Elderly patients: In view of the limited experience in patients aged over 75 years, caution must be exercised and these patients closely monitored.

Children and adolescents: As no specific studies have been performed, use in children and adolescents is not recommended.”

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

C : Cardiovascular system
C07 : Beta-blockers
C07B : Beta-blockers and thiazide diuretics
C07BB : Selective beta-blockers and thiazide diuretics

2.2. Medicines in the same therapeutic category

Separate administration of nebivolol 5 mg (TEMERIT, NEBILOX) and 25 mg/day of hydrochlorothiazide (ESIDREX).
No proprietary medicine containing 12.5 mg of hydrochlorothiazide is available on the market.

Fixed-dose combinations of a beta-blocker and a diuretic:

Bisoprolol 2.5 / 5 /10mg + HCTZ 6.25 mg	:	LODOZ, WYTENS
Metoprolol 200 mg + chlortalidone 25 mg	:	LOGROTON
Atenolol 50 mg + chlortalidone 12.5 mg	:	TENORETIC
Oxprenolol 160 mg + chlortalidone 20 mg	:	TRANSITENSINE
Pindolol 10 mg + clopamide 5 mg	:	VISKALDIX

2.3. Medicines with a similar therapeutic aim

All medicinal products indicated in the treatment of essential hypertension as monotherapy or in combination.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The evaluation of efficacy and safety is based on the results of two studies:

- a bioequivalence study (NEBIZ-01) which showed the bioequivalence of the NEB/HCTZ 5 mg/12.5 mg and 5 mg/25 mg combinations and the free combination of their respective monotherapies on the kinetic parameters studied [Cmax, AUC (0→t) and AUC].
- A randomised, double-blind, phase III study (NEB-CAN-3)[1], in 240 patients with hypertension, followed up for 12 weeks with the objective of determining efficacy in terms of a reduction in diastolic blood pressure (DBP) relative to baseline.

Study NEB-CAN-3

Method: 12-arm factorial design (placebo, nebivolol 1, 5 and 10 mg, HCTZ 12.5 and 25 mg, nebivolol + HCTZ 1 mg/12.5 mg, 1 mg/25 mg, 5 mg/12.5 mg, 5 mg/25 mg, 10 mg/12.5 mg, 10 mg/25 mg) performed in 240 patients followed up for 12 weeks.

Inclusion criteria: adult patients (aged 18 to 70 years) with a DBP of between 95 and 110 mmHg.

1 Lacourcière et al. "Treatment of ambulatory hypertensives with nebivolol or hydrochlorothiazide alone and in combination" Am. Journal of hypertension 1994,7:137-45.

Treatments:
- Placebo (n =20)
- nebivolol 1 mg, n=20,
- nebivolol 5 mg, n=20,
- nebivolol 10 mg, n=20,
- HCTZ 12.5 mg, n=20,
- HCTZ 25 mg, n=20,
- nebivolol + HCTZ 1 mg/12.5 mg, n= 20,
- nebivolol + HCTZ 1 mg/25 mg, n= 20,
- nebivolol + HCTZ 5 mg/12.5 mg, n= 20,
- nebivolol + HCTZ 5 mg/25 mg, n= 20,
- nebivolol + HCTZ 10 mg/12.5 mg, n= 20,
- nebivolol + HCTZ 10 mg/25 mg, n= 20,

NB: in this study, the distribution of treatments and doses administered did not take the patient blood pressure status into account .

Primary efficacy endpoint: mean change (fall) in DBP (in mmHg) relative to baseline at 4 weeks; an "additional" analysis was carried out on the data obtained at the "last available visit".

RESULTS: ITT Analysis (see Table 1).

Table 1: Mean change in DBP (in mmHg) at 4 weeks.

Treatment	Baseline Mean ± SD	4 weeks Mean ± SD	Difference Mean ± SD	p	Last available visit Mean ± SD	Difference Mean ± SD
Placebo	104.2 ± 4.54	98.7 ± 8.17	5.1 ± 8.13	0.0162	102.8 ± 8.98	1.4 ± 8.99
NEB 1 mg	101.1 ± 8.16	97.4 ± 10.69	3.7 ± 6.63	0.0212	95.6 ± 9.60	5.5 ± 5.48
NEB 5mg	97.5 ± 8.52	88.1 ± 7.26	9.4 ± 5.83	0.0001	88.2 ± 7.83	8.5 ± 6.93
NEB 10 mg	99.8 ± 5.88	86.5 ± 8.38	13.3 ± 5.61	0.0001	86.0 ± 7.89	13.8 ± 7.16
HCTZ 12.5 mg	99.8 ± 5.40	95.1 ± 7.04	5.0 ± 5.77	0.0013	95.2 ± 6.46	4.6 ± 4.71
HCTZ 25 mg	100.1 ± 5.28	93.9 ± 9.13	6.1 ± 7.01	0.0009	94.3 ± 7.15	5.8 ± 5.75
NEB 1/HCTZ 12.5	98.6 ± 7.61	90.7 ± 7.61	7.8 ± 7.76	0.0002	89.1 ± 6.31	9.4 ± 7.05
NEB 1/HCTZ 25	101.9 ± 7.30	92.0 ± 9.61	9.9 ± 9.19	0.0001	91.6 ± 9.51	10.3 ± 9.02
NEB 5/HCTZ 12.5	102.5 ± 7.26	92.6 ± 6.50	9.8 ± 8.25	0.0001	92.6 ± 7.34	9.9 ± 8.60
NEB 5/HCTZ 25	99.3 ± 7.07	86.0 ± 7.12	13.3 ± 5.40	0.0001	86.9 ± 7.82	12.4 ± 6.51
NEB10/HCTZ 12.5	102.1 ± 6.73	87.9 ± 5.41	14.1 ± 6.56	0.0001	89.5 ± 6.49	12.6 ± 6.19
NEB 10/HCTZ 25	102.4 ± 5.60	86.3 ± 9.36	16.1 ± 8.83	0.0001	87.1 ± 5.50	15.3 ± 7.25

NEB : nebivolol

After 4 and 12 weeks of treatment, a fall in DBP was observed in all treatment groups relative to baseline.

As no statistical test was performed to compare groups, no conclusion may be made about the reduction in DBP between the combinations and the active ingredients alone.

3.2. Adverse effects

The study data showed that no new adverse effects were observed after coadministration of these two active ingredients.

According to the SPC, the most commonly observed adverse effects (> 10%) were: headaches, vertigo, paraesthesia, dyspnoea, constipation, nausea, vomiting, asthenia, and oedema.

3.3. Conclusion

TEMERIT DUO is a fixed-dose combination of nebivolol (beta-blocker) and hydrochlorothiazide (diuretic) available at two dosage strengths: 5 mg/12.5 mg and 5 mg/25 mg.

One study (NEBIZ-01) showed the bioequivalence of the nebivolol/HCTZ 5 mg/12.5 mg and 5 mg/25 mg combinations and their respective monotherapies.

The efficacy and safety of these proprietary medicines were evaluated during study NEB-CAN-3. A fall in DBP relative to baseline was observed in all treatment groups after 4 and 12 weeks of treatment. As no statistical test was performed to compare groups, no conclusions may be drawn about the reduction in DBP between the combinations and the active ingredients alone.

Study NEB-CAN-3 evaluated the nebivolol/HCTZ combination given in separate doses; no comparative efficacy study with the fixed-dose combination (TEMERIT DUO) is available. The value of administering these two antihypertensive agents as a fixed-dose combination rather than in separate doses was not established.

Moreover, the impact of the combination of 5 mg of nebivolol with 12.5 mg or 25 mg of HCT on reduction in morbidity and mortality has not been established.

The usefulness of this combination compared to other antihypertensive combinations (medicinal products in the same class or other classes) is not documented.

The safety profile of the nebivolol/HCTZ (5 mg/12.5 mg, 5 mg/25 mg) combinations in the studies was not different from the known profiles of the two active ingredients. The most commonly observed adverse effects (> 10%) were headaches, vertigo, paraesthesia, dyspnoea, constipation, nausea, vomiting, asthenia and oedema.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Essential hypertension may have life-threatening complications.
These proprietary drugs are intended for preventive treatment.

The efficacy/adverse effects ratio evaluated from the reduction in blood pressure values induced by TEMERIT DUO fixed-dose combinations is high. These fixed-dose combinations were not shown to have any benefit in terms of a reduction in morbidity and mortality.

These proprietary medicines are intended for 3rd-line treatment of patients whose blood pressure is controlled by concomitant administration of:
- 5 mg of nebivolol and 12.5 mg of hydrochlorothiazide for TEMERIT DUO 5 mg / 12.5 mg,
- 5 mg of nebivolol and 25 mg of hydrochlorothiazide for TEMERIT DUO 5 mg / 25 mg,

There are many alternative medications with a demonstrated benefit in terms of a reduction in morbidity and mortality.

The actual benefit of TEMERIT DUO is substantial.

4.2. Improvement in actual benefit

The proprietary medicines TEMERIT DUO, fixed-dose combinations of nebivolol and hydrochlorothiazide (5 mg/12.5 mg and 5 mg/25 mg) do not provide any improvement in actual benefit (IAB V) compared to the combined use of each of the ingredients taken separately at the same unit doses in the treatment of essential hypertension.

4.3. Therapeutic use

Antihypertensive medication aims to prevent the cardiovascular and renal complications of hypertension. The objective of these agents is to restore normal blood pressure values. Diuretics, beta-blockers, calcium channel blockers and renin-angiotensin system antagonists have been shown to reduce the occurrence of cardiovascular complications. For these reasons, the national or international recommendations propose that antihypertensive treatment is initiated with one of these products.

TEMERIT DUO 5 mg/12.5 mg is intended for 3rd-line treatment and may only be prescribed in patients whose blood pressure is controlled by concomitant administration of 5 mg of nebivolol and 12.5 mg of hydrochlorothiazide

TEMERIT DUO 5 mg/25 mg is intended for 3rd-line treatment and may only be prescribed in patients whose blood pressure is controlled by concomitant administration of 5 mg of nebivolol and 25 mg of hydrochlorothiazide

Moreover, the Committee pointed out that the value of fixed-dose combinations in the management of hypertensive patients in comparison with separate administration of (two) drugs has not been established. Moreover, this proprietary medicine is not adapted for the management of all patients.

4.4. Target Population

The prevalence of diagnosed and/or treated high blood pressure is about 6.5 to 7.4 million patients (HCSP 2002 and CREDES 1999 data extrapolated to the French population in 2003, THALES/CEMKA 2001).
However, the real prevalence of hypertension may be higher than that of diagnosed and/or treated hypertension. The MONICA study showed that only 52.2% of hypertensive patients aged 35-64 years knew about their hypertension.
If the MONICA data are extrapolated assuming that only 52.2% of patients with high blood pressure are actually diagnosed and/or treated, the real prevalence of hypertension could be about 12.5 to 14.2 million persons.

It should be noted for information purposes that a study on the management of hypertension in general medicine (THALES/CEMKA 2001) showed that 49% of patients are treated by monotherapy, 34% by bitherapy, 13% by triple-agent therapy and 4% by four agents or more.

There is no data with which to estimate the percentage of patients treated in France by 5 mg of nebivolol and 12.5 or 25 mg of HCTZ and whose blood pressure is controlled. The target population of TEMERIT DUO (5mg/12.5 mg and 5 mg/25 mg) cannot therefore be calculated.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Health Insurance and on the list of medicinal products approved for use by hospitals and various public services in the indication and at the dosages in the marketing authorisation.

Packaging: Appropriate for the prescription conditions.

Reimbursement rate: 65%

APPENDIX

Dosage of nebivolol (TEMERIT/NEBILOX) in hypertension (SPC):

The dosage is one tablet per day (5 mg), preferably at the same time of day. The tablets may be taken with meals.
The blood pressure lowering effect becomes evident after 1-2 weeks of treatment.
Occasionally, the optimal effect is reached only after 4 weeks.

Dosage of HCTZ (ESIDREX) in hypertension (SPC):

The currently recommended doses in arterial hypertension are 12.5 to 25 mg/day and 6.25 to 12.5 mg/day in combination with another antihypertensive.
The dosage should not exceed 25 mg/day (increase in adverse effects with no gain in efficacy).