HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

16 June 2010

ALTEISDUO 40 mg/12.5 mg, film-coated tablets
B/30 (CIP: 350 238-6)
B/50 (CIP: 576 792-4)
B/90 (CIP: 350 239-2)

ALTEISDUO 40 mg/25 mg, film-coated tablets
B/30 (CIP: 350 242-3)
B/50 (CIP: 576 793-0)
B/90 (CIP: 350 244-6)

Applicant: A. MENARINI FARMACEUTICA INTERNAZIONALE SRL

olmesartan medoxomil / hydrochlorothiazide

ATC code: C09DA08

List I

Date of Marketing Authorisation: 10/03/2010

Reason for request: Inclusion on the list of medicines reimbursed by National Health Insurance and approved for use by hospitals (pack of 30 and pack of 90). Inclusion on the list of medicines approved for use by hospitals (pack of 50)

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
olmesartan medoxomil/hydrochlorothiazide

1.2. Indication
"Treatment of essential hypertension.
ALTEIS DUO 40 mg/12.5 mg and 40 mg/25 mg fixed dose combinations are indicated in patients whose blood pressure is not adequately controlled by olmesartan medoxomil 40 mg alone."

1.3. Dosage
"The recommended dose of ALTEIS DUO 40 mg/12.5 mg and 40 mg/25 mg is 1 tablet per day.
ALTEIS DUO 40 mg/12.5 mg may be administered in patients whose blood pressure is not adequately controlled by olmesartan medoxomil 40 mg alone.
ALTEIS DUO 40 mg/25 mg may be administered in patients whose blood pressure is not adequately controlled by ALTEIS DUO 40 mg/12.5 mg fixed dose combination.
For convenience, patients receiving olmesartan medoxomil and hydrochlorothiazide from separate tablets may be switched to ALTEIS DUO 40 mg/12.5 mg and 40 mg/25 mg tablets containing the same component doses.

Method of administration:
The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water). The tablet should not be chewed and should be taken at the same time each day. ALTEIS DUO 40 mg/12.5 mg and 40 mg/25 mg can be taken with or without food.

Elderly (age 65 years or over): In elderly patients the same dosage of the combination is recommended as for adults. Blood pressure should be closely monitored.

Renal impairment: ALTEIS DUO is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min). The maximum dose of olmesartan medoxomil in patients with mild to moderate renal impairment (creatinine clearance of 30–60 mL/min) is 20 mg olmesartan medoxomil once daily, owing to limited experience of higher dosages in this patient group, and periodic monitoring is advised. ALTEIS DUO 40 mg/12.5 mg and 40 mg/25 mg are therefore contraindicated in all stages of renal impairment.

Hepatic impairment: ALTEIS DUO 40 mg/12.5 mg and 40 mg/25 mg should be used with caution in patients with mild hepatic impairment. Close monitoring of blood pressure and renal function is advised in hepatically-impaired patients who are receiving diuretics and/or other antihypertensive agents. In patients with moderate hepatic impairment, an initial dose of 10 mg olmesartan medoxomil once daily is recommended and the maximum dose should not exceed 20 mg once daily. There is no experience of olmesartan medoxomil in patients with severe hepatic impairment. ALTEIS DUO 40 mg/12.5 mg and 40 mg/25 mg therefore should not be used in patients with moderate and severe hepatic impairment, as well as in cholestasis and biliary obstruction.

Children and adolescents: ALTEIS DUO 40 mg/12.5 mg and 40 mg/25 mg are not recommended for use in children below 18 years due to a lack of data on safety and efficacy."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

C : Cardiovascular system
C09 : Agents acting on the renin-angiotensin system
C09D : Angiotensin II antagonists, combinations
C09DA : Angiotensin II antagonists and diuretics
C09DA08 : Olmesartan medoxomil and diuretics

2.2. Medicines in the same therapeutic category

2.2.1 Comparator medicines

Aside from separate doses of 40 mg/day of olmesartan and hydrochlorothiazide 12.5 mg or 25 mg, the list of comparator medicines consists of fixed-dose combinations of angiotensin II receptor antagonists (sartans) and hydrochlorothiazide.

Hydrochlorothiazide 12.5 mg combined with:

- Candesartan cilexetil (8 mg, 16 mg): COKENZEN, HYTACAND
- Eprosartan (600 mg): COTEVETEN
- Irbesartan (150 mg, 300 mg): COAPROVEL
- Losartan: HYZAAR (50 mg), FORTZAAR (100 mg)
- Olmesartan (20 mg): ALTEIS DUO, CO-OLMETEC
- Valsartan (80 mg, 160 mg): COTAREG, NISISCO
- Telmisartan (40 mg, 80 mg): MICARDISPLUS, PRITORPLUS

Hydrochlorothiazide 25 mg combined with:

- Irbesartan (300 mg): COAPROVEL
- Losartan (100 mg): FORTZAAR
- Olmesartan (20 mg): ALTEIS DUO, CO-OLMETEC
- Telmisartan (80 mg): MICARDISPLUS, PRITORPLUS
- Valsartan (160 mg): COTAREG, NISISCO

2.2.2 Medicines with a similar therapeutic aim:

All medicinal products indicated for the treatment of essential hypertension.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The dossier includes:

- 2 studies (SE-866-CMB/02 and SE-866/318[1]), the aim of which was to demonstrate the benefit provided by the addition of each component to the other. These studies were previously presented in the opinion on ALTEIS DUO 20/12.5 and 20/25 dated 29/03/2006 and will not be covered in this opinion.
- Three new phase III studies (303, 301 and 302). Studies 301 and 302, which evaluated the efficacy of ALTEIS DUO 40/12.5 and 40/25 mg in patients with moderate to severe hypertension that is not sufficiently controlled on olmesartan 40 mg alone, and study 303, which compared the efficacy of ALTEIS DUO 40/12.5 mg with olmesartan 40 mg alone.
- 5 short-term titration studies, in which the dose titration levels were as follows: olmesartan 20 mg, olmesartan 40 mg, olmesartan 40 mg/HCTZ 12.5 mg and olmesartan 40 mg/HCTZ 25 mg, which assessed the percentage of responders (those who reached the blood pressure objectives at the end of the studies). These studies will not be further examined in this opinion.

- **Study 303**

Design: a randomised, double-blind, parallel-group, comparative study of ALTEIS DUO 40/12.5 versus olmesartan 40 mg, carried out in 838 patients with moderate to severe hypertension who were followed up for 8 weeks.

Inclusion criteria: adults aged over 18 with essential hypertension.

Treatments:
After two weeks of placebo treatment, two treatment phases were begun:
Phase A (8 weeks): patients were randomly divided into 2 groups:

- ALTEIS DUO 40/12.5 mg, n=556
- Olmesartan 40 mg, n=282.

Note: during this treatment phase, ALTEIS DUO 40/12.5 was not administered in compliance with the indication that is validated in the marketing authorisation, which states that it should be reserved "for patients whose blood pressure is not adequately controlled by olmesartan 40 mg alone".

Phase B (8 weeks): responders continued their treatment, while non-responders had their treatments changed. Analysis of results from this phase, which formed a secondary endpoint for this study, will not be examined in this opinion.

Primary endpoint: change in residual mean seated DBP (diastolic blood pressure) after 8 weeks of treatment (phase A).

[1] Ball et al., "Relative efficacy of an angiotensin II antagonist compared with other antihypertensive agents. Olmesartan medoxomil versus antihypertensives", J Hypertens Suppl. 2001 Jun;19(1):S49-56.

RESULTS: Intention-to-treat analysis

	ALTEIS DUO Olmesartan 40mg/ HCTZ 12.5 mg (n = 556)	Olmesartan 40mg (n = 282)	Difference [95% CI] p
DBP (mmHg)			
- mean at randomisation (SD)	104.6 (4.21)	104.5 (3.87)	
- after 8 weeks (SD)	85.7 (10.33)	88.7 (10.80)	
- mean change (SD)	-18.9 (9.32)	-15.8 (9.71)	-3.1 [-4.47; -1.76] p<0.0001

After 8 weeks of treatment, a significantly greater reduction in DBP was observed with ALTEIS DUO 40/12.5 than with olmesartan 40 mg alone: the difference was -3.1 mmHg [-4.47, -1.76], p<0.0001.

- **Study 301**

Design: a randomised, double-blind, parallel-group, comparative study of ALTEIS DUO 40/25, 40/12.5 and 20/12.5 versus olmesartan 40 mg, carried out in 970 patients with moderate to severe hypertension not adequately controlled by olmesartan 40 mg, who were followed up for 8 weeks.

Inclusion criteria: adults aged 18 or over, mean seated DBP of between 90 and 115 mmHg and mean seated SBP of between 140 and 180 mmHg.

Treatments:
After 8 weeks of treatment with olmesartan 40 mg alone, non-responders were randomised into 4 groups and were followed up for 8 weeks:
- ALTEIS DUO 40/25 mg, n=140
- ALTEIS DUO 40/12.5 mg, n=277
- ALTEIS DUO 20/12.5 mg, n=279
- Olmesartan 40 mg, n=274.

Note: the various different treatments were given without regard to the patients' blood pressure levels.

Primary endpoint: change in residual mean seated DBP after 8 weeks of treatment (week 16 in comparison with week 8).

RESULTS: intention-to-treat

	ALTEIS DUO Olmesartan 40mg/ HCTZ 25 mg (n = 140)	ALTEIS DUO Olmesartan 40mg/ HCTZ 12.5 mg (n = 277)	ALTEIS DUO Olmesartan 20mg/ HCTZ 12.5 mg (n = 279)	Olmesartan 40mg (n = 274)
DBP (mmHg) - mean at randomisation (SD) - after 8 weeks (SD) - mean change (SD)	98 (5.56) 86.9 (9.01) -11.16 (8.796)	97.5 (5.96) 88.3 (9.04) -9.13 (8.622)	97.2 (6.25) 89.1 (9.23) -8.10 (7.968)	97.3 (5.81) 91.6 (9.64) -5.66 (8.546)
Inter-arm comparisons	Comparison with olmesartan 40 mg -5.3 [-6.97; -3.6] p<0.0001	Comparison with Olmesartan 40 mg -3.4 [-4.79; -2.03] p<0.0001 Comparison with Olmesartan 20mg/ HCTZ 12.5 mg -0.9 [-2.32; 0.43] NS	-	-

After 8 weeks of treatment, in patients whose blood pressure was inadequately controlled by olmesartan 40 mg, a significantly greater reduction in seated DBP in comparison with olmesartan 40 mg alone was observed in the following arms:

- ALTEIS DUO 40/12.5: difference -3.4 mmHg [-4.79; -2.03] p<0.0001,
- ALTEIS DUO 40/25: difference -5.3 mmHg [-6.97; -3.6] p<0.0001.

No statistically significant difference was observed between the ALTEIS DUO 40/12.5 and ALTEIS DUO 20/12.5 arms.

- **Study 302**

Design: a randomised, double-blind, parallel-group, comparative study of ALTEIS DUO 40/25 versus ALTEIS DUO 20/25, carried out in 1010 patients with moderate to severe hypertension not controlled by olmesartan 40 mg who were followed up for 8 weeks.

Inclusion criteria: adults aged 18 or over, mean seated DBP of between 90 and 115 mmHg and mean seated SBP of between 140 and 180 mmHg after 8 weeks of treatment with olmesartan 40 mg.

Treatments:
After 8 weeks of treatment with olmesartan 40 mg alone, non-responders were randomised into 2 groups and were followed up for 8 weeks:

- ALTEIS DUO 40/25 mg, n=502;
- ALTEIS DUO 20/25 mg, n=508.

Note: the various different treatments were given without regard to the patients' blood pressure levels.

Primary endpoint: change in residual mean seated DBP after 8 weeks of treatment (week 16 in comparison with week 8).

RESULTS: Intention-to-treat analysis

	ALTEIS DUO Olmesartan 40mg/ HCTZ 25 mg (n = 502)	ALTEIS DUO Olmesartan 20mg/ HCTZ 25 mg (n = 508)	Difference [95% CI] p
DBP (mmHg)			
- mean at randomisation (SD)	97.0 (5.62)	96.8 (5.55)	
- after 8 weeks (SD)	85.9 (8.67)	86.3 (7.64)	-0.5
- mean change (SD)	-11.16 (8.851)	-10.45 (7.928)	[-1.51; 0.42] NS

After 8 weeks of treatment, in patients whose blood pressure was inadequately controlled by olmesartan 40 mg, no significant difference was observed between the ALTEIS DUO 40/25 and ALTEIS DUO 20/25 arms: difference -0.5 mmHg [-1.51, 0.42], NS.

3.2. Adverse effects

In study 303, 5/336 patients (1.5%) receiving ALTEIS DUO 40/12.5 and 1/129 patients (0.8%) receiving olmesartan 40 mg experienced adverse events.
The most frequent adverse events (≥ 0.5%) were:

- nervous system disorders (headaches, drowsiness): 1 patient in the ALTEIS DUO 40/12.5 arm versus 0 patient in the olmesartan 40 mg arm.
- renal disorders (elevated blood urea levels): 0 patient versus 1 patient.

In study 301, 5/140 patients (3.6%) in the ALTEIS DUO 40/25 arm, 7/278 patients (2.5%) in the 40/12.5 arm, 8/279 patients (2.9%) in the 20/12.5 arm and 9/274 patients (3.3%) in the olmesartan 40 mg arm experienced adverse events.
The most frequent adverse events (≥ 0.5%) were:

- hypertension: 1 versus 0 versus 2 versus 3 patients,
- hypotension: 1 versus 1 versus 1 versus 0 patient,
- nervous system disorders (drowsiness): 1 versus 1 versus 1 versus 0 patient,
- dizziness: 1 versus 1 versus 0 versus 0 patient,
- raised gamma GT levels: 0 versus 2 versus 0 versus 0 patient.

In study 302, 30/502 patients (6%) in the ALTEIS DUO 40/25 arm and 26/508 patients (5.1%) in the ALTEIS DUO 20/25 arm experienced adverse events.
The most frequent adverse events (≥ 0.5%) were:

- dizziness: 2 versus 3 patients,
- raised blood uric acid levels: 3 versus 0 patient.

According to the SPC, the tolerance of ALTEIS DUO 40/12.5 and 40/25 has been assessed in clinical trials involving 3709 patients. The most commonly occurring adverse events were: dizziness, headache, asthenia, peripheral oedema and chest pain.

3.3. Conclusion

The efficacy and tolerance of fixed-dose combinations of olmesartan 40 mg + HCTZ 12.5 mg and olmesartan 40 mg + HCTZ 25 mg have been assessed in 2 studies (301 and 302) which involved patients with moderate to severe hypertension which was inadequately controlled by olmesartan 40 mg alone. Study 303 assessed the efficacy and tolerance of the 40/12.5 mg fixed-dose combination in comparison with olmesartan 40 mg.

In study 303, after 8 weeks of treatment, a significantly greater reduction in sitting DBP was observed with ALTEIS DUO 40/12.5 than with olmesartan 40 mg alone: the difference was -3.1 mmHg [-4.47. -1.76], p<0.0001.

In study 301, after 8 weeks of treatment, a significantly greater reduction in sitting DBP was observed with ALTEIS DUO than with olmesartan 40 mg alone: the difference was -3.4 mmHg [-4.79; -2.03], p<0.0001 with ALTEIS DUO 40/12.5 and -5.3 mmHg [-6.97; -3.6], p<0.0001 with ALTEIS DUO 40/25. No statistically significant difference was observed between the ALTEIS DUO 40/12.5 and ALTEIS DUO 20/12.5 arms.

In study 302, after 8 weeks of treatment, no statistically significant difference was observed between the ALTEIS DUO 40/25 and ALTEIS DUO 20/25 arms: difference -0.5 mmHg [-1.51, 0.42], NS.

In studies 301 and 302, no statistically significant difference was observed between ALTEIS DUO 40/12.5 and ALTEIS DUO 20/12.5, or between ALTEIS DUO 40/25 and ALTEIS DUO 20/25. Given these results, it remains to be seen whether there is any added benefit of the ALTEIS DUO 40/12.5 and 40/25 fixed-dose combinations in comparison with the 20/12.5 and 20/25 combinations in patients with moderate to severe hypertension which is inadequately controlled by olmesartan 40 mg alone.

The most commonly observed adverse events were: dizziness, headache, asthenia, peripheral oedema and chest pain.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Essential hypertension can be life-threatening, because of its complications.

These products come within the scope of preventive treatment.

The efficacy/adverse effects ratio, assessed by measuring reduction in blood pressure, is high.
These fixed-dose combinations have not been shown to have an effect in terms of reduction in morbidity and mortality.

These medicinal products are second-line therapies.

There are many alternatives that have been shown to provide a reduction in morbidity and mortality (diuretics, beta-blockers, calcium channel blockers and other renin-angiotensin system antagonists).

> Public health benefit:
> Essential hypertension and cardiovascular disease (for which hypertension is a significant risk factor) represent a significant public health burden.
> Reducing the morbidity and mortality attributed to hypertension is a public health need (a priority identified in the GTNDO* and the Public Health Act**).
> However, existing treatments (including flexible combinations of olmesartan medoxomil and hydrochlorothiazide) already help to meet this need.
> There is no indication that these fixed-dose combinations have any added benefit (even in terms of increased compliance) over flexible combinations of the two active substances.
> Consequently, ALTEIS DUO is not expected to benefit public health in this indication.
> ***** GTNDO: National Technical Group for Defining Objectives (DGS-2003)
> ** Public Health Law 2004 no. 2004-806, dated 9 August 2004.

The actual benefit of these medicinal products is substantial.

4.2. Improvement in actual benefit (IAB)

"ALTEIS DUO products, which are fixed-dose combinations of olmesartan 40 mg and hydrochlorothiazide 12.5 mg or 25 mg, does not provide improvement in actual benefit (IAB V) in comparison with concurrent use of their separate components."

4.3. Therapeutic use

Antihypertensive treatment aims to prevent the cardiovascular and renal complications of hypertension. The goal should be to normalise blood pressure. Diuretics, beta-blockers, calcium channel antagonists and renin-angiotensin system antagonists have been shown to reduce the occurrence of cardiovascular complications. For these reasons, national and international guidelines suggest that one of these treatments should be used as initial treatment for hypertension.

ALTEIS DUO (40/12.5 and 40/25) are second-line therapies for the treatment of hypertension, indicated for patients whose blood pressure is not adequately controlled on olmesartan medoxomil 40 mg alone. The usefulness of a fixed-dose combination in the

management of patients, in comparison with separate doses of the two drugs, has not been established.
In addition, these products are not suitable for all patients to take.

4.4. Target population

The prevalence of diagnosed and/or treated hypertension in France appears to be between 6.5 and 7.4 million patients (HCSP data 2002 and CREDES 1999, extrapolated to the French population in 2003, THALES, CEMKA 2001).
However, the actual prevalence of hypertension could be higher than the prevalence of diagnosed and/or treated hypertension. The MONICA survey showed that only 52.2% of people with hypertension aged between 35 and 64 were aware of their hypertension.
If the MONICA data are extrapolated, and if we assume that only 52.2% of patients with hypertension are diagnosed and/or treated, the real prevalence of hypertension could be of the order of 12.5-14.2 million individuals in France.
For information, a study on treatment methods for hypertension in general practice (THALES/CEMKA 2001) showed that:

- 49% of patients were treated with a monotherapy, 34% with a dual therapy, 13% with triple therapy and 4% with four or more agents;
- 31% of patients were treated with beta-blockers, 27% with ACE inhibitors (alone or in combination) and 26% with calcium channel blockers.

No data are available concerning the percentage of patients whose hypertension is inadequately controlled by 40 mg of olmesartan medoxomil alone and who would be eligible to receive a fixed-dose combination. The target population for ALTEIS DUO cannot be calculated.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Health Insurance (packs of 30 and 90) and on the list of medicinal products approved for use by hospitals and various public services (packs of 30, 50 and 90) for the indication and at the dosage given in the marketing authorisation.

Packaging: appropriate for the prescription conditions.

Reimbursement rate: 65%