

**COZAAR-COMP 100MG/12.5MG FILM-COATED TABLETS
(LOSARTAN POTASSIUM / HYDROCHLOROTHIAZIDE)**

PL 00025/0473

UKPAR

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Merck Sharp & Dohme Limited a Marketing Authorisation (licence) for the medicinal product Cozaar-Comp 100mg/12.5mg film-coated tablets (PL 00025/0473) on 17th October 2007. This is a prescription-only medicine (POM) used for the treatment of high blood pressure and stroke.

Cozaar-Comp 100mg/12.5mg film-coated tablets contain two active ingredients, losartan potassium and hydrochlorothiazide. Losartan belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin II is a chemical occurring in the body, which tightens your blood vessels making it harder for the blood to pass through them and causing your blood pressure to increase. Losartan blocks this effect of angiotensin II, causing the blood vessels to relax. Hydrochlorothiazide works by making your kidneys pass more water and salt. The combined effect of losartan and hydrochlorothiazide lowers high blood pressure.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Cozaar-Comp 100mg/12.5mg film-coated tablets outweigh the risks, hence a Marketing Authorisation has been granted.

**COZAAR-COMP 100MG/12.5MG FILM-COATED TABLETS
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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Merck Sharp & Dohme Limited a Marketing Authorisation for the medicinal product Cozaar-Comp 100mg/12.5mg film-coated tablets (PL 00025/0473) on 17th October 2007. This is a prescription-only medicine (POM) used for the treatment of high blood pressure and stroke.

Cozaar-Comp 100mg/12.5mg film-coated tablets contain two active ingredients, losartan potassium and hydrochlorothiazide. Losartan belongs to a group of medicines known as angiotensin-II receptor antagonists and is approved as a single agent and in combination with hydrochlorothiazide for treatment of hypertension. Hydrochlorothiazide is a thiazide diuretic used for many years in treatment of hypertension.

This is a national, abridged, application, submitted as a line extension for a fixed dose combination product containing 100mg losartan potassium and 12.5mg hydrochlorothiazide made under article 8.3(i)(a) of directive 2001/83/EC (as amended). The application cross-refers to “Cozaar Comp” (50mg losartan potassium/12.5mg hydrochlorothiazide; PL 00025/0338) which is also held by the proposed MA holder. In addition to “Cozaar Comp” Merck, Sharp and Dohme Ltd. also hold a Marketing Authorisation for “Fortzaar” (PL 00025/0374) which contains 100mg losartan/25mg hydrochlorothiazide.

The application was referred to the Commission for Human Medicines (CHM) in March 2006 for consideration whether the safety, quality and efficacy of the product was demonstrated. At that time, the Commission advised that a marketing authorisation should not be approved.

The applicants’ response and further data were considered at the CHM meeting in June 2007. Following consideration of the additional data, the Commission advised the approval of the marketing authorisation.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

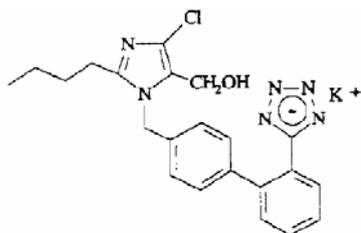
Losartan potassium

Nomenclature:

INN: Losartan potassium

Chemical name: 2-Butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol, monopotassium salt

Structure:



Molecular formula: $C_{22}H_{22}ClKN_6O$

Molecular weight: 461.0

CAS No: 124750-99-8

Physical form: White to off-white free flowing crystalline powder

Solubility: Freely soluble in water

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate active substance specification has been provided based on USP and Ph Eur. monographs.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active losartan potassium is stored in appropriate packaging under ambient conditions of temperature and humidity. It is packed in double polyethylene bags. Specifications and certificates of analysis have been provided. The polyethylene bags in direct contact with the drug substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Batch analysis data are provided and comply with the proposed specification. Satisfactory certificates of analysis have been provided for standards used by the active substance manufacturer during validation studies.

Appropriate stability data have been generated for drug substance stored in the same immediate packaging as the commercial packaging. This data demonstrate the stability of the drug substance and supports a retest period of 4 years when stored in the proposed packaging.

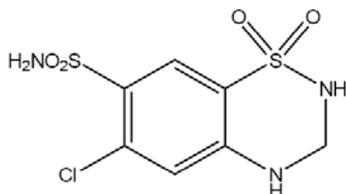
ACTIVE SUBSTANCE**Hydrochlorothiazide**

Nomenclature:

INN: Hydrochlorothiazide

Chemical name: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide

Structure:

Molecular formula: C₇H₈ClN₃O₄S₂

Molecular weight: 297.7

CAS No: 58-93-5

Physical form: White to off-white odourless crystalline powder

Solubility: Very slightly soluble in water, soluble in aqueous solutions of inorganic bases, e.g. sodium hydroxide / ammonium hydroxide, and in organic bases like n-butylamine

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate active substance specification has been provided based on USP and European Pharmacopeia requirements.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active hydrochlorothiazide is stored in appropriate packaging for long-term storage. It is packed in double polyethylene liners. Specifications and certificates of analysis have been provided. The polyethylene bags in direct contact with the drug substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for standards used by the active substance manufacturer during validation studies.

Appropriate stability data have been generated for active substance stored in similar immediate packaging to the commercial packaging. This data demonstrate the stability of the drug substance and supports a retest period of 5 years when stored in the proposed packaging.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely hydroxypropylcellulose (E463), hypromellose (E464), lactose monohydrate, magnesium stearate (E572), microcrystalline cellulose (E460), pregelatinised maize starch, titanium dioxide (E171), and carnauba wax. Appropriate justification for the inclusion of each excipient has been provided.

The excipients used comply with their respective European Pharmacopoeia monographs. Satisfactory certificates of analysis have been provided for all excipients.

Magnesium stearate is of vegetable origin. The applicant has confirmed that lactose is derived from healthy animals and is collected under the same conditions as milk for human consumption. The lactose is not prepared using other ruminant materials.

There were no novel excipients used and no overages.

Pharmaceutical development

Details of the pharmaceutical development of the drug product have been supplied and are satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls have been provided and are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on validation batches. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any standards used.

Container Closure System

The tablets are packed in white, opaque PVC (polyvinylchloride) / PE (polyethylene) /PVDC (polyvinylidene chloride) blisters with aluminium foil lidding. The calendar blister strips are packaged with the PIL into cardboard boxes. The product is packaged in a pack size of 28 tablets. In-house specifications, and certificates of analysis, for all packaging types and components used have been provided. These are satisfactory.

All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 36 months has been set, which is satisfactory. Storage conditions are “Do not store above 30°C”, “Store in the original packaging”.

Efficacy Studies

The applicant provided results from a bioequivalence study where the proposed combination product was compared against co-administration of corresponding monotherapies. In the course of assessment, the applicant provided a further efficacy study (P264) using a formulation representative of that intended for marketing. The formulation intended for marketing is justified considering the evidence of efficacy provided and supporting quality data.

Clinical efficacy study P264:

Composition - The composition of each of the formulations used in the study has been provided. The composition of Losartan Potassium Tablets 100 mg is identical to that of the UK market product (Cozaar 100mg film-coated tablets), except that carnauba wax is omitted. The composition of Losartan Potassium-Hctz Tablets 100-12.5 mg is identical to that of the proposed market product.

Manufacturing sites - The proposed market product is manufactured by the same manufacturers as the Losartan Potassium-Hctz Tablets 100-12.5 mg used in the efficacy study.

Finished product specifications - Specifications are generally identical for the Losartan potassium tablets-Hctz 100-12.5 mg and Losartan potassium tablets 100mg used in the efficacy study, and for the products intended to market.

Dissolution profiles - The dissolution profile of Losartan Potassium tablets-Hctz 100-12.5 mg used in the efficacy study versus the product intended for marketing is comparable.

Expert report

A detailed quality overall summary has been provided, which has been prepared by an appropriately qualified expert.

Conclusion

The grounds for this application are considered adequate. It is recommended that a Marketing Authorisation is granted for this application.

PRECLINICAL ASSESSMENT

This is a national, abridged, application, submitted as a line extension for a fixed dose combination product containing 100mg losartan potassium and 12.5mg hydrochlorothiazide made under article 8.3(i)(a) of directive 2001/83/EC (as amended).

No new preclinical data have been supplied with this application and none are required for an application of this type. A preclinical expert report has been written by a suitably qualified person and is satisfactory.

CLINICAL ASSESSMENT

INTRODUCTION

This is a national, abridged, application, submitted as a line extension (new combination of strengths of known active ingredients) for Cozaar compound. Two other strengths for the same combination of actives (losartan and hydrochlorothiazide), 50/12.5 and 100/25 mg have already been approved since 1996. The applicant (MSD) claims this strength (100/12.5) on the basis of clinical use, posology approved based on LIFE study data and the currently approved SmPCs.

As the applicant claims the legal basis of the application to be a line extension, most data submitted in the dossier were bibliographic, except for the clinical efficacy studies.

CLINICAL BACKGROUND

The applicant argues that addition of low dose diuretic (hydrochlorothiazide) to a renin-angiotensin blocker such as losartan provides additional antihypertensive efficacy over that provided by monotherapy with either agent. The availability of the intermediate strength of 100/12.5 mg combination (to those already approved (50/12.5 and 100/25mg) achieves or offers greater flexibility for titration to physicians who prefer to use the lower dose of hydrochlorothiazide (12.5mg). The applicant also argues that there is wealth of evidence supporting the use of 100/12.5 mg combination and that this new combination will permit a step wise titration from 100mg losartan in those who show inadequate response.

INDICATIONS

For the treatment of hypertension in patients whose blood pressure is not adequately controlled on hydrochlorothiazide or losartan monotherapy.

In hypertensive patients with left ventricular hypertrophy a reduced risk of stroke was demonstrated with losartan administered usually in combination with Hctz. The data do not support the use of losartan for this indication in black patients (LIFE study).

Assessor's Comment: These indications are identical to the currently authorised strengths and are acceptable.

The first is a non-responder indication and would need data in those not responding to monotherapy with losartan 100mg or hydrochlorothiazide 12.5mg as per the CHMP guidance note hypertension (CHMP/EWP/238/95 Rev.2) "two add on studies one in non-responders to X and one with non-responders to Y should be carried out".

In this context, the 100+25mg combination has already been authorised and therefore it seems established that addition of 100mg losartan to those not responding to 25mg of hydrochlorothiazide is beneficial. It would not be unreasonable to infer that addition of 100mg to those not responding to 12.5mg would also derive a clinically meaningful benefit. The question is whether addition of 12.5mg hydrochlorothiazide to those non-responding to 100mg losartan monotherapy produces a clinically meaningful benefit.

The second indication is supported by the LIFE study. The approved SmPCs (50/12.5 & 100/25 strengths) suggest a place for the 100/12.5mg strength that was accepted at the time of authorisation of these, based on data from the LIFE study. This fact permits a conclusion that data were supportive of the use of 100/12.5mg in this indication and therefore no new studies are required.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The two actives used in this product have been in clinical use (separately) for a number of years. Indeed, the diuretic, hydrochlorothiazide has been in use for over 25 years in various forms and combinations all over the EU and world wide. Losartan has been used as a first line antihypertensive agent for nearly 10 years worldwide including EU member states.

The pharmacokinetics of the actives are well established and no new data are presented in the dossier. This is considered acceptable.

Bioequivalence

The applicant provided results from a bioequivalence study where the proposed combination product was compared against co-administration of corresponding monotherapies. This bioequivalence study was supplanted by the clinical efficacy study P264 subsequently submitted by the MAH.

Pharmacodynamics

The combination is a line extension of two existing approved combinations that differ only in the individual strengths. The pharmacodynamic interaction is expected in the form of additional reduction in blood pressure and this has been well established for the approved combinations.

EFFICACY

As this is a line extension of existing combinations that have been previously approved, general effectiveness and logic of such a combination could be considered established. As two other strengths of the same actives are already approved (50/12.5mg & 100/25mg) and the SmPCs are identical, the applicant seeks to retain the same indications and posology. Therefore, efficacy of this particular combination strength (100/12.5mg) will be addressed in relation to the claimed indications and posology.

Treatment of hypertension in patients not adequately controlled by monotherapy

This is the primary indication for this combination and the applicant's clinical overview discusses the rationale for the combination in terms of those not responding to losartan monotherapy of 100mg and the need for an intermediate strength of the combination (between 50/12.5 and 100/25 that are already approved).

The CHMP guidance notes (CHMP/EWP/238/95.Rev 2 on hypertension) state that for a fixed dose combination to obtain an indication in non-responders to products X or Y monotherapy, *“two add on studies one in non-responders to ‘X’ and one in non-responders to ‘Y’ should be carried out”*. An alternative scenario that one non-responder study combined with a factorial design study might be considered when adequately justified. It is expected that the addition of the second agent should produce a statistically significant improvement that is clinically meaningful / relevant.

In an ideal application therefore, an analysis of the addition of losartan 100mg to 12.5mg Hctz, and the addition of 12.5mg Hctz to 100mg losartan, should be presented. These scenarios are discussed below.

Addition of losartan 100mg to 12.5mg hydrochlorothiazide monotherapy:

It is anticipated that during approval of the 100/25mg combination that is already marketed, evidence that non-responders to 25mg Hctz benefited from addition of 100mg losartan was provided and therefore this could be considered established/proven with a positive risk: benefit ratio. From the above, it would be safe to conclude that those not responding to 12.5mg Hctz would derive clinically meaningful benefit with the addition of 100mg losartan.

Assessor's Comment: In view of the above, the 12.5mg Hctz non-responder study is not considered mandatory.

Addition of hydrochlorothiazide 12.5mg to 100mg losartan monotherapy:

The applicant has provided several studies in which one could be considered pivotal and a meta-analysis, and reference to the LIFE study is made. A statistical response-surface model is utilised that estimates the anticipated BP reduction with the currently proposed strength.

Estimated benefit of losartan/ hydrochlorothiazide 100/12.5 mg (Meta-analysis):

The estimated benefit was derived using a meta-analysis of 3 studies that randomised subjects to various monotherapies or combination of losartan and Hctz for periods of up to 12 weeks. Using the data from all 3 studies, the estimated benefit in blood reduction (systolic and diastolic) relative to placebo for each combination was derived using a quadratic function model. Effects of combinations not included in the studies were also estimated. The overall effect was a reduction of 9.6 mmHg diastolic and 17.0 mmHg for systolic blood pressures.

Assessor's Comment: Following review of the studies and meta-analysis, it was considered that for the non-responder indication, a clinical efficacy study is required in those not adequately controlled on losartan monotherapy.

LIFE study:

The applicant makes references to the LIFE (Losartan Intervention for Endpoint reduction in Hypertension) study in supporting efficacy of the 100/12.5mg combination. This was a triple blind, stepped care approach, active controlled (atenolol) study in 9193 subjects. The exact titration of doses is as indicated in the SmPC; commence with 50mg losartan or atenolol, addition of 12.5 mg Hctz after 2 months, and if needed losartan or atenolol doses were increased to 100mg. Subsequently, other agents (or increase of Hctz to 25mg) were permitted to achieve target BP. The mean follow up was 48 months. The overall benefit after titration to losartan 100 + Hctz 12.5 was -12 ± 23 mmHg systolic from baseline, and -5.4 ± 14 mmHg for diastolic BP. The change from 50/12.5 dose was -6.3 ± 14 mmHg and -3.4 ± 7.8 mmHg for systolic and diastolic respectively.

Assessor's Comment: The LIFE study addresses an important issue of end point reduction and was considered as positive to support the indication of prevention of stroke in hypertensive patients with left ventricular hypertrophy. The LIFE study does not address the issue of non-responders to 100mg losartan monotherapy. These points support the view that a new clinical study in non-responders is needed to support the indication 'treatment of hypertension in patients not adequately controlled by monotherapy'.

Clinical efficacy study P264:

This comparative clinical efficacy study, a randomised, double blind, parallel filter study, evaluated the antihypertensive efficacy of losartan 100mg-hydrochlorothiazide 12.5mg combination therapy compared to losartan 100mg monotherapy in 292 patients with essential hypertension. A parallel group, double dummy design was adopted with a filter approach in the initial 4 weeks for non-responders to losartan monotherapy.

Statistical Assessor's discussion of study:

The applicant has conducted a study with the requested design. The results from this trial allow assessment of the benefit of adding Hctz 12.5mg to patients not adequately controlled on losartan 100mg monotherapy.

Patients with sitting diastolic blood pressure (SiDBP) in the range 90-120 mmHg after 4 weeks of treatment with losartan 100mg monotherapy were randomised to either continue on losartan 100mg or switch to the combination of losartan 100mg + Hctz 12.5mg for the next 6 weeks.

This was a randomised, double-blind, double-dummy trial aiming to show the benefit of the combination tablet in patients not responding to losartan monotherapy. There were 292 patients randomised into the trial, 147 to the combination and 145 to remain on losartan monotherapy.

The primary analysis population of efficacy was the modified intention-to-treat (MITT) population, which included all randomised patients who received at least one dose of randomised treatment and provided at least one valid blood pressure measurement in the double-blind treatment phase. One patient was excluded from each treatment group for not providing efficacy data. The vast majority of patients provided data till the end of the 6-week randomised treatment period. For patients with missing data at 6-weeks last observation carried forward was used to include the patient in the analysis. As there were not many missing data the imputation method is not of great importance. Analyses including only patients who completed the trial gave similar results.

| | <i>Los 100/HCTZ 12.5</i> | <i>Los 100</i> |
|--------------------------------|--------------------------|------------------|
| <i>Randomised</i> | <i>147</i> | <i>145</i> |
| <i>MITT population</i> | <i>146 (99%)</i> | <i>144 (99%)</i> |
| <i>Provided data at week 6</i> | <i>139 (95%)</i> | <i>135 (93%)</i> |

The change from baseline to week 6 in SiDBP and SiSBP was analysed using ANCOVA with terms for treatment and baseline value. The primary analysis was SiDBP with SiSBP being the main secondary analysis.

Mean (sd) trough sitting blood pressure – MITT population

| | <i>Los 100/Hctz 12.5</i> | <i>Los 100</i> | <i>Difference (95% CI)</i> | <i>p-value</i> |
|-----------------|--------------------------|---------------------|----------------------------|-------------------|
| <i>SiDBP</i> | | | | |
| <i>Baseline</i> | <i>97.5 (5.9)</i> | <i>97.0 (5.3)</i> | | |
| <i>Week 6</i> | <i>89.3 (9.1)</i> | <i>91.8 (8.8)</i> | | |
| <i>Change</i> | <i>-8.3 (7.3)</i> | <i>-5.2 (6.4)</i> | <i>-3.0 (-4.6, -1.4)</i> | <i>p<0.001</i> |
| <i>SiSBP</i> | | | | |
| <i>Baseline</i> | <i>147.3 (15.1)</i> | <i>144.3 (12.1)</i> | | |
| <i>Week 6</i> | <i>137.9 (15.9)</i> | <i>139.4 (14.8)</i> | | |
| <i>Change</i> | <i>-9.4 (12.4)</i> | <i>-4.9 (11.8)</i> | <i>-3.8 (-6.5, -1.1)</i> | <i>p=0.006</i> |

p-values, differences and confidence intervals from ANCOVA with terms for treatment and baseline

Significant differences were also seen at week 3 - differences of -3.1 and -5.7 mmHg in SiDBP and SiSBP respectively ($p < 0.001$ for both). Consideration of responder rates can sometimes assist in assessing the clinical relevance of a difference in change from baseline. Analyses of responder rates and patients achieving target levels were provided. These were conducted using logistic regression with terms for treatment and baseline SiDBP and/or SiSBP.

Responder rates at week 6

| | Los 100/HCTZ 12.5 | Los 100 | Odds ratio (95% CI) | p-value |
|-------|-------------------|--------------|---------------------|-------------|
| SiDBP | 92/146 (63%) | 64/144 (44%) | 2.6 (1.5, 4.3) | $p < 0.001$ |
| SiSBP | 63/146 (43%) | 37/144 (26%) | 2.0 (1.2, 3.4) | $p = 0.007$ |

SiDBP responder = mean trough SiDBP < 90 mmHg or a decrease of ≥ 10 mmHg from baseline

SiSBP responder = mean trough SiSBP < 140 mmHg (provided baseline value ≥ 140 mmHg) or a decrease of ≥ 20 mmHg from baseline

Patients achieving blood pressure targets

| | Los 100/HCTZ 12.5 | Los 100 | Odds ratio (95% CI) | p-value |
|-------------------|-------------------|--------------|---------------------|-------------|
| SiDBP < 90 mmHg | 81/146 (55%) | 61/144 (42%) | 2.3 (1.3, 4.0) | $p = 0.004$ |
| SiSBP < 140 mmHg | 53/100 (53%)* | 30/88 (34%)* | 2.8 (1.5, 5.4) | $p = 0.002$ |
| Both of the above | 39/100 (39%)* | 19/88 (22%)* | 2.7 (1.3, 5.6) | $p = 0.005$ |

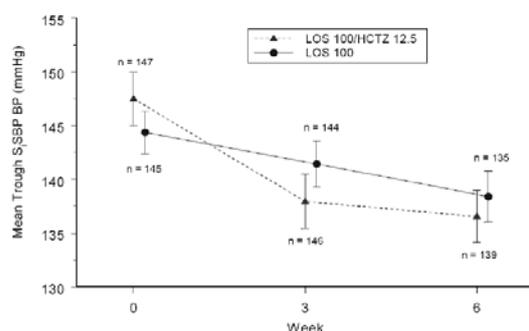
* includes only patients with SiSDP ≥ 140 mmHg at baseline

All the analyses showed a clear reduction in blood pressure from baseline for the combination compared to monotherapy, with a higher proportion of patients achieving target levels.

Clinical Assessor's discussion of study:

The aim of the study P264 was to demonstrate additional benefit of Hctz (12.5mg) when added to losartan monotherapy (100mg). The percentage of responders might have been a little higher than noted currently if the duration of the study was 8-12 weeks. However, as the odds ratios for those achieving target BP (DBP or SBP) are clearly in favour of the combination, the shorter duration has not influenced the impact of the results seen. It is well recognised from other doses that as a general principle, the combination therapy (Los+Hctz) performs better than monotherapy.

Mean Trough Systolic Blood Pressure with 95% Confidence Interval at Pre-randomization baseline, Week 3 and Week 6 by Treatment Group (Data-as-Observed Approach)



To summarise, the efficacy of the combination therapy in those with inadequate response to losartan monotherapy is shown. The efficacy of the combination is sustained for at least up to 6 weeks and a clear longitudinal trend is established. The formulation used is the one intended for marketing and is similar to the existing formulations in the UK. The clinical efficacy study obviates the need for a bioequivalence study.

Reduction of the risk of stroke in hypertensive patients with left ventricular hypertrophy

This is the second indication sought by the applicant in line with already approved SmPC for other strengths (50/12.5 and 100/25mg) of the combination (Cozaar Comp). The already approved SmPCs contain the following text;

“Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy; The usual starting dose is 50mg of Losartan once daily. If goal BP is not reached, therapy should be titrated using a combination of Losartan and a low dose hydrochlorothiazide (12.5mg) and, if needed the dose should then be increased to Losartan 100mg/hydrochlorothiazide 12.5mg once daily. If necessary, the dose should be increased to Losartan 100mg/hydrochlorothiazide 25mg daily.”

The text is based on the dosing schedule used in the LIFE study that showed benefit in terms of end point reduction to be greater with losartan+Hctz than with atenolol+Hctz, using a similar scheme of titration. The 48 month follow up period was clearly in favour of using the losartan+Hctz combination. Subgroup analysis based on dose has not been provided, but it should be noted that the text for indication and posology has been approved in the SmPCs of existing strengths. Approximately 1500 participants received this combination some time during the study.

Assessor’s Comment: The fact that the approved SPCs already contain the text, suggests a place for this particular combination (100/12.5mg) in this indication (reduction of stroke). There is no reason to request new efficacy data for this indication.

SAFETY

Both the actives (losartan and Hctz) of this product have been in widespread clinical use for some years. Hydrochlorothiazide has been used as a single agent for nearly 25 years in various doses since its approval and more recently, its use in combination with other antihypertensive agents such as ACE inhibitors or ARBs (Angiotensin Receptor Blockers) has increased. The recognised scientific society guidelines such as JNC VII and ESC/EHS guidelines recommend use of thiazide diuretics in the treatment of hypertension especially when it is poorly controlled with single agents. Losartan is also well established in the treatment of hypertension as first line treatment.

This application relates to a combination of 100/12.5 mg of losartan/Hctz, where the Hctz dose is small, while for losartan, it is the maximal approved dose. The combination of losartan and Hctz has been authorised in a number of EU member states at doses of 50/12.5 mg and 100/25 mg. Whilst the higher dose combination is limited for use in those responding poorly to monotherapy with lower doses or low dose combinations, the fact that the 100/25 mg combination has been approved implies that the higher doses were considered to have a positive risk: benefit ratio.

Patient exposure

According to the applicant and the expert, a large number of patients have been exposed to the actives either alone or in combination during many clinical trials. Overall in the LIFE study, of the 4605 patients randomised to the losartan based therapy group, 2579 (56%) received the combination of Los 100/Hctz 12.5 mg at some time during the study. At the end of follow up, it is projected that ~1500 patients

were exposed to the combination of interest (100/12.5 mg) for at least 1 year. It is unclear how many subjects were actually exposed to 100/25 mg or other combinations.

In the worldwide marketing authorisation (WMA) applications (integrated summary), 409 were exposed to the 100/12.5 mg combination while 783 were exposed to 100mg losartan monotherapy.

Deaths /Serious adverse events

No deaths have been reported in the clinical trials so far. From the worldwide MA applications and post marketing surveys (1995 to 2004) 9 serious adverse event reports were identified where subjects received the Los 100/Hctz 12.5 mg dose (achieved using marketed tablets of either 50/12.5 + 50mg losartan, or 50+50 of losartan + 12.5mg of Hctz). No unusual pattern of events was noted on review of these reports by the applicant.

Common adverse events

In the LIFE study, there were 23% withdrawals from the losartan based therapy group (n=1043). The losartan group experienced less ADRs than the atenolol group (37.2 vs 45.2%; a composite of definite, probable or possible active related events). The most common adverse events reported in the losartan group were; dizziness 5.3%, asthenia/fatigue 5.0%, and vertigo 3.1%. These were apparently less than that noted in the atenolol group.

From the WMA, the overview reports that 134 (32.8%; for losartan+Hctz) and 314 (40.1% for losartan alone) experienced at least one adverse event respectively. In those taking the combination the following ADRs were reported with higher frequency than for those taking 100mg losartan monotherapy; muscle cramps (1.5% vs 0.3%) and dizziness (6.1% vs 2.2%).

Discontinuation due to adverse events

The LIFE study report showed approximately 23% withdrawals, compared to 26% in the atenolol based group.

Laboratory findings

Rare minor laboratory abnormalities have been noted (increased liver enzymes-transient; 1 of 77 subjects in biostudy).

Safety in special populations

Special populations have not been specifically addressed and there are no data in children.

Assessor's overall conclusions on clinical safety: From the data provided, no specific concerns arise regarding the use of this particular dose combination more so than the existing approved combinations. The combination is likely to have marginally more adverse events than monotherapy in terms of cramps or dizziness, which is not unexpected based on the pharmacodynamic interaction of the two actives included in the combination. The studies have not highlighted any new specific major issues. The SmPC includes the appropriate warnings regarding ADRs and interactions in line with the already approved SmPC for other dose combinations.

EXPERT REPORT

The expert report (clinical overview, clinical efficacy and safety summaries) is provided, and has been prepared by an appropriately qualified expert.

PRODUCT INFORMATION:**Summary of Product Characteristics**

The approved SPC is satisfactory.

Patient Information Leaflet

The approved PIL is in line with the approved SPC and is satisfactory.

Labelling

Colour mock-ups of the label and carton have been provided. The labelling is medically satisfactory.

CONCLUSION

Based on the fact that a losartan 100mg / hydrochlorothiazide 25mg combination is already approved and marketed, it was accepted that those not responding to 12.5mg hydrochlorothiazide monotherapy would derive clinically meaningful benefit in the treatment of their hypertension with the addition of 100mg losartan.

The clinical efficacy study P264 has demonstrated the efficacy of the combination therapy (losartan 100mg + hydrochlorothiazide 12.5mg) in the treatment of hypertension in those with inadequate response to losartan 100mg monotherapy.

Following review of the approved SmPCs for other combinations of losartan + hydrochlorothiazide therapy (50/12.5 and 100/25 mg), which were based on the dosing schedule used in the LIFE study, it was accepted that this particular combination (100/12.5 mg) can be used to reduce the risk of stroke in hypertensive patients with left ventricular hypertrophy.

Sufficient clinical information and bibliographic analysis has been submitted to support this application. A Marketing Authorisation may, therefore, be granted on medical grounds.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Cozaar-Comp 100mg/12.5mg film-coated tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

Products containing losartan and hydrochlorothiazide as monotherapies and combination therapy have been available in the UK for many years. Their use is well established with recognised efficacy and acceptable safety.

The applicant has submitted adequate clinical information and analysis, as well as bibliographic review for this application. The information submitted confirms the therapeutic effectiveness of a losartan potassium 100mg / hydrochlorothiazide 12.5mg combination therapy, and no new safety issues have arisen.

PRODUCT LITERATURE

The approved SPC, PIL and labelling are satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

RISK: BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with losartan and hydrochlorothiazide as monotherapies and combination therapy, and the efficacy study submitted, are considered to have demonstrated the therapeutic value of the medicinal product as a combination therapy. The risk: benefit is, therefore, considered to be positive.

**COZAAR-COMP 100MG/12.5MG FILM-COATED TABLETS
(LOSARTAN POTASSIUM / HYDROCHLOROTHIAZIDE)****PL 00025/0473****STEPS TAKEN FOR ASSESMENT**

- 1 The MHRA received the marketing authorisation application on 11th April 2005
- 2 Following standard checks and communication with the applicant the MHRA considered the application valid on 22nd August 2005
- 3 Following assessment of the application the MHRA requested further information relating to the quality dossier on 29th November 2005
- 4 The applicant responded to the MHRA's request, providing further information for the quality sections on 21st December 2005
- 5 Advice was sought from the Commission on Human Medicines with regards to issues raised during assessment of the application. The Commission met in March 2006 and issued their advice
- 6 The applicant responded to the CHM advice, providing further information for the clinical sections and quality sections on 1st December 2006
- 7 The Commission on Human Medicines met again in June 2007 to review the application and issued further advice to the applicant
- 8 The applicant responded to the CHM advice, providing further information for the quality sections on 6th August 2007
- 9 The application was determined on 17th October 2007

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Cozaar-Comp 100mg/12.5mg film-coated tablets is as follows:

1 NAME OF THE MEDICINAL PRODUCT

COZAAR®-Comp 100 mg/12.5 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 91.5 mg of losartan, present as 100 mg of losartan potassium, and 12.5 mg hydrochlorothiazide.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Oval, white, film-coated tablets with '745' on one side and plain on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the treatment of hypertension in patients whose blood pressure is not adequately controlled on hydrochlorothiazide or losartan monotherapy.

In hypertensive patients with left ventricular hypertrophy a reduced risk of stroke was demonstrated with losartan administered usually in combination with HCTZ. The data do not support the use of losartan for this indication in black patients (see section 4.4 Special warnings and Precautions for Use-*Race* and section 5.1 Pharmacodynamic Properties, LIFE study, *Race*).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Where possible titration with the individual components (ie losartan and hydrochlorothiazide) is recommended.

When clinically appropriate direct change from monotherapy to the fixed combinations may be considered in patients whose blood pressure is not adequately controlled.

The usual starting and maintenance dose is losartan 50 mg/hydrochlorothiazide 12.5 mg once daily for most patients. For patients who do not respond adequately, the dosage may be increased to losartan 100mg/ hydrochlorothiazide 25 mg once daily. The maximum dose is losartan 100 mg/hydrochlorothiazide 25 mg once daily. In general, the antihypertensive effect is attained within three weeks after initiation of therapy. 'Cozaar'-Comp 100 mg /12.5 mg (losartan 100 mg /hydrochlorothiazide 12.5 mg) is available for those patients titrated to 100 mg of 'Cozaar' who require additional blood pressure control.

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy

The usual starting dose is 50 mg of losartan once daily. If goal blood pressure is not reached with losartan 50 mg, therapy should be titrated using a combination of losartan and a low dose of hydrochlorothiazide (12.5 mg) and, if needed the dose should then be increased to losartan 100 mg/hydrochlorothiazide 12.5 mg once daily. If necessary, the dose should be increased to losartan 100 mg/ hydrochlorothiazide 25 mg daily.

Use in the elderly: Patients over 75 years: Presently there is limited clinical experience in this group. Any therapy involving the angiotensin II antagonist, losartan, should be initiated with 25 mg losartan in these patients.

Use in renal impairment: No initial dosage adjustment is necessary in patients with mild renal impairment (i.e. creatinine clearance 20-50 ml/min). 'Cozaar'-Comp is not recommended for patients with moderate to severe renal impairment (i.e. creatinine clearance <20 ml/min) or patients on dialysis.

Use in patients with intravascular volume depletion: 'Cozaar'-Comp should not be initiated in patients who are intravascularly volume depleted (e.g. those treated with high-dose diuretics).

Use in hepatic impairment: 'Cozaar'-Comp is not recommended for patients with hepatic impairment.

Concomitant therapy: 'Cozaar'-Comp may be administered with other antihypertensive agents.

'Cozaar'-Comp may be administered with or without food.

Use in children: Safety and efficacy in children have not been established.

4.3 CONTRAINDICATIONS

'Cozaar'-Comp is contra-indicated in pregnancy (see 4.6 'Pregnancy and lactation'), in patients who are hypersensitive to any component of this product, in patients with anuria, and in patients who are hypersensitive to other sulphonamide-derived drugs.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Losartan and hydrochlorothiazide combination tablet

Hypersensitivity: Angioedema. See 4.8 'Undesirable effects'.

Hepatic and renal impairment: 'Cozaar'-Comp is not recommended for patients with hepatic impairment or moderate to severe renal impairment (creatinine clearance <20 ml/min). (See 4.2 'Posology and method of administration'.)

Losartan

Renal function impairment: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function, including renal failure, have been reported (in particular, in patients whose renal function is dependent on the renin-angiotensin-aldosterone system, such as those with severe cardiac insufficiency or pre-existing renal dysfunction).

As with other drugs that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy.

Caution is required in patients with significant renal disease and renal transplant recipients as there have been reports of anaemia developing in such patients treated with 'Cozaar'.

Hydrochlorothiazide

Hypotension and electrolyte/fluid imbalance: As with all antihypertensive therapy, symptomatic hypotension may occur in some patients. This was rarely seen in uncomplicated hypertensive patients, but was more likely in the presence of fluid depletion or electrolyte imbalance. Periodic determination of serum electrolytes should be performed at appropriate intervals, as in any patients receiving diuretics.

Metabolic and endocrine effects

Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required (see 4.5 'Interaction with other medicinal products and other forms of interaction').

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Thiazide therapy may precipitate hyperuricaemia and/or gout in certain patients. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricaemia.

Other

In patients receiving thiazides, hypersensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

The use of 'Cozaar' in patients with haemodynamically significant obstructive valvular disease and cardiomyopathy has not been adequately studied.

Race (Black patients):

There is no evidence that losartan reduces the risk of stroke in black hypertensive patients with LVH (see section 5.1 Pharmacodynamic Properties, LIFE Study Race).

Cozaar-comp tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Losartan

In clinical pharmacokinetic trials no drug interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital (phenobarbitone), (see **Hydrochlorothiazide**; *Alcohol, barbiturates, or narcotics* below) ketoconazole and erythromycin. Rifampicin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

As with other drugs that block angiotensin II or its effects, concomitant use of other drugs which retain potassium or may increase potassium levels (e.g. potassium-sparing diuretics, potassium supplements, or salt substitutes containing potassium) may lead to increases in serum potassium. Co-medication is not advisable.

Combination with NSAIDs: When Angiotensin II antagonists are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. selective COX-2 inhibitors, acetylsalicylic acid (> 3 g / day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.

As with ACE inhibitors, concomitant use of Angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme (ACE) inhibitors. Very rare cases have also been reported with angiotensin II receptor antagonists. Co-administration of lithium and losartan should be undertaken with caution. If this combination proves essential, serum lithium level monitoring is recommended during concomitant use.

Hydrochlorothiazide

When given concurrently, the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics—potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)—dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs—there may be an additive effect.

Colestyramine and colestipol resins—absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either colestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastro-intestinal tract by up to 85% and 43%, respectively.

Corticosteroids, ACTH—there may be intensified electrolyte depletion, particularly hypokalaemia.

Pressor amines (e.g. adrenaline)—possible decreased response to pressor amines, but not sufficient to preclude their use.

Skeletal muscle relaxants, non-depolarising (e.g. tubocurarine)—possible increased responsiveness to the muscle relaxant.

Lithium—diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Therefore, concomitant use is not recommended. Refer to the prescribing information for lithium preparations before use of such preparations.

Non-steroidal anti-inflammatory drugs—in some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of diuretics.

Drug/laboratory test interactions

Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (see 4.4 'Special warnings and precautions for use').

4.6 PREGNANCY AND LACTATION

Use during pregnancy

Although there is no experience with the use of 'Cozaar'-Comp in pregnant women, animal studies with losartan potassium have demonstrated foetal and neonatal injury and death, the mechanism of which is believed to be pharmacologically mediated through effects on the renin-angiotensin system.

In humans, foetal renal perfusion, which is dependent upon the development of the renin-angiotensin system, begins in the second trimester; thus, risk to the foetus increases if 'Cozaar'-Comp is administered during the second or third trimesters of pregnancy.

Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and foetus to unnecessary hazard, including foetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult. Diuretics do not prevent development of toxæmia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxæmia.

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing foetus. When pregnancy is detected, 'Cozaar'-Comp should be discontinued as soon as possible.

Use during lactation

It is not known whether losartan is excreted in human milk. Significant levels of losartan and the active metabolite were shown to be present in rat milk. Thiazides appear in human milk. Because of the potential for adverse effects on the breast-feeding infant, a decision should be made whether to discontinue breast-feeding or discontinue the drug, taking into account the importance of the drug to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are no data to suggest that 'Cozaar'-Comp affects the ability to drive and use machines. However, patients who experience dizziness while taking 'Cozaar'-comp should refrain from driving or operating machinery.

4.8 UNDESIRABLE EFFECTS

In clinical trials with the combination tablet of losartan and hydrochlorothiazide, no adverse experiences peculiar to this combination drug have been observed. Adverse experiences have been limited to those that were reported previously with losartan potassium and/or

hydrochlorothiazide. The overall incidence of adverse experiences reported with the combination was comparable to placebo. The percentage of discontinuations of therapy was also comparable to placebo. For the most part, adverse experiences have been mild and transient in nature and have not required discontinuation of therapy.

In controlled clinical trials for essential hypertension, dizziness was the only adverse experience reported as drug related that occurred with an incidence greater than placebo in 1% or more of patients treated with losartan potassium-hydrochlorothiazide.

In a controlled trial in hypertensive patients with left ventricular hypertrophy, losartan used usually with hydrochlorothiazide was generally well tolerated. The most common drug-related side effects were dizziness, asthenia/fatigue, and vertigo.

The following adverse reactions have been reported in post-marketing experience:

Hypersensitivity

Anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Vasculitis including Henoch-Schonlein purpura, has been reported rarely with losartan.

Gastro-intestinal: Hepatitis has been reported rarely in patients treated with losartan, diarrhoea.

Respiratory: Cough has been reported with losartan.

Skin: Urticaria

Additional side effects that have been seen with one of the individual components and may be potential side effects with 'Cozaar'-Comp are the following:

Losartan

Dose-related orthostatic effects, liver function abnormalities, myalgia, migraine, rash, anaemia, pruritus.

Hydrochlorothiazide

Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhoea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialoadenitis, vertigo, paraesthesiae, headache, xanthopsia, leucopenia, agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, purpura, photosensitivity, fever, necrotising angitis, respiratory distress (including pneumonitis and pulmonary oedema), anaphylactic reactions, toxic epidermal necrolysis, hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia and hypokalaemia), renal dysfunction, interstitial nephritis, renal failure, muscle spasm, weakness, restlessness, transient blurred vision.

Laboratory test findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of losartan potassium-hydrochlorothiazide. Hyperkalaemia (serum potassium >5.5 mmol/l) occurred in 0.7% of patients, but in these trials discontinuation of losartan potassium-hydrochlorothiazide due to hyperkalaemia was not necessary. Serum potassium should be monitored, particularly in the elderly and patients with renal impairment. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy.

4.9 OVERDOSE

No specific information is available on the treatment of overdosage with 'Cozaar'-Comp. Treatment is symptomatic and supportive. Therapy with 'Cozaar'-Comp should be discontinued and the patient observed closely. Suggested measures include induction of emesis if ingestion is recent, and correction of dehydration, electrolyte imbalance, hepatic coma, and hypotension by established procedures.

Losartan

Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor the active metabolite can be removed by haemodialysis.

Hydrochlorothiazide

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalaemia may accentuate cardiac arrhythmias.

The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ATC CODE: C09DA01

Losartan and hydrochlorothiazide combination tablet

The components of 'Cozaar'-Comp have been shown to have an additive effect on blood-pressure reduction, reducing blood pressure to a greater degree than either component alone. This effect is thought to be a result of the complimentary actions of both components. Further, as a result of its diuretic effect, hydrochlorothiazide increases plasma-renin activity, increases aldosterone secretion, decreases serum potassium, and increases the levels of angiotensin II. Administration of losartan blocks all the physiologically relevant actions of angiotensin II and through inhibition of aldosterone could tend to attenuate the potassium loss associated with the diuretic.

Losartan has been shown to have a mild and transient uricosuric effect. Hydrochlorothiazide has been shown to cause modest increases in uric acid; the combination of losartan and hydrochlorothiazide tends to attenuate the diuretic-induced hyperuricaemia.

The antihypertensive effect of 'Cozaar'-Comp is sustained for a 24-hour period. In clinical studies of at least one year's duration, the antihypertensive effect was maintained with continued therapy. Despite the significant decrease in blood pressure, administration of 'Cozaar'-Comp had no clinically significant effect on heart rate. 'Cozaar'-Comp is effective in reducing blood pressure in males and females, and in younger (<65 years) and older (≥65 years) patients and is effective in all degrees of hypertension.

Losartan

Losartan is an oral, specific angiotensin-II receptor (type AT₁) antagonist. Angiotensin II binds to the AT₁ receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth-muscle proliferation.

Losartan binds selectively to the AT₁ receptor and does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore, losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, effects not directly related to blocking the AT₁ receptor, such as the potentiation of bradykinin-mediated effects or the generation of oedema (losartan 1.7%, placebo 1.9%), are not associated with losartan.

In an overall analysis of 16 double-blind clinical trials in 4,131 patients, the incidence of spontaneously reported cough in patients treated with losartan was similar (3.1%) to that of patients treated with placebo (2.6%) or hydrochlorothiazide (4.1%), whereas the incidence with ACE inhibitors was 8.8%.

In non-diabetic hypertensive patients with proteinuria, the administration of losartan potassium significantly reduces proteinuria, fractional excretion of albumin and IgG. Losartan maintains glomerular filtration rate and reduces filtration fraction. Generally, losartan causes a decrease in serum uric acid (usually <24 micro mol/l) which was persistent in chronic therapy.

In clinical studies of once-daily administration of losartan to patients with mild to moderate essential hypertension, statistically significant reductions in systolic and diastolic blood pressure were produced with relatively smooth blood pressure reduction over 24 hours. Discontinuation of losartan in hypertensive patients did not result in an abrupt rebound of blood pressure.

Although losartan is antihypertensive in all races, as with other drugs that affect the renin-angiotensin system, black hypertensive patients have a smaller average response to losartan monotherapy than non-black patients.

LIFE Study

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomised to once daily 'Cozaar' 50 mg or atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of 'Cozaar' or atenolol was then increased to 100 mg once daily. Other antihypertensives (e.g., increase in dose of hydrochlorothiazide therapy to 25 mg or addition of other diuretic therapy, calcium channel blockers, alpha blockers, or centrally acting agents, but not ACE inhibitors, angiotensin II antagonists or beta-blockers) were added if necessary to reach the goal blood pressure. In efforts to control blood pressure, the patients in both arms of the LIFE study were coadministered hydrochlorothiazide the majority of time they were on study drug (73.9% and 72.4% of days in the losartan and atenolol arms respectively). The mean length of follow up was 4.8 years.

The primary endpoint was the composite of cardiovascular morbidity and mortality as measured by a reduction in the combined incidence of cardiovascular death, stroke and myocardial infarction. Blood pressure was significantly lowered to similar levels in the two groups. Treatment with 'Cozaar' resulted in a 13.0% risk reduction ($p=0.021$, 95% confidence interval 0.77-0.98) compared with atenolol for patients reaching the primary composite endpoint. This was mainly attributable to a reduction of the incidence of stroke. Treatment with 'Cozaar' reduced the risk of stroke by 25% relative to atenolol ($p=0.001$ 95% confidence interval 0.63-0.89). The rates of cardiovascular death and myocardial infarction were not significantly different between the treatment groups.

Race: There were 533 black patients in the study. In this group, treatment with 'Cozaar' resulted in a 67% increase in risk compared with atenolol for the primary composite endpoint ($p=0.033$, 95% confidence interval 1.04-2.66) and a 118% increase relative to atenolol in the risk of stroke ($p=0.030$, 95% confidence interval 1.08-4.40).

Hydrochlorothiazide

The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not usually affect normal blood pressure.

Hydrochlorothiazide is a diuretic and antihypertensive. It affects the distal renal tubular mechanism of electrolyte reabsorption. Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate.

After oral use, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Losartan:

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. There was no clinically significant effect on the plasma-concentration profile of losartan when the drug was administered with a standardised meal.

Distribution

Losartan:

Both losartan and its active metabolite are $\geq 99\%$ bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Hydrochlorothiazide:

Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Biotransformation

Losartan:

About 14% of an intravenously or orally administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of ^{14}C -labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about 1% of individuals studied.

In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.

Elimination

Losartan:

Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6-9 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of ^{14}C -labelled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the faeces.

Hydrochlorothiazide:

Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61% of the oral dose is eliminated unchanged within 24 hours.

Characteristics in Patients

Losartan and hydrochlorothiazide combination tablet:

The plasma concentrations of losartan and its active metabolite and the absorption of hydrochlorothiazide in elderly hypertensives are not significantly different from those in young hypertensives.

Losartan:

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1.7-fold greater than those seen in young male volunteers.

Neither losartan nor the active metabolite can be removed by haemodialysis.

5.3 PRECLINICAL SAFETY DATA

The toxic potential of losartan potassium and hydrochlorothiazide was evaluated in repeated-dose oral toxicity studies for up to six months in rats and dogs. There were no findings that would preclude administration to man at the therapeutic dosage level.

There was no evidence of direct genotoxicity in studies conducted with the losartan and hydrochlorothiazide combination.

Losartan potassium and hydrochlorothiazide administration had no effect on the reproductive performance or fertility in male rats at dosage levels of up to 135 mg/kg/day losartan in combination with 33.75 mg/kg/day hydrochlorothiazide. These dosage levels provided respective plasma concentrations (AUC) for losartan, the active metabolite and hydrochlorothiazide that were approximately 260-, 120-, and 50-fold greater than those achieved in man with 50 mg losartan potassium in combination with 12.5 mg hydrochlorothiazide. In female rats, however, the coadministration of losartan potassium and hydrochlorothiazide (10/2.5 mg/kg/day) induced a slight but statistically significant decrease in fecundity and fertility indices. Compared to plasma concentrations in man (see above) these dosage levels provided respective increases in plasma concentration (AUC) for losartan, the active metabolite, and hydrochlorothiazide of approximately 15-, 4-, and 5-fold.

There was no evidence of teratogenicity in rats or rabbits treated with losartan potassium and hydrochlorothiazide combination. Foetal toxicity in rats, as evidenced by a slight increase in supernumerary ribs in the F₁ generation, was observed when females were treated prior to and throughout gestation. As observed in studies with losartan alone, adverse foetal and neonatal effects, including decreased bodyweight, mortality and/or renal toxicity, also occurred when pregnant rats were treated with losartan potassium and hydrochlorothiazide combination during late gestation and/or lactation.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Hydroxypropylcellulose E463

Hypromellose E464

Lactose monohydrate

Magnesium stearate E572

Microcrystalline cellulose E460

Pregelatinised maize starch

Titanium dioxide E171

It may also contain carnauba wax.

'Cozaar'-Comp 100 mg /12.5 mg also contains 8.48 mg (0.216 mmol) of potassium.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE
36 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 30°C
Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER
White, opaque PVC/PE/PVDC blisters with aluminium foil lidding.
Available in blister calendar packs of 28 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
None.

7 MARKETING AUTHORISATION HOLDER
Merck Sharp & Dohme Limited
Hertford Road
Hoddesdon
Hertfordshire
EN11 9BU
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 00025/0473

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
17/10/2007

10 DATE OF REVISION OF THE TEXT
17/10/2007

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

COZAAR® Comp 100 mg / 12.5 mg Film-Coated Tablets (losartan potassium 100 mg and hydrochlorothiazide 12.5 mg)

Please read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may want to read it again.
- If you have further questions ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side-effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Cozaar-Comp is and what it is used for
2. Before you take Cozaar-Comp
3. How to take Cozaar-Comp
4. Possible side effects
5. How to store Cozaar-Comp
6. Further Information

1. What COZAAR-COMP is and what it is used for

Cozaar-Comp contains two active ingredients. These are losartan potassium and hydrochlorothiazide. Losartan belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin II is a chemical occurring in the body, which tightens your blood vessels making it harder for the blood to pass through them and causing your blood pressure to increase. Cozaar-Comp blocks this effect of angiotensin II, causing the blood vessels to relax. Hydrochlorothiazide works by making your kidneys pass more water and salt. Together, losartan and hydrochlorothiazide lower high blood pressure.

In patients with high blood pressure who have developed thickening of the heart muscle, Cozaar-Comp may help to lower the risk of stroke. There is no data to support this effect in Black patients.

What is high blood pressure?

Blood pressure is the term given to the pressure produced by your heart pumping blood to all parts of your body. Your blood pressure is measured by two numbers, e.g. 120/80 mm Hg. The top number measures the pressure while your heart beats and the bottom number measures the pressure in between heartbeats.

Normal blood pressure is part of good health. High blood pressure is caused when the blood vessels tighten and the measurement goes above the normal range for your age. There are usually no symptoms of high blood pressure and you will only know you have it if you have had your blood pressure measured.

Although you might feel quite well, if your high blood pressure is not treated, it can damage your heart and kidneys, and in some cases lead to stroke, heart attack, heart and/or kidney failure, or blindness.

High blood pressure can be treated and controlled with medicines such as Cozaar-Comp. Your doctor may also recommend that you make some changes to your lifestyle to help your high blood pressure, such as losing weight, keeping alcohol intake moderate or avoiding it altogether, stopping smoking, and reducing the amount of salt in your diet. Your doctor may also encourage you to take more mild exercise.

2. Before you take COZAAR-COMP

Do not take Cozaar-Comp:

- if you are allergic to any of the ingredients
- if you are allergic to any sulphonamide-derived medicines (ask your doctor if you are not sure what sulphonamide-derived drugs are)
- if you are not passing urine
- if you have liver problems
- if you have kidney problems or are on dialysis

This medicine should not be given to children.

If you think any of these apply to you, do not take the tablets. Talk to your doctor first and follow the advice given.

Take special care with Cozaar-Comp:

If you have any of the following conditions and you have not discussed it with your doctor, go back to your doctor and ask for advice. Your doctor may need to adjust the dose of your medications or regularly monitor you.

- gout
- diabetes
- lupus erythematosus
- recent excessive vomiting and/or diarrhoea
- parathyroid problems. This is a condition which is associated with high calcium levels in your blood.

- 'aortic stenosis' or 'outflow obstruction'. This is a condition where one of the valves in your heart doesn't open fully and blocks the flow out of the heart.
- if you are being treated with other diuretics (water tablets).
- if you have had a kidney transplant
- if you know that you have high levels of potassium in your blood (hyperkalaemia) or you are on a low potassium diet.

Before surgery and anaesthesia (even at the dentist), tell the doctor or dentist that you are taking this medicine, as there may be a sudden fall in blood pressure associated with the anaesthesia

If you are going to have a blood test, let your doctor know that you are taking Cozaar-Comp. This medicine can affect the results of some diagnostic tests.

Taking other medicines:

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

In particular tell your doctor if you are taking any of the following as they may affect how Cozaar-Comp works

- potassium supplements, potassium sparing agents, or potassium-containing salt substitutes; taking these with Cozaar-Comp is not advised
- rifampicin, a drug used in the treatment of tuberculosis (TB)
- fluconazole, a drug used for treating fungal infections such as thrush
- non-steroidal, anti-inflammatory painkillers (such as ibuprofen, naproxen or diclofenac), COX-2 inhibitors (such as celecoxib, etoricoxib or lumiracoxib) or more than 3 g of aspirin per day
- barbiturates, sedative drugs which may be used in the treatment of sleeplessness or epilepsy
- narcotics, morphine like drugs used for severe pain
- medicines for diabetes including oral treatments to lower blood sugar as well as insulin.
- other drugs used to reduce blood pressure
- other diuretics (water tablets)
- resins such as colestyramine and colestipol, which are used to reduce high cholesterol levels
- ACTH, used to test whether your adrenal glands are working properly
- corticosteroids, anti-inflammatory medicines used to treat various conditions including rheumatism, arthritis, allergic conditions, certain skin diseases, asthma or certain blood disorders
- pressor amines such as adrenaline used for the treatment of hypotension, shock, cardiac failure, asthma or allergies
- lithium, a drug used to treat certain mental disorders: lithium containing medicines should not be taken with Cozaar-Comp without dose medical supervision
- alcohol: when some people take a medicine to lower their blood pressure, they can feel dizzy or faint, particularly if they stand up quickly. This effect can be exaggerated in some patients shortly after drinking alcohol. If this happens to you, then you should avoid drinking alcohol.

Pregnancy and breast feeding

The use of Cozaar-Comp while you are pregnant or breast feeding is not recommended. If you are pregnant or become pregnant while taking Cozaar-Comp, stop taking the tablets and talk to your doctor as soon as possible.

Driving and using machines

Dizziness has been reported in some patients taking Cozaar-Comp. Do not drive if you experience dizziness.

Do not use any tools or machines if you experience dizziness.

Important information about some of the ingredients of Cozaar-Comp

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product



REDUCE YOUR RISK OF STROKE



Untreated high blood pressure is an important risk factor for stroke. Other factors which can increase your chance of having a stroke include smoking, lack of exercise, heavy drinking, and a history of heart disease, stroke, or mini-stroke (TIA).

The Stroke Association produces FREE leaflets which could help you reduce your risk of stroke. We also have information on why it's important to keep taking your blood pressure drugs.

If you would like to receive these publications, please complete the coupon overleaf and send it to:

THE STROKE ASSOCIATION,
STROKE HOUSE, 240 CITY ROAD, LONDON, EC1V 2PR
TEL: 020 75660300. REGISTERED CHARITY NO. 2111015.

The Stroke Association aims to prevent strokes. It also provides practical support, advice and information to people who have had strokes and to their carers. The association funds research into all aspects of stroke illness.

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3. How to take COZAAR-COMP

Always take Cozaar-Comp exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

'Cozaar'-Comp should be taken by mouth.

You must keep taking 'Cozaar'-Comp every day and it is important that you take this medicine for as long as your doctor prescribes.

High blood pressure

Cozaar-Comp will usually be prescribed by your doctor when your previous treatment for high blood pressure has not provided appropriate blood pressure reduction. You may have previously been given losartan on its own or in a lower strength combination tablet with hydrochlorothiazide (Cozaar-Comp 50/12.5 mg). Your doctor will instruct you on how to switch from your previous treatment to Cozaar-Comp 100 mg /12.5 mg and you will need to take one tablet once a day.

High blood pressure and a thickening of the heart muscle

The usual starting dose is 50 mg of losartan once daily. If goal blood pressure is not reached with losartan 50 mg, your doctor may prescribe a combination of losartan and low dose hydrochlorothiazide (12.5 mg). Your doctor will increase the amounts of losartan and hydrochlorothiazide step by step until the dose that is right for you has been achieved.

If you are aged over 75 years you should check with your doctor before taking your tablets.

Cozaar-Comp should not be given to children.

You can take Cozaar-Comp with or without food. It is recommended that you take your tablet at the same time each day.

If you take more Cozaar-Comp than you should:

If you take too many tablets by mistake, contact your doctor immediately.

If you forget to take Cozaar-Comp:

Try to take Cozaar-Comp daily as prescribed. However, if you miss a dose, just carry on with the next dose as normal. Do not take an extra tablet to make up.

4. Possible side effects

Like all medicines, Cozaar-Comp can cause side-effects, although not everybody gets them.

They are generally mild and do not normally require treatment to be interrupted. Some patients may experience dizziness, cough, diarrhoea and rarely hepatitis (inflammation of the liver, symptoms of which are yellowing of the whites of the eyes and skin and flu-like symptoms).

Some patients may present with hives. Rarely, patients have reported developing an allergic reaction involving swelling of the face, lips, tongue, and/or throat which may cause difficulty in breathing or swallowing, and/or inflammation of blood vessels including inflammation of small veins, causing hard, purple blotches on the skin. If you develop any of these symptoms stop taking your tablets and contact your doctor immediately.

Additional side-effects that have been seen with either losartan or hydrochlorothiazide alone (the two active ingredients in Cozaar-Comp), and may be potential side effects with this medicine, are as follows:

Losartan: Few patients have reported a rapid lowering in blood pressure (symptoms of which may be lightheadedness or dizziness, particularly when standing up); rash, itching; muscle pain; migraines; liver problems (signs of which may be yellowing of the eyes and skin and flu-like symptoms), or an anaemia (symptoms may be tiredness or shortness of breath caused by the number of red blood cells or amount of haemoglobin in the blood being below normal) which are usually detected by blood tests.

Hydrochlorothiazide: loss of appetite; stomach upsets; nausea; vomiting; stomach cramps; constipation; jaundice seen as yellowing of the skin and/or whites of the eyes; an inflamed pancreas marked by pain in the abdomen and back; swelling of the salivary glands; vertigo (spinning sensation); pins and needles; headache; visual changes which can make objects appear yellow; anaemia marked by unusual tiredness and a loss of colour in the linings of the eyes and skin; other blood disorders which can result in fever; sore throat or prolonged bleeding after injury; increased skin sensitivity to sunlight; purplish or reddish-brown marks on the skin; fever; hives or a nettle-like rash, inflammation of blood vessels; breathing problems due to inflamed or swollen lungs; allergic reactions marked by rash, hives, or difficulties in breathing or swallowing; blistering or peeling of the skin, mouth, eyes or genitals; changes in the levels of certain chemicals in the blood and urine which are usually detected by blood and urine tests; kidney problems; muscle spasm; weakness; restlessness; blurred vision.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store COZAAR-COMP

Keep your tablets out of the reach and sight of children.
Do not store above 30°C.
Store in the original package.

Do not use Cozaar-Comp after the expiry date, which is stated on the carton.

6. Further information

What Cozaar Comp contains

The active substances are losartan potassium and hydrochlorothiazide.

The other ingredients are: hydroxypropylcellulose; hypromellose; lactose monohydrate; magnesium stearate; microcrystalline cellulose; pregelatinised maize starch; titanium dioxide; carnauba wax.

What Cozaar-Comp looks like and contents of the pack

'Cozaar'-Comp 100 mg /12.5 mg is available as white, oval, film-coated tablets marked '745' on one side, containing 91.5 mg of losartan, present as 100 mg of losartan potassium and 12.5 mg of hydrochlorothiazide.

Pack size: 28 tablets

Marketing Authorisation Holder and Manufacturer

The Marketing Authorisation Holder is Merck Sharp & Dohme Limited, Hertford Road, Huddersdon, Hertfordshire EN11 9BU, UK.

The Manufacturer is Merck Sharp & Dohme Limited, Shotton Lane, Cramlington, Northumberland NE23 3JL, UK.

This leaflet was last approved in

For further information on High Blood Pressure please contact the Blood Pressure Association on 020 8772 4994.

The Blood Pressure Association is an independent charity not associated with Merck Sharp & Dohme Limited.

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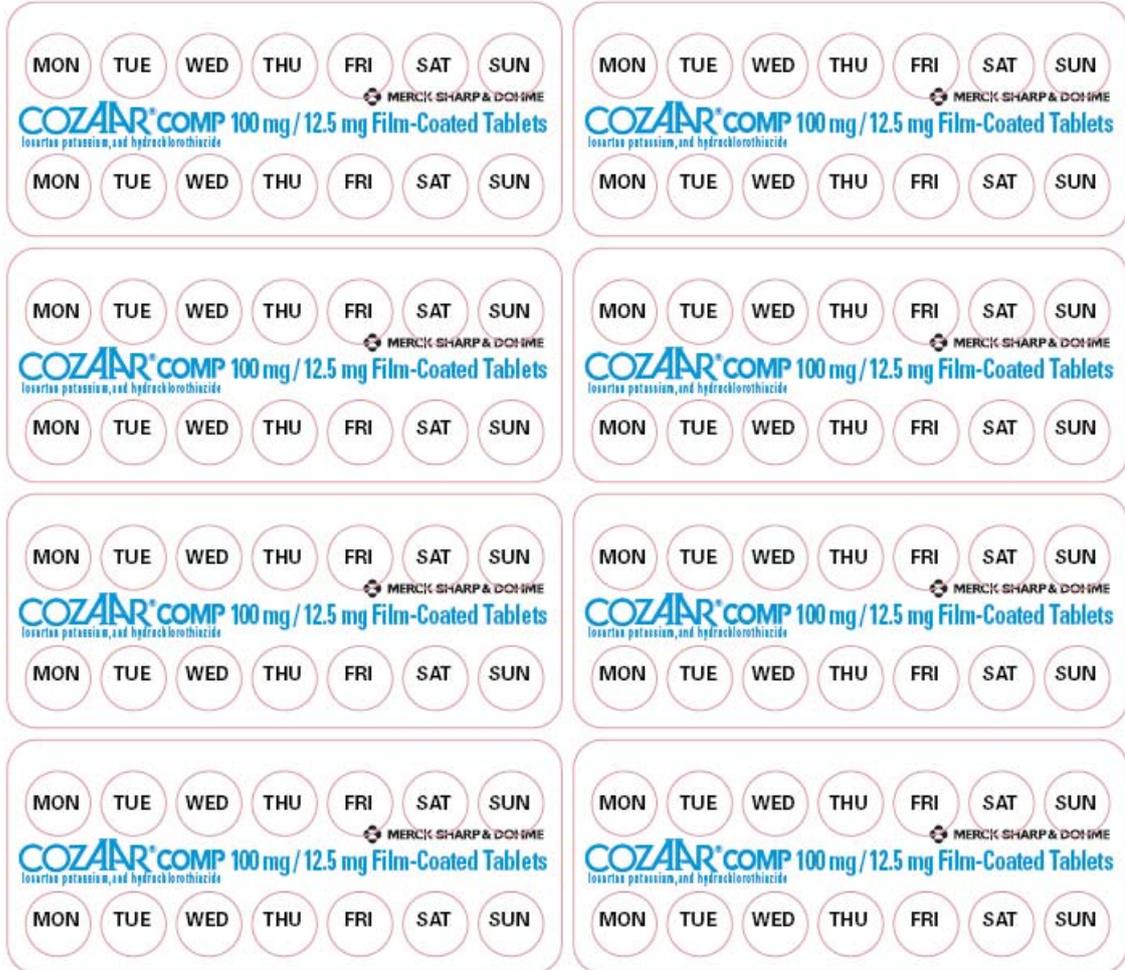
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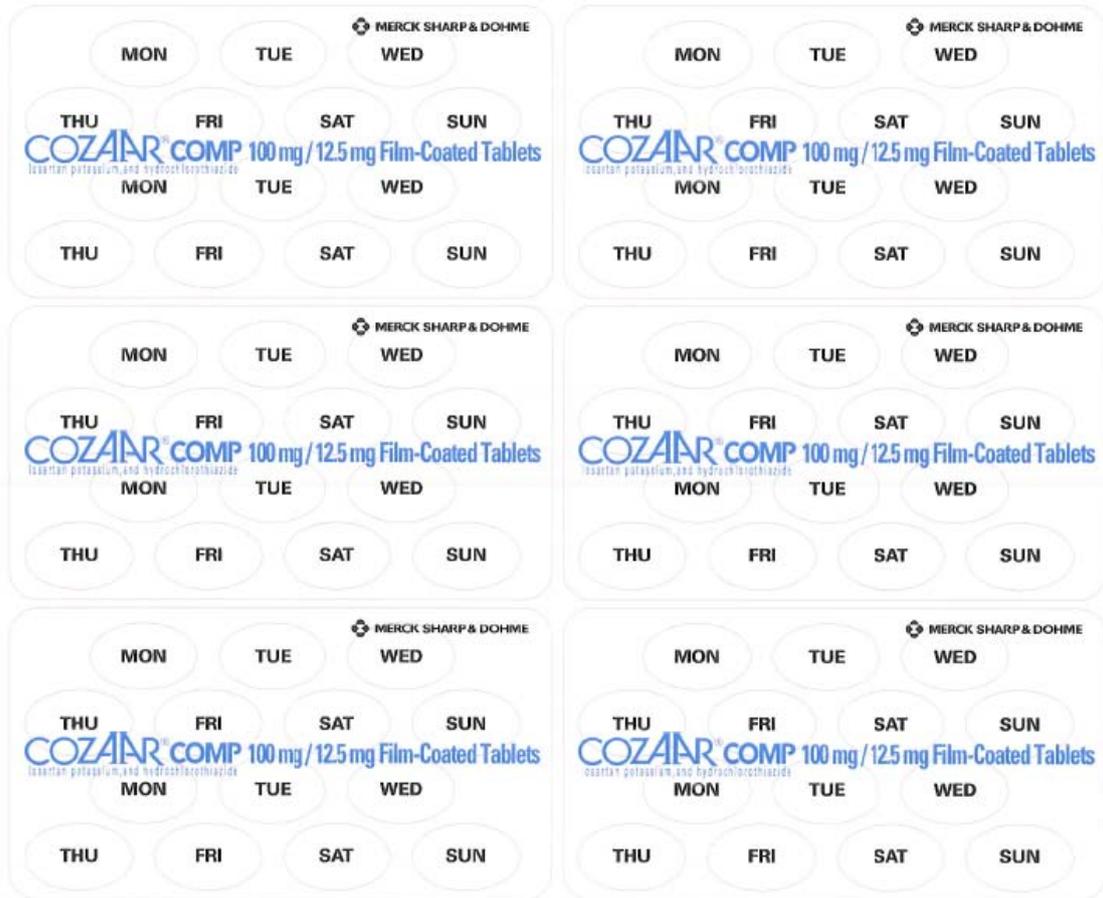
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LABELLING

Blister



Blisters – alternative design



Mock up carton artwork, with braille

