SCHEDULING STATUS S3

PROPRIETARY NAME AND DOSAGE FORMS:

CO-ZOMEVEK 80/12,5 TABLET

CO-ZOMEVEK 160/12,5 TABLET

CO-ZOMEVEK 160/25 TABLET

COMPOSITION:

Active ingredients:

Co-Zomevek 80/12,5 tablet: One tablet contains 80 mg valsartan and 12, 5 mg hydrochlorothiazide.

Co-Zomevek 160/12,5 tablet: One tablet contains 160 mg valsartan and 12, 5 mg hydrochlorothiazide.

Co-Zomevek 160/25 tablet: One tablet contains160 mg valsartan and 25 mg hydrochlorothiazide.

List of excipients:

Colloidal silicon dioxide; crospovidone; hydroxypropyl-methylcellulose; magnesium stearate; microcrystalline cellulose; polyethylene glycol; talc; titanium dioxide (E171) (Co-Zomevek 80/ 12,5 tablet, Co-Zomevek 160/12,5 tablet, Co-Zomevek 160/25 tablet); red iron oxide (E172) (Co-Zomevek 80/12,5 tablet, Co-Zomevek 160/12,5, Co-Zomevek 160/ 25); black iron oxide (E172) (Co-Zomevek 160/25 tablet) and yellow iron oxide (E172) (Co-Zomevek 80/12,5 tablet, Co-Zomevek 160/25 tablet).

The tablets are sugar free.

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.3 Vascular medicines - other hypotensives

PHARMACOLOGICAL ACTION:

Valsartan is an orally active, specific Angiotensin II (Ang II) receptor antagonist. It acts selectively on the Angiotensin I receptor subtype, which is responsible for the known actions of Angiotensin II. Valsartan does not exhibit any partial agonist activity at the Angiotensin I receptor and has much (about 20 000 fold) greater affinity for the Angiotensin I receptor than for the Angiotensin II receptor.

Administration of valsartan to patients with hypertension results in reduction of blood pressure without affecting pulse rate.
In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours and the peak action is achieved within 4 to 6 hours. The effect persists over 24 hours after dosing. During repeated dosing, the maximum reduction in blood pressure with any dose is generally attained within 2 to 4 weeks and is sustained during long-term therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.

Hydrochlorothiazide is a thiazide diuretic.
The site of action of the diuretic effect of thiazide diuretics is primarily in the renal distal convoluted tubule. It has been shown that there is a high affinity receptor in the renal cortex with the primary binding site for the thiazide diuretic action and inhibition of NaCℓ transport in the distal convoluted tubule. The mechanisms of the antihypertensive effects of the thiazide diuretics are not fully known.

Pharmacokinetics:

Valsartan:

Valsartan is absorbed after oral administration, although the amount absorbed varies widely. Mean absolute bioavailability for Valsartan is 23 %. Valsartan shows multi-exponential decay kinetics ($t_{1/2}$ alpha < 1 hour and $t_{1/2}$ beta about 9 hours).

The pharmacokinetics of valsartan is linear in the dose range tested. There is no change in the

kinetics of valsartan on repeated administration and little accumulation when dosed once daily. Plasma concentrations were observed to be similar in males and females.

Valsartan is highly bound to serum protein (94 to 97 %), mainly serum albumin. Steady-state volume of distribution is low (about 17 ℓ). Plasma clearance is relatively slow (about 2 ℓ/h) when compared with hepatic blood flow (about 30 ℓ/h). Of the absorbed dose of valsartan 70 % is excreted in the faeces and 30 % in the urine, mainly as unchanged compound.

When valsartan is given with food, the area under the plasma concentration curve (AUC) of valsartan is reduced by 48 %, although from about 8 hours post dosing plasma valsartan concentrations are similar for the fed and fasted group. This reduction in AUC, however, is not accompanied by a clinically significant reduction in the therapeutic effect.

Hydrochlorothiazide:

The absorption of hydrochlorothiazide, after an oral dose, is rapid (t_{max} about 2 hours). The distribution and elimination kinetics is described by a bi-exponential decay function, with a terminal half-life of 6 to 15 hours. The increase in mean AUC is linear and dose proportional in the therapeutic range. There is no change in the kinetics of hydrochlorothiazide on repeated dosing and accumulation is minimal when dosed once daily.

Absolute bioavailability of hydrochlorothiazide is 60 to 80 % after oral administration, with > 95 % of the absorbed dose being excreted as unchanged compound in the urine and about 4 % as the hydrolysate, 2-amino-4-chloro-*m*-benzenedisulfonamide.

Concomitant administration with food has been reported to both increase and decrease the systemic availability of hydrochlorothiazide compared with the fasted state. The magnitude of these effects is small and has little clinical importance.

Valsartan/hydrochlorothiazide:

The systemic availability of hydrochlorothiazide is reduced by about 30 % when co-administered

with valsartan. The kinetics of valsartan is not markedly affected by the co-administration of hydrochlorothiazide. This observed interaction has no impact on the combined use of valsartan and hydrochlorothiazide.

Elderly:

A significantly higher systemic exposure to valsartan was observed in elderly patients than in young patients.

Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly patients compared to young healthy volunteers.

Renal Impairment:

At the recommended dose of CO-ZOMEVEK no dose adjustment is required for patients with mild renal impairment.

In patients with moderate to severe renal impairment (creatinine clearance < 70 mℓ/min) and patients undergoing dialysis no data are available for CO-ZOMEVEK. Valsartan is highly bound to plasma protein and is not removed by dialysis whereas clearance of hydrochlorothiazide will be achieved by dialysis.

Renal clearance of hydrochlorothiazide is composed of passive filtration and active secretion into the renal tubule. As expected for a compound, which is cleared almost exclusively via the kidneys, renal function has a marked effect on the kinetics of hydrochlorothiazide (See "CONTRA-INDICATIONS").

Hepatic impairment:

In patients with mild to moderate hepatic dysfunction, exposure to valsartan is increased approximately 2-fold. There is no data available on the use of valsartan in patients with severe hepatic dysfunction.

Hepatic disease does not significantly affect the pharmacokinetics of hydrochlorothiazide and no dose reduction is considered necessary.

INDICATIONS:

Treatment of mild to moderate hypertension.

CO-ZOMEVEK is indicated for the treatment of hypertension in patients whose blood pressure has been stabilized at the same dosages of the individual components given together.

CONTRA-INDICATIONS:

Hypersensitivity to valsartan or hydrochlorothiazide or to any of the excipients of CO-ZOMEVEK.

The use of CO-ZOMEVEK during pregnancy and lactation is contra-indicated (See "PREGNANCY AND LACTATION"). CO-ZOMEVEK should be discontinued as soon as possible when pregnancy is suspected.

The safety in lactation has not been established.

A history of angioedema related to previous therapy with angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.

Hereditary or idiopathic angioedema.

Severe hepatic impairment, biliary cirrhosis and cholestasis.

CO-ZOMEVEK should not be given to patients with Addison's disease.

Anuria, moderate to severe renal impairment (creatinine clearance less than 30 mℓ/min).

Lithium therapy: Concomitant administration with CO-ZOMEVEK may lead to toxic blood concentrations of lithium (See "INTERACTIONS").

Refractory hypokalaemia, hyponatraemia, hypercalcaemia and symptomatic hyperuricaemia.

Safety and efficacy have not been established in children.

Safety has not been established in porphyria.

Hypertrophic obstructive cardiomyopathy (HOCM).

Bilateral renal artery stenosis.

Renal artery stenosis in patients with a single kidney.

Aortic stenosis.

Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride.

WARNINGS AND SPECIAL PRECAUTIONS:

Women of childbearing age should ensure adequate contraception. CO-ZOMEVEK is contra-indicated in pregnancy and should be used with care, if at all, during breast feeding.

Sodium and/or volume depleted patients:

In sodium-depleted and/or volume-depleted patients such as those receiving doses of diuretics, and/or patients with moderate to severe renal impairment, symptomatic hypotension may occur after initiation of therapy with CO-ZOMEVEK. Sodium and/or volume depletion should be corrected before starting treatment with CO-ZOMEVEK.

If hypotension occurs, symptomatic treatment should be given. Treatment can be continued once the blood pressure has stabilised.

CO-ZOMEVEK should be used with caution in patients with bilateral renal arterial stenosis or stenosis of an artery to a single kidney, aortic valve stenosis or hypertrophic obstructive cardiomyopathy. Reduced doses must be considered in patients with hepatic impairment.

Serum electrolyte changes:

Concomitant use with potassium supplements, potassium sparing diuretics, salt substitutes containing potassium, or other drugs that may increase potassium levels (heparin, etc.) should be used with caution. Hypokalaemia has been reported under treatment with thiazide diuretics. Frequent monitoring of serum potassium is recommended.

Treatment with hydrochlorothiazide diuretics as in CO-ZOMEVEK has been associated with

hyponatraemia and hypochloroaemic alkalosis. Thiazides increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Hydrochlorothiazide as in CO-ZOMEVEK may decrease urinary calcium excretion. Hydrochlorothiazide as in CO-ZOMEVEK may cause elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. CO-ZOMEVEK should be discontinued before carrying out tests for parathyroid function.

Renal artery stenosis:

In patients with unilateral or bilateral renal artery stenosis or stenosis to a solitary kidney, the safe use of CO-ZOMEVEK has not been established.

Renal impairment:

No dosage adjustment is required for patients with mild renal impairment.

Hepatic impairment:

As the majority of valsartan is eliminated in the bile, patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders, showed lower valsartan clearance. Care should be exercised in administering CO-ZOMEVEK to these patients.

Systemic lupus erythematosus:

Hydrochlorothiazide diuretics as in CO-ZOMEVEK have been reported to exacerbate or activate systemic lupus erythematosus.

Other metabolic disturbances:

Thiazide diuretics may alter glucose tolerance and raise serum levels of cholesterol, triglycerides, and uric acid.

Effect on ability to drive and use machinery:

It is advisable to exercise caution when driving or operating machinery

INTERACTIONS:

The antihypertensive effect may be increased with concomitant use of other antihypertensive drugs. Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicines that may alter potassium levels (heparin, etc.) should be used with caution and with frequent monitoring of potassium.

Non-steroidal anti-inflammatory medicines (NSAID's) may antagonise the antihypertensive effect of CO-ZOMEVEK.

Concurrent use with sympathomimetics may reduce the antihypertensive effects of CO-ZOMEVEK.

Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors and thiazides. There is no experience with concomitant use of CO-ZOMEVEK and lithium. Therefore monitoring of serum lithium concentrations is recommended during concurrent use.

Increased mortality has been reported with CO-ZOMEVEK in patients with heart failure also receiving ACE inhibitors or beta blockers. Concurrent use of CO-ZOMEVEK is not recommended in these patients.

The following potential substance interactions may occur due to the thiazide component of CO-ZOMEVEK:

Thiazides potentiate the action of curare derivatives.

Concomitant administration of non-steroidal anti-inflammatory agents (e.g. salicylic acid derivatives, NSAID's) may weaken the diuretic and antihypertensive activity of CO-ZOMEVEK. Concurrent hypovolemia may induce acute renal failure.

The hypokalaemic effect of diuretics may be increased by kaliuretic diuretics, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G and salicylic acid derivatives.
Thiazide-induced hypokalaemia or hypomagnesaemia may occur as unwanted effects, favouring the onset of digitalis-induced cardiac arrhythmias.

It may prove necessary to readjust the dosage of insulin and of oral antidiabetic agents.
Co-administration of thiazide diuretics such as in CO-ZOMEVEK may increase the incidence of hypersensitivity reactions to allopurinol and may increase the risk of adverse effects caused by amantadine and may enhance the hyperglycaemic effect of diazoxide, and may reduce the renal excretion of cytotoxic medicines (such as cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

The bioavailability of thiazide-type diuretics such as in CO-ZOMEVEK may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach-emptying rate.

Haemolytic anaemia may occur with concomitant use of hydrochlorothiazide such as in CO-ZOMEVEK and methyldopa.

Absorption of hydrochlorothiazide diuretics as in CO-ZOMEVEK is decreased by cholestyramine.
Administration of hydrochlorothiazide diuretics as in CO-ZOMEVEK with vitamin D or with calcium salts may potentiate the rise in serum calcium.

Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.
Alcohol, barbiturates or narcotics may potentiate orthostatic hypotension.

PREGNANCY AND LACTATION:

Pregnancy: (See "CONTRA-INDICATIONS").

CO-ZOMEVEK should be discontinued as soon as possible, when pregnancy is suspected.

CO-ZOMEVEK should not be used in pregnancy as teratogenicity has been shown in experimental animals.

Lactation:

Safety has not been established.

Hydrochlorothiazide crosses the placenta and is excreted in breast milk. Thus, it is not advisable to use CO-ZOMEVEK in lactating mothers.

DOSAGE AND DIRECTIONS FOR USE:

CO-ZOMEVEK is initiated once the patient has been stabilised on the individual components taken concomitantly and at the same dosages as the combination.

No dosage adjustment is required for patients with mild renal impairment (creatinine clearance > 70 mℓ/min). No dosage adjustment is required in patients with mild to moderate hepatic insufficiency of non-biliary origin and without cholestasis. A lower dose should be considered for patients with a history of hepatic impairment (See "WARNINGS AND SPECIAL PRECAUTIONS").

The safety and efficacy of CO-ZOMEVEK have not been established in children.

SIDE EFFECTS:

Adverse reactions have been ranked under headings of frequency using the following convention: very common (> 1/10); common (> 1/100, < 1/10); uncommon (> 1/1 000, < 1/100); rare (> 1/10 000, <1/1 000); very rare (< 1/10 000), including isolated report.

In clinical trials the overall incidence of adverse events with CO-ZOMEVEK was similar to placebo. All adverse experiences showing an incidence of 1 % or more in the CO-ZOMEVEK group are included in table 1.

Table 1:

	CO-ZOMEVEK ***N = 4372 ᵗ***	***Placebo*** ***N= 262***
Headaches	3.7	14.5
Dizziness	3.5	3.8
Nasopharyngitis ǂ	2.4	1.9
Fatigue	1.6	1.5
Upper Respiratory tract Infection	1.2	3.4
Cough	1.2	0.8
Diarrhoea	1.1	1.1
Arthralgia	1.0	1.1
Back pain	1.2	2.7
ᵗ Includes all combinations of valsartan 80 and 160 mg with HCT 12.5 and 25 mg ǂ Nasopharyngitis including pharyngitis + rhinitis HCTZ = Hydrochlorothiazide		

Other uncommon adverse experiences included abdominal pain, abdominal pain upper, anxiety, arthralgia, arthritis, asthenia, bronchitis, bronchitis acute, chest pain, dizziness postural, dyspepsia, dysnoea, dry mouth, hyperhidrosis, hypoaesthesia, hypokalemia, hypotension, influenza, insomnia, muscle strain, nasal congestion, neck pain, oedema peripheral, otitis media, pain in extremity, palpitations, paraethesia, pyrexia, rash, sinus congestion, somnolence, sprains and strains, tachycardia, tinnitus, urinary tract infection, viral infection, oedema, asthenia, blurred vision, vertigo.

Post marketing data revealed cases of angioneurotic oedema, rash, pruritus, and other hypersensitivity/ allergic reactions including serum sickness, and vasculitis.

Cases of renal impairment and myalgia have also been reported.

There have also been reports of hydrochlorothiazide-induced pulmonary oedema with granulocytic infiltration and lgG deposition in alveolar membranes. Non-cardiogenic pulmonary oedema may be an immunologically mediated rare idiosyncratic reaction to hydrochlorothiazide.

Laboratory findings:

Potassium levels may rise or fall and should be frequently monitored (See "WARNINGS AND SPECIAL PRECAUTIONS*")*. A greater than 20 % decrease in serum potassium was observed in 3,7 % of patients receiving CO-ZOMEVEK as compared to placebo (3,1 %) (See "WARNINGS AND SPECIAL PRECAUTIONS"*)*.

Elevations in creatinine and blood urea occurred in 1,9 % and 14,7% respectively, of patients taking CO-ZOMEVEK and 0,4 % and 6,3 % respectively given placebo in controlled clinical trials. Neutropenia was observed in 0,1 % of patients treated with CO-ZOMEVEK versus 0,4% of patients treated with placebo.

Valsartan:

Other additional adverse experiences reported with valsartan monotherapy were, with a frequency below 1 %: decreased libido, renal failure, acute occasional elevations in liver function values.

Hydrochlothiazide:

The following adverse reactions have been reported in patients treated with thiazide diuretics alone, including hydrochlorothiazide:

Electrolytes and metabolic disorders: *(*See "WARNINGS AND SPECIAL PRECAUTIONS"*)*.

***Others*:**

Common: Urticaria and other forms of rash, decreased appetite, mild nausea and vomiting, orthostatic hypotension, which may be aggravated by alcohol, anesthetics or sedatives, and erectile dysfunction.

Rare: Photosensitivity reactions, abdominal discomfort, constipation, diarrhoea, cholestasis or jaundice, dysrhythmias, headache, dizziness, sleep disorder, depression, paresthesia, visual disturbance, thrombocytopenia, sometimes with purpura, gout.

Very rare: Vasculitis necrotizing and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, pancreatitis, leucopenia, agranulocytosis, bone marrow depression, haemolytic anaemia, hypersensitivity reactions, respiratory distress including pneumonitis and pulmonary oedema.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Overdose with valsartan may result in marked hypotension which could lead to depressed levels of consciousness, circulatory collapse and/shock. If the ingestion is within one hour and level of consciousness is adequate, vomiting should be induced. Otherwise, the usual treatment would be intravenous infusion of normal saline solution.

Valsartan cannot be eliminated by means of haemodialysis because of its strong plasma binding behavior whereas clearance of hydrochlorothiazide will be achieved by dialysis.

IDENTIFICATION:

Co-Zomevek 80/12,5 tablet:

Light orange, ovaloid, convex tablet. One side bears the imprint "HGH", the other "CG". Film-coating is intact and shows no signs of cracks.

Co-Zomevek 160/12,5 tablet:

Dark red, ovaloid, convex film-coated tablet. One side bears the imprint "HHH", the other "CG". Film-coating is intact and shows no signs of cracks.

Co-Zomevek 160/25 tablet*:*

Brown orange, ovaloid, film-coated tablet which have slightly convex faces, imprinted with "HXH" on the one side and "NVR" on the reverse side. Film-coating is intact and shows no signs of cracks.

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PRESENTATIONS:

28 tablets in PVC/PE/PVDC aluminium foil blisters (Triplex) or PA/Al/PVC aluminium foil blisters

(alu-alu or double-sided aluminium blisters) or PVC/PVDC with aluminium foil (Duplex) blisters. The aluminium foil is silver and the PVC/PVDC is clear colourless.

The outer container is a printed cardboard box.

STORAGE INSTRUCTIONS:

Protect from moisture and, store at or below 25 ^{0}C. Keep containers well closed.

Keep the blisters in the outer carton until required for use, to protect the tablets from moisture.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS:

Co-Zomevek 80/12,5 tablet: 43/7.1.3/0080

Co-Zomevek 160/12,5 tablet: 43/7.1.3/0081

Co-Zomevek 160/25 tablet: 43/7.1.3/0082

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION:

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[1] Company Reg. No.: 1990/001979/07