Module 2.5

Clinical Overview

XXX

(oral and parenteral formulations)

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Appendix I shows the results of computer-assisted investigations for publications on the subject of clinical pharmacology, clinical efficacy, and adverse drug reactions following administration of XXX, that appeared in the period of 01/01/1968 to 01/02/2016.

2.5.1 Product Development Rationale

Pharmacological Class
XXX, 1-yyy-N-yyy-acid, belongs to the pharmacological group of loop diuretics and is a cardiovascular agent.

Indication
XXX as an oral formulation is currently used for edema resulting from cardiac or hepatic disease, edema resulting from renal disease (in nephrotic syndrome, priority should be given to treatment of the primary disease), arterial hypertension, and edema resulting from burns.

Scientific Background
The kidneys remove water and salt as urine and return water that has been filtered to the blood plasma, thus helping to maintain the water and electrolyte balance of the body. Diuretics enhance the urinary excretion of salt and secondarily of water by directly or indirectly impairing sodium chloride reabsorption in the renal tubules. This causes reduction of volume of the extracellular fluid. Frequently used diuretics include thiazide-type diuretics (e.g. hydrochlorothiazide), potassium sparing diuretics (e.g. spironolactone), loop diuretics (e.g. XXX) and carbonic anhydrase inhibitors (e.g. acetazolamide) which act on different sites of the nephron, resulting in different pharmacological effects. The specific drug to be used is selected according to the action desired and the patient's physical status.

Loop diuretics act at the luminal surface of the thick ascending limb of the loop of Henle by blocking the sodium-potassium-chloride ($Na^+/K^+/2Cl^-$) active reabsorption. They possess a potent diuretic effect and are used in patients with high interstitial fluid retention (edema or ascites) due to cardiac, renal, hepatic diseases or other conditions of disturbed fluid balance. In addition, loop diuretics provide extrarenal effects which are favorable especially in cardiac diseases. Potential benefits and risks of XXX administration, either alone or in combination with other drugs, are studied in patients with various edematous disease states.

XXX can be applied by various routes of administration (oral, intravenous). However, the diuretic is used orally by a large number of patients on a long term basis, and oral therapy with XXX usually replaces parenteral therapy as soon as it is practical.

Concordance with Current Standard Research Approaches
Not applicable for generic products (see *Guidelines CTD-Module 2*).

2.5.2 Overview of Biopharmaceutics

XXX is characterized by a large degree of pharmacokinetic variability and its absorption is known to be erratic. The absorptive behaviour of XXX differs between dosage forms weather comparing a solution and a tablet, comparing tablets formulated by different manufacturers or comparing immediate- or sustained-release preparations (*XXX*).

However, XXX-tablets (batch N° yyyy) have been proved to be bioequivalent to the reference product Lasix® (40 mg tablets) according to requirements of the CPMP-note for guidance (III/54/89-EN). In contrast, bioequivalence for XXX-ratiopharm® (batch N° yyyy) and Lasix® could not be stated. According to these results, interchangeability of the test preparation (batch N° zzzz) and Lasix® is concluded (*Pharmakin 1997b*).

Controlled release formulations of XXX with a low and extended rate of dissolution lead to a more prolonged absorption and subsequent diuresis, but still maintain a similar cumulative response, due to their higher diuretic efficiency. Substantial differences in XXX recovery and diuretic efficiency were observed between one reference formulation of XXX (60 mg) with a low rate of dissolution and three different XXX extended-release formulations (60 mg of ER1Tab, ER2Tab and ER3Caps) in a single-dose, double-blind, 4-way cross-over study (n=12). At 24 hours, mean total XXX recoveries of ER1Tab, ER2Tab and ER3Caps were 52%, 36% and 57% lower, respectively, compared to reference ($p<0.01$). Also, mean total diuretic efficiency for ER1Tab, ER2Tab and ER3Caps was 83%, 31% and 135% higher, respectively, compared to reference. The rapid dissolution and absorption of reference XXX resulted in a high diuretic response from 0 to 3 hours after dosing. However, from 0 to 24 hours, there were no differences in diuretic response between the formulations (*XXX et al. 1999*).

A crossover study compared a XXX (60 mg) gastro-retentive dosage form (releasing the drug during 6 hours in vitro) and an immediate-release tablet in healthy males (n=14). The unfolding controlled-release form of XXX improved the pharmacodynamic actions due to the sustained absorption in the stomach and jejunum, which delayed the body's counteractivity to the drug effect. The sustained input of the drug significantly improved diuretic and natriuretic efficiencies during the first 5 hours and thereby increased the total effects measured over 24 hours (*XXX et al. 2003*).

2.5.3 Overview of Clinical Pharmacology

Pharmacodynamics

Mechanism of Action

The exact mechanism of action of XXX is not fully understood, but the drug is believed to act at the luminal surface of the thick ascending limb of the loop of Henle by blocking the sodium-potassium-chloride ($Na^+/K^+/2Cl^-$) active reabsorption (*XXX er 1991*, *XXX 1996*). There are two major lines of evidence. First, micropuncture experiments demonstrate a greatly enhanced delivery of sodium and chloride to the beginning of the distal tubule after XXX. Second, in microperfusion experiments *in vitro* there is a complete inhibition of sodium chloride transport in the thick ascending limb at luminal drug concentrations in the range of those expected to occur *in vivo* (*XXX 1990*).

The molecular mechanism by which XXX blocks the $Na^+/K^+/2Cl^-$ reabsorptive pump is unknown but there is evidence for drug attachment to Cl^--binding site of the transporter. XXX must reach the tubular lumen to exert its effect on the $Na^+/K^+/2Cl^-$ reabsorptive pump (*XXX 1979*, *XXX and XXX 1980*), it is not effective at the basal side of the cells of the loop of

Henle (*XXX and XXX 1997*). XXX is secreted into the lumen of the proximal tubule by the organic secretory mechanism, where it flows to its site of action at the thick ascending limb of the loop of Henle. Its effect depends on its concentration in the tubular lumen. This has been demonstrated by inhibiting the secretion of XXX into the tubular urine using probenecid. As a result the dose-response curve of XXX is shifted to the right when expressed in terms of sodium excretion rate related to plasma concentration of XXX. However, when the response is plotted as a function of the urinary rate of excretion of XXX, the response curve remains unchanged indicating that the same XXX concentration at the luminal site of action also produced the same effect (*XXX et al. 1998*, *XXX 1991*, *XXX and XXX 1997*, *XXX and XXX 1985*).

Adrenocorticosteroids and/or endogenous ouabain-like substances may play an important role in the mechanism of XXX diuretic action. It was reported that the drug is highly bound in the adrenals, lungs, kidney, spleen, and liver. In patients with liver cirrhosis, XXX exerted a markedly decreased natriuretic effect compared with normal subjects, and the plasma levels of circulating endothelin and atrial natriuretic factor (ANF) were significantly elevated. In neonates, after administration of XXX, the urinary excretion of endothelin-1 and aldosterone increased markedly, and it is known that endothelin may release ANF and aldosterone in a dose-dependent manner. XXX was used to stimulate zona glomerulosa, whereas ANF decreased the production of steroids in zona glomerulosa and fasciculata cell culture owing to stimulation by various factors. Because the concomitant use of ANF and XXX appeared to be diuretically effective in newborns after cardiac surgery, it was suggested that XXX competes with ANF for its effects on the adrenals (*XXX 2002*, *XXX 2001*).

Onset and Duration of Action

Initial response to XXX is obtained 30–60 minutes after oral administration, peak response after 1–2 hours, and return to baseline within another 2-3 hours. Diuresis after a single oral dose lasts for 6 to 8 hours. The duration of diuresis may be prolonged up to 10 hours in patients with chronic renal failure and may be prolonged following a myocardial infarction. After intravenous administration the onset of diuresis occurs within 2-5 minutes, peaking at 30 minutes and reaching baseline within 2-3 hours (*XXX 1993*, *Drugdex 2007* [from *XXX* and *XXX* 1988, *XXX* et al. 1984, *XXX* and *XXX* 1971, *XXX* et al. 1966a]).

Effect on Urinary Excretion

Subsequently to its effect on the $Na^+/K^+/2Cl^-$ cotransport system, XXX enhances the excretion of chloride, sodium (up to 25% of the filtered load of sodium, compared to normal values of 0.5%-2%), potassium and hydrogen. Since greater amounts of sodium are available in the distal tubule, an increased exchange of sodium against potassium and hydrogen is favorised. Abolition of the transmembrane potential difference also results in marked increases in the excretion of calcium and magnesium. XXX has also a weak carbonic anhydrase-inhibiting activity which leads to an increased excretion in bicarbonate and phosphate (*XXX and XXX 1997*, *XXX 1996*).

By allowing the delivery of isotonic tubular fluid to the distal tubule, XXX causes a fall in volume absorption along the early distal convolution in proportion to its baseline water permeability. It increases urine flow by abolishing the interstitial hypertonicity and, consequently, the osmosis driven solvent flow across the distal epithelium and collecting ducts. Therefore the urine flow rate during XXX closely approximates volume delivery out of the proximal tubule (*XXX et al. 1998*, *XXX 1996*).

Acutely, XXX, as all loop diuretics, increases the excretion of uric acid, whereas chronic administration reduces excretion of uric acid. The chronic effect of XXX on uric acid excretion may be due to enhanced transport in the proximal tubule secondary to volume depletion, leading to increased reabsorption of uric acid, or to competition between XXX and

uric acid for the organic acid secretory mechanism in the proximal tubule (*XXX 1990a*, *XXX 1996*). XXX affects the plasma concentration and urinary excretion of purine bases and oxypurinol by acting on their common renal pathways. In allopurinol-treated healthy subjects XXX (20 mg intravenously) significantly decreased urinary excretion of uric acid, hypoxanthin, xanthin and oxypurinol. Moreover, it increased plasma concentration of uric acid 1.5 hours after administration. It did not affect adenosine and uridine excretion (*XXX et al. 2001*, *XXX et al. 2000*).

Effect on Renal Hemodynamics

XXX transiently enhances renal blood flow without increasing filtration rate, especially after intravenous application. This increase in renal blood flow is relatively short (5-15 min). Such a change in renal hemodynamic reduces fluid and electrolyte reabsorption in the proximal tubule and may augment the initial diuretic response. With the reduction of extracellular fluid volume resulting from diuresis, there is a tendency for renal blood flow to decrease. The intrarenal blood flow is preferentially increased in the inner cortical zones, and this increase is abolished by prostacyclin inhibitors in humans and animals (*XXX et al. 1978*, *XXX and XXX 1980*, *XXX et al. 1984*, *XXX et al. 1983*, *XXX 1990*, *XXX et al. 1975*). Since the capacity of XXX to increase renal blood flow is related to the initial resistance of certain vascular segments within the kidney, it is concluded that, the higher the initial resistance the greater the potential effect (*XXX and XXX 1990a*).

XXX (20 mg orally or 20 mg intravenously) immediately after administration produced a significant decline in glomerular filtration rate in healthy subjects (p=0.03) and in subjects with diastolic dysfunction (p=0.0002; both p-values versus baseline). A greater post-XXX decline of glomerular filtration rate is seen in subjects with diastolic dysfunction compared with healthy subjects (25.5 vs. 14.6 ml/min, respectively, p=0.12) (*XXX et al. 2007*).

Effects on Systemic and Pulmonary Hemodynamics

Differential systemic and pulmonary hemodynamic effects of torasemide and XXX have been observed in patients with secondary pulmonary hypertension. Results of a double-blind controlled comparison of diuretics showed that torasemide increased cardiac output (relative treatment effect over the time between groups; p=0.03), whereas treatment with XXX significantly increased arterial angiotensin-II plasma levels compared with torasemide (p=0.031). A possible explanation for these findings might be activation of the renin-angiotensin system by XXX. However, the underlying pathomechanism remains to be established and evidence from an adequately powered trial is needed to determine if XXX aggravates cardiac function by increasing angiotensin-II plasma levels (*von XXX et al. 2008*).

Cardiovascular Effects

XXX produces a rise in peripheral venous capacitance and a decrease in forearm blood flow. Left ventricular filling pressure is decreased, earlier than diuresis, which is beneficial in patients with pulmonary edema. These effects are dependent on functional kidneys, a salt-retaining state and prostaglandin synthesis capability. Improvement in cardiovascular hemodynamics are observed following long-term use of XXX subsequent to contraction of the extracellular fluid, increased venous capacitance, reduced cardiac preload and afterload. Some investigators have identified significant improvements in the left ventricular ejection fraction with XXX (*XXX and XXX 1990a*, *XXX et al. 1984*, *XXX et al. 1983*).

In vitro, XXX exerted an anti-vasoconstrictor effect independent of its diuretic properties. At concentrations in the therapeutic range, XXX (10^{-5} M) inhibits angiotensin II-induced contraction on human isolated internal mammary artery and saphenous vein. This inhibitory effect is cyclooxygenase independent and appears mediated, at least in part, by inhibition of $Na^+/K^+/2Cl^-$ symport. Reduction in the vasoconstrictor effect of angiotensin I may be involved

in the therapeutic efficacy of XXX (*XXX et al. 1998*).

XXX at high concentrations inhibited thromboxane A2-induced contraction in isolated human internal mammary artery and saphenous vein by mechanisms independent of the release of relaxant prostaglandins. *In vitro* results suggest that blockade of thromboxane A2 receptors by XXX may contribute to the therapeutic effects of XXX in the treatment of severe heart failure (*XXX et al. 2000*). In patients with heart failure, counteraction of the increased oxidative stress by vitamin C appears to augment the natriuretic effects of XXX probably via the renal kinin-nitric oxide pathway (*XXX et al. 2003*).

Hormonal Effects

XXX produces an increase in the plasma renin activity, plasma noradrenaline levels and plasma arginine vasopressin levels. These alterations are dependent upon the route of administration. After oral administration, the increased hormone release appears to be related to the cumulative sodium excretion (*XXX and XXX 1990a*, *XXX and XXX 1997*). A majority of patients with suppressed plasma renin activity has high levels of atrial natriuretic peptide and can respond to oral XXX therapy with a rise in plasma renin activity and a fall in atrial natriuretic peptide, suggesting a physiologic suppression of the renin system by volume expansion (*XXX et al. 1998*).

Additionally, the secretion of prostaglandins is enhanced by XXX. It is unknown whether XXX may promote the synthesis of prostaglandins or inhibit the prostaglandin degradation enzymes. Prostaglandins A and E however, exhibit natriuretic and diuretic activity. Conflicting data exist on the effect of XXX on kallikrein and kallikrein-like activity (*XXX and XXX 1990a*, *XXX and XXX 1990b, XXX and XXX 1997*).

Antihypertensive Effects

In hypertensive patients XXX reduces blood pressure which seems to work, initially, via reduction in extracellular volume and cardiac output, and during long-term therapy through reduction of vascular resistance. During effective therapy, plasma volume remains about 5% below pretreatment values and plasma renin activity remains elevated, confirming a persistent reduction in total sodium. Diuretics do not relax vascular smooth muscle in vitro, and hemodynamic effects of diuretics on vascular resistance can also be reproduced by restriction of salt. Potential mechanisms for reduction in vascular resistance suggested are a reduction in body sodium, a decrease in interstitial fluid volume, a fall in smooth muscle sodium concentration that may secondarily reduce intracellular calcium concentration, so that the cells are more resistant to contractile stimuli, and a change in the affinity and response of the cell surface to vasoconstrictor hormones (*XXX 1996*).

After XXX treatment, in 67% of elderly patients (n=12) with initial low plasma renin activity, decreases in systolic blood pressure, diastolic blood pressure and mean arterial pressure, were associated with increases in plasma renin activity and serum aldosterone and with decreases in atrial natriuretic peptide and body weight. In the remaining 33% of patients, blood pressure also decreased significantly, but there were no other significant changes in parameters (*XXX et al. 2003*).

Effect on Respiratory System

XXX (40 mg) affects ion and water movement across the respiratory epithelium. A controlled study in young healthy subjects (n=14) showed impairment of mucociliary clearance (assessed by saccharine test). XXX prolonged saccharine test and this effect was not prevented by fluid replacement, suggesting a direct effect of XXX on the respiratory epithelium (*XXX et al. 2010*).

Moreover, XXX appears to possess antiinflammatory and bronchodilating properties. A protective action from bronchospasm has been discovered. XXX shows no acute

bronchodilator effect, but prevents or attenuates bronchospasm caused by many factors, such as hyperpnea, drugs (metabisulphite, bradykinin), physical agents (hypo- and hypertonic aerosols), and allergen challenge in asthmatic patients. XXX is also active on upper airway mucosa, on which the drug decreases nasal resistance in patients affected by non-allergic rhinitis and exhibits a protective effect on nasal mucosa reactivity to the specific allergen in atopic subjects. The mechanism of action of XXX on airways has not yet been fully cleared and interference with electrolyte epithelial transport, prostaglandins, inflammatory cell activity, vascular and neural regulation has been hypothesized (*XXX and XXX 2002*, *XXX 2002*).

Antiepileptic Effects

In patients suffering from neocortical and mesial temporal lobe epilepsy, studies on drug induced modulation of volume and water content of the extracellular space have shown possible antiepileptic properties of XXX. A single intravenous dose (20 mg) significantly suppressed spontaneous epileptic spikes and electrical stimulation-evoked epileptiform (XXX *and* XXX *2005*). XXX was not found to alter synaptic field responses, excitatory postsynaptic currents or intrinsic membrane properties of principal hippocampal neurons. *In vitro* studies indicate that XXX does not abolish spontaneous epileptiform bursting during co-application of Ba^{2+} or Cs^{+} ions (to block inwardly rectifying potassium channels). Astrocytes appear to mediate the antiepileptic actions of XXX *in vitro* (*XXX et al. 2004*).

Other Effects

A modest effect on salivary flow rate and a more pronounced effect on saliva composition, especially in submandibular-sublingual secretion during treatment of healthy volunteers with therapeutic doses of XXX (40 mg once daily) has been demonstrated in a placebo-controlled study (*XXX et al. 2004*).

Loop diuretics increase renal calcium loss and may thereby affect calcium homeostasis and bone metabolism. In postmenopausal women receiving XXX (40 mg daily) therapy, it was demonstrated that the increased renal calcium losses are compensated by a parathyroid hormone-dependent increase in 1,25 dihydroxyvitamin D levels. Thereby calcium balance remains neutral without major effects on bone metabolism (*XXX et al. 2005*).

XXX has been shown effective in reversing multidrug resistance status in bladder cancer cell lines *in vitro*. It may also have an increment of intrinsic cytotoxicity, but only at higher concentrations (*XXX et al. 2006*).

Dose-effect Relationship

The rate of sodium excretion as a function of dose and plasma concentrations of XXX shows a typical sigmoidal curve with an EC_{50} value of approximately 1 µg/ml (*XXX 1983*, *XXX et al. 1978*, *XXX et al. 1978*, *XXX and XXX 1985*). No relationship exists between plasma levels and therapeutic effect. Since XXX acts on the tubular site of the loop of Henle, its excretion rate into urine determines the natriuretic response. Thus, when the tubular secretion of XXX is blocked by probenecid, there is a shift to the right of the plasma concentration/effect relationship while the relationship between urinary excretion rate and effect remained unaltered. The diuretic response is determined by the amount of drug reaching the renal tubule, not by the amount present in the plasma (*XXX and XXX 1990a*, *XXX 1983*, *XXX et al. 1982*).

The response to a given dose is modulated by the fluid and electrolyte balance of the individual. Acute tolerance and delayed tolerance have been demonstrated in animals and humans. This tolerance is postulated to be due to the intervention of homeostatic mechanism influencing extracellular fluid volume and electrolyte balance (*XXX and XXX 1990a*).

Resistance to Loop Diuretics

The mechanism by which resistance to loop diuretics occurs has been elucidated in several clinical conditions. Most often, it is due to a non-justified prescription of diuretics (e.g., obesity, edema due to lymphatic or venous insufficiency), non-compliance of the patient, concomitant administration of non-steroidal anti-inflammatory drugs, and a sodium rich diet (*XXX and XXX 1997*). Food significantly affects the pharmacokinetics of oral loop diuretics in healthy individuals (*XXX et al. 2004*).

In the elderly and in patients with moderate renal insufficiency, the mechanism of the resistance appears to be purely pharmacokinetic, involving altered access of the diuretic in the urine (*XXX 1985*). In contrast, patients with nephrotic syndrome manifest a purely pharmacodynamic form of resistance due to the binding of XXX to luminal albumin (*XXX 1993*, *XXX et al. 1982*).

In patients with chronic heart failure, intrarenal diuretic resistance was reported to be the main factor. Gross non-adherence was less important in response to chronic XXX therapy (*XXX et al. 2004*).

Pharmacokinetics

Absorption

The absorption of XXX is variable and exhibits great inter- and intra-individual differences. It depends on the formulation used, the time of administration (fasting or post-prandial), the age of the patient, and the underlying disease. From tablets XXX is rapidly absorbed. After administration (80 mg tablet) to healthy subjects in fasting state, serum concentrations of XXX were detected 10 minutes after ingestion and peak serum concentrations (mean 2.3 µg/ml) occurred between 60 and 70 minutes. The drug was no more detectable between 3-4 hours after administration (*XXX et al. 1974*). In healthy subjects XXX obeys absorption rate-limited kinetics with a mean absorption time of 84 minutes after oral doses compared to a mean residence time after intravenous dosing of 51 minutes (*XXX et al. 1984*).

Bioavailability of XXX between subjects ranges from 20% to 80% (*XXX et al. 1982*, *XXX et al. 1975*, *XXX et al. 1984*, *XXX et al. 1984*, *XXX et al. 1974*, *XXX 1988*, *XXX et al. 1980*). The maximal intra-subject difference in bioavailability was 20% to 61% (*XXX et al. 1984*). The relative bioavailability of XXX of a 40-mg tablet compared to an aqueous solution was 89% (*XXX et al. 1988*).

Controlled-release formulations of XXX (60 mg) with a low and extended rate of dissolution lead to a more prolonged absorption and subsequent diuresis (*see 2.5.2*.) (*XXX et al. 1999*, *XXX et al. 2003*).

Food may affect the rate, but not the extent of absorption. Other investigators state that bioavailability (oral solution and tablets) is significantly ($p<0.01$) reduced by 30% when administered with food. This decrease in the bioavailability of XXX probably results from decreased absorption. In addition, administration with meals significantly reduces the mean peak plasma level (C_{max}) ($p<0.001$) and significantly delays the time to peak level (T_{max}) ($p<0.01$) (*Drugdex 2007* [from *XXX* and *XXX* 1986a; *XXX* et al. 1996a, *XXX* and *XXX* 1990a]).

The rate of absorption may be decreased in patients with edema, but total bioavailability remains unchanged (*Drugdex 2007* [from *XXX* et al. 1995]).

Distribution

In normal patients, the distribution phase averages 7 minutes (*Drugdex 2007* [from Kelly et al. 1974, Calesnick et al. 1966]). XXX is highly bound to plasma proteins which restricts its

apparent volume of distribution. Ranges of volume of distribution equal to 0.18 to 0.07 l/kg in normal adult patients have been found at steady-state (*XXX et al. 1996*, *XXX 1993*).

Passage across Placenta and into Breast Milk

XXX crosses the placental barrier. Following oral doses of 25-40 mg, peak concentrations in cord serum of 330 ng/ml were recorded at 9 hours. Maternal and cord levels were equal at 8 hours (*Briggs et al. 1994*). XXX is excreted into breast milk (*Drugdex 2007*, *Briggs et al. 1994*). Elimination of XXX in the mother may be abolished or diminished during delivery, so that the new-born is exposed to the risk of dehydration and electrolyte loss when XXX is administered to the mother before term (*XXX et al. 1978*).

Protein Binding

XXX is highly bound to plasma proteins (91%-99%), primarily to albumin which is reduced in patients with uremia, nephrotic syndrome, cirrhosis, hypoalbuminemia, hyperbilirubinemia, and in the elderly (*Drugdex 2007*, *XXX and XXX 1990a*). In theory, good perfusion and albumin are required for the XXX to be secreted at the tubular lumen. Thus, in the situation of low glomerular filtration rate and hypoalbuminemia, the efficacy of XXX alone might be limited. In hypoalbuminemic chronic kidney disease patients, the addition of albumin to XXX provided a superior short-term diuretic efficacy over XXX alone (*XXX and XXX 2012*).

Metabolism

A glucuronide metabolite has been identified (*XXX et al. 1975*) which appears to be the only or at least the only significant metabolite, however, of unknown activity (*Drugdex 2007*). XXX conjugated with glucuronic acid is excreted via the urine and the feces. In the presence of severe renal failure, the liver may play a significant role. Patients receiving the drug for > 6 month have significantly greater production of XXX glucuronide and nonrenal elimination is reported to be increased by more than 4 times that of normal. Newborn infants substantially metabolize XXX to an acid metabolite (1-*XXX* 8-*XXX*-yyy acid) and glucuronide conjugate (*Drugdex 2007* [from *XXX* and *XXX* 1990, *XXX* et al. 1974, *XXX* et al. 1982]).

A metabolite called CSA (4-chloro-5-sulfamoyl-anthranilic acid) has been identified by some investigators, but others have found no evidence of the existence of this possible metabolite. Urinary levels of CSA were identified when large doses of XXX (100 to 500 mg intravenously) were administered to a patient with advanced renal failure (*Drugdex 2007* [from *XXX* and *XXX* 1990, *XXX* 1990, *XXX* 1985a, *XXX* et al. 1988]).

Elimination

XXX is eliminated by the renal and extra-renal routes. The mean value of total plasma clearance of XXX is 2 ml/min/kg (*Drugdex 2007*, *XXX et al. 1996*, *XXX 1993*, *XXX et al. 1984*, *XXX and XXX 1989*). Renal clearance accounted for 72% and the non-clearance for 28% in normal subjects (*XXX et al.1984*). Administration of the oral solution with food significantly reduced renal excretion compared with fasting ($p<0.001$) (*Drugdex 2007* [from *XXX* et al. 1996b]). Significantly more is excreted in urine following intravenous than after oral administration. Since XXX is highly bound to plasma protein, XXX is actively eliminated in the lumen of the proximal tubule by the organic secretory mechanism.

In normal subjects, the elimination half-life of XXX ranges from approximately 30 to 120 minutes. Calculation of mean residence time has been proposed as alternative to half-life and was, after oral administration, 135 and 195 minutes in fasting and postprandial state, respectively (*Drugdex 2007*, *XXX and XXX 1990a*, *XXX 1993*). Approximately 58.8% of a dose is recovered in the urine as unchanged drug in 24 hours in normal subjects. About 14% of the available dose was excreted as XXX glucuronide after both, intravenous and oral doses of XXX to healthy subjects (*XXX et al. 1980*). The ratio of the amount of XXX

glucuronide to unchanged XXX in the urine has been calculated to be 0.22-0.3. The sum of unchanged and glucuronidated XXX accounted for 80% of an intravenous dose in young subjects (*XXX et al. 1981*). The remaining proportion of the dose is probably biliary excreted into the feces either as unchanged XXX or as the glucuronide conjugate (*XXX 1989*). After intravenous administration, 7% to 9% of the administered dose has been found to be eliminated in the feces (*XXX et al. 1975*). Active secretion into the intestinal lumen has not been proven to be a potential mechanism of the appearance of XXX in the gut. Passive diffusion from plasma into the lumen is believed to be the source of fecal XXX concentrations (*XXX et al. 1986*).

The acyl glucuronide is formed in part by the kidney tubules and it is possible that the compound is pharmacologically active through inhibition of the $Na^+/2Cl^-/K^+$ co-transport system. Up to now the mechanism of action has been solely attributed to XXX. The total body clearance of XXX occurs by hepatic and renal glucuronidation (50%) and by renal excretion (50%). Enterohepatic cycling of XXX acyl glucuronide, followed by hydrolysis, results in a second and slow elimination phase with a half-life of 20-30 hours. This slow elimination phase coincides with a pharmacodynamic rebound phase of urine retention. After each dosage of XXX, there is first a short stimulation of urine flow (4 hours), which is followed by a 3-day recovery period of the body (*XXX and van der XXX 1999*).

Pharmacokinetics in Premature/Full-term Infants

A volume of distribution of 0.173 to 0.24 l/kg has been reported in newborn infants aged 1 day to 4 months (*Drugdex 2007* [from *XXX* et al. 1983, *XXX* et al. 1980a]). Newborns substantially metabolize XXX to 1-*XXX*-8-*XXX*-5-YYY acid and glucuronide conjugate (*Drugdex 2007* [from *XXX* et al. 1982]).

Important pharmacokinetic differences between adults and infants include a reduced clearance and prolonged half-life of XXX (*XXX and XXX 1998*).

An inverse relationship between half-life of XXX and gestational age of birth appears to exist. In a group of neonates (n=21) who received XXX (1 mg/kg intravenously) after birth, half-lives ranged from 8.4 to 44 hours in prematures, whereas full-term newborns showed shorter half-lives ranging from 4.7 to 29 hours (*XXX et al. 1982*). Neonates younger than 31 weeks frequently exhibited half-lives of > 24 hours (*XXX et al. 1988*). In neonates plasma clearance was 15.3 ml/kg/h, renal clearance was 14.9 ml/kg/h and 99% of total clearance of XXX consisted of renal elimination of unchanged drug. In consistancy with the immature glucuronidation capacity in newborns, no glucuronide metabolite was found in the urine (*XXX et al. 1983*). It is suggested that the reason of the prolonged half-life in newborns is a slow renal excretion due to an immature renal function associated with the absence of non-renal elimination.

Pharmacokinetics in the Elderly

After single dose administration of XXX (40 mg intravenously) geriatric patients as compared to young adults displayed a prolonged plasma elimination half-life due to a significantly reduced renal clearance. The nonrenal clearance and the volume of distribution calculated for the β-phase were not significantly changed (*XXX et al. 1984*).

Pharmacokinetics in the Presence of Various Disorders

Liver Cirrhosis

In patients with liver cirrhosis who are hypoalbuminemic, protein binding is decreased causing increases in volume of distribution and clearance based on total drug. If assessed for unbound XXX, these parameters are not changed in cirrhotic patients. In one study, the percentage of unbound XXX in cirrhotic patients was 10.2% compared with 4% in normal subjects (*Drugdex 2007* [from *XXX* et al. 1982], *XXX et al. 1981*, *XXX et al. 1981*, *XXX et al.*

1986, *XXX et al. 1982*).

Although the amount of drug absorbed is not affected, the rate of absorption is slowed. The mean absorption time in cirrhosis was 203 minutes compared to 84 minutes in healthy subjects (*XXX et al. 1991*, *XXX et al. 1984*).

The half-life in cirrhotic patients is only slightly greater compared to normal patients (81 vs. 60.2 minutes, respectively). Approximately 58.8% and 53.1% of a dose is recovered in the urine as unchanged drug in 24 hours in normal subjects and cirrhotic patients, respectively. The 24-hour percentage urinary recovery of glucuronide metabolite was nonsignificantly different between cirrhotic (21.3%) and normal subjects (17.8%) (*Drugdex 2007* [from *XXX* et al. 1982]).

Renal Disorders
Bioavailability is reduced to 43% to 46% in patients with end-stage renal disease (*Drugdex 2007* [from AMA Department of Drugs 1990a; *XXX* and *XXX* 1988]).

XXX protein binding is reduced in patients with renal disorders (uremia, nephrotic syndrome). In patients with severe renal insufficiency, accumulated organic acids may displace XXX from albumin increasing the unbound fraction and protein binding can be reduced by up to 10%. In the presence of severe renal failure, the liver may play a significant role and nonrenal elimination is reported to be increased by more than 4 times that of normal (*Drugdex 2007* [from *XXX* and *XXX* 1990, Kelly et al. 1974]). Total clearance of XXX in renal insufficiency was reported 0.3-0.8 ml/kg/min compared to 2 mg/kg/min in healthy subjects (*XXX 1993*).

As a result of the decreased total clearance, the elimination half-life may increase to 4 to 6 hours (*Drugdex 2007* [from *XXX* 1991, *XXX* 1989, *XXX* et al. 1987, *XXX* and *XXX* 1980]). In anephric patients, the average plasma half-life ranges between 1.5 and 9 hours (*Drugdex 2007* [from *XXX* et al. 1974]). In children with nephrotic syndrome half-life is longer compared to healthy children (38.5 vs. 28 minutes, respectively) (*Drugdex 2007* [from *XXX* et al. 1983).

Clinical implications arise from the elimination kinetics of XXX. Repetitive dosing must result in accumulation of the recovery period. Accumulation of XXX and its acyl glucuronide in patients with end-stage renal failure results from infinite hepatic cycling. Impaired kidney function may result in impaired glucuronidation and diuresis. While kidney impairment normally requires a dose reduction for those compounds which are mainly eliminated by renal excretion, for diuretics, a dose increment is required in order to maintain a required level of diuresis (*XXX 1999*).

In patients with nephrotic syndrome, which is characterized by proteinuria, hypoalbuminemia and edema, a mean value of nonrenal clearance of 154 ml/min was found versus 56 ml/min in healthy volunteers (*XXX et al. 1982*). Based on free drug, unbound renal clearance is unchanged (*XXX et al. 1982*, *XXX et al. 1978*) or reduced depending on the degree of renal impairment. This reflects some impairment of the tubular secretory mechanism which secretes XXX into the tubular fluid. Secreted XXX may bind to protein within the tubular fluid. This process further diminishes the pharmacological effect. Both mechanisms may thus explain the diuretic resistance often observed in these patients (*XXX 1993*, *XXX et al. 1982*).

Dialysis
Oral XXX is not significantly removed by hemodialysis. Elimination of approximately 10% of the substance during hemodialysis has been found (*XXX et al. 1982*). The distribution of XXX in the peritoneal cavity is low, 0.9% of an oral dose if found in the peritoneal fluid within

24 hours. Clearance through peritoneal dialysis, 0.5 ml/min, is approximately 10% of peritoneal creatinine clearance (*XXX et al. 1985*).

Congestive Heart Failure
The inter-individual variations in XXX absorption observed in patients with congestive heart failure has been reported to be greater than those in healthy subjects (*XXX 1979*, *XXX et al. 1982*, *XXX et al. 1987*, *XXX et al. 1979*). Oral absorption is slower in patients with decompensated congestive heart failure as compared to patients with compensated heart failure. As compared to decompensated patients, a 57% decrease in lag time, a 27% decrease in time to peak serum levels, and a 29% increase in peak serum levels were observed in compensated patients. Absorption appears abnormal in patients with decompensated congestive heart failure (*Drugdex 2007*) however, the extent of absorption of XXX as judged by the area under the plasma concentration-time curve is unaffected (*XXX et al. 1982*, *XXX et al. 1985*). Diuresis altered the pharmacokinetics of XXX in only a small percentage of patients with marked fluid overload. Maximum plasma concentration increased from 3.1 to 3.9 μg/ml (p=0.16). Maximum concentration increased by > 30% in only one third of the patients. Total absorption increased by 7% (p=0.63) (*XXX et al. 1998*).

Compared to normal patients, total and renal clearance of XXX is reduced patients with congestive heart failure (2 vs. 0.8 ml/min/kg) and elimination half-life is prolonged (mean 205 minutes) (*Drugdex 2007* [from *XXX* et al. 1987], this is due to altered renal function secondary to severe heart failure (*XXX et al. 1981*).

Cystic Fibrosis
Clearance is increased in patients with cystic fibrosis, which is related to an increase in nonrenal clearance (*Drugdex 2007* [from *XXX* et al. 1990, *XXX* et al. 1988]).

2.5.4 Overview of Efficacy

Clinical Overview

General

XXX is effective in the treatment of edema associated with congestive heart failure, hepatic disease, renal failure, even if the glomerular filtration rate is greatly reduced, and in pulmonary edema. Clinically, XXX does not differ significantly from other loop diuretics. XXX may be effective alone, but is primarily used in combination therapy for the treatment of hypertension. The loop diuretics have a shorter duration of action than thiazide-type diuretics and appear to be less effective in controlling blood pressure. XXX should be reserved for hypertensive patients with fluid retention refractory to thiazide diuretics or those with renal impairment. Edema and hypertension in patients with chronic renal failure can only be controlled with loop diuretics; large doses may be required, but the depletion of blood volume should be avoided (*Drugdex 2007*, *XXX 1996*).

The use of XXX (alone or in combination with other hypotensive agents) in chronic hypertensive patients is usually reserved for those patients with reduced renal function (creatinine clearance < 30 ml/min). XXX is a useful adjunct in the management of hypertensive crisis in doses of 40 to 80 mg intravenous over a period of 1 to 2 minutes. Larger doses are required in patients with reduced renal function. XXX is a useful adjunct in the reduction of intracranial pressure in patients undergoing surgery for intracranial hematomas or repair of a ruptured intracranial aneurysm (*Drugdex 2007*).

Additionally, XXX may be administered to diagnose acute renal failure and prevent acute tubular necrosis (*Drugdex 2007*). Beyond it, XXX may have antiinflammatory properties and has been used in respiratory tract diseases in adults and children. A recent study has shown that XXX can reduce the risk of hospitalization for prostatism (*XXX 2002*, *XXX 2001*, *XXX et al. 2006*).

Hypertension

A similar antihypertensive effect has been shown for XXX (25 mg and 40 mg twice daily) and hydrochlorothiazide (12.5 mg twice daily) during 4 weeks of treatment in a crossover study (*XXX 1975*). Hypertensive patients who are not adequately controlled with thiazides alone will probably not respond well to monotherapy with XXX either. However, the substitution of XXX (40 mg daily) for thiazide diuretics was successful in controlling blood pressure in 18 patients with mild-to-moderate hypertension receiving a multi-drug regimen (*Drugdex 2007* [from *XXX* et al. 1987]).

XXX (20 mg daily) combined with ramipril (5 mg daily) was as effective as ramipril (10 mg daily) in reducing blood pressure. The rate of responders (with diastolic blood pressure ≤ 90 mmHg) was 45% for XXX-ramipril and 47% for ramipril (10 mg). The incidence of cough was 8% in the XXX group and 12% in the 10-mg ramipril group (*XXX et al. 1992*). A similar decrease in systolic and diastolic blood pressure was induced by XXX (20 mg daily) alone, in combination with ramipril (1.25 mg daily), or with ramipril (5 mg daily) after 6 month of therapy. The left ventricular hypertrophy was reduced only in the group receiving XXX plus 5-mg ramipril (*XXX et al. 1995*).

XXX (20 mg daily) combined with penbutolol (40 mg daily) was more effective in reducing systolic and diastolic blood pressure than either of the drugs given alone (*XXX and XXX 1983*). In a non-comparative study in hypertensive patients (n=1563), the responder rate to the combination XXX (10 mg daily) and penbutolol (20 mg daily) was 78% (*XXX 1989*).

XXX (25 to 40 mg daily) combined with propranolol (40 mg three times daily) was superior to hydrochlorothiazide (25-50 mg daily) combined with propranolol (40 mg three times daily),

responder rates were 58% vs. 33%, respectively (*XXX et al. 1981*). Responder rates of 59% were observed for XXX (30 mg daily) combined with beta-blockers and of 29% for hydrochlorothiazide (25 mg daily) combined with beta-blockers (*XXX et al. 1987*).

After XXX treatment, in 67% of elderly patients (n=12) with initial low plasma renin activity, decreases in systolic blood pressure, diastolic blood pressure and mean arterial pressure, were associated with increases in plasma renin activity and serum aldosterone and with decreases in atrial natriuretic peptide and body weight. In the remaining 33% of patients, blood pressure also decreased significantly, but there were no other significant changes in parameters (*XXX et al. 2003*).

Brief postpartum XXX for patients with severe preeclampsia seems to enhance recovery by normalizing blood pressure more rapidly and reducing the need for antihypertensive therapy. Only postpartum patients (n=70) who received XXX (20 mg daily orally for 5 days) had significantly lower systolic blood pressure by postpartum day 2 compared with untreated controls and required less antihypertensive therapy during hospitalization and at discharge. No benefit was shown for patients with mild preeclampsia (n=169) or superimposed preeclampsia (n=25). There was no benefit on length of hospitalization or frequency of delayed postpartum complications (*XXX et al. 2005*).

Hypertension and Chronic Kidney Disease

According to a small clinical study (n=7), hydrochlorothiazide increased the fractional excretion of sodium and chloride more than XXX (60 mg daily) in hypertensive patients with severe renal failure. However, the combination of the two diuretics had no additional effect on the increase in sodium and chloride fractional excretion. Either monotherapy or the combination of XXX and hydrochlorothiazide decreased mean arterial blood pressure by the same extent (*XXX et al. 2005*). XXX is the diuretic of choice for the treatment of hypertension in chronic kidney disease but the adaptive changes in the distal nephron may decrease its efficacy. Hydrochlorothiazide is not believed to be efficient in this setting. A pilot double-blind cross-over study (n=23) comparing XXX (60 mg) and hydrochlorothiazide (25 mg) showed a trend towards an increase in the fractional excretion of sodium and chloride with XXX and hydrochlorothiazide (p=not significant), whereas the association of the two diuretics increased the fractional excretions of sodium and chloride from 3.4 to 4.9 and from 3.8 to 6.0, respectively ($p<0.05$). The two drugs decreased mean blood pressure by the same extent. The association of the two diuretics more efficiently reduced blood pressure (*XXX et al. 2012*).

In hypertensive chronic kidney disease patients treated with renin-angiotensin system inhibitors (n=40), add-on XXX efficaciously reduced left ventricular mass index independently from blood pressure changes. Extracellular water decreased from 18.7 to 17.7 l in XXX-treated patients while remaining unchanged (from 19.5 to 19.6 l) in controls Absolute change of left ventricular mass index correlated with changes of extracellular water in XXX-treated patients ($r=0.458$, $p=0.042$) but not in controls, suggesting a better control of volume expansion (*XXX et al. 2011*).

Edema due to Congestive Heart Failure

Numerous studies have documented the efficacy of XXX in patients with edema due to cardiac failure who are unresponsive to thiazide diuretics, especially in the case of renal impairment. Frequently, high doses (250 to 4000 mg daily) are required (*Drugdex 2007*). Current evidence suggests that continuous infusions are a potentially effective method for delivering high daily doses of diuretics and rapidly removing large amounts of excess sodium and water, and may shorten hospitalizations of patients with severe heart failure (*XXX 2006*). The addition of hydrochlorothiazide to high-dose XXX therapy produces a significant synergistic diuretic effect. In an open study in patients with severe refractory congestive

heart failure (NYHA class III to IV) (n=20), the combination of XXX (250-4000 mg daily orally or intravenously) and hydrochlorothiazide (25-100 mg daily orally) produced a reduction in mean body weight and a significant increase in mean daily urine volume and mean fractional sodium excretion (p<0.001) in patients resistant to high-dose XXX therapy alone. However, hypokalemia occurred in 75% of patients (*Drugdex 2007* [from *XXX* and *XXX* 1996]).

Most patients who were clinically stabilized on high doses of XXX (83%) remained stable on a maintenance dose equal to one-third of the dose needed for their stabilization. Remaining patients unable to tolerate the dose reduction regained their previous clinical status following the resumption of the prior diuretic doses (*XXX et al. 2003*).

Randomized studies in patients with congestive heart failure compared the effects of oral XXX with those of other diuretics like amiloride, bendroflumethiazide, bumetanide, hydrochlorothiazide, ibopamine, muzolimine and torasemide. In most of the studies, a treatment with digitalis was given. In addition to XXX, potassium or amiloride was administered in some trials to prevent hypokalemia (*XXX et al. 1990*, *XXX et al. 1981*). The duration of the treatments with XXX ranged from 8 days to 12 weeks. Oral XXX was effective in a dose range of 20-80 mg daily (median daily dose 40 mg) in significantly reducing the peripheral edema, reducing body weight, increasing urine volume and sodium excretion. It also improved other clinical symptoms of congestive heart failure (e.g. hepatomegaly, heart rate, dyspnea, hepato-jugular reflux, pulmonar and cardiac auscultation, exercise test, heart size) (*XXX et al. 1990*, *XXX et al. 1994*, *XXX 1985*, *XXX et al. 1987*, *XXX and XXX 1982*). The efficacy of XXX on cardiac edema was found to be similar or below to that of comparator diuretics (*XXX 1993*, *XXX et al. 1981*).

The short-acting XXX (40-60 mg daily), had a greater influence on heart rate variability and fluid balance than azosemide (60-90 mg daily), a long-acting loop diuretic, in patients with mild to moderate chronic congestive heart failure (n=19) in a crossover study. The 24-hour urinary sodium excretion was similar during the XXX and azosemide treatment periods but was significantly greater in the first 2 hours after XXX administration. Plasma renin activity and hematocrit level increased and high-frequency power significantly decreased 2 hours after the administration of XXX only (p<0.05) (*XXX et al. 1999*).

In patients with compensated chronic cardiac failure (NYHA class III), the natriuresis that accompanies oral XXX dosing was enhanced when given just prior to a period of timed semirecumbency. With each patient serving as his or her own control, both urine flow rate and urinary sodium excretion rate were markedly increased when XXX was given prior to bed rest as compared to its dosing prior to upright activity (*XXX et al. 2006*).

Available data from 4- to 6-week controlled studies, including patients unresponsive to optimal doses of digitalis, do not suggest a significant advantage of oral torasemide (5-20 mg once daily) over oral XXX (20-40 mg daily) in congestive heart failure. Body weight was reduced and New York Heart Association class was improved to a similar degree with both agents; decreases in serum potassium were minimal and similar; hospitalizations due to heart failure were similar. Some preliminary studies have shown that higher doses of torasemide (20 mg daily) produce greater reductions in body weight, edema, pulmonary congestion, and cardiomegaly than XXX (40 mg daily) (*Drugdex 2007*). In a pilot study, torasemide showed more abilities to reverse myocardial fibrosis in patients with chronic heart failure than did XXX. In torasemide-treated patients (n=19), collagen volume fraction in right septal endomyocardial biopsies decreased from 7.96% to 4.48% (p<0.01), and procollagen type I decreased from 143 µg/l to 111 µg/l (p<0.01) compared to no significant change in XXX-treated patients (n=17). In all patients, collagen volume fraction was directly correlated with procollagen type I (r=0.88; p<0.001) before and after treatment (*XXX et al. 2004*).

Torasemide-treated patients with chronic heart failure, but not XXX-treated patients, showed

decreased serum concentrations of the C-terminal propeptide of procollagen type I, a biochemical marker of myocardial fibrosis (*XXX et al. 2016*). According to a more recent study, long-term administration of either prolonged-release torasemide (n=77) or XXX (n=78) was not associated with significant effects on myocardial fibrosis in hypertensive patients with mild and clinically stable heart failure (*XXX Investigators Group 2011*).

Acute Decompensated Heart Failure

Results of a prospective double-blind randomized study in patients with acute decompensated heart failure and moderate-to-high baseline diuretic requirements (n=308) indicate no significant differences in patients' global assessment of symptoms or in the change in renal function with either bolus as compared with continuous infusion of XXX or at a high dose (2.5 times the previous oral dose) as compared with a low dose (equivalent to the patient's previous oral dose). The high-dose strategy was associated with greater diuresis and more favorable outcomes in some secondary measures but also with transient worsening of renal function (*XXX et al. 2011*). According to a subsequent study, admission diuretic dose was associated with an increased risk of death or re-hospitalization at 60 days. Patients on higher doses of XXX were less frequently on renin-angiotensin system inhibitors (p=0.01) and had worse renal function and more advanced symptoms (*XXX et al. 2012*).

Acute Renal Failure

Several uncontrolled reports have described the benefits of XXX therapy in preventing or reversing the course of acute renal failure. All studies comparing XXX and torsemide in chronic renal failure have involved small numbers of patients, and have not shown significant advantages of torsemide, particularly with regard to potassium and calcium balance (*Drugdex 2007*).

Data of a placebo-controlled study showed no differences in survival and renal recovery rates between patients with acute renal failure (n=383) requiring dialysis therapy who were treated either with XXX either intravenously (25 mg/kg daily) or orally (35 mg/kg daily). Time to achieve a 2-liter daily diuresis was shorter with XXX than placebo. An urine output of at least 2 liter daily during the study period achieved 57% XXX-treated patients versus 33% placebo-treated patients (p<0.001). High-dose XXX maintains urinary output, but does not have an impact on survival and recovery. There were no significant differences in number of dialysis sessions and time on dialysis therapy between groups, even in the subgroup of patients reaching a 2-liter daily diuresis (*XXX et al. 2004*). Moreover, a meta-analysis of 9 randomized controlled trials (n=849) confirmed that XXX is not associated with significant clinical benefits in the prevention and treatment of acute renal failure in adults. High doses helped maintain urinary output, but may be associated with an increased risk of ototoxicity (*XXX 2006*).

The severity of acute kidney injury has a significant effect on the diuretic response to XXX; a good response may indicate some residual renal function. The current evidence does not suggest that XXX can reduce mortality in patients with acute kidney injury. In patients with acute lung injury without hemodynamic instability, XXX may be useful in achieving fluid balance to facilitate mechanical ventilation according to the lung-protective ventilation strategy (*XXX 2010*). Data from the Fluid and Catheter Treatment Trial obtained from patients with acute lung injury (n=306) showed that a positive fluid balance after acute kidney injury was strongly associated with mortality. Higher XXX doses had a protective effect on mortality (60-day survival) but no significant effect after adjustment for post-acute kidney injury fluid balance. There was no threshold dose of XXX above which mortality increased (*XXX et al. 2011*).

Post-Transplantation Renal Edema

XXX is effective to treat fluid overload and hypertension following renal transplantation. However, its efficacy varies widely, with many patients requiring much higher doses. One study reported that nonresponder have a decreased ability to secrete XXX into tubular fluid, as well as a lower ability to respond to the drug, than responders. Giving the drug intravenously offers no real advantage over oral administration (*Drugdex 2007* [from Smith et al. 1981]).

Chronic Kidney Disease and Dialysis

In patients with renal edema due to advanced chronic renal failure, glomerulonephritis or nephrotic syndrome, XXX therapy (dose range of 40 to 1000 mg daily orally for 1 to 4 weeks) has been shown to reduce edema, body weight and to increase diuresis and natriuresis. However, body weight and edemas were less decreased with XXX than with torasemide (100-400 mg daily orally), bumetanide (1-10 mg daily orally) and xipamide (40 mg daily orally) (*XXX et al. 1988*, *XXX et al. 1988*, *XXX et al. 1981*, *XXX and XXX 1982*, *XXX 1981*).

Elevated extracellular fluid volume could be corrected acutely with XXX and torasemide. In patients with chronic kidney disease persistent diuretic use resulted in dynamic changes in extracellular water and other body fluid compartments that translated into chronic blood pressure reduction. Over 3 weeks, XXX reduced mean 24-hour ambulatory blood pressure from 147/78 to 138/74 mmHg (p=0.021) and torasemide reduced it from 143/75 to 133/71 mmHg (p=0.007) (*XXX and XXX 2003*). However, bioequivalent doses of torasemide and XXX failed to demonstrate superiority of torasemide with respect to natriuresis or 24-hour ambulatory blood pressure control in subjects with stage 2 or 3 chronic kidney disease (n=14) (*XXX et al. 2003*).

High-dose XXX (2 g) was effective in patients on continuous ambulatory peritoneal dialysis (n=7) in increasing urine volume (average 400 ml) and electrolyte excretion (54 mmol) without affecting urea and creatinine clearance. In these patients, the individual response to an identical high dose of XXX is dependent on the magnitude of residual glomerular filtration rate (*van XXX et al. 2003*). Long-term XXX (250 mg daily for 1 year) produces a significant increase in urine volume over 12 months when on continuous ambulatory peritoneal dialysis (n=61), and may result in clinically significant improvement in fluid balance. However, XXX has no effect on preserving residual renal function (*XXX et al. 2001*).

Use of small doses of XXX (40 mg daily for 3 months) in chronic kidney disease patients with residual renal function undergoing hemodialysis (n=10) could significantly increase urinary volume (p=0.008) and sodium excretion (p=0.02) compared to patients who did not use this drug (n=9) (*XXX et al. 2011*).

Children with Nephrotic Syndrome

In children (2-16 years of age) with edemas due to nephrotic syndrome or glomerulonephritis, XXX (2 mg/kg bodyweight daily orally) decreased body weight and increased urine flow rates (*XXX et al. 1978*). Combination therapy with metolazone (0.2 to 0.4 mg/kg daily) and XXX (2 to 4 mg/kg daily) was reported effective in children with edema resistant to XXX alone. However, 5 of 7 episodes of edema (71%) in children with both nephrotic syndrome and chronic renal insufficiency did not respond to combination diuretic therapy (*Drugdex 2007* [from *XXX* 1984]).

Severe edema in children with nephrotic syndrome may be associated with volume contraction or volume expansion. Usually, severe edema in children is treated with intravenous albumin and diuretics, which is appropriate for volume contraction patients. However, in volume expansion patients, this can precipitate fluid overload. According to a

recent prospective study, the use of diuretics alone (intravenous XXX and oral spironolactone) is safe and effective in the treatment of children with volume expansion as compared to albumin plus XXX which is appropriate for patients with volume contraction (*XXX et al. 2016*).

Ascites or Edema associated with Cirrhosis

Randomized studies have been performed in nonazotemic cirrhotic patients with ascites. The proportion of patients with peripheral edema is often not reported. Cirrhosis was caused in most cases by alcohol abuse, in rare cases it occurred post-necrotic, or resulted from chronic hepatitis B infection or hemochromatosis. The resorption of ascites fluid by the peritoneal membrane cannot exceed 0.9 l per day, approximately 200 to 300 g per day is mobilized in patients without peripheral edema and 1 kg in the presence of peripheral edema (*XXX et al. 1990*, *van XXX and XXX 1991*). The aim of the treatment is to mobilize the intraabdominal fluid by creating a net negative balance of sodium. Best rest and low-sodium diet (maximum 40-60 mEq/d) can induce the disappearance of the ascites in 10% of patients (*XXX et al. 1993*). In the nonresponders, these measures should be associated to a diuretic treatment. XXX alone has been shown to be effective in only 50-70% of patients, indicating a moderate diuretic effect (*XXX et al. 1983*). One possible cause for the reduced effectiveness of XXX in ascites may be that the sodium which is not reabsorbed in the loop of Henle due to the action of XXX may be reabsorbed in the collecting duct due to hyperaldosteronism observed in cirrhotic patients (*XXX et al. 1993*). The responder rate to aldosterone antagonists e.g. spironolactone (150-500 mg daily orally) has been found to be higher (57-95%) (*XXX et al. 1991*, *XXX et al. 1983*). The simultaneous administration of XXX (40 to 160 mg daily orally) and spironolactone (100 to 400 mg daily orally) has been shown to increase the natriuretic effect of both drugs and to reduce the incidence of hypo- or hyperkalemia (*XXX et al. 1992*, *XXX et al. 1993*).

The effect of XXX has been compared to that of torasemide in several studies resulting in an overall similar effectiveness of the two drugs (*Drugdex 2007*). In a small study (n=14), single dose XXX (80 mg) induced a lower 24-hour cumulative diuresis than a single dose of torasemide (20 mg) in patients with ascites (*XXX et al. 1993*). Also, the combination of XXX (50 mg daily) and the aldosterone antagonist potassium canrenoate (200 mg daily) seems to induce a lower diuresis and natriuresis than the combination torasemide (20 mg daily) and potassium canrenoate (200 mg daily) (*XXX et al. 1993*). However, in a longterm study over 70 days in cirrhotic patients with controlled ascites, combined spironolactone (200 mg daily) with either XXX (50 mg daily) or torasemide (20 mg daily) induced similar increase in urine volume and factional excretion of sodium and were both able to avoid an increase in body weight (*XXX et al. 1993*).

Diuretic-Resistant Edema

A frequent cause of diuretic-resistant ascites is inadequate sodium restriction. Once the ascites has disappeared, most cirrhotic patients continue to require a low-sodium diet and low doses of diuretics to prevent re-accumulation of ascites (*XXX et al. 1992*). In patients who are resistant to XXX, a successful use of the combination of metolazone and XXX is well documented and commonly reported in both adults and children. Patients, who were resistant to oral or intravenous XXX (80 to 1060 mg), responded to the addition of metolazone (2.5 to 40 mg) which produced a rapid and significant diuresis. The mechanism of this synergistic effect is probably related to their different sites of action in the nephron. Metolazone blocks sodium reabsorption in the distal convoluted tubule, while XXX acts at the ascending loop of Henle (*Drugdex 2007*).

Studies on combined XXX and human albumin treatment for diuretic-resistant edema in patients with nephrotic syndrome and cirrhosis report conflicting results. However, it appears

the combination may provide clinical benefits for selected patients. The addition of albumin to enhance diuretic efficacy should be reserved for patients with recalcitrant edema or ascites in whom diuretic doses have been maximized and those with severe hypoalbuminemia (*XXX et al. 2003*). The combination of XXX and albumin has a superior short-term efficacy over XXX alone in enhancing water and sodium diuresis in hypoalbuminemic chronic kidney disease patients (*XXX and XXX 2012*).

Edema as a Result of Burns

XXX is used especially for the supportive treatment of edema following second- and higher degrees of burns. It should be adapted to the individual's clinical symptoms and begun only after correction of a volume deficiency (*Aufbereitungskommission 1986*, *BfArM 1996*). In electrical injuries, XXX was used in patients with acidosis or with a marked myoglobinuria (*XXX 1994*).

Postoperative Pleural Effusion

Retrospective analysis of postoperative XXX (n=29) versus no-XXX therapy (n=161) indicate that postoperative XXX in patients who undergo significant pleural manipulation during spinal deformity surgery may decrease the incidence of clinically symptomatic pleural effusion requiring thoracocentesis. In the respective groups, 3.4% vs. 16% patients underwent thoracocentesis (*XXX and XXX 2011*).

Thyroidectomy Pretreatment

Recombinant human TSH (rhTSH) can be used for post-surgical radioiodine (I^{131}) thyroid remnants ablation in differentiated thyroid cancer patients after surgery. Radioiodine ablation during rhTSH stimulus can be improved by reducing the circulating iodine pool and by increasing thyroid cell uptake and retention of I^{131} obtained by administering XXX and lithium. According to results of a controlled study, in low-risk thyroid cancer patients the pre-treatment with XXX seems to play an important role to further improve the outcome of ablation by reducing the iodine pool (*XXX et al. 2010*).

2.5.5 Overview of Safety

Adverse Drug Reactions

General

The most common adverse effects of XXX therapy are primarily related to fluid or electrolyte disturbances (e.g. dehydration, hypokalemia). Hypokalemia occurred in 75% of patients (*Drugdex 2007* [from *XXX* and *XXX* 1996]). Excessive diuresis can lead to circulatory disorders manifesting mainly as headache, dizziness, visual disorders, dry mouth and thirst, hypotension and disorders of orthostatic regulation. Excessive diuresis can result in dehydration and hypovolemia, circulatory collapse and hemoconcentration are possible. There may be an increased tendency to thrombosis, especially in older patients (*Drugdex 2007*, *XXX 1985*).

As a result of increased renal sodium losses, hyponatremia and corresponding symptoms can occur, especially, if sodium chloride intake is restricted. Frequently observed symptoms of sodium deficiency are apathy, calf cramps, loss of appetite, weakness, drowsiness, vomiting, and confusion. Hypokalemia can occur as a result of increased renal potassium loss, particularly if potassium intake is reduced at the same time, and/or if extrarenal potassium losses are increased (e.g. resulting from vomiting or chronic diarrhea) (*XXX et al. 1992*, *XXX et al. 1970*). Diuretic-induced hypokalemia is dose-related, generally mild and has been observed in 14% to 60% of ambulatory hypertensive patients. Potassium losses

can lead to cardiac symptoms (e.g. conduction disturbances), renal (polyuria, polydipsia) and neuromuscular symptoms (vomiting, constipation, meteorism). Severe potassium losses can result in paralytic ileus or disturbances of consciousness (*Drugdex 2007*). Dyskalemic paralysis has been observed as the prominent clinical symptom of hypokalemia in XXX therapy and simultaneous laxative abuse (*XXX et al. 1999*).

Overall, the majority of adverse effects are due to the pharmacological properties of XXX, only a small percentage accounts for other adverse reactions. As reviewed by *XXX and XXX 1990a*), of 2367 XXX recipients 10.1% had an adverse reaction probably or definitely due to XXX. Of these, 4.6% exhibited some manifestation of volume depletion, 3.6% developed hypokalemia, 1.5% developed another form of electrolyte or metabolic disturbance and 0.4% experienced other adverse reactions (e.g. rash, CNS disturbances, flushing, dry mouth). In 14 of 239 cases, the severity was considered to be life-threatening with 2 subsequent deaths.

According to a retrospective cohort study (n=244), higher XXX doses (> 80 mg daily) are associated strongly and independently with adverse long-term outcome in chronic heart failure. For each 40-mg XXX tablet, there was a 67% increase in risk of an adverse outcome within 2 years. The increase in risk was independent of other variables crudely associated with prognosis. Among euvolemic patients, those on ≤ 80 mg/day XXX performed better than those on higher doses. Among hypervolemic patients, the diuretic dose had no prognostic implications (*XXX et al. 2011*).

Endocrine/Metabolic Effects

Like the thiazide diuretics, XXX causes increased glucose levels. Hyperglycemia usually presents after 2 to 4 weeks of treatment and is manifested by mild increases in fasting blood sugar. It is usually reversible, most significant in prediabetic patients or diabetics which can experience deterioration in metabolic status (*Drugdex 2007*, *XXX et al. 1968*, *XXX 1985*, *XXX and* XXX *1978*). XXX can cause increases in serum lipid levels. Increases in cholesterol, triglycerides and transient increases in serum creatinine and serum urea have been observed (*Drugdex 2007*, *XXX et al. 1998*, *XXX et al. 1988*). XXX influences serum lipid levels markedly less than thiazide diuretics or chlorthalidone (*van der XXX et al. 1998*). In patients with congestive heart failure, long-term treatment with oral XXX (80-240 mg daily for 3-14 months) may be associated with clinically significant vitamin deficiency due to excessive urinary excretion of thiamine (*Drugdex 2007*). Severe thiamine deficiency was found in 98% patients receiving 80 mg daily of XXX and in 57% patients taking 40 mg daily (*XXX et al. 2003*). The elderly patients with heart failure treated with XXX, thiamine deficiency is assumed to derive from an altered metabolism of thiamine, which is not understood at present (*XXX et al. 2000*). However, in patients with chronic renal failure, in addition to the increased urinary excretion of vitamin B6 and vitamin C and increased urinary excretion of oxalic acid has been a new positive side effect (*XXX et al. 1999*).

Hyperuricemia secondary to XXX occurs in about 40% of men and less frequently in women. The effect is persistent, but reversible with discontinuation of the drug. In predisposed patients this can lead to attacks of gout (*Drugdex 2007*, *XXX et al. 1978*, *XXX and XXX 1982*).

XXX can cause hypermagnesuria which can result in hypomagnesemia, arrhythmias, and tetany. In a study involving congestive heart failure patients (n=404) who received XXX (≥ 40 mg daily for > 3 months) normomagnesemia, hypermagnesemia, and hypomagnesemia were reported in 82.6%, 4.9%, and 12.3% of patients, respectively. However, after adjusting for age, severity of disease, and renal failure, only hypomagnesemia was significantly associated with shortened survival (p=0.009) (*Drugdex 2007* [from *XXX* et al. 2003]).

Renal Effects

XXX induced hypercalciuria and calcium renal stones in premature infants, and in neonates renal calcification, accompanied by bone demineralization, has been reported by a number of investigators. XXX induced renal calcifications in very low birth weight infants may be associated with long-term glomerular and tubular dysfunction (*Drugdex 2007*, *XXX et al. 1988*, *XXX et al. 1984*). Long-term XXX treatment in full-term infants (median age 2.9 months; n=72) with congestive heart failure entails a considerable risk of developing nephrocalcinosis (XXX 14% vs. untreated 0%) and may increase with higher dosages (*XXX 1999*). XXX may increase the risk for hip fractures. In postmenopausal women (n=280), however, renal calcium losses in XXX users are compensated by a parathyroid hormone-dependent increase in 1,25 dihydroxy-vitamin D levels. Thereby calcium balance remains neutral without major effects on bone metabolism (*Drugdex 2007*, *XXX et al. 2005*). An unusual case of XXX-induced nephrolithiasis causing ureteral obstruction, urinoma, and acute renal failure in a preterm neonate was presented by (*XXX and XXX 2004*).

Renal function after cardiac surgery may be adversely affected by XXX (*XXX et al. 2003*). Most patients with chronic congestive heart failure (n=29) who were clinically stabilized on high doses of XXX remained stable on a maintenance dose equal to one-third of the dose needed for their stabilization (*XXX et al. 2003*). One case of interstitial nephritis and membrane glomerulonephritis after daily oral administration of XXX (40 mg for 5 months) is described (*XXX and XXX 1986*). According to an analysis of patients in an intensive care unit (n=132), age, use of XXX, and septic shock were predictors of acute kidney injury in critically ill patients. Use of XXX in the subgroup of patients with sepsis/septic shock increased (68.4%) the chance of development of acute kidney injury when compared to the cohort as a whole (43.9%) (*XXX et al. 2012*).

Ototoxic Effects

Ototoxicity (tinnitus, hearing loss) has been reported with XXX following oral and intravenous administration. Reversible losses of hearing intravenous administration of 1000 mg XXX over 40 minutes occurred in 9 of 15 patients. In contrast, no effect on hearing occurred in 10 patients after oral or slow intravenous administration of high doses of XXX over a longer period of time (*Drugdex 2007*, *XXX and XXX 1985*). Evidence from a meta-analysis of 9 controlled trials suggested an increased risk of temporary deafness and tinnitus in patients treated with high doses of XXX. A sensation of pressure in the ears and dizziness may occur due to a change in the electrolyte composition of the endolymph. XXX inhibits adenylate cyclase in the inner ear, and to a lower degree sodium-potassium-ATPase. In addition to the resultant deterioration in energy balance, morphological changes to the inner ear can also occur. In most cases symptoms are reversible however, permanent damage can occur. Predisposing risk factors include high doses (serum levels of ≥ 50 μg/ml increase the risk of ototoxicity), renal, cardiac, or liver impairment, hypoproteinemia, and concomitant administration of other ototoxic drugs. Premature infants appear to be at the greatest risk to develop ototoxicity (*Drugdex 2007*, *XXX 2006*, *de XXX and XXX 1983*, *XXX et al. 1979*). Furthermore, aminoglycoside followed by XXX may increase the risk for ototoxicity. A case summary showed auditory toxicity occurring after only 5 days of gentamicin therapy and one single dose of XXX (*XXX et al. 2002*).

Dermatologic Effects

A variety of dermatologic adverse effects such as rash, pruritus, urticaria, purpura, photosensitivity reactions, exfoliative dermatitis, and necrotizing angiitis have been reported with XXX use as well as several cases of erythema multiforme secondary to XXX have been reported. Rare cases of bullous pemphigoid have been reported in association with XXX (*Drugdex 2007*, *XXX and XXX 2006*, *XXX et al. 1999*, *XXX et al. 1984*). XXX may give rise to symptoms of Stevens-Johnson syndrome. There are 5 case reports of reversible tissue

necrosis from elderly patients (ages 71 to 85) (*Drugdex 2007*) and one case of acute generalized exanthematic pustulosis (*XXX et al. 2000*).

Allergic Effects

Allergic reactions occasionally occur during treatment with XXX. These can manifest themselves as febrile conditions, skin reactions (bullous exanthema, purpura, erythema exsudativum multiforme, exfoliative dermatitis, photo-sensitivity) vasculitis, interstitial nephritis, thrombocytopenia leucopenia or hemolytic anemia, occasionally as aplastic anemia or agranulocystitis (*Drugdex 2007*, *XXX 1990*, *XXX 1985*). One case of anaphylaxis to oral XXX has been reported (*XXX et al. 2003*). A fatal immunocytopenic purpura and cerebral hemorrhage following intake of XXX is described. The patient probably had been sensitized to XXX 18 month before the development of purpura (*XXX and XXX 2004*). Several cases of XXX-associated fever in infants have been reported, which appears dose-related and without allergic manifestations (*Drugdex 2007*). One case of Sweet syndrome related to the use of XXX is described (*XXX et al. 2005*). Pseudoporphyria cutanea tarda was induced by XXX (500 mg daily) in a patient undergoing peritoneal dialysis (*XXX et al. 1988*).

Cardiocascular Effects

XXX may adversely influence patency rate for the immature ductus arteriosus (*Drugdex 2007* [from Green et al. 1981]). In premature infants with respiratory distress syndrome, diuretic treatment with XXX during the first weeks of life can increase the risk of persistent arterial Botallo's duct (*XXX 1983*). In chronic heart failure high daily doses of XXX have been associated with increased mortality. Normalized XXX dose (mean, 15 mg/m^2) was a major determinant of prognosis in patients with chronic heart failure but without ongoing signs and symptoms, and this suggests a possible negative interaction of this drug in clinically stable patients (*XXX et al. 2012*).

Gastrointestinal Effects

Gastrointestinal disorders (e.g. nausea, vomiting, diarrhea) seldom occur (*Drugdex 2007*, *XXX 1989*). A case of drug related non-occlusive, ulcerative-stricturing, ischemic colitis, masquerading as colonic cancer is reported in association with XXX intake (*XXX et al. 2004*).

Other Effects

There have been individual observations of acute pancreatitis, for which there appears to be a causal connection with XXX treatment lasting several weeks (*Drugdex 2007*, *XXX and XXX 1975*). A recent review did not recommend oral XXX as treatment for newborns with transient tachypnea. Infants with transient tachypnea (n=50) who received oral XXX (2 mg/kg followed by 1 mg/kg 12 hours later), showed greater weight loss in the first 24 hours than placebo-treated infants, but there was no evidence of a difference between the groups in duration of tachypnea or severity of symptoms or length of hospitalization (*XXX and XXX 2002*).

ADR Reports

Summary of Listed Adverse Drug Reactions (ADRs)

The most common XXX adverse effect is fluid and electrolyte imbalance including hyponatremia, hypokalemia, and hypochloremic alkalosis, particularly after large doses or prolonged use. Signs of electrolyte imbalance include headache, hypotension, muscle cramps, dry mouth, thirst, weakness, cardiac arrhythmias, and gastrointestinal disturbances. Hypovolemia and dehydration may occur, especially in the elderly. XXX increases the urinary excretion of calcium and nephrocalcinosis has been reported in preterm infants. XXX may

cause hyperuricemia and precipitate gout in some patients. It may provoke hyperglycemia and glycosuria. Pancreatitis, cholestatic jaundice, tinnitus* and deafness* may occur (*in particular during rapid high-dose parenteral XXX). Other adverse effects include blurred vision, yellow vision, dizziness, headache, fever, orthostatic hypotension, bone marrow depression, and hypersensitivity reactions (include interstitial nephritis and vasculitis). Rashes and photosensitivity reactions may be severe. There have been reports of agranulocytosis, thrombocytopenia, and leucopenia (see *Addendum to Clnical Overview (AddCO) [154/02/16]* from 31/01/2016 [Data Lock Point]).

Detailed Unlisted Adverse Drug Reactions (ADRs)
According to the cummulative summary tabulation of serious symptoms from spontaneous, regulatory, and literature source (time period: 01/01/2002–31/01/2016), adverse drug reactions like **Blood/Lymphatic system disorders** (Agranulocytosis, Anaemia, Aplastic anaemia, Disseminated intravascular coagulation, Granulocytopenia, Haemolytic anaemia, Heparin-induced, thrombocytopenia, Leukopenia, Neutropenia, Pancytopenia, Thrombocytopenia, Thrombocytopenic purpura), **Cardiac disorders** (Arrhythmia, Atrial fibrillation, Bradycardia, Bradycardia foetal, Cardiac arrest, Cardiac disorder, Cardiac failure, Cardiac failure congestive, Cardiac flutter, Cardiogenic shock, Cardiomegaly, Cardio-respiratory arrest, Extrasystoles, Left ventricular dysfunction, Left ventricular failure, Left ventricular hypertrophy, Long QT syndrome, Mitral valve incompetence, Myocardial infarction, Myocardial ischaemia, Sinus tachycardia, Stress cardiomyopathy, Tachycardia, Torsade de pointes, Tricuspid valve incompetence, Ventricular dysfunction, Ventricular tachycardia), **Congenital/Familial/Genetic disorders** (Acrodermatitis enteropathica, Adrenogenital syndrome, Microcephaly, Porencephaly), **Ear/Labyrinth disorders** (Deafness, Deafness bilateral, Deafness unilateral, Ear disorder, Hearing impaired, Ototoxicity, Tinnitus, Vertigo), **Endocrine disorders** (Inappropriate antidiuretic hormone secretion), **Eye disorders** (Blindness, Choroidal detachment, Conjunctivitis, Miosis, Retinal artery occlusion, Retinal vein occlusion, Visual impairment), **Gastrointestinal disorders** (Abdominal pain , Abdominal pain upper, Colitis, Colitis ischaemic, Diarrhoea, Duodenal ulcer, Dyspepsia, Dysphagia, Faecaloma, Gastric dilatation, Gastritis, Gastrointestinal disorder, Gastrointestinal haemorrhage, Gastrointestinal tract mucosal pigmentation, Large intestinal ulcer, Lip erosion, Lip swelling, Lower gastrointestinal haemorrhage, Nausea, Pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Swollen tongue, Tongue dry, Vomiting), **General disorders/Administration site conditions** (Asthenia, Chest pain, Condition aggravated, Death, Drug effect decreased, Drug ineffective, Drug interaction (see 2.1 *Overview of Safety / Subtitle – Drug Interactions*)**,** Drug withdrawal syndrome, Enanthema, Face oedema, Fatigue, Feeling abnormal, Feeling cold, Food interaction, General physical health deterioration, Generalised oedema, Hyperthermia, Hypothermia, Malaise, Mucosal inflammation, Multi-organ failure, Oedema, Oedema peripheral, Pain, Product substitution issue, Pyrexia, Therapeutic response decreased, Ulcer haemorrhage), **Hepatobiliary disorders** (Cholelithiasis, Cholestasis, Granulomatous liver disease, Hepatic failure, Hepatic function abnormal, Hepatic necrosis, Hepatitis, Hepatitis acute, Hepatitis cholestatic, Liver disorder, Liver injury), **Immune system disorders** (Anaphylactic reaction, Autoimmune disorder, Drug hypersensitivity), **Infections/Infestations** (Bacterial infection, Bacteriuria, Campylobacter gastroenteritis, Clostridium difficile colitis, Infection, Infective exacerbation of chronic obstructive airways disease, Lower respiratory tract infection, Oral candidiasis, Pneumonia, Rash pustular, Sepsis, Staphylococcal scalded skin syndrome, Urinary tract infection, Wound infection pseudomonas), **Injury, Poisoning/Procedural complications** (Accidental overdose, Autonomic dysreflexia, Contusion, Fall, Fracture, Humerus fracture, Intentional overdose, Laceration, Maternal exposure during pregnancy, Medication error, Neuromuscular block prolonged, Overdose, Toxicity to various agents), **Investigations** (Alanine aminotransferase increased, Aspartate aminotransferase increased,

Blood alkaline phosphatase increased, Blood calcium increased, Blood creatine phosphokinase increased, Blood creatinine increased, Blood electrolytes abnormal, Blood glucose decreased, Blood glucose increased, Blood osmolarity decreased, Blood potassium decreased, Blood potassium increased, Blood pressure decreased, Blood sodium decreased, Blood urea abnormal, Blood urea increased, Blood uric acid increased, Breath sounds abnormal, Carbon dioxide increased, Cardiac murmur, Cardioactive drug level increased, Crystal urine present, Drug level increased, Ejection fraction decreased, Electrocardiogram abnormal, Electrocardiogram QT prolonged, Eosinophil count increased, General physical condition abnormal, Glomerular filtration rate decreased, Haemoglobin decreased, Heart rate increased, Heart rate irregular, International normalised ratio increased, Liver function test abnormal, Sinus rhythm, Transaminases increased, Venous pressure jugular increased, Weight decreased, Weight increased), **Metabolism/Nutrition disorders** (Alkalosis hypokalaemic, Decreased appetite, Dehydration, Electrolyte imbalance, Fluid imbalance, Fluid retention, Gout, Hypercalcaemia, Hyperglycaemia, Hyperkalaemia, Hyperuricaemia, Hypocalcaemia, Hypochloraemia, Hypoglycaemia, Hypokalaemia, Hypokalaemic syndrome, Hypomagnesaemia, Hyponatraemia, Hypophagia, Hypophosphataemia, Hypovolaemia, Lactic acidosis, Metabolic acidosis, Metabolic alkalosis), **Musculoskeletal/Connective tissue disorders** (Arthralgia, Muscle disorder, Muscle twitching, Rhabdomyolysis, Tendonitis), **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** (Colon cancer, Mesothelioma, Myelodysplastic syndrome), **Nervous system disorders** (Akinesia, Altered state of consciousness, Aphasia, Balance disorder, Brain injury, Burning sensation, Carotid artery stenosis, Cerebral ischaemia, Coma, Complex partial seizures, Convulsion, Coordination abnormal, Diabetic coma, Dizziness, Dyskinesia, Encephalopathy, Epilepsy, Grand mal convulsion, Haemorrhage intracranial, Headache, Hypersomnia, Hypoglycaemic coma, Incoherent, Ischaemic stroke, Lethargy, Loss of consciousness, Lupus encephalitis, Mental impairment, Osmotic demyelination syndrome, Paraesthesia, Paralysis, Parkinsonism, Presyncope, Somnolence, Syncope, Transient ischaemic attack), **Psychiatric disorders** (Agitation, Anxiety, Apathy, Completed suicide, Confusional state, Delirium, Depression, Dissociation, Drug abuse, Drug dependence, Emotional distress, Hallucination, Intentional drug misuse, Nervousness, Panic attack, Psychotic disorder, Restlessness, Sleep disorder, Suicide attempt), **Renal/Urinary disorders** (Anuria, Glomerulonephritis, Haematuria, Nephrocalcinosis, Nephrogenic diabetes insipidus, Nephrolithiasis, Oliguria, Renal cyst, Renal disorder, Renal failure, Renal failure acute, Renal failure chronic, Renal impairment, Renal injury, Renal tubular acidosis, Ureteric stenosis, Urinary retention), **Reproductive system/Breast disorders** (Genital erythema, Genital lesion, Gynaecomastia), **Respiratory/Thoracic/Mediastinal disorders** (Acute pulmonary oedema, Acute respiratory distress syndrome, Asthma, Bronchospasm, Chronic obstructive pulmonary disease, Cough, Dyspnoea, Dyspnoea exertional, Eosinophilic pneumonia acute, Laryngeal oedema, Laryngospasm, Obstructive airways disorder, Oropharyngeal pain, Orthopnoea, Pleural effusion, Pulmonary oedema, Rales, Respiratory arrest, Respiratory failure, Stridor), **Skin/Subcutaneous tissue disorders** (Acute febrile neutrophilic dermatosis, Acute generalised exanthematous pustulosis, Alopecia, Angioedema, Blister, Cold sweat, Dermatitis bullous, Drug eruption, Drug rash with eosinophilia and systemic symptoms, Erythema, Erythema multiforme, Generalised erythema, Henoch-Schonlein purpura, Hirsutism, Hyperhidrosis, Leukocytoclastic vasculitis, Lichenoid keratosis, Pemphigoid, Photosensitivity reaction, Pruritus, Pruritus generalised, Pseudoporphyria, Purpura, Rash, Rash erythematous, Rash generalised, Rash macular, Rash maculo-papular, Rash papular, Skin burning sensation, Skin disorder, Skin exfoliation, Stevens-Johnson syndrome, Swelling face, Telangiectasia, Toxic epidermal necrolysis, Toxic skin eruption, Urticaria, Vasculitic rash), **Social circumstances** (Treatment noncompliance), **Surgical and medical procedures** (Coronary artery bypass, Off label use), **Vascular disorders** (Aortic dissection,

Circulatory collapse, Haematoma, Haemorrhage, Hypertension, Hypotension, Jugular vein distension, Orthostatic hypotension, Shock, Thrombosis, Vasculitis), and **Pregnancy** (Peripartum cardiomyopathy) have been described in ADR reports (see *Addendum to Clnical Overview (AddCO) [154/02/16]* from 31/01/2016 [Data Lock Point]).

No change in characteristics of listed adverse drug reactions was observed and the safety profile of XXX has not changed in a fundamental way. The data described in this report did not change the risk/benefit balance of XXX. Therefore, no immediate actions are regarded as necessary. However, based on the review of safety data following PSUR evaluation and requirements from the regulatory authority relevant topics like renal failure (acute), renal calculi and nephrocalcinosis in other populations than premature infants will be closely monitored further by the Pharmacovigilance Unit of MAH (see *Addendum to Clnical Overview (AddCO) [154/02/16]* from 31/01/2016 [Data Lock Point]).

No signal justifying a change of the CCSI (Company Core Safety Information)/RSI (Reference Safety Information) arose from these mostly single listed symptoms. There is no evidence of any significant increase in the frequency of any adverse drug reaction due to XXX. The symptoms mentioned above refer to adverse drug reactions from serious cases that are already in this or in a similar form included in the CCSI (Company Core Safety Information), RSI (Reference Safety Information), ISE (Information Sheet for Experts) and PIL (Patient Information Leaflet).

Based on results of computer-assisted investigations for publications on the subject of adverse drug reactions, no new information regarding the benefit-risk-ratio of XXX could be found in the international literature (see *Appendix I*).

Drug Interactions

Antibiotic Drugs

Considerably higher tissue and plasma concentrations of the antibiotic were determined after concomitant use of cephalosporins and XXX, than after cephalosporin alone. XXX can potentiate the toxic effects of nephrotoxic antibiotics (e.g. aminoglycosides), cephalosporines, polymyxines (XXX *et al. 1978*, XXX *et al. 1977*, XXX *et al. 1984*, XXX *1985*, XXX *and* XXX *1976*).

Antihypertensive Drugs

XXX is able to potentiate the effect of antihypertensive drugs. Severe postural hypotension (first dose) has been reported when ACE inhibitors are added to loop diuretic therapy. Significantly higher propranolol blood levels have been reported when both, propranolol and XXX are given orally (*Drugdex 2007*). XXX does not influence the pharmacokinetic parameters of atenolol and the pharmacokinetic of XXX is not influenced by captopril in hypertensive patients (XXX *et al. 1981*, XXX *et al. 1990*). Hypokalemia and subsequent cardiotoxicity (torsades de pointes, QT prolongation) may result from interaction of XXX with calcium channel blocker bepidril (*Drugdex 2007*). Coadministration of the direct renin inhibitor aliskiren and XXX reduced XXX exposure and had a minor effect on aliskiren pharmacokinetics. The clinical significance of reduced systemic exposure to XXX during coadministration of aliskiren is uncertain (XXX *et al. 2008*).

Diuretics

Hydrochlorothiazide addition to high-dose XXX therapy produces a significant synergistic diuretic effect (*Drugdex 2007*, XXX *et al. 2012*). No clinically significant interactions were noted after coadministration of XXX and the non-peptide active vasopressin receptor antagonist tolvaptan. Tolvaptan did not significantly affect the natriuretic activity of XXX. XXX did not significantly affect the aquaretic activity of tolvaptan (XXX *et al. 2007*).

NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) have been reported to reduce both the diuretic and antihypertensive effects of loop diuretics, which appear to relate to effects on chloride delivery to the distal tubule as well as to effects on renal prostaglandins (*Drugdex 2007*). The natriuretic effect of XXX can be attenuated by NSAIDs (e.g. indomethacin) and probenecid (XXX *1987*, XXX *et al. 1975*, XXX *et al. 1983*, XXX *1990*). Aspirin can decrease the effectiveness of XXX and this is less pronounced with low doses of aspirin. In patients who develop hypovolemia during XXX therapy, concomitant administration of NSAID can cause acute renal failure. Due to competition for renal elimination sites, patients receiving high-dose salicylates concurrently with XXX may experience potentiated salicylate toxicity (e.g. at lower aspirin doses than expected) (*Drugdex 2007*, XXX *1987*, XXX *1985*, XXX *et al. 1992*). An open-label 5-way crossover study in healthy adults (n=40), showed pharmacodynamic interactions of XXX with oral diclofenac (decrease of urine output) and ibuprofen (increase of urine sodium excretion). XXX also affected plasma and urine pharmacokinetic profiles. Diclofenac epolamine topical patch had no effect on XXX pharmacodynamics; total systemic exposure to diclofenac during topical treatment was < 1% that of oral diclofenac (XXX *et al. 2011*).

Ototoxic, Nephrotoxic Drugs (eg. Cisplatin, Aminoglycosides)

Concurrently administered XXX and aminoglycosides or cisplatin may increase the risk of nephrotoxicity and ototoxicity. The aminoglycoside interacts with the cell membranes in the inner ear, increasing their permeability. This theoretically allows the loop diuretic to penetrate into the cells in higher concentrations, causing more severe damage up to irreversible hearing disorder. Moreover, ethacrynic acid may produce additive or synergistic ototoxic effects in the stria vascularis (*Drugdex 2007*, XXX *et al. 2002*, XXX *et al. 1987*).

Corticosteroids

Concomitant loop diuretic and corticosteroid therapy has been reported to result in excessive potassium loss (*Drugdex 2007*, XXX *and* XXX *1976*).

Glycosides

Hypokalemia and/or hypomagnesemia increase the sensitivity of the myocardium for cardiac glycosides. Concomitant XXX and digitalis or digoxin therapy can result in digitalis toxicity (nausea, vomiting, cardiac arrhythmias) secondary to hypokalemia and possibly hypomagnesemia (*Drugdex 2007*, XXX *and* XXX *1976*).

Uricostatic, Uricosuric Drugs

The interaction between allopurinol and XXX results in increased serum urate and plasma oxypurinol. The exact mechanisms remain unclear but complex interactions that result in attenuation of the hypouricemic effects of oxypurinol are likely (XXX *et al. 2012*). Probenecid blocks the pump for organic acids, and thus inhibits the tubular secretion of XXX. This leads to elevated plasma concentration and decreased tubular fluid concentraton of XXX resulting in a decreased diuretic effect (XXX *and* XXX *1990a, b*).

Vasodilatory Drugs

Concomitant hydralazine increased XXX renal clearance and enhanced diuretic response (*Drugdex 2007*).

Antiarrhythmic Drugs

According to a retrospective study, addition of nitroglycerin to early loop diuretic therapy in patients with chronic kidney disease and acute decompensated heart failure (n=430) decreased length of hospital stay. A trend toward a decrease in the composite endpoint of all-cause mortality and acute heart failure readmission is observed. Survival at 24 months

was higher with combined treatment (87%) compared with untreated (79%) and diuretic only (82%) groups (XXX *et al. 2011*). Cardiovascular toxicity may result from XXX interaction with dofetilide and the antipsychotic drug droperidol (*Drugdex 2007*, XXX *and* XXX *1976*).

Antithrombotic Drugs
Coadministration of phenprocoumon and XXX can lead to altered protein binding of either drug. However, it is concluded that XXX may be safely administered to patients receiving phenprocoumon therapy (*Drugdex 2007*).

Antidiabetic Drugs
The effect of antidiabetic drugs can be attenuated by concomitant XXX (XXX *and* XXX *1985*, XXX *and* XXX *1976*).

Clofibrate
The concurrent administration of XXX and clofibrate has resulted in muscular pain and stiffness, general malaise, pronounced diuresis, and elevated levels of serum transaminases and creatine phosphokinase. These effects are more prominent in patients with nephrotic syndrome, hypoalbuminemia, and hyperlipoproteinemia (*Drugdex 2007*).

Colestipol, Cholestyramine
Decreased XXX effectiveness may also result from pharmacokinetic drug interactions. Colestipol reduced the bioavailability of XXX by 80% (*Drugdex 2007* [from XXX et al. 1988a]). A marked decrease in XXX serum concentrations due to the interference of the anion-exchange resin cholestyramine with XXX has been shown (*Drugdex 2007* [from XXX 1974a]).

Phenytoin
Phenytoin may reduce the gastrointestinal absorption (*Drugdex 2007* [from XXX et al. 1977a]).

Lithium, Theophylline, Tubocurarine, Succinylcholine
The concomitant administration of XXX and lithium may potentiate lithium toxicity (weakness, tremor, excessive thirst, confusion) probably as a result of decreased lithium clearance. XXX can also potentiate the effects of theophylline or curare-like muscle relaxants (*Drugdex 2007*, XXX *et al. 1984*). Low doses of XXX have been reported to enhance the neuromuscular blockade of tubocurarine and succinylcholine, while high doses (1 to 4 mg/kg) of XXX have been reported to antagonize neuromuscular blockade (*Drugdex 2007*).

Albumin
Added-up albumin enhanced the diuretic effect of XXX in patients with hypo-albuminemic chronic kidney disease in a controlled cross-over study versus XXX alone (XXX *and* XXX *2012*).

Adrenaline, Noradrenaline
The effect of adrenaline and noradrenaline can be attenuated by concomitant XXX (XXX *and* XXX *1985*, XXX *and* XXX *1976*).

Ephedra, Yohimbine
The hypotensive effect of XXX may be reduced by the sympathomimetic activity of ephedrine and pseudoephedrine in Ma Huan (Ephedra). Yohimbine may directly counteract the hypotensive effect of diuretics, resulting in inadequate blood pressure control in hypertensive patients (*Drugdex 2007*).

Germanium, Ginseng

Germanium and ginseng-germanium combination decreased diuretic effectiveness and increase the risk of resistance to XXX. Germanium may damage cells of the thick ascending limb of the loop of Henle, diminishing the cells' responsiveness to loop diuretics (*Drugdex 2007*).

Other Drugs

Concomitant loop diuretic and carbenoxolone or laxatives has been reported to result in excessive potassium loss. Hypokalemia and subsequent cardiotoxicity (torsades de pointes, QT prolongation) may also result from interaction of XXX with arsenic trioxide. Concurrent use of licorice and diuretics should be avoided since pseudoaldosteronism from licorice ingestion results in hypokalemia and decrease XXX efficacy (*Drugdex 2007*). In patients with heart failure, counteraction of the increased oxidative stress by vitamin C appears to augment the natriuretic effects of XXX (XXX *et al. 2003*).

Contraindications

XXX is contraindicated in renal failure with anuria. It is also contraindicated in cases of hypersensitivity to XXX or sulfonamides (*Drugdex 2007*).

Precautions

Administration of XXX has to be monitored very carefully in patients with diabetes mellitus, fluid or electrolyte imbalance (eg, hypokalemia or hyponatremia), hepatic coma and pre-coma, hyperglycemia, hyperuricemia or gout, hypovolemia, with or without hypotension, liver disease, ototoxicity (tinnitus, reversible/irreversible hearing impairment), renal impairment, severe hypokalemia or hyponatremia, and systemic lupus erythematosus (*Drugdex 2007*).

Safety during Pregnancy and Lactation

XXX crosses the placental barrier. However, maternal use of XXX during pregnancy has not been associated with toxic or teratogenic effects, although metabolic complications have been observed. Among newborns who had been exposed to XXX during the 1st trimester (n=350) a total of 5.1% major birth defects were observed (18 observed vs. 15 expected) including 2/4 cardiovascular defects, 1/1 oral cleft, 0/0 spina bifida, 1/1 polydactyly, 1/1 limb reduction, and 3/1 hypospadias. No fetal or newborn adverse effects were associated with XXX use after the 1st trimester. Administration of the drug does not significantly alter amniotic fluid volume. Serum uric acid levels, which are increased in toxemia, are further elevated by XXX. Neonatal thrombocytopenia has not been reported (*Drugdex 2007*, *Briggs et al. 1994*).

However, elimination of XXX in the mother may be abolished or diminished during delivery and the newborn is at risk of dehydration and electrolyte loss when the drug is administered to the mother before term (XXX *et al. 1978*). In neonates the plasma elimination half-life is prolonged 8-fold, and a possible inhibition of the closure of the ductus arteriousus Botalli has been discussed (XXX *1983*). In addition, in neonates after administration of XXX (1mg/kg bodyweight intravenously at intervals of < 12 hours) the incidence of metabolic alkalosis was increased, probably caused by increased excretion of potassium and hydrogen ions (XXX *et al. 1984*). XXX may be cleared from the circulation considerably more slowly in the neonates and there is a risk of developing electrolyte disturbances. Therefore, XXX should be given only if the potential benefit justifies the potential risk to the fetus (*Drugdex 2007*).

XXX is excreted into breast milk. Concomitant XXX administration and restriction of fluids appear to inhibit post-partum lactation in breast-feeding mothers, although changes in serum prolactin level were not observed (XXX *et al. 1976*, XXX *et al. 1977*). There are no reports on adverse effects in nursing infants. It is not known if XXX affects the quantity and

composition of breastmilk. Until more data are available, potential benefits and risks have to be evaluated when considering the use of XXX in lactating women (*Drugdex 2007*, *Briggs et al. 1994*).

Dosage

For the treatment of edema, associated with congestive heart failure, hepatic cirrhosis, and renal dysfunction, the dose of XXX should be individualized.

Adult Dosage

The usual initial dose for *adults* is 20 to 80 mg orally as a single dose, which is generally followed by prompt diuresis. Depending on the response, the same dose may be administered 6 to 8 hours later. The dose may be increased by 20 to 40 mg at 6- to 8-hour intervals after the previous dose, until the desired diuretic effect has been achieved. This individually determined single dose (maintenance dose) should then be given once or twice daily. Mobilization of edema may be most efficiently and safely accomplished by using intermittent dosing schedules (e.g. administration of XXX for 2 to 4 consecutive days each week) (*Drugdex 2007*).

The usual oral maintenance dosage is 40 to 120 mg daily. The weight loss resulting from increased diuresis should not exceed 1 kg daily. To treat clinically severe edematous states, XXX may be carefully titrated up to the maximal possible dose of 600 mg daily. (*Drugdex 2007*).

In hypertension, the dose of XXX should be individualized. The usual initial oral dose is 80 mg daily. XXX (40 mg twice daily) appears to be the optimal dose and the use of higher doses generally does not provide any additional benefit (*Drugdex 2007* [from Valmin et al. 1980]). If the response is inadequate, other antihypertensive agents should be added to the regimen.

No specific dosage adjustment of XXX is necessary for dialysis patients, in the elderly, in patients with renal failure (glomerular filtration rate < 10 ml/min) (*Drugdex 2007*).

Dosage adjustments may be necessary in patients with cirrhosis and in patients with combined hepatic and renal insufficiency. Patients with chronic renal insufficiency may require higher than usual doses to induce diuresis (80 to 120 mg daily initially, increasing up to 800 mg daily, maximal 1500 mg daily) (*Drugdex 2007*).

For the oral treatment of refractory edema and refractory heart failure, high-dose XXX of 250 to 4000 mg daily may be required (*Drugdex 2007*).

According to the Diuretic Optimization Strategies Evaluation (DOSE) trial, a clinical trial of various diuretic strategies for patients with acute decompensated heart failure, there were no significant differences in patients' global assessment of symptoms or in the change in renal function when diuretic therapy was administered by bolus as compared with continuous infusion or at a high dose as compared with a low dose of XXX (XXX *et al. 2011*). Patients on higher diuretic doses at admission have greater disease severity and may benefit from an initial bolus strategy (XXX *et al. 2012*).

Pediatric Dosage

Premature neonates initially receive an oral dose of 1-2 mg/kg. Dosing may be repeated every 24 hours in neonates less than 29 weeks gestation, and every 12 to 24 hours in those > 29 weeks gestation. In cases of insufficient diuresis the dosis may increase up to 6 mg/kg. Since the bioavailability of XXX in premature infants is generally poor doses exceeding 6 mg/kg may be required (*Drugdex 2007*).

Neonates are treated with 1-3 mg/kg orally every 8 hours as needed (*Drugdex 2007*).

Infants and children, initially receive an oral dose of 2 mg/kg. If the response is inadequate, the dose may be increased by 1-2 mg/kg no sooner than 6-8 hours following the previous dose. The maximal dose is 6 mg/kg. For maintenance therapy, the lowest effective XXX dose should be used. The usual dosing interval is once to twice daily (*Drugdex 2007*).

Children with chronic renal failure undergoing regular hemodialysis have the same dose schedule of XXX, despite a 5-fold increase in the half-life of the drug (*Drugdex 2007* [from XXX et al. 1982])

Overdosage

Careful clinical observation and laboratory monitoring is required if high XXX doses (> 80 mg daily) are used for a prolonged period of time. For maintenance therapy, the lowest effective XXX dose should be used (*Drugdex 2007*).

Patients with chronic congestive heart failure stabilized on a standard regimen (i. e., ACE inhibitor, digoxin, nitrates, XXX) for at least 3 months may tolerate a reduction in the daily dose of XXX to 1/3 of the previous dose or discontinued if the initial daily dose was 40 mg or less, while the concomitant therapy remains unchanged (*Drugdex 2007* [from van XXX et al. 2000], XXX *et al. 2003*).

According to results on subjects who habitually took XXX (40 to 2800 mg daily) to control weight or edema for long periods of time (range 3-25 years), long-term XXX abuse can cause medullary nephrocalcinosis in adults, and the risk of developing of nephrocalcinosis seems to be correlated with the daily dose of XXX (XXX *et al. 2001*).

Dyskalemic paralysis has been observed as a prominent clinical symptom of hypokalemia following XXX abuse (XXX *et al. 1999*).

2.5.6 Benefits and Risks Conclusion

XXX, 6-VVVV)-2-VVVV, is a highly potent diuretic agent which belongs to the loop diuretics. XXX acts at the luminal surface of the thick ascending limb of the loop of Henle by blocking the sodium-potassium-chloride ($Na^+/K^+/2Cl^-$) active reabsorption. The exact mechanism of action has not been fully elucidated, but evidence suggests that XXX attaches to the Cl^--binding site of the $Na^+/K^+/2Cl^-$-pump thereby inhibiting the active reabsorption of these ions. The inability to reabsorb salt therefore results in a higher osmolality and subsequently, the kidney's ability to reabsorb water decreases. XXX enhances the excretion of chloride, sodium (up to 25% of the filtered load of sodium as compared to normal values of 0.5%-2%), also the elimination of potassium, hydrogen, calcium, magnesium, bicarbonate, and possibly phosphate.

The diuretic response is related to the concentration of XXX in urine rather than in plasma. After oral administration, the onset of diuresis occurs within 30-60 minutes, peak response at 30-120 minutes and return to baseline within another 2-3 hours. Acutely, XXX increases the excretion of uric acid, whereas chronic administration results in reduced excretion of uric acid. XXX transiently (for 5-15 minutes) enhances renal blood flow, without increasing filtration rate. Acute administration of XXX declines glomerular filtration rate, and this acute decline appears to be greater in subjects with diastolic dysfunction than in healthy subjects.

In addition to its diuretic action XXX has been shown to exert an anti-vasoconstrictor effect. Cardiovascular hemodynamic is improved following long-term use of XXX subsequent to contraction of the extracellular fluid, increased venous capacitance, reduced cardiac preload and afterload. XXX reduces high blood pressure which seems to occur in long-term therapy through a reduction of vascular resistance. There is evidence for differential hemodynamic effects of XXX and torasemide. When the two diuretics were compared in patients with secondary pulmonary hypertension XXX significantly increased arterial angiotensin-II plasma levels, whereas, torasemide increased cardiac output over the time. However, it remains to be established whether or not XXX aggravates cardiac function by increasing angiotensin-II plasma levels.

Other pharmacodynamic actions of XXX have been demonstrated, including antiepileptic, antiinflammatory and bronchodilating effects. Beyond it, XXX appears to directly affect ion and water movement across the respiratory epithelium and thereby impairs nasal mucociliary clearance.

The pharmacokinetic behaviour of XXX is characterized by a large degree of variability. Great inter-subject and intra-subject differences are observed in the absorption of XXX. Moreover, absorptive behaviour differs between oral dosage forms, and also between fasting and postprandial states. Food appears to delay absorption but may not reduce the amount of drug absorbed. An oral dose of XXX (80 mg tablet) administered in the fasting state to healthy subjects produced a detectable serum concentrations within 10 minutes, peak concentrations between 60 and 70 minutes, and was undetectable between 3 to 4 hours after ingestion. The bioavailability of oral dosage forms of XXX is highly variable and may range from 20% to 80% between subjects.

XXX is highly (up to 99%) bound to plasma proteins, almost exclusively to albumin. High protein binding restricts the apparent volume of distribution at steady-state (0.07-0.2 l/kg). A high risk of clinically relevant drug interactions due to competition for binding sites on protein may arise from the high rate of plasma protein binding.

XXX glucuronide has been identified as metabolic product with possible pharmacological activity in human. Healthy subjects excrete about 14% of an oral or intravenous dose as

XXX glucuronide. A second metabolite has been described however, its status is unclear.

XXX is eliminated by the renal and extrarenal routes (72% and 28%, respectively in normal subjects). The excretion processes are of dual importance. First, both active and passive processes contribute to remove XXX from the body, and secondly, specifically renal excretion (active secretion and glomerular filtration) provide the means by which XXX is transported to its site of action. Up to one-third of an oral dose will actually be available at the site of action, but, this finding is altered by factors which alter the bioavailability and/or urinary delivery of the drug. The elimination half-life of XXX in normal subjects ranges from 0.3 to 1.7 hours and is changed depending on the age and diseases of the patients.

Prolonged plasma elimination half-life of XXX in geriatric patients is due to a reduced renal clearance. In the newborn half-life is prolonged due to the immaturity of organs involved in the elimination of the drug. In renal insufficiency, diminished renal and non-renal clearance results in a decrease in the total amount of XXX reaching the site of action and in a less intense and more prolonged diuretic effect. In nephrotic syndrome, the response to XXX is reduced due to the binding of XXX to luminal albumin. However, add-up albumin in kidney disease patients with hypoalbuminemia may improve XXX transport to its site of action and thus increase diuretic efficacy. In patients with heart failure absorption is slowed down, elimination half-life is prolonged and clearance is reduced.

Clinically, oral XXX still proves useful and effective in the treatment of edema associated with congestive heart failure, renal impairment, and hepatic disease. XXX administration significantly increases urine volume and sodium excretion and reduces peripheral edema and body weight. Patients with refractory heart failure may benefit from higher doses or addition of hydrochlorothiazide or metozalone to XXX especially in cases of renal failure.

In the treatment of ascites or edema due to cirrhosis, XXX as monotherapy exhibits a moderate diuretic effect. When XXX is combined with spironolactone effectiveness increases and dyskalemia may be largely prevented. Also, for the treatment of chronic hypertension, XXX is effective alone, but may be more effectively used in combination with other antihypertensive drugs. XXX has a shorter duration of action than thiazide-type diuretics and appears to be less effective in controlling blood pressure. Therefore, XXX should be reserved for hypertensive patients with fluid retention refractory to thiazide diuretics or those with renal impairment.

XXX is the diuretic of choice for the treatment of hypertension in chronic kidney disease where it efficaciously reduces left ventricular mass index independently from blood pressure changes, but the adaptive changes in the distal nephron may decrease its efficacy. The addition of hydrochlorothiazide may balance this effect. Patients on continuous ambulatory peritoneal dialysis experience a clinically significant improvement in fluid balance. Recent results from patients with residual renal function undergoing hemodialysis show an increase of urinary volume and sodium excretion with the use of low dose XXX. High doses help to maintain urinary output, but for patients with renal failure it does not appear to provide a significant clinical benefit.

There is preliminary evidence for benefit of postoperative XXX in the treatment of pleural effusion following spinal deformity surgery in children and adolescents. Beyond it, pretreatment with XXX in thyroid cancer patients undergoing thyroidectomy may play an important role to further improve the outcome of ablation by reducing the iodine pool.

A great number of potential drug interactions with XXX may be of clinical relevance. XXX may potentiate the effects of antihypertensive drugs and act synergistic with other diuretics as outlined above. Early administration of nitroglycerin and XXX to chronic kidney disease patients with acute decompensated heart failure may improve survival. Non-steroidal anti-

inflammatory drugs may reduce both, the diuretic and hypotensive effect of the diuretic. XXX may be applied with caution in multidrug treatment regimen since it can potentiate the effects and toxicity of concomitantly used drugs including salicylate, aminoglycoside antibiotics, cardiac glycosides, muscle relaxants and some other drugs. XXX may reduce the hypoglycemic effect of antidiabetic drugs.

In general, XXX is a well-tolerated diuretic. Contraindicated is XXX only for patients with renal failure and anuria, and in cases of hypersensitivity to XXX or sulfonamides. Its potential benefits and harm depend on the fluid balance in the body. The most common adverse effects attributable to XXX therapy are extensions of the therapeutic effects, specifically water and electrolyte depletion and include dehydration, hyponatremia, hypokalemia, hypocalcemia or hypomagnesemia. Excessive diuresis can lead to headache, dizziness, visual disorders, dry mouth and thirst, hypotension and disturbances of the orthostatic regulation. Hyperuricemia, hyperglycemia or increase in serum lipid levels may occur during chronic treatment especially with high doses. In patients with renal failure and/or receiving high doses, signs and symptoms of hearing loss, tinnitus, and vertigo may develop with XXX therapy. Ototoxicity occurs frequently in patients who are treated with high doses or concomitantly receive other ototoxic drugs (e.g. aminoglycosides). Premature infants appear to be at the greatest risk. Therefore, monitoring is recommended in predisposed patients. In maintenance treatment the lowest effective dose should be used (e.g. in heart failure after clinical stabilization).

The role of XXX is controversial with respect to longterm outcome and survival. Prior studies have suggested no long-term mortality benefit and that high-dose treatment is associated with worsening of renal function. Recent results indicate a possible negative interaction of XXX in clinically stable patients with chronic heart failure. However, in chronic heart failure it has been demonstrated that the diuretic dose has no prognostic implications in hypervolemic patients and that high-dose XXX (> 80 mg per day) may produce poor long-term outcome in euvolemic patients. There is also evidence that the use of high doses of XXX may indicate a greater severity of illness rather than being a mediator of adverse outcomes. This may be supported by the finding that XXX is associated with acute kidney injury in critically ill patients but the subgroup of patients with sepsis or septic shock is at high risk for development of acute kidney injury.

XXX crosses the placental barrier and passes into breast milk. Since the drug may be cleared from the circulation in the neonate more slowly, XXX should be given to pregnant or lactating women only if the potential benefit justifies the potential risk (dehydration/loss of electrolytes) to the fetus.

Based on the cummulative summary of serious/non-serious symptoms, a total of 1040 serious and 619 non-serious adverse drug reactions from 739 spontaneous reports (from regulatory, literature and healthcare professional source) were notified to the drug safety department of MAH in ratio to approximately 7,25 billion defined daily doses (corresponding with about 19,85 million patient-years; calculated with a defined daily dose of 40 mg according to the ATC Index (WHO) and an average number of 365 days) (see *Addendum to Clnical Overview (AddCO) [154/02/16]* from 31/01/2016 [Data Lock Point]).

Furthermore, the current clinical data on XXX do not give any clues which would alter the past clinical evaluation (i.e. the clinical assessment of the risk-benefit ratio for the therapeutic use of XXX). Therefore, it can be stated that the risk-benefit ratio of XXX is positive and has been unchanged over time in the periods evaluated.

In the most recent and approved PSUR, CCSI, RSI, ISE and PIL of XXX formulations therapeutic indications, drug induced adverse effects, interactions and precautions are appropriately summarized. Most reports refer to adverse drug reactions already included,

either in this form or a similar form (see 2.1 *Overview of Safety* / *Subtitle – Detailed Unlisted Adverse Drug Reactions;* 2.2 *Summary of Safety*).

With regard to place renal failure (acute), renal calculi and nephrocalcinosis in other populations than premature infants as possible XXX-induced adverse drug reaction under close surveillance (see *Addendum to Clnical Overview (AddCO) [154/02/16]* from 31/01/2016 [Data Lock Point]), no modifications in the CCSI, RSI, ISE and PIL are considered necessary.

In summary, for none of the possible drug adverse reactions reported above an increased development during therapeutical use of XXX seems probable (see 2.5.5 *Overview of Safety*).

In conclusion, XXX exhibits a favorable risk-benefit ratio. Efficacy, safety and clinical benefits of oral XXX in the treatment of ascites/edema due to cardiac, liver and renal diseases as well as in arterial hypertension have been confirmed repeatedly. Considering the long period of its clinical use and, although being a highly potent diuretic, serious adverse effects attributable to XXX are extremely rare. Therefore, the use of XXX for the indications mentioned is judged to be therapeutically appropriate, effective and well-tolerated. On the basis of the comprehensive scientific documentation currently available, a marketing authorization for XXX containing preparations can be approved.

2.5.7 References

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Enclosures

Appendix I: Results from international literature investigation for publications on pharmacology, pharmacokinetics, toxicology, therapeutical effectiveness and adverse drug reactions following administration of XXX