Redacted under Section 40, Section 41 and Section 43 of the Freedom of Information Act.

2.5 Clinical overview

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List of Abbreviations

Abbreviation	Definition
ACE	Angiotensin Converting Enzyme
AE	Adverse Event
$AUC_{0\rightarrow48}$	Area under the plasma concentration time curve from zero to the last measurable concentration
$AUC_{0-\infty}$	Area under the plasma concentration time curve from zero to infinity
AUC_{0-inf}	Area under the plasma concentration time curve from zero to infinity
CL/F	Clearance Rate
C_{max}	Maximum Concentration
EU	European Union
GFR	Glomerular Filtration Rate
GCP	Good Clinical Practice
hCA	Human Carbonic anhydrase
IC_{50}	Half maximal inhibitory concentration
INR	International Normalized Ratio
IQR	Interquartile Range
Ki	Inhibitory Constant
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MRT	Mean Residence Time
PC	Primary Care
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
$t_{1/2}$	Half life
t_{max}	Time to Maximum Concentration
UK	United Kingdom
V_d/F	Apparent Volume of distribution

1 Product development rationale

1.1 Metolazone

Diuresis is directed toward reducing extracellular fluid volume by decreasing total-body NaCl content. Although continued administration of a diuretic causes a sustained net deficit in total-body Na^+, the time course of natriuresis is finite because renal compensatory mechanisms bring Na^+ excretion in line with Na^+ intake. Diuretics not only alter the excretion of Na^+ but also may modify renal handling of other cations (e.g., K^+, H^+, Ca^{2+}, and Mg^{2+}), anions (e.g., Cl^-, HCO_3^-, and $H_2PO_4^-$) and uric acid. In addition, diuretics may alter renal hemodynamics indirectly, by reducing the glomerular filtration rate (GFR) due to their hypovolaemic action.

Benzothiadiazides (usually referred as "thiazides") are sulfonamide derivatives initially synthesized in an effort to enhance the potency of the diuretics inhibiting human carbonic anhydrase (hCA). However, unlike hCA inhibitors (that primarily increase $NaHCO_3$ excretion), benzothiadiazides predominantly increase NaCl excretion, an effect shown to be independent of hCA inhibition. Thiazides increase the rate of urine flow, together with an increase the rate of excretion of Na^+, in parallel with excretion of Cl- (a Na^+ Cl^- "symport"). At maximal therapeutic dosages all thiazides are approximately equal in diuretic efficacy. This holds true, also for the so called "thiazide-like diuretics", which act with the same mechanism despite their slightly different chemical structure. In this group belong metolazone and quinethazone (quinazoline sulfonamides), chlorthalidone (a phthalimidine derivative) and indapamide (an indoline). With the possible exceptions of the thiazide-like diuretics metolazone and indapamide, most thiazide diuretics are ineffective when the GFR is <30-40 mL/min (Reilly & Jackson, 2011).

Thiazide and thiazide-like diuretics are used for the treatment of hypertension, oedema associated with cardiac insufficiency (congestive heart failure) and renal disease (nephrotic syndrome, chronic renal failure, and acute glomerulonephritis) (Martindale, 2009).

Controlled clinical trials have demonstrated a reduced morbidity and mortality with diuretics exhibiting a Na^+ and Cl^- symport (thiazides and thiazide-like diuretics), but not with Na^+, K^+, $2Cl^-$ symport inhibitors (loop diuretics). Nonetheless, Na^+, K^+, $2Cl^-$ symport inhibitors appear to lower blood pressure as effectively as Na^+, Cl^- symport inhibitors, while causing smaller perturbations in the lipid profile. However, the relative potency and short elimination half-lives of loop diuretics render them less useful for hypertension than thiazide-type diuretics (Reilly & Jackson, 2011).

Metolazone [7-chloro-1,2,3,4-tetrahydro-2-methyl-3-(2-methylphenyl)-4-oxo-6-quinazoline-sulfonamide, $C_{16}H_{16}ClN_3O_3S$, CAS Registry Number 17560-51-9; molecular weight 365.83 g/mol] belongs to the pharmacotherapeutic group of sulfonamides (ATC code:

C03BA08). Due to its diuretic properties, metolazone is used for the treatment of oedema, as well as an antihypertensive drug. Chemically, it is a quinazoline derivative with the following structure:

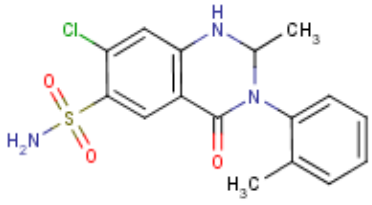


Figure 2.5 - 1 Chemical structure of metolazone

The present clinical overview concerns the product metolazone 5 mg tablets which is formulated in tablets containing metolazone as the active ingredient (5 mg). The excipients are microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, and sodium stearyl fumarate.

1.2 Approval status

Metolazone was developed in the 1970s. Currently, it is available as tablets for oral administration in several countries (Table 2.5 - 1). In the European Union, metolazone has a reference date of January 1st 1991.

[redacted] he tablet is indicated in the treatment of oedema of kidney diseases, including nephrotic syndrome and states of impaired renal function as well as for oedema of cardiac insufficiency. The recommended dose for adults is 2.5 to 5 mg once daily.

[redacted]

[redacted]

[redacted]

In the United Kingdom, Metenix was approved until discontinuation in 2012 for both oedema and hypertension. [redacted]

Table 2.5 - 1 International approval status of metolazone tablets

Drug	Country
[redacted]	[redacted]

1.3 Drug development rationale

The marketing authorisation application for metolazone 5 mg tablets is submitted under Directive 2001/83/EC Article 10(a) (well-established use application).

A comparative bioavailability study was performed to the formulation marketed in the United Kingdom (UK) by Sanofi-Aventis, Metenix 5 mg tablets, prior to its discontinuation. Metenix 5 mg tablets were authorized in the UK prior to 2001 and continuously marketed in the European Union (EU) for more than ten years; the product was withdrawn from the UK market in 2012. Thus, therapeutic equivalence to Metenix 5 mg tablets was demonstrated with metolazone 5 mg tablets.

Still today metolazone is of clinical importance in treating oedema related to kidney diseases, including nephrotic syndrome and states of impaired renal function. It is also effective in cases of oedema caused by congestive heart failure. Another indication of metolazone is the mild and moderate hypertension, alone or in combination with other antihypertensive medicines of different class (Bond & Crew, 2018).

The combined use of metolazone and loop diuretics (so called sequential nephron blockade) is recommended by the European Society of Cardiology (ESC) as a guiding principle for

therapy in treating heart failure (ESC Guidelines, 2016; ESC Guidelines, Web Addenda, 2016). Unlike other thiazide diuretics, metolazone retains effectiveness at glomerular filtration rate below 30 mL/min/1.73 m2 and thus is a preferred diuretic in patients with chronic kidney disease (CKD) stage 1-3 (NKF Guidelines, 2004). It represents an effective, patient friendly and affordable alternative to the administration of intravenous loop diuretics, which has to be carried out under stationary conditions.

1.4 Search strategy and selection of pertinent references

As an application for a medicinal substance of well-established use, documentation of this Clinical Overview was based on bibliographical data. The clinical overview for metolazone has been submitted to provide an integrated and critical assessment of the clinical efficacy and safety data of the proposed medicinal product. The literature search strategy used for the drafting of this clinical overview includes a review of the relevant published literature data taking into account the following criteria:

a. Most recent and relevant publications available;
b. Peer reviewed clinical journals;
c. Evidence in the proposed therapeutic indication.

To obtain an updated and complete view of the literature, a review of a series of databases was performed focussing on the efficacy and safety of this drug substance.

The literature search strategy applied was focused mainly on Medline (Pubmed), which cites journals publishing only peer-reviewed scientific papers. This was selected as the broadest

and most accepted scientific database. Searches were also done in reliable databases, such as “Biosis”, “Drugs.com”, “PubChem” and “Toxnet”, during the time period between the 10th and 30th of June 2020.

Medical Subject Headings (MeSH) and search terms were as follows: Metolazone, thiazides, thiazide-like diuretics, diuretic, oedema, oedema of kidney diseases, nephrotic syndrome, impaired renal function, oedema of cardiac insufficiency, hypertension, heart failure, hepatic cirrhosis. pharmacology, mechanism of action, efficacy, pharmacodynamics, pharmacokinetics, safety, clinical trials, adverse drug reactions, adverse events and interactions.

References were evaluated according to the content and scope of the Clinical Overview and their relevance to pharmacokinetics, pharmacological properties, clinical indications, and safety issues (side effects, interactions with other medicinal products, pregnancy and breastfeeding). Priority was given to papers of high quality, taking into consideration their methodological efficiency. Papers with apparent drawbacks (e.g. open label non-randomized clinical trials) failed to meet the necessary quality standards and have been rejected.

2 Overview of biopharmaceutics

2.1 Bioavailabilitiy

Metolazone is absorbed by the gastrointestinal tract and it is readily distributed in the body, with a rather long half-life (8-14 hours). The high volume of distribution, as well as the significant scale of the renal clearance of metolazone, explain the prolonged diuretic effect during monotherapy, as well as combination therapy (Sica, 2003; Sica & Gehr, 1996).

Bioavailability of metolazone ranges from 40% to 65% (Hughes, 2008). Due to its long duration of action, metolazone can be administered as a single daily dose, improving the compliance of the patient. Early clinical trials have shown that different formulations of the drug may exhibit considerable variation in the onset, the potency and the duration of their effect (Gunstone et al, 1971; Sica, 2003; Martindale, 2009). These observations necessitate an individual titration of patients, starting with a low dosing (see also Section 4.2 Posology).

According to the Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease of the US National Kidney Foundation, variation in absorption of metolazone is less relevant when dosing has been ongoing for a sufficiently long enough time to have established a steady-state blood level (NKF Guidelines, 2004).

2.2 Comparative bioavailability study [redacted]

An open label, single dose, randomized, two-period, two-treatment, two-sequence, and crossover bioequivalence study [redacted] compared the bioavailability of two formulations of metolazone 5 mg tablets ([redacted] and Metenix).

The drug was initially given as a single dose of 5 mg metolazone ([redacted] tablets, the test product, and Metenix tablets, the reference product). There were two treatment periods and two sequences of administration to 24 healthy volunteers (eventually, 22 were evaluable). The administration of the two products was separated by a washout period of 10 days. Plasma levels were measured before administration, and between 15 minutes and 72 hours after administration (in total 18 blood samples for both tested drugs, as follows: one sample before intake and then samples at 0.25, 0.50, 1.0, 1.5, 2.0, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, and 72 hours after intake).

In comparison to the reference product metolazone 5 mg tablets all in all appeared to possess a higher bioavailability, which was outside the predefined criteria for bioequivalence (80–125% for C_{max}) as well as for the area under the curve from zero to infinity ($AUC_{0\text{-}inf}$). C_{max} and $AUC_{0\text{-}inf}$ of metolazone 5 mg tablets ([redacted]) were on average 2.54 times and 1.93 times higher, respectively. The time to maximum concentration (t_{max}) of the two test drugs was comparable (2.0 versus 2.25 hours; median values), the half-life ($t_{1/2}$) of metolazone 5 mg tablets ([redacted] was significantly shorter (median 8.54 hours) compared to the reference product (14.56 hours), so that 16 hours after administration of metolazone 5 mg tablets only slightly higher plasma concentrations could be detected (Table 2.5 - 2).

Table 2.5 - 2 Main pharmacokinetic parameters of metolazone 5 mg tablets [redacted] (test) and Metenix (reference) following single dose 5 mg (n=22, mean±SD)

Parameters	[redacted] (Test)	Metenix (Reference)
	5 mg	5 mg
C_{max} (ng/mL)	78.46±21.42	39.45±6.76
t_{max} (h)	2.00±0.72	2.46±0.69
$t_{1/2}$ (h)	8.47±1.62	14.81±7.82
$AUC_{0\rightarrow last}$ (µg·h/L)	498.48±128.89	256.85±58.45
$AUC_{0\rightarrow inf}$ (µg·h/L)	511.28±126.59	279.93±60.24
$AUC_{0\rightarrow last}$: area under the plasma concentration time curve from zero to the last measurable concentration; $AUC_{0\text{-}inf}$: area under the plasma concentration time curve from zero to infinity; C_{max}: maximum concentration; $t_{1/2}$: half-life; t_{max}: time to maximum concentration		

Despite the different bioavailability, the tolerability profiles of both products were comparable; none of the occurring adverse events (AEs) were judged as serious, unexpected or clinically significant.

2.3 Dose proportionality study [redacted]

A dose proportionality study [redacted] was conducted with the primary goal to characterize the relative bioavailability as well as to assess the dose proportionality between 5 mg and 2.5 mg metolazone administered as one tablet (5 mg) and one-half tablet (2.5 mg) of metolazone 5 mg tablets [redacted]).

The study was designed as an open-label, laboratory-blind, single dose, randomized, two periods, two sequences, cross-over dose proportionality study. It consisted of two treatment phases of 24 hours each and two single dose administrations of 5 mg and 2.5 mg metolazone, separated by a wash-out phase of 1 week. Twelve male healthy Caucasian subjects were randomly assigned to the treatment sequences.

In summary, dose proportionality was shown with respect to $AUC_{0\rightarrow tlast}$ (93.3% power). Unfortunately, dose proportionality could not be demonstrated for C_{max} with respect to the criteria set for dose proportionality. The administration of 5 mg metolazone resulted in a

mean C_{max} value of 34.29 mg/mL, instead of calculated doubled value of 38.65 mg/mL after treatment with reference (2.5 mg metolazone) (Table 2.5 - 3).

Table 2.5 - 3 Main pharmacokinetic parameters of one metolazone 5 mg tablet and one-half tablet (2.5 mg metolazone) (n=12, mean±SD)

Parameters	[redacted] **(Test)**	[redacted] **(Reference)**
	5 mg	**2.5 mg**
C_{max} (ng/mL)	34.3±6.69	19.3±5.51
t_{max} (h)	2.92±1.38	2.17±0.72
$AUC_{0\rightarrow tlast}$ (ng·h/mL)	202.7±25.91	105.2±23.64
C_{last} (ng/mL)	7.19±1.82	3.62±1.46
$AUC_{0\rightarrow last}$: area under the plasma concentration time curve from zero to the last measurable concentration; C_{max}: maximum concentration; t_{max}: time to maximum concentration; C_{last} concentration at the last time quantifiable point (C LLOQ).		

All study procedures were highly standardized and performed in accordance with the clinical trial protocol and the Good Clinical Practice (GCP) regulations.

In total 10 AEs were reported. One type of AE, namely headache, was reported 5 times in four volunteers and accounted for 50% of the total AEs assessed and 100% of the certainly study related AEs. In total two AEs (headache) were classified as certainly study drug related. There were two probably and one possibly study drug related AEs (headache). All four related AEs that were classified as severe (vasovagal syncope and circulatory dysregulation) were judged as not related with the drug studied. All AEs were followed up and the outcome was assessed “recovered” in every single case.

Within the course of the study no Serious Adverse Events (SAEs) occurred. There were no new or unexpected findings observed or reported during the course of the study. The risk-benefit relationship stated prior to conduct of the present study was not affected by the results obtained.

These observations necessitate an individual titration of patients, starting with a low dosing (see also Section 4.2 Posology).

2.4 Summary of recommended posology according to the Indications

In a comparative bioavailability study, the applicants Metolazone 5 mg tablet was compared with Metenix 5 mg tablets from the UK market.

The applicants Metolazone tablet was shown to be supra-bioavailable compared with the former Metenix 5 mg tablets. The AUC and C_{max} were 1.9 times and 2.5 times higher after administration of the applicants Metolazone 5 mg than after 5 mg of the Metenix formulation. More importantly, given that the product is dosed on a daily basis, the time to maximum concentration (tmax) of the two test drugs was comparable. Half-life ($t_{1/2}$) of applicants metolazone 5 mg tablets was significantly shorter (median 8.54 hours) compared to the reference product (14.56 hours), so that 16 hours after administration of metolazone 5 mg tablets only slightly higher plasma concentrations could be detected.

Furthermore, breakability of the tablet has been satisfactorily demonstrated. Dose proportionality was shown for AUC between a half and a whole Metolazone 5 mg tablet, but dose-corrected C_{max} increased somewhat when the tablet was halved. Thus, half a tablet of applicants Metolazone 5 mg would be expected to lead to an AUC that is about 90% and to a C_{max} that is about 140% of the AUC and C_{max} obtained after a dose of 5 mg administered as the former Metenix tablets.

[redacted] The posology in all these markets remains to initiate treatment on a 2.5mg Tablet and the dose adjusted according to the individual reaction of the patient. Once the desired therapeutic effect has been achieved, it may be advisable to reduce the maintenance dose if possible. This posology is consistent with existing clinical application of Metolazone Tablets and elaborated across a selection of referenced clinical guidelines and clinical practice regimens (see also 4.2 Posology).

A selection has been tabulated below for ease of reference:

Clinical Guidelines	Therapeutic Indications	Posology
European Society of Cardiology	Oedema related to congestive heart failure	2.5mg to 10mg (Maximum recommended total daily dose)
Central London CCG's Clinical Reference Group	Oedema related to congestive heart failure	2.5mg to 10mg (Titrate to symptoms)
American College of Cardiology	Hypertension	2.5mg to 10mg

Clinical Guidelines	Therapeutic Indications	Posology
South East London guidance on the pharmacological management of Heart Failure	Oedema related to congestive heart failure	2.5mg (If no improvements occur after 7 days, increase dosing to twice weekly for 2 weeks.)
Wirral Shared Care Guidelines	Oedema related to kidney diseases	2.5mg (titrate to a maximum of 7.5mg)
Kidney Foundation Clinical Practise Guidelines	Oedema related to kidney diseases	2.5mg to 5mg (titrate up to 10 to 20 mg)
American National Heart, Lung, and Blood Institute	Hypertension	2.5mg to 5mg

3 Overview of clinical pharmacology

3.1 Pharmacokinetics

3.1.1 Absorption

The pharmacokinetic parameters of metolazone tablets were studied in two Chinese studies, which have given similar results. Both studies originate from the Department of Pharmacy at the Research Laboratory of the Xijing Hospital in the Fourth Military Medical University of China (Jia et al, 2011; Li et al, 2017).

In the first study (Jia et al, 2011), 30 healthy male and female Chinese subjects randomly divided into three groups (five males and five females in each group). Subjects were administered a single dose of metolazone tablet 0.5, 1.0 and 2.0 mg, respectively. It is important to note that metolazone tablets and metolazone reference standard (99.3% purity) were obtained from a manufacturer in China (Xi'an Libang Pharmaceutical Co.). No other information has been provided for the tablets used in the pharmacokinetic studies cited above (Jia et al, 2011; Li et al, 2017).

For studying the pharmacokinetics of multiple doses, the 1.0 mg group received 1 mg metolazone for six consecutive days. The main pharmacokinetic parameters are presented in Table 2.5 - 2. Single dosing with 0.5 mg, 1 mg, or 2 mg metolazone yielded linear plasma pharmacokinetic curves. Multiple oral dosing did not show any difference in the distribution and the elimination characteristics, compared with single dosing (Table 2.5 - 4). The investigators did not address the questions whether gender or food might influence the pharmacokinetics (Jia et al, 2011).

Table 2.5 - 4 Main pharmacokinetic parameters of metolazone following single dose of 0.5, 1 and 2 mg and multiple dose of 1 mg (n=10, mean±SD)

Parameters	Single dose			Multiple dose
	0.5 mg	**1 mg**	**2 mg**	**1 mg**
C_{max} (ng/mL)	6.9±2.6	20.6±4.8	36.8±7.1	22.4±5.0
t_{max} (h)	1.55±0.9	1.60±0.6	1.45±1.3	2.4±1.4
$t_{1/2}$ (h)	6.6±2.8	7.9±1.2	7.6±1.9	8.9±1.4
MRT (h)	5.7±1.0	8.1±1.3	6.8±1.5	8.5±1.0
CL/F (L/h)	15.6±4.1	7.9±1.2	12.5±2.1	6.5±1.5
Vz/F (L)	158.4±115.2	100.5±36.3	135.2±33.3	84.0±2.4
$AUC_{0\rightarrow48}$ (ng·h/mL)	33.9±9.2	122.5±36.3	162.4±26.9	156.8±31.6
$AUC_{0\rightarrow\infty}$ (ng·h/mL)	34.2±8.9	123.9±37.0	164.1±27.5	160.8±21.1
$AUC_{0\rightarrow48}$: area under the plasma concentration time curve from zero to the last measurable concentration; $AUC_{0-\infty}$: area under the plasma concentration time curve from zero to infinity; CL/F: clearance rate; C_{max}: maximum concentration; MRT: mean residence time; $t_{1/2}$: half-life; t_{max}: time to maximum concentration; V_d/F= apparent volume of distribution.				
(Jia et al, 2011).				

The second study (Li et al, 2017) followed exactly the same protocol, with the exception of the group of the multiple dosing, where subjects received for six consecutive days a dose of 0.5 mg (instead of the dose of 1 mg used in the first study). The findings of these two studies were very similar, as can be seen in Table 2.5 - 4 and Table 2.5 - 5.

Table 2.5 - 5 Primary pharmacokinetic parameters of metolazone after single-dose administration of 0.5 mg, 1 mg, and 2 mg metolazone tablets and multiple-dose administration of 0.5 mg metolazone tablets in healthy Chinese volunteers

PK parameter	Single dose			Multiple dose
	0.5 mg (n = 10)	1 mg (n = 10)	2 mg (n = 10)	0.5 mg (n = 10)
K_{el} (L/h)	0.1002 ± 0.0309	0.0966 ± 0.0123	0.0969 ± 0.0181	0.0957 ± 0.0227
C_{max}(ng/mL)	8.2252 ± 2.7712	13.8666 ± 4.3227	28.8775 ± 11.3863	8.1967 ± 2.0941
t_{max}(h)	1.63 ± 0.46	1.43 ± 0.39	2.05 ± 1.11	1.63 ± 0.41
$t_{1/2}$(h)	7.47 ± 2.06	7.28 ± 0.93	7.42 ± 1.60	7.61 ± 1.76
AUC_{0-t}(ng/mL/h)	49.68 ± 14.16	91.31 ± 30.39	184.84 ± 52.39	51.35 ± 15.02
$AUC_{0-\infty}$(ng/mL/h)	50.51 ± 14.60	92.41 ± 31.38	186.58 ± 52.50	52.26 ± 15.28
V_d (L/Kg)	108,732 ± 21,357	120,081 ± 23,585	126,326 ± 53,382	122,125 ± 38,729
CL(mL/h)	10,645.1 ± 3021.0	11,755.6 ± 3252.2	11,630.7 ± 3726.0	11,267.2 ± 2770.6
C_{avg}(ng/mL)	\	\	\	1.9595 ± 0.5118
C_{min}(ng/mL)	\	\	\	0.3962 ± 0.2258
AUC_{ss}(ng/mL/h)	\	\	\	1.9595 ± 0.5118
All values are mean (±SD) K_{el} Rate constant for elimination, C_{max} Maximum plasma concentration, t_{max} Time to maximum plasma concentration, $t_{1/2}$ Apparent plasma terminal elimination half-life, AUC_{0-t} AUC from 0 h to time t, $AUC_{0-\infty}$ AUC from time 0 extrapolated to infinity, V_d Volume of distribution during terminal elimination phase, CL Apparent clearance, C_{avg} Average plasma concentration, C_{min} Minimum observed concentration, AUC_{ss} AUC of distribution at steady state.				
(Li et al, 2017)				

Both studies have demonstrated that oral doses of metolazone for six consecutive days do not seem to significantly influence the absorption, the distribution or the elimination characteristics of the drug. Additionally, the authors did not report any significant side effects in the participating volunteers (Jia et al, 2011; Li et al, 2017).

Li and co-workers (2017) examined also the role of food in the bioavailability of metolazone. For details, see below Table 2.5 - 6 and Section 3.1.7 Pharmacokinetics and food.

Table 2.5 - 6 Pharmacokinetic parameters of metolazone after a single oral 1 mg dose: effect of food

Parameter	Parameter	
	Fasted (n = 10)	**Fed (n = 10)**
K_{el} (L/h)	0.0966 ± 0.0123	0.0892 ± 0.0113
t_{max} (h)	1.43 ± 0.39	2.83 ± 1.12
$t_{1/2}$(h)	7.28 ± 0.93	7.86 ± 0.82
C_{max} (ng/mL)	13.8666 ± 4.3227	11.4826 ± 3.5083
AUC_{0-t} (h•ng/mL)	91.31 ± 30.39	88.55 ± 27.28
$AUC_{0-\infty}$ (h•ng/mL)	92.41 ± 31.38	89.72 ± 27.63
V_d(L/Kg)	120,081 ± 23,585	135,593 ± 39,880
CL(mL/h)	11,755.6 ± 3252.2	11,930.9 ± 3017.5
MRT_{0-t} (h)	8.80 ± 1.50	9.90 ± 1.32
$MRT_{0-\infty}$ (h)	9.31 ± 1.77	10.54 ± 1.48
All values are mean (±SD) K_{el} Rate constant for elimination, $t_{1/2}$ Apparent plasma terminal elimination half-life, t_{max} Time to maximum plasma concentration, C_{max} Maximum plasma concentration, AUC_{0-t} AUC from 0 h to time t, $AUC_{0-\infty}$ AUC from time 0 extrapolated to infinity, V_d Volume of distribution during terminal elimination phase, CL Apparent clearance, MRT_{0-t} The average residence time of zero time to t, $MRT_{0-\infty}$ The average residence time of zero time to infinite time.		
(Li et al, 2017)		

3.1.2 Distribution

Metolazone is extensively distributed in the body. As an organic acid it is highly protein-bound (95%). In an early study with dogs ^{14}C-labelled metolazone, given either orally or intravenously, was highly distributed in the body and showed a remarkable extent of membrane binding. Typically, in the blood 80% of radioactivity was found in the red blood cells, 15% in the plasma proteins, and only 5% circulated as a free drug (Cohen et al, 1973).

In the classic pharmacokinetic model of two compartments, protein binding in the peripheral compartment gives rather high values for the apparent volume of distribution for metolazone. This is shown in the two Chinese studies with the human volunteers mentioned above

(Jia et al, 2011; Li et al, 2017) and has been also documented by other investigators who have reported values in humans as high as 113 L/kg (Table 2.5 - 7) (Hughes, 2008).

Metolazone crosses the placental barrier and it is also excreted into the breast milk (Martindale 2009).

Table 2.5 - 7 Pharmacokinetics of metolazone

Diuretic	Oral Bioavailability (%)	Half-Life	Elimination	Volume Of Distribution (L/Kg)
Metolazone	40-65%	8-14	Largely renal	113
(Hughes, 2008)				

3.1.3 Metabolism

Experimental data from dogs has shown that the drug is extensively hydroxylated to yield inactive metabolites (Cohen et al, 1973). In humans, metabolism of metolazone has not been studied in detail. However, it is estimated that only a 10% of the dose is metabolized by hydroxylation (Reilly & Jackson, 2011) and it should be considered highly improbable that hydroxylated metabolites could be reconverted back to the parent compound.

Banerjee and Chen (2014) have shown that metolazone binds to human Pregnane X receptor (hPXR), a soluble protein which induces the expression of several target genes, including those encoding the drug metabolism enzyme cytochrome P450 3A4 (CYP3A4) and the drug transporter multidrug-resistance protein 1 (MDR1). These molecules are involved in the metabolism and the elimination of many pharmaceuticals and xenobiotics. The induction of CYP3A4 by metolazone implies that this isozyme may also catalyse the hydroxylation of this drug, but until now there has been no research data on this issue.

3.1.4 Elimination

According to the findings in studies with dogs, metolazone is mainly excreted into the urine, by glomerular filtration and also by active tubular secretion (Belair et al, 1972). As mentioned above (Cohen et al, 1973), metolazone is extensively bound to proteins (95%), a fact leading to a considerable delay in its elimination, because only the free drug (5%) is cleared by the kidney or the liver.

In humans, elimination has been estimated to be mainly renal (~90%) and to a lesser extent biliary (~10%) (Tilstone et al, 1974; Hughes, 2008; Reilly & Jackson, 2011). Following a single oral dose of ^{14}C-labelled metolazone (2.5 mg) to five healthy volunteers it was found that the drug excreted into the urine was unmetabolized. Continuous measurements of

radioactivity after administration showed that 30% and 56% of the dose was excreted in urine during 24 and 144 hours, respectively (Tilstone et al, 1974).

Vose and collaborators by using a less accurate fluorimetric technique, showed that daily doses of metolazone (10 mg, p.o.) led to similar renal excretion rates on day 8 and on day 13 (about 30% of the administered dose). Concomitant daily administration of spironolactone (50 mg, p.o.) did not affect the excretion of metolazone. These findings show that chronic dosing has no pharmacokinetic implications, and also that metolazone and spironolactone do not interact, as far as renal elimination is concerned (Vose et al, 1980).

3.1.5 Half-life ($t_{1/2}$)

In the literature, values of the half-life of metolazone vary from 8 to 14 hours (Martindale, 2009; Hughes, 2008). The two Chinese pharmacokinetic studies presented above (Jia et al, 2011; Li et al, 2017) give average estimations for half-life of about 8 hours, when metolazone was given as a single dose, or in multiple doses up to six consecutive days. A similar value of half-life was found in the bioavailability study [redacted] of the formulation examined in the current application (see Table 2.5 - 2).

3.1.6 Pharmacokinetics and gender

Li and co-workers investigated also the possible differences between the male and female participants, but they could not find any statistically significant deviation (data not shown here) (Li et al, 2017).

3.1.7 Pharmacokinetics and food

As mentioned above, the intake of food as a possible factor in producing pharmacokinetic changes was examined by Li and co-workers (2017). According to the published data, most pharmacokinetic parameters of metolazone were very similar in fasting and fed volunteers, except the value of t_{max} which was almost doubled when metolazone was administered with a high-fat food. It must be noted, however, that despite this significant delay in the absorption, the important parameters of total exposure (AUC_{0-t} and $AUC_{0-\infty}$) and C_{max} were not influenced by food (Table 2.5 - 6). Based on their findings, the authors suggested that metolazone should be taken at the same time of day in relation to food (Li et al, 2017). This is in accordance with the texts of the SmPCs of the products already marketed in the EU for at least ten years [redacted]

3.1.8 Pharmacokinetics of special patient groups

3.1.8.1 Patients with renal disease

Nephropathies hinder the absorption of metolazone and also its elimination from the body. Especially in patients with severe renal insufficiency, clearance has been found to be only 20 mL/min, compared to 110 mL/min in normal subjects, despite the significant increase of the proportion of the removable free drug in the plasma (from 3% in normal subjects to 10% in severe renal disease). Absorption was also reduced to about 40% in some patients with renal disease, compared to 64% in healthy individuals (Tilstone et al, 1974).

The US National Kidney Foundation (NKF) has issued the following guidelines on metolazone treatment in chronic kidney disease: "Metolazone retains effectiveness at GFR below 30 mL/min/1.73 m^2. Absorption should be taken into account when both a dose and frequency of dosing are being determined. Metolazone can be started at a dose of 2.5 to 5.0 mg daily and titrated to 10 to 20 mg daily, though these higher doses are seldom needed. Once metolazone has enhanced diuresis, it can typically be dosed as infrequently as two to three times a week because of its very long half-life. In terms of pharmacokinetics it should be pointed out that, at least partly metolazone is metabolised in the normal kidneys" (NKF Guidelines, 2004).

3.1.8.2 Patients with heart disease

According to the study mentioned already above (Tilstone et al, 1974), patients with heart insufficiency had a markedly reduced absorption of metolazone, but elimination was found to be normal.

3.1.8.3 Patients with liver disease

In patients with ascites due to liver disease, metolazone has been used as a potent diuretic, with an initial daily dose of 5 mg which may be escalated (Hillenbrand & Sherlock, 1971). In theory, several pharmacokinetic parameters might be different, mainly due to significant hemodynamic changes and also due to the fall of plasma albumins. There are no scientific reports on these issues.

3.1.8.4 Elderly patients

In the old age, possible pathophysiological conditions of the kidneys, the liver and the heart, as well as a decrease of the albumin fraction of the plasma proteins, may influence pharmacokinetic and pharmacodynamic parameters related with metolazone. To date, these

parameters have not been specifically addressed, despite the frequent use of metolazone in diseases of the elderly.

3.1.8.5 Paediatric patients

Metolazone has been used in paediatric patients, but there is no data concerning the pharmacokinetics of metolazone in children (Segar et al, 1992; Segar et al, 1997; Garin, 1987).

3.1.9 Conclusions on pharmacokinetics

After oral administration, metolazone is almost completely absorbed from the gastrointestinal tract and reaches a peak in the plasma in about two hours. Food with high fat content has been reported to prolong the time needed for the drug to reach maximal plasma concentration (t_{max}). However, food does not seem to influence the parameters reflecting total exposure to the drug (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$).

Metolazone is given as a single daily dose. In order to avoid possible variation in its bioavailability, intake should be at the same time in relation to food.

Despite extensive binding to plasma proteins and erythrocytes (95%), metolazone is highly distributed into the body (V_d/F=113 L). It also crosses the placenta and passes into breast milk.

Metolazone has a $t_{1/2}$ of 8-10 hours. About 70% of the absorbed dose is excreted into urine unchanged. It is estimated that less than 20% undergoes biotransformation to yield metabolites, deprived of any pharmacological or toxic action. A minimal proportion of the dose is also excreted with the faeces.

3.2 Pharmacodynamics

Metolazone is a sulfonamide diuretic with a mechanism of action similar to the one of thiazides. Metolazone decreases sodium reabsorption along the renal tubules, but it is acting mostly in the distal convoluted tubule. The enhancement of sodium excretion results also to an increased loss of chloride and water. During sustained maximal water diuresis metolazone has been shown to produce a mean increment in sodium excretion of 3.5% of filtered load (Steinmuller & Puschett, 1972). The shift in water and electrolytes results in hypovolaemia, keeping the peripheral vascular resistance low and normalizing the cardiac output. The increased water excretion resolves oedema and lowers blood pressure. While metolazone is similar to thiazide diuretics in its mechanism of action, it does differ in its use in patients with impaired renal function. Thiazide diuretics decrease GFR and are therefore less

effective in patients with renal impairment. Because metolazone works primarily in the distal convoluted tubule, rather than the proximal convoluted tubule, it has little effect on GFR and can be used in patients with a reduced GFR. Metolazone stimulates diuresis in patients with a very low glomerular filtration rate (less than 30-40 mL/min/1.73 m^2) (Craswell et al, 1973; Reilly & Jackson, 2011; Bond & Crew, 2018).

Metolazone shares with thiazides, furosemide and acetazolamide the presence of an unsubstituted sulfamoyl group (-SO_2NH_2), which is known to exert an inhibitory action on the enzyme hCA (Carta & Supuran, 2013). However, metolazone does not seem to lead to any overt alteration in urinary pH or bicarbonate excretion. On the other hand, metolazone induces a slight phosphaturia which is believed to be due to the inhibition of a sodium transport mechanism linked to that of phosphate in the proximal tubule. So, metolazone exerts its major effect in the cortical diluting segment, where it inhibits sodium re-absorption in the distal tubule, but also in the proximal tubule and the ascending branch of the loop of Henle (Steinmuller & Puschett 1972; Reilly & Jackson, 2011). Potassium excretion is affected by metolazone to a lesser extent (Puschett & Rastegar, 1974).
At the optimal therapeutic dosage metolazone leads to approximately the same diuretic activity as the thiazides. Diuresis starts within the first hour after administration, reaches a maximum effect at two hours, and continues for 12 to 24 hours depending on the dose, and the formulation (see Section 4.2 Posology).
Metolazone qualifies as a strong diuretic which·has been shown to be clinically effective in oedematous patients with renal disease, uncompensated heart failure and also in hypertensive patients, as monotherapy, or in combination with loop diuretics and spironolactone (Paton & Kane, 1977; Reilly & Jackson, 2011; Fuchs, 2009; Goyfman et al, 2017).

4 Overview of efficacy

4.1 Indications

Metolazone 5 mg tablets are indicated for the treatment of the following:

1. Oedema related to kidney diseases, including nephrotic syndrome and states of impaired renal function.
2. Oedema related to congestive heart failure.
3. Mild and moderate hypertension, alone or in combination with other antihypertensive medicines of a different class.

4.1.1 Oedema related to kidney disease

Several early clinical trials have demonstrated the beneficial effect of oral thiazide therapy in oedematous patients with nephropathy, even with severe nephrotic syndrome, either they are complicated with hypertension or not (e.g. Craswell et al, 1973; Paton & Kane, 1977). Despite their important findings, these early studies cannot be easily evaluated, because they were open-label, uncontrolled trials, and usually the patients were not randomized (Sinha & Agarwal, 2015).

Gunstone and collaborators used metolazone to treat 52 oedematous patients (gender not specified) in the hospital of the Makerere University Medical School, (Kampala, Uganda). The first group (35 patients) received metolazone, while the second group (17 patients) received a combined treatment of metolazone with spironolactone or furosemide. Dosages differed from patient to patient, depending on the response and the diagnosed cause of the oedema. Despite serious methodological drawbacks, this paper clearly demonstrated the synergistic effect of thiazides and loop diuretics (Gunstone et al, 1971).

Especially the combination metolazone-furosemide is very useful when removal of volume overload becomes necessary, as is the case in chronic renal insufficiency, nephrotic syndrome, congestive heart failure, or cirrhosis. The efficacy of this combination is independent of patient age (Sica, 2003).

4.1.1.1 Nephrotic syndrome

Metolazone monotherapy was proven successful in the control of oedema in nephrotic syndrome (Gunstone et al, 1971; Craswell et al, 1973; Paton & Kane, 1977) with or without renal failure (Ghose & Gupta, 1981; Paton & Kane, 1977). In patients with nephrotic syndrome who are resistant to loop diuretics, the addition of metolazone frequently produces an impressive diuretic response (Allen et al, 1981; Ghose & Gupta, 1981).

In a crossover, randomized study in nephrotic patients with oedema (n=9) it has been shown that the combination metolazone-furosemide was equally effective with the combination chlorothiazide-furosemide. The patients were treated with furosemide (2 mg/kg per dose) and either metolazone (dose varied according to weight: 14-28 kg, 1.0 mg; 28-40 kg, 2.0 mg 40-55 kg, 3.0 mg; and 55-68 kg, 4:0 mg.) or chlorothiazide (10 mg/kg per dose). An additive natriuretic and diuretic effect was observed after both metolazone and chlorothiazide were combined with furosemide. Both diuretic combinations were associated with marked kaliuresis (Garin, 1987). This is a well-designed crossover randomized clinical trial, that should be considered pivotal in showing that patients with nephrotic syndrome respond equally well to the co-administration of either metolazone or chlorothiazide with furosemide.

4.1.1.2 Chronic renal failure

Although this is not a rule with the classic thiazides, metolazone monotherapy is able to elicit a diuretic response in advanced renal failure (Craswell et al, 1973; Paton & Kane, 1977). As has been mentioned already above, a diuretic response has been demonstrable even with a very low GFR (Black et al, 1978; Craswell et al, 1973), as well as in patients undergoing maintenance hemodialysis (Sica & Gehr, 1996).

The doses of metolazone needed for a satisfactory diuretic response in renal failure, may be surprisingly variable, and typically do not have a defined relationship to the GFR. For instance, doses as high as 100-200 mg have been reported (Gunstone et al, 1971). Several different parameters have been proposed as an explanation to this variation, such as the rate and extent of metolazone absorption, its prolonged elimination half-life, and the rather modest tubular delivery rate necessary for a threshold diuretic response (Sica, 2003).

Paton and Kane have reported the case of a hypertensive patient with oedema, nephrocalcinosis, and cardiac decompensation, who did not respond during 11 months of metolazone therapy at 40 mg/day. The addition of furosemide 160 mg/day to metolazone resulted in a dramatic diuresis. A subsequent trial of furosemide 360 mg/day alone failed to prevent recurrent fluid retention and heart failure; combined treatment again reproduced the earlier dramatic response. The patient was subsequently stabilized without oedema receiving 10 mg/day of metolazone and 160 mg/day of furosemide (Paton & Kane, 1977). In combined administration with loop diuretics, one might expect that overdiuresis and subsequent hypovolaemia would reduce the GFR and the filtered load of sodium, hindering eventually the osmotic excretion of water. However, this has not always been the case. The extremely prolonged elimination half-life of metolazone in the presence of moderate-to-severe renal insufficiency (Tilstone et al, 1974) can explain the protracted diuretic response, which has been reported in such patients (Stern, 1976; Black et al, 1978).

In a meta-analysis of clinical trials concerning thiazides and thiazide-like diuretics in nephropathies, the authors concluded that even in patients with stage 4 chronic kidney disease thiazides are useful and effective drugs in controlling oedema and hypertension (Sinha & Agarwal, 2015).

4.1.2 Oedema related to congestive heart failure

4.1.2.1 Chronic heart failure

Combination diuretic therapy seems to have been most frequently employed in the management of the volume overload characteristic of advanced chronic heart failure (CHF). Metolazone potentiates the effect of loop diuretics and is effective in oedema associated with heart insufficiency resistant to other therapy. It has been shown that combining metolazone

with furosemide does not change the metabolism or urinary excretion of the latter. The combination of loop diuretics with metolazone exerts concomitant actions at three segments of the nephron: the proximal tubule, the thick ascending limb of the loop of Henle, and the distal tubule. This multi-segmental blockade diminishes the physiological renal countereffects observed when using metolazone or a loop diuretic as monotherapy. It is postulated, that thiazide-type diuretics counteract the enhanced sodium reabsorption seen in the distal tubules due to treatment with a loop diuretic (Marone et al, 1985).

The efficacy of co-administered metolazone together with other diuretics and especially loop diuretics is well-established and supported by many clinical trials and case studies in patients with chronic heart failure (Gunstone et al, 1971; Black et al, 1978; Allen et al, 1981; Ghose & Gupta, 1981; Aravot et al, 1989; Kiyingi et al, 1990; Rosenberg et al, 2005; Lee et al, 2010; Qavi et al, 2015).

In chronic heart failure, an aggressive dosage regimen with metolazone is usually applied, so that diuresis is elicited and maintained. For example, Kiyingi and collaborators initiated combination therapy with metolazone 1.25 mg/day and 200–500 mg/day of furosemide in a group of patients with severe chronic heart failure (n=17). Metolazone was titrated to a maximum dose of 10 mg/day according to the desired response. Ultimately, 12 of the 17 patients responded with diuresis within 72 hours of starting therapy. Failure to respond to combination therapy was an ominous prognostic finding (Kiyingi et al, 1990). This is a well-designed pivotal clinical trial showing the clinical efficacy of diuresis in patients with chronic heart failure after the combined administration of metolazone and furosemide.

In patients with class III and IV refractory heart failure (Classes Of Heart Failure, 2017), a randomised, blind, controlled trial compared the sodium excreting efficacy of a “furosemide plus indapamide” combination vs. “furosemide plus metolazone”. The patients included (n=150) had not responded to intravenous furosemide doses of 120 mg (40 mg Q8hr). The subjects were randomly put into two groups (75 in each group). Both groups received intravenous furosemide (40 mg Q12hr), while group 1 received also metolazone (5 mg Q24hr) and group 2 received also indapamide (2.5 mg Q24hr). Analysis of the results revealed that both combinations had comparable efficacy and safety profiles. Moreover, indapamide and metolazone were effective even in patients with severe renal dysfunction (GFR<30 mL/min). Hypokalaemia was the most common adverse event (Shah et al, 2019). Due to the large number of patients included in this clinical trial, the reported results are very important, because they give further support to earlier observations on the beneficial effects of metolazone and indapamide, even in cases of refractory cardiac insufficiency with a severe decrease of GFR (Goodman & Gilman, 2011).

A retrospective study of hospitalized acute heart failure patients (n=242) compared the diuretic effect of three different regimens: (a) continuous infusion furosemide (n=160), (b) furosemide plus metolazone (n=42), (c) continuous infusion bumetanide (n=40). Primary

end points were the change of mean hourly urine output and evaluation of renal function. Compared to baseline, all regimens increased mean hourly urinary output ($p < 0.0001$ for all). Most effective was the treatment "furosemide plus metolazone" (109+171 mL), followed by "bumetanide" (90+90 mL) and "furosemide" (48+103 mL; $p = 0.009$). No difference in the incidence of worsening renal function was found; however, electrolyte abnormalities may be more prevalent when furosemide is combined with metolazone or when bumetanide is used (Ng et al, 2013). This investigation would have been more informative by adding a group of patients treated with bumetanide plus metolazone.

Several retrospective cohort studies have compared chlorothiazide vs. metolazone as adjunct treatments for patients with loop diuretic resistance (Moranville et al, 2015; Shulenberger et al, 2016; Bohn et al, 2019).

Moranville and collaborators evaluated the efficacy and safety of oral metolazone versus intravenous chlorothiazide as add-on therapy to loop diuretics in patients hospitalized with acute decompensated heart failure and renal dysfunction. The primary endpoint was net urine output at 72 h after initiation of thiazide-like diuretics. Safety endpoints were also included, with regard to renal function, blood pressure and electrolyte balance. Of the 55 patients enrolled, 33 were receiving metolazone and 22 chlorothiazide. When diuretic dosing was examined by each individual day of the 72-h study period, the median daily dose of metolazone was 2.5 mg (IQR 2.5-2.5 mg). The median daily dose of chlorothiazide was 500 mg (IQR 500-875 mg) on day 1, 750 mg (IQR 500-1000 mg) on day 2, and 1000 mg (625-1000 mg) on day 3. Analysis of the data revealed that sequential nephron blockade with either metolazone or chlorothiazide appears to be efficacious and safe in acute decompensated heart failure, renal dysfunction, and loop diuretic resistance. There was no significant difference in the defined safety endpoints (hypotension, worsening renal function, hyponatraemia, or hypokalaemia). Hospital length of stay was shorter in the metolazone cohort (median 7 days) compared to chlorothiazide (median 15 days) (Moranville et al, 2015).

In a similar retrospective cohort study, the efficacy and safety of intravenous chlorothiazide was assessed versus oral metolazone when added in patients with acute decompensated heart failure and loop diuretic resistance. The patients evaluated were adults with diagnosis of acute decompensated heart failure who were treated in a San Francisco hospital between 2005 and 2015, and they did not respond to intravenous furosemide (160 mg/day or higher) or to an equivalent dose of intravenous bumetanide, during hospitalization, and who then received at least one dose of intravenous chlorothiazide (88 patients) or oral metolazone (89 patients) to augment diuresis. Mean doses were 491±282 mg for chlorothiazide and 5.8±3.5 mg for metolazone. Analysis of the data showed that oral metolazone was equally effective to intravenous chlorothiazide for enhancing net urine output in patients with acute decompensated heart failure and loop diuretic resistance. No major adverse events were noted in either group (Shulenberger et al, 2016).

The third study, by Bohn and collaborators, had the same methodology and the same endpoints with the two previous studies. Patients (n=168) with heart failure and reduced ejection fraction, received either chlorothiazide (at least one dose ≥500 mg) or metolazone (at least one dose ≥5 mg). Both metolazone and chlorothiazide increased in a similar way the 24-hour total urine output (Bohn et al, 2019).

These data support the use of oral preparations of metolazone instead of intravenous formulations of thiazides. However, a prospective, randomized, controlled trial would be ideal to determine whether an efficacy difference exists between chlorothiazide and metolazone.

4.1.3 Mild and moderate hypertension

Diuretics still remain useful drugs for the treatment of hypertension, as monotherapy, but more frequently in combination with drugs of other categories, depending on the underlying pathophysiological mechanism for the increased blood pressure (Groth et al, 1985; Fuchs, 2009).

In an early double-blind clinical trial, metolazone (1.0, 2.5 or 5 mg p.o., daily) was compared with chlorthalidone (100 mg p.o., daily) for the treatment of non-oedematous hypertensive patients (n=57). Both drugs significantly reduced blood pressure, to the same extent. They also produced equally frequent hypokalaemia (Fotiu et al, 1974).

Another study compared metolazone (5 mg p.o. daily) with hydrochlorothiazide (25 mg p.o. twice daily) in hypertensive patients (n=22). Each patient received a separate 6-week treatment with metolazone or hydrochlorothiazide in random order. Each treatment was separated from the other by a washout period of 2 weeks (single-blind cross-over clinical trial). Metolazone was shown to be more potent than hydrochlorothiazide in that it caused a greater reduction in both systolic and diastolic blood pressure. Significant decreases in plasma potassium were observed with both treatments (Reda et al, 1983).

In the “Cochrane Database of Systematic Reviews”, thiazides and thiazide-like diuretics when applied as antihypertensive monotherapy in primary hypertension are reported to exert similar maximal blood pressure-lowering effects. Overall, thiazides have been found to reduce average blood pressure by 9 mmHg/4 mmHg (systolic/diastolic), compared to placebo (Musini et al, 2014). According to Musini and collaborators, for the evaluation of metolazone as an antihypertensive monotherapy, only a clinical trial fulfilled the necessary minimum quality criteria for being included. In this placebo-controlled trial, metolazone was given orally at daily doses 0.5 to 2.0 mg to 105 patients, 46 males and 59 females, with a baseline blood pressure 150/98 mmHg (systolic/diastolic). Metolazone was administered as monotherapy for six weeks. The placebo-corrected systolic/diastolic blood pressure-

lowering with metolazone was 11.6/5.8 mmHg. Direct comparison of doses did not show any significant differences in systolic or diastolic blood pressure-lowering between the different doses used (Curry et al, 1986).

4.1.4 Special groups of patients

4.1.4.1 Elderly

The therapeutic indications of metolazone refer to diseases and pathological conditions occurring mostly in the old age. The side effects of metolazone reported in clinical trials concern as a rule elderly people who are statistically more prone to suffer from cardiovascular and renal diseases coexisting with hypertension or oedema. The situation becomes more complicated when a kidney disease ends up to a complete renal insufficiency necessitating dialysis. Equally problematic are patients with ascites due to liver cirrhosis (see below). Elderly patients (n=3) with renal failure and refractory fluid overload resistant to oral furosemide were successfully treated with short-term (2-5 days) metolazone administration (2.5 to 5 mg). Oedema was clinically improved and the drug was well tolerated, without any significant blood pressure fluctuations or electrolyte disturbances (Cheng et al, 2014).

4.1.4.2 Severe renal insufficiency

In patients with very low GFR, the thiazide-like diuretics indapamide and metolazone may retain their natriuretic effect (Craswell et al, 1973; Reilly & Jackson, 2011). However, when hypovolaemia has been established after chronic treatment, lowering of blood pressure may lead to a further decrease of glomerular filtration rate and possibly to histological renal damage.

In a review, Chan and collaborators (2012) evaluated the antihypertensive effect of thiazides in patients with renal insufficiency. The objective was to determine whether thiazides have a chronic antihypertensive effect, in the absence of diuresis, in patients with severe renal disease (creatinine clearance <30 mL/min) or in those receiving dialysis. Thiazide diuretics are associated with a chronic reduction in peripheral vascular resistance secondary to a purported vasodilatory effect. However, their antihypertensive effect is mediated though diuresis secondary to natriuresis. Hydrochlorothiazide, chlorothiazide, and indapamide provided long-term blood pressure reduction in patients with severe renal disease who were not on dialysis. In studies involving patients on dialysis, hydrochlorothiazide 50 mg daily and metolazone 5 mg daily did not affect blood pressure, with the exception of one study suggesting that indapamide 2.5 mg daily may confer an antihypertensive effect. All studies were small (<12 subjects) and had methodological limitations. The authors concluded that

thiazide diuretics cannot be routinely recommended for chronic antihypertensive treatment in patients with severe renal disease or in those on dialysis (Chan et al, 2012).

In patients with chronic renal failure and hypertension (n=35), the efficacy of increasing doses of metolazone (5, 10, 20 mg) were compared with those of furosemide (40, 80, 160 mg). Both diuretics were given as a monotherapy. Antihypertensive potency was comparable during a treatment period of up to 12 weeks. Maximal response was achieved with 10 mg of metolazone or 160 mg of furosemide. However, only in 25% of the cases blood pressure could be normalized with the monotherapy of metolazone or furosemide (diastolic blood pressure <95 mm Hg) (Groth et al, 1985).

4.1.4.3 Hepatopathy

In patients with ascites due to liver disease, metolazone has been used as a potent diuretic, with an initial daily dose of 5 mg which may be escalated. When metolazone is used alone the high incidence of hypokalaemia (80%), hypochloraemia (35%), and encephalopathy (35%) compared with the results of other series is a major disadvantage and indicates that this drug should be used with caution in patients with liver disease. Hypokalaemia can usually be prevented by the simultaneous administration of amiloride or spironolactone (Hillenbrand & Sherlock, 1971).

4.1.4.4 Paediatric use

Possible changes in the pharmacokinetic parameters of metolazone in paediatric patients have not been studied. At least furosemide, after repetitive administration to neonates has been associated with ear toxicity due to accumulation (Mirochnick et al, 1988). The risk of significant systemic accumulation of a loop diuretic can be lessened with a prolonged time interval between doses, or with co-administration with thiazides allowing a decrease in the dose of furosemide. Furosemide and metolazone have been employed regularly in the management of the full spectrum of oedematous conditions found in childhood (Sica 2003).

Segar and collaborators (1992) evaluated the response in infants with bronchopulmonary dysplasia (n=24) to furosemide, metolazone, or their combination. Although the initial doses of either furosemide (1 mg/kg. i.v. daily) or metolazone (0.2 mg/kg p.o. daily) alone elicited a diuretic response, this quickly disappeared with succeeding doses. The physiologic tolerance to repetitive administration of either furosemide or metolazone was overcome when both drugs were administered together (Segar et al, 1992).

Combination diuretic therapy should be undertaken cautiously in the paediatric population. Administration of metolazone to paediatric patients usually occurs on a milligram per kilogram basis, extrapolated arbitrarily from doses given to adults, since formal dose-ranging studies have not been conducted in children. Moreover, when small amounts of metolazone

are given either to neonates or to children under 1 year of age, tablets must be crushed before administration to provide the prescribed dose (Sica 2003).

A descriptive, retrospective study carried out in patients less than a year old (n=97, age: 0.32±0.25 years), that had received metolazone over a 2-year period in a paediatric cardiac intensive care unit. The study categorised a total of 66 patients (68.0%) as responders. Changes in urine output were not associated with the dose of metolazone (Wise et al, 2018).

In conclusion, the use of metolazone in paediatric patients is not recommended due to lack of sufficient clinical data.

4.1.5 Overall conclusions on efficacy

Despite the limited data on metolazone monotherapy in hypertension, it has to be noted that increased blood pressure is a common finding in many oedematous patients, as a complication of cardiac and kidney diseases. In such cases, combined antihypertensive therapy with metolazone and loop diuretics is very effective, as has been already described in detail above.

The published scientific data support the use of metolazone in the proposed indications (1. Oedema related to kidney diseases, including nephrotic syndrome and states of impaired renal function. 2. Oedema related to congestive heart failure, and 3. Mild and moderate hypertension, alone or in combination with other antihypertensive medicines of a different class).

4.2 Posology

Metolazone is given orally and it is available in divisible tablets of 5 mg. The therapy should be initiated with a dose of 2.5 mg/day and the dose must be individualized according to the severity of the condition of the patient and his reaction to the treatment. Once the desired therapeutic effect has been achieved, it may be advisable to reduce the maintenance dose if possible.

It is important to note that different metolazone products have different bioavailability. Therefore, the dose in mg can differ between products (see above Section 2 Overview of biopharmaceutics). Once the appropriate dose has been identified for a patient with a certain product (brand), this product cannot readily be exchanged with another.

Usual dose ranges for metolazone 5 mg tablets for adults are as follows:

Oedema related to congestive heart failure: 2.5–5 mg daily.

In acute heart failure, doses of metolazone as high as 5 mg p.o. (twice daily) or even 10 mg p.o. (twice daily) have been reported (Goyfman et al, 2017).

Oedema related to kidney disease: 2.5-5 mg daily.
Hypertension: 2.5 mg/day.

Metolazone should be given in the morning, due to its prolonged absorption and duration of action (Bond & Crew, 2018). The tablet should always be taken at the same conditions in relation to food (e.g. in the morning with breakfast).

4.2.1 Special populations

Metolazone should be used with caution in elderly patients, in patients with impaired renal or hepatic function and in patients with electrolyte disturbances. There is no conclusive data on the use and dosage of metolazone in paediatric patients (the drug is not recommended for use in patients under 18 years of age).

4.3 Drug Interactions

Thiazide diuretics may interact with other medicinal products through various mechanisms related with pharmacodynamic as well as with pharmacokinetic factors. Considering the fact that metolazone and other diuretics are often used in patients with renal impairment, pharmacokinetic interactions become more complicated when the involved drugs are known to be excreted mainly into the urine (Khoyi & Westfall, 2008; Goodman & Gilman, 2011).

4.3.1 Drugs affecting metolazone

Anticholinergics

May increase metolazone absorption, by decreasing the motility of the gastrointestinal system (Goodman & Gilman, 2011).

Cholestyramine and colestipol

Bind metolazone and may reduce its gastrointestinal absorption (Goodman & Gilman, 2011).

Ethanol

Potentiation of the hypotensive effect due to vasodilation. Moreover, it may enhance diuresis, by inhibiting the secretion of antidiuretic hormone (ADH) (Goodman & Gilman, 2011).

Opioids

Therapeutic doses of morphine-like opioids can produce peripheral vasodilation and reduced peripheral resistance. This may lead to a potentiation of the hypotensive effect of diuretics in general (Goodman & Gilman, 2011).

Nonsteroidal anti-inflammatory drugs

Salicylates and related anti-inflammatory drugs decrease sodium excretion and reduce the natriuretic and antihypertensive effects of thiazides (Goodman & Gilman, 2011).

4.3.2 Drugs affected by metolazone

4.3.2.1 Pharmacodynamic interactions

Metolazone influences the action of several other drugs, through various mechanisms of physiological antagonism or through synergy.

Hypokalemia

Hypokalemia associated with thiazides or metolazone may increase the cardiotoxicity of sotalol and digitalis glycosides (severe arrhythmias and syncope) and may also increase the risk of arrhythmias with drugs prolonging the QT interval, such as astemizole, terfenadine, halofantrine and pimozide. Corticosteroids and ACTH may enhance the hypokalemic effect of the above mentioned diuretics (Martindale, 2009; Goodman & Gilman, 2011).

Anticoagulants (thrombin inhibitors)

Metolazone enhances the anti-thrombin action of the newer anticoagulants, because it also inhibits thrombin. It has been found to exert inhibitory activity almost similar to that of a well-known thrombin inhibitor argatroban (Nair et al, 2015).

Anticoagulants (coumarin derivatives)

It has been reported that metolazone may potentiate the effect of warfarin (Trewin 1988), but the mechanism of this interaction could not be clarified (Wells et al, 1994; Holbrook et al, 2005). Knowing the ability of metolazone to inhibit thrombin, the enhancement of warfarin action can be easily explained (Nair et al, 2015).

Antidiabetic agents

Metolazone may increase blood-glucose concentration, especially in prediabetic and diabetic patients. Thiazide diuretics impair glucose tolerance and deteriorate insulin resistance, but these effects are largely and possibly wholly reversible (Bengtsson et al, 1992; Ramsay et al, 1992; Gurwitz et al, 1993; Harper et al, 1994; Siegel et al, 1994).

Antigout agents

Due to its similarities to thiazides, metolazone may increase blood uric acid levels (Goodman & Gilman, 2011).

Calcium salts

Metolazone increases distal Ca++ reabsorption, so concomitant administration of preparations of calcium salts may lead to extreme hypercalcaemia, as is the case with the thiazide diuretics in general (Goodman & Gilman, 2011).

Cyclosporine

Thiazides combined with cyclosporine have been reported to increase the risk of renal toxicity. In a patient with a renal transplant, the addition of a low dose of metolazone (2.5 mg/day) for two weeks caused an increase of serum creatinine concentrations from 193 to 449 mcmol/L. The discontinuation of metolazone resulted in a return of serum creatinine concentration to the previous value. The bioavailability of cyclosporine was not changed (Christensen & Leski, 1987). The underlying mechanism of this interaction is not fully understood. To date, we do not know whether it is correlated with an enhancement of cyclosporine metabolism due to the induction of CYP3A4 by metolazone (Banerjee & Chen, 2014). Monitoring of serum creatinine levels is recommended when metolazone is given to patients under cyclosporine treatment.

Methenamine

Efficacy may be decreased, presumably due to the urinary alkalizing effect of metolazone (Goodman & Gilman, 2011).

Norepinephrine and other pressor amines

The effect of pressor amines may be decreased by metolazone, as has already been documented for other antihypertensives. Hydrochlorothiazide (50 mg daily for a week) attenuated the pressor responses to infusions of norepinephrine (2 to 10 mcg/min) (Fruncillo et al, 1985). Also, the pressor response to norepinephrine was significantly reduced after prolonged treatment with lisopril and hydrochlorothiazide (Malini et al, 1990). It is recommended to adjust the dosage of metolazone in patients who are to undergo surgery.

Tubocourarine

The effect of non-depolarizing skeletal muscle relaxants may be potentiated by diuretics due to electrolyte imbalance and especially hypokalaemia. This concerns mainly patients with renal impairment treated with the loop diuretics. Hypokalaemia affects neuromuscular function and may be manifested as a minimal weakness but also as a frank paralysis (Miller et al, 1976). No report of such an interaction exists for metolazone.

4.3.2.2 Pharmacokinetic interactions

Metolazone can induce the expression of CYP3A4 and MDR1 (multidrug-resistance protein 1, p-glycoprotein) through activation of the human pregnane X receptor (hPXR) (Banerjee & Chen, 2014). CYP3A4 is a cytochrome involved in the microsomal oxidation of many medicinal products of common use (Ogu & Maxa, 2000). At least in theory, acceleration of hepatic metabolism might necessitate dosage readjustment of the following drugs: alprazolam, astemizole, buspirone, calcium channel blockers (felodipine, nidedipine), carbamazepine, cisapride, cyclosporine, doxorubicin, erythromycin, etoposide, fentanyl,

HIV protease inhibitors, ifosfamide, lovastatin, midazolam, pimozide, quinidine, quinine, simvastatin, tacrolimus, terfenadine, and triazolam.

Lithium salts.

Thiazide diuretics and metolazone may lead to a relative increase of lithium blood levels, with possibly toxic consequences. Metolazone decreases tubular excretion of lithium on one hand and on the other hand by increasing diuresis it leads to a restricted volume for its distribution (Timmer & Sands, 1999).

4.3.3 Drugs mutually affected with metolazone

Diuretics

Combination of loop diuretics with thiazides produces synergy, leading to large and prolonged losses of fluid and electrolytes. With furosemide, complications occurring may include severe natriuresis and hypokalaemia. Dosage titration may be necessary, according to urine volume and changes in body weight. It is important to supplement potassium in diuretic-induced hypokalaemia (serum potassium less than 3.5 mmol/L) (Maronde et al, 1986). Despite this possible pharmacodynamic interaction, it has been reported that metolazone does not affect the pharmacokinetics of furosemide (Marone et al, 1985).

Antihypertensives

There is a mutual potentiation in reducing the systolic and diastolic blood pressure between thiazides and other antihypertensives. Symptomatic hypotension may be expected to occur in patients who are volume and/or sodium depleted (Todd & Heel, 1986).

Deterioration of renal function has been reported in patients treated with thiazides and inhibitors of angiotensin converting enzyme (ACE) (Funck-Brentano et al, 1986; Hogg & Hillis, 1986). It has been suggested that natriuresis and a fall in blood pressure caused by the diuretic might have compromised an already low renal perfusion pressure when auto-regulatory mechanisms were blocked by captopril or other ACE inhibitors. Restoration of normal synthesis of angiotensin represents a necessary compensatory mechanism. Analysis of data from 74 patients showed that acute renal failure was diagnosed only in 2.4% of individuals treated with ACE inhibitors alone, while this percentage was 33% in patients with combined treatment of an ACE inhibitor and a diuretic (Mandal et al, 1994). Nearly all patients who developed acute renal failure in the context of ACE inhibition were consuming salt-restricted diets or receiving diuretic therapy. In clinical practice, older individuals should be monitored carefully for intercurrent volume depletion when they are taking ACE inhibition (Bennett, 1997). The preservation of a positive sodium balance promotes the recovery of renal function after the combined administration of ACE inhibitors and diuretics, which is a rather common fixed combination for treating hypertension. It should be noted, that to date such interaction with ACE inhibitors has not been reported for metolazone.

Similarly, any interaction of metolazone with the inhibitors of the angiotensin-II-receptors is only theoretical.

Corticosteroids or ACTH

These drugs may lead to severe hypokalaemia, with symptoms of weakness and muscle cramps, and with the serious risk of cardiac arrhythmias (especially when metolazone is combined with furosemide, a rather common practice). On the other hand, retention of sodium and water antagonizes he action of metolazone (Goodman & Gilman, 2011).

5 Overview of safety

5.1 Adverse effects

5.1.1 Electrolyte imbalance

Metolazone can be followed by serious electrolyte abnormalities, especially when it is combined with a loop diuretic. In order to avoid serious electrolyte disturbances when metolazone is introduced in patients taking loop diuretics, the metolazone should be given in low doses to start with in hospital, and at the same time the dosage of the loop diuretic should be reduced under careful biochemical monitoring (Allen et al, 1981; Ghose & Gupta,1981; Oster, 1983; Odlind et al, 1987; Kiyingi et al, 1990; Filippone et al, 2020). Weight loss of more than 2–3 pounds daily in an oedematous patient marks those patients predisposed to the development of more severe electrolyte abnormalities. In this regard, careful selection of starting doses of a loop diuretic and metolazone and monitoring of the rate of body weight loss are important safety considerations (Sica, 2003).

The most common electrolyte abnormalities with combination diuretic therapy include hypokalaemia, hypomagnesemia, contraction alkalosis and, occasionally, hyponatraemia (Black et al, 1978; Allen et al, 1981; Brisco-Bacik et al, 2018). Supplemental potassium may be necessary. Patients with a persistent need for large amounts of supplemental potassium are not uncommonly hypomagnesemic, in that hypomagnesemia hinders renal potassium-conserving ability (Sica, 2003).

In a retrospective cohort study of Shulenberger and collaborators, patients with acute decompensated heart failure and loop diuretic resistance were treated with chlorothiazide (n=88) or metolazone (n=89) at a mean dosage of 491±282 mg (chlorothiazide, i.v.) and 5.8±3.5 mg (metolazone, p.o.). Safety outcomes were similar between the two groups. No significant differences in renal function were observed (serum creatinine concentration, blood urea nitrogen concentration, and glomerular filtration rate). The incidence of acute kidney injury was also similar (17.1% and 23.6% in the chlorothiazide and metolazone groups, respectively). Rates of severe hypokalaemia did not significantly differ between the

two groups, nor did the rates of severe hyponatraemia, or severe hypomagnesemia (Shulenberger et al, 2016).

5.1.2 Cardiovascular system

Patients hospitalized with acute decompensated heart failure were evaluated post hoc in data from ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure). Analysis of the data showed that among factors associated with hypotension was chronic metolazone therapy (odds ratio, 1.74; 95% CI, 1.17–2.60; $P<0.001$) (Patel et al, 2014).

5.1.3 Endocrine system

Thiazide diuretics can precipitate hyperosmolar non-ketotic diabetes mellitus in susceptible individuals, and this has been reported also for metolazone (Rowe & Mather, 1985). In a literature search (from 1966 to 2004), Zillich and collaborators identified 59 clinical trials constituting 83 thiazide diuretic study arms. Trial size, length, type of thiazide diuretic, and dose varied substantially among the studies. There was an association between average changes in potassium and glucose in the study arms, supported by a sensitivity analysis, by subset analyses of the effect of covariates, as well as by an inverse-variance weighting. The authors suggested that treatment of thiazide-induced hypokalaemia may reverse glucose intolerance and possibly prevent the future development of diabetes (Zillich et al, 2006).

5.1.4 Idiosyncratic reactions

Some case reports imply that metolazone, similarly to the thiazides in general (Seçen & Karaca, 2016), may elicit idiosyncratic reactions, of unknown aetiology, although in some reports they are characterized as "autoimmune" without any further elaboration on their mechanism. Such reports refer to aplastic normochromic anaemia (Suh & Sood, 1979), neutropenia (Donovan, 1989), vasculitis (Cox & Hodkin, 1991), hypercalcemia and acute pancreatitis (Anderson et al, 1991), cholestatic liver disease (Gabrielli et al, 2001), and Stevens-Johnson Syndrome (toxic epidermal necrolysis) (Kumar et al, 2016; Meyler's Side Effects of Drugs, 2016).

5.2 Overdose

Symptoms and Findings

Overdosing may lead to dehydration and electrolyte disturbances (primarily hyponatraemia, but also loss of potassium and magnesium). The symptoms include thirst, nausea, vomiting,

disorientation, somnolence, headache, muscle cramps, arterial hypotension, and arrhythmias (in severe cases of hypokalaemia).

Treatment

Within the first hour of ingestion the absorption may be reduced by administration of medicinal charcoal (1 g/kg body weight). Thereafter priority should be given to establish adequate hydration and re-establishment of the electrolyte balance [redacted]

5.3 Pregnancy and Breastfeeding

5.3.1 Pregnancy

If administration of a thiazide is begun during pregnancy, there is a risk of transient volume depletion that may result in placental hypoperfusion (Al-Balas et al, 2009). Metolazone crosses the placenta and appears in cord blood (Martindale, 2009). Therefore, administration to women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the foetus. As a matter of fact, the potential effects on the foetus include foetal or neonatal jaundice, thrombocytopenia, electrolyte imbalance, and possibly other adverse reactions known to occur in the adult (Al-Balas et al, 2009; Martindale, 2009; Product Monograph Zaroxolyn, 2018).

Teratogenicity studies in mice, rats and rabbits treated with oral doses ranging from 0.2 to 50 mg/kg showed no evidence of teratogenic effects. Reproductive studies in mice and rats have shown no evidence of altered reproductive capacity in mice. However, in a rat study in which males were treated orally with metolazone at doses of 2, 10 and 50 mg/kg for 127 days prior to mating with untreated females, an increased number of resorption sites were observed in dams mated with males from the 50 mg/kg group. In addition, the fetal weight was decreased and the pregnancy rate was reduced in dams mated with males from the 10 and 50 mg/kg group (Module 2.4 Non-Clinical Overview, Section 5.5. Reproductive and Developmental Toxicity).

Metolazone is considered as non-teratogenic in humans (FDA pregnancy category B: “Animal reproduction studies have failed to demonstrate a risk to the foetus and there are no adequate and well-controlled studies in pregnant women”) (Goodman & Gilman, 2011).

5.3.2 Breastfeeding

Metolazone, like the thiazide diuretics and the loop diuretics, appears in breast milk and it is possible to affect the newborn. The risk of exposure to the infant should be weighed against

the benefit of treatment for the mother. If the use of metolazone is absolutely necessary for the nursing mother, then she should stop nursing (Martindale, 2009; Reilly & Jackson, 2011; Bond & Crew, 2018).

5.4 Contraindications, special warnings and precautions for use

5.4.1 Contraindications

Metolazone is contraindicated in patients with:

- Hypersensitivity to the active substance, sulfonamides, thiazides or to any of the excipients of the tablet.
- Anuria, hepatic coma or precomatose conditions.
- Severe disturbances of the electrolyte balance

[redacted]

5.4.2 Special warnings and precautions for use

5.4.2.1 Electrolyte imbalance

Fluid and electrolyte balance should be carefully monitored during treatment with metolazone in all patients, especially if the drug is used at high doses or if is administered concurrently with loop diuretics and corticosteroids (risk of hypokalaemia). Hyponatraemia or hypochloraemia may occur. Hyponatraemia is accompanied by neurological symptoms (nausea, debility, progressive disorientation, apathy). Cases of hypomagnesemia have also been observed. In some patients (as it may happen also with other diuretics) serious hyponatraemia and hypokalaemia may occur immediately after the beginning of treatment. An individually adjusted dosage of a concurrently administered oral potassium salt (e.g. potassium chloride) may be considered for patients receiving digitalis or showing signs of coronary heart disease. Potassium supplements should be avoided in patients concurrently treated with an ACE inhibitor or with an angiotensin-II-antagonist, because these drugs produce hyperkalaemia. An individually adjusted dosage may also be considered for patients who are being treated with a high dose beta-adrenergic agonist, and in all cases when the potassium concentration in the serum is below 3.0 mmol/L.

In all cases of combined treatment, the maintenance or normalization of the potassium balance should be monitored closely. If hypokalaemia is accompanied by clinical signs of potassium shortage (for instance muscular weakness, paresis or ECG-alterations) the administration of metolazone should be discontinued.

5.4.2.2 Patients with kidney and liver disease

Monitoring of serum electrolytes is particularly advisable in the elderly. Also, in patients with ascites due to liver cirrhosis, or in patients with oedema as a consequence of a nephrotic syndrome. For the latter condition, metolazone should be used only under control in

normokalaemic patients who show no signs of volume depletion or hypoalbuminaemia. In case the condition of a patient with kidney insufficiency, oliguria or azotaemia deteriorates, the treatment should be discontinued.

There have been cases with renal failure mostly in the context of dehydration, aggravated by concomitant medication such as ACE-inhibitors, angiotensin-II-antagonists, aldosterone-antagonists and/or NSAIDs. Concurrent treatment with lithium should be avoided (see above Section 4.3 Drug Interactions).

5.4.2.3 Cross-reactivity with sulfonamides

Cross reactivity may occur in patients who are allergic to sulfonamides or thiazides.

5.4.2.4 Metabolic and endocrine effects

Thiazide diuretics tend to reduce glucose tolerance and raise serum levels of cholesterol, triglycerides, and uric acid. These effects are usually minor, but frank gout or overt diabetes may be precipitated in susceptible patients.
In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Latent diabetes mellitus may become manifest during thiazide therapy.

5.4.2.5 Primary adrenal insufficiency

Diuretics should be avoided for the treatment of hypertension if the patient has primary adrenal insufficiency, known as Addison's disease.

5.4.2.6 Gouty attacks

Like other diuretics, metolazone may raise the serum uric acid level, which in rare instances may lead to acute attacks of gout (Martindale, 2009).

5.4.2.7 Choroidal effusion, acute myopia and secondary angle-closure glaucoma

Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing

acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy (PRAC Recommendations on signals, 2020).

5.4.2.8 Glucose metabolism

Metolazone has only a slight effect on the glucose metabolism. In patients suffering from diabetes, treatment with antidiabetic drugs may have to be readjusted. In cases with latent diabetes, glycosuria and hyperglycaemia may occur. The blood sugar level should therefore be checked on a regular basis (Martindale, 2009).

5.4.2.9 Laboratory values

Insignificant and partly reversible increases in the plasma concentration of total cholesterol, triglycerides, or LDL-cholesterol were observed during long term treatment with thiazide or thiazide-like diuretics. The clinical relevance of these observations is unclear (Martindale, 2009).

5.4.2.10 Excipients

This product contains lactose. Patients with hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine [redacted]

5.4.2.11 Elderly

Regular ongoing monitoring and blood tests are to be performed in elderly patients and patients who are on long term treatment with metolazone.

5.4.2.12 Children

There is insufficient clinical experience for using metolazone in paediatric population (patients under 18 years of age).

6 Benefits and risks conclusions

Metolazone is a quinazoline derivative related to the thiazide diuretics in terms of pharmacological actions. It has been used in many countries for almost fifty years to treat salt and water retention, in oedematous situations accompanying congestive heart failure or kidney disease. Metolazone inhibits sodium transport across the epithelial cells of the renal tubules, mostly in the distal convoluted tubules. By decreasing the reabsorption of sodium,

it enhances the excretion of sodium, chloride, and water. The shift in water and electrolytes results in hypovolaemia, keeping the peripheral vascular resistance low and returning the cardiac output to normal. Diuresis resolves oedema and contributes to the antihypertensive effect. While metolazone is similar to thiazides in its mechanism of action, it does differ in its use in patients with impaired renal function. Thiazide diuretics decrease GFR and are therefore less effective in patients with renal impairment. On the contrary, metolazone has been shown to retain a satisfactory diuretic effect in patients with a reduced GFR.

Metolazone 5 mg tablets are indicated for the treatment of oedema related to kidney diseases, including nephrotic syndrome and states of impaired renal function, and for patients with severe chronic congestive heart failure. It is also indicated in cases of mild and moderate hypertension. Metolazone is administered alone, or in combination with other diuretic or antihypertensive drugs. It has been used together with loop diuretics in patients refractory to loop diuretics alone.

Metolazone is given orally as a single daily dose, which should always be taken at the same time in relation to food. Diuresis begins within two hours and persists for 24 hours in normal subjects. Dose-response studies in normal subjects show that a maximum diuretic activity is observed on raising the dose to 10 mg ([redacted]). Metolazone is bound to plasma proteins and erythrocytes (to about 95%) and it is virtually not metabolized.

The starting dose should be 2.5 mg in order to titrate administration according to the response of the patient. Therapy is then continued at the lowest dose needed to maintain diuresis. For the treatment of oedema associated with congestive heart failure or kidney disease, a dose of 2.5-5 mg once daily is recommended as the initial treatment. For the treatment of hypertension, 2.5 mg once daily is recommended initially, with titration of the dose as above. The drug is not recommended for paediatric patients, because safety and efficacy have not been established in individuals under the age of 16 years.

Adverse effects concern usually fluid and electrolyte imbalances, especially hyponatraemia, hypokalaemia, and hypomagnesemia. It is essential that any electrolyte imbalances be corrected before starting treatment. A common adverse effect is hyperuricaemia, due to competitive inhibition of uric acid secretion and a decrease in extracellular fluid from diuresis. Metolazone may impair glucose tolerance, causing hyperglycaemia and glycosuria. Diabetic patients should have their blood and urine glucose levels monitored while on this therapy. Diuretic therapy may be associated with increased serum cholesterol and triglycerides.

The patient may experience orthostatic hypotension, which can be worsened by other antihypertensive agents, alcohol, or narcotic medications. Hypotension may be more common in the elderly. Rare adverse effects include agranulocytosis, aplastic anaemia and toxic epidermal necrolysis.

Metolazone passes the barrier of the placenta and it is also excreted into milk. As a rule, it should be avoided during pregnancy and breastfeeding.

Therapy is contraindicated in those with known metolazone hypersensitivity. There is limited evidence of cross-reactivity between sulfonamide derivatives and metolazone, because metolazone contains the sulfamoyl moiety in its structure. Therefore, it should be used with caution in patients known for sulfonamide allergy. Metolazone should not be used in patients who are experiencing a hepatic coma or hepatic encephalopathy because the possible electrolyte disturbances may exacerbate or worsen the underlying disease.

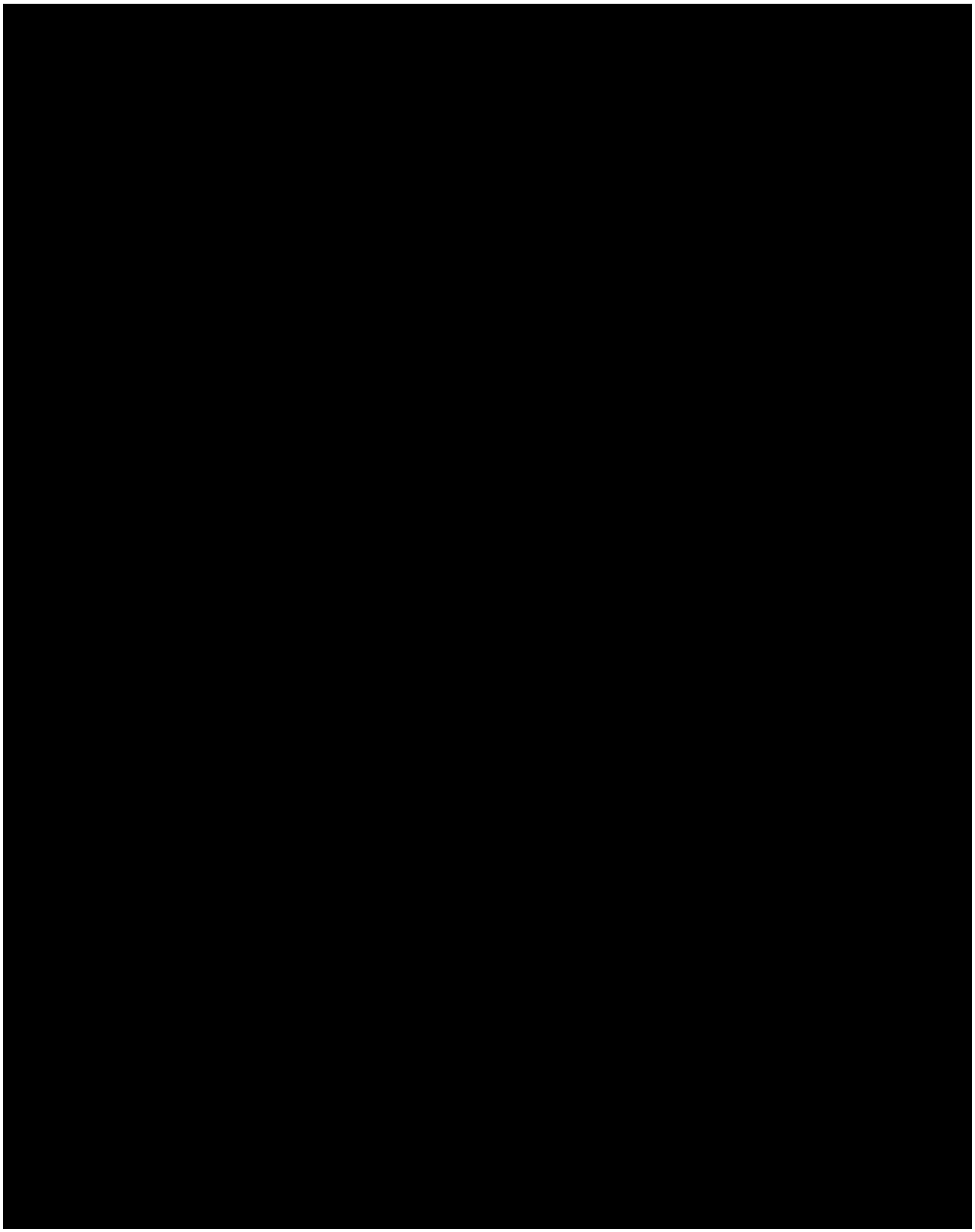
Metolazone is excreted mainly into the urine. Its use is safe in mild to moderate renal impairment, unlike other thiazide diuretics. Extreme caution is needed in patients with severe renal impairment or anuria. Anuric patients do not respond to treatment and they should have metolazone withheld.

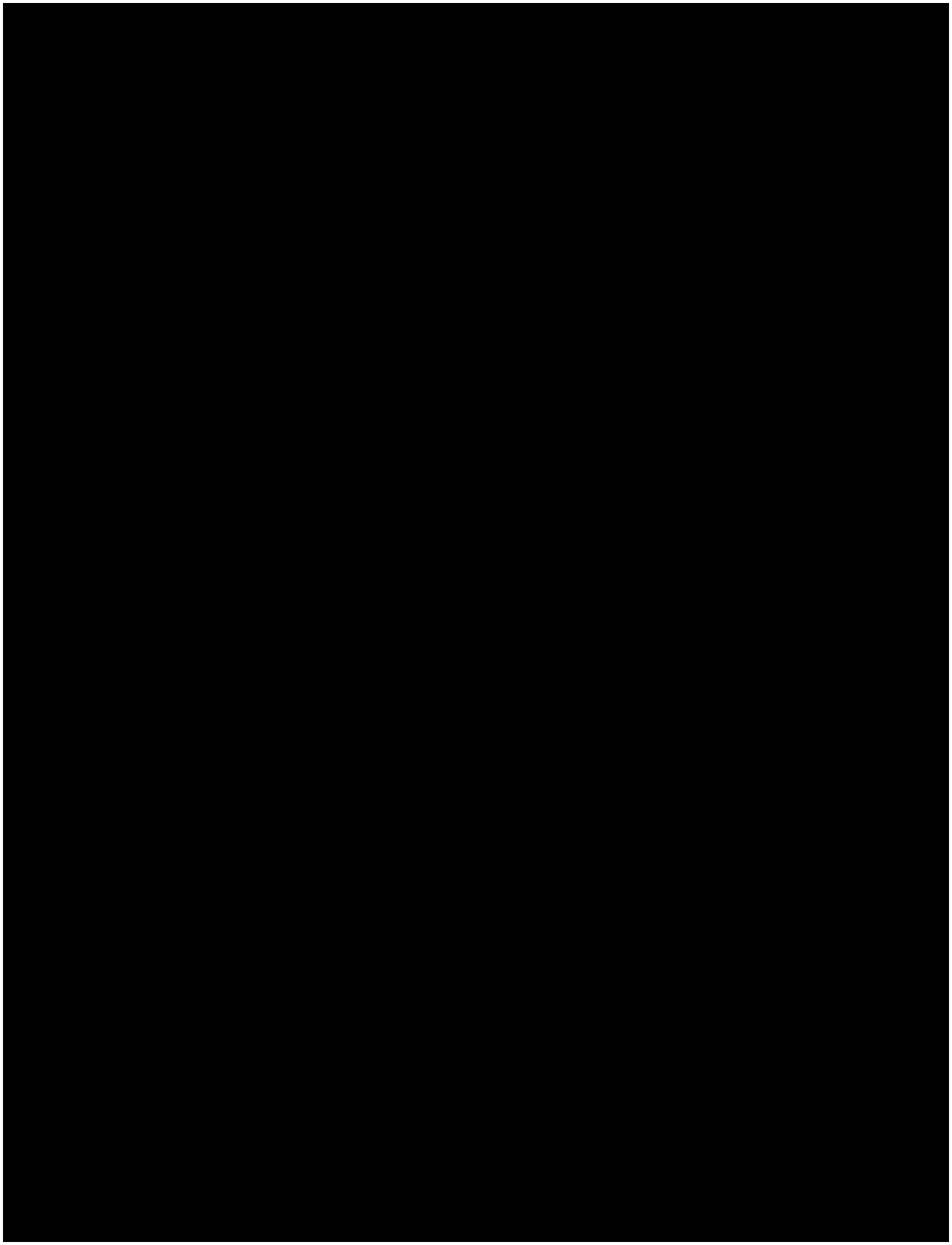
To monitor the effectiveness of therapy in the treatment of oedema, the patient should show an increase in urine output and a decrease in total body weight. Additionally, because of the adverse effects associated with metolazone, serum electrolytes (sodium, potassium, magnesium, and chloride) should be monitored at baseline and routinely while continuing therapy. Adequate fluid replacement and correction of possible electrolyte imbalances during diuresis will prevent most common adverse effects. Although evidence is controversial in the incidence of hyperglycaemia with metolazone, diabetic patients should monitor their serum glucose regularly while on this medication.

In conclusion, metolazone is a medicinal agent with a long clinical application and a well-established use for the proposed indications. Furthermore, metolazone 5 mg tablets formulation as proposed by this application is the same qualitative and quantitative formulation approved and marketed in several other member states for at least 10 years. The assessment of the available data in terms of pharmacological and clinical documentation, shows a favourable risk/benefit ratio with a therapeutic efficacy and an acceptable level of safety.

7 Literature references

[redacted]





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