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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 31 of Directive 2001/83/EC

Metformin containing medicinal products

Procedure number: EMEA/H/A-31/1432

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Note:
Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Information on the procedure

Metformin, alone or in combination with other medicines, is considered the first choice in the treatment for Type 2 diabetes mellitus (T2DM) and it is widely used in the EU. Currently the use of metformin in patients with renal failure is not harmonised across the EU, being contraindicated in patients with different stages of moderate renal failure depending on the member state and product. It is considered in the interest of the Union that the adequacy of the current recommendations for metformin containing products is re-evaluated with respect to the use in patients with moderate renal failure, taking into account the available information on the risk of lactic acidosis. These patients form a large population which currently may have not access to the benefits of metformin across the Union.

On 25 January 2016 the Netherlands therefore triggered a referral under Article 31 of Directive 2001/83/EC, and requested the CHMP to assess the impact of the above concerns on the benefit-risk balance of metformin containing products and to issue an opinion on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

Metformin is indicated in the treatment of Type 2 Diabetes Mellitus (T2DM) in adults, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycemic control. Metformin is considered the first choice in the treatment for T2DM and it is widely used in the EU.

Metformin may be used as monotherapy or in combination with other antidiabetic agents or with insulin. Metformin-containing medicines have been authorised in the EU either nationally or through the centralise procedure from 1959 to 2014. Metformin is available as 250 mg, 500 mg, 850 mg and 1000 mg tablets. This referral covers all medicines containing metformin, either as a single agent or in combination:

Metformin single agent (originator product Glucophage)

Pioglitazone/metformin (Competact, Glubrava)

Dapagliflozin/metformin (Ebymect, Xigduo)

Sitagliptin/metformin (Efficib, Janumet, Ristfor, Velmetia)

Linagliptin/metformin (Jentadueto)

Saxagliptin/metformin (Komboglyze)

Alogliptin/metformin (Vipdomet)

Canagliflozin/metformin (Vokanamet)

Vildagliptin/metformin (Eucreas, Icandra, Zomarist)

Empagliflozin/metformin (Synjardy)

Glibenclamide/metformin (Glucovance)

Lactic acidosis is an adverse drug reaction associated with the use of metformin. It is a very rare but serious metabolic complication that can occur with metformin accumulation, being associated with a

high mortality rate in the absence of prompt treatment. Because metformin is cleared by the kidneys, it may accumulate when renal function decreases, with the potential for exposure-dependent toxicity that could precipitate lactate accumulation.

The different stages of renal function are as follows:

Grade	GFR (ml/min)	Interpretation
1	>90	Normal kidney function
2	60-89	Mild renal impairment
3a	45-59	Moderate renal impairment
3b	30-44	
4	15-29	Severe renal impairment

* All GFR values are normalized to an average surface area (size) of 1.73m^2. Chronic kidney disease (CKD) is defined as either kidney damage or GFR < 60 ml/min for 3 for more months.

In order to provide a safety margin to minimise the risk of metformin-associated lactic acidosis, stringent prescribing criteria based on kidney function were implemented in the EU in 2001 following a previous referral procedure. During this procedure, the product information of metformin containing medicinal products in the EU was revised to include a contra-indication in all patients with moderate and severe renal impairment.

In 2014, a worksharing variation procedure was finalised for the brand leader product Glucophage concluding on the extension of the use in moderate renal failure Stage 3a (GFR 45-59ml/min).

In December 2015, during a recent Periodic Safety Update Report Single Assessment (PSUSA) procedure for metformin it became apparent that the product information of metformin containing products with regards to the cut-off value for creatinine clearance where metformin is contra-indicated was not consistent between member states and among metformin containing products. In addition, there were a number of metformin containing products, including fixed dose combinations (FDC), where both moderate Stages 3a and 3b (GFR < 60 mL/min) were still contra-indicated for use.

Moreover, the current product information approved in the EU for the use of metformin containing medicinal products significantly differs from the therapeutic recommendations in the majority of European and international treatment guidelines in diabetes mellitus that recommend the use of metformin in all stages of moderate renal impairment.

In view of the above, taking into account that metformin is the considered the first choice in the treatment for Type 2 diabetes mellitus (T2DM) in the EU, the Netherlands considered that it was in the interest of the Union to re-evaluate the adequacy of the current contra-indication of metformin in patients with moderate renal impairment of all metformin containing products taking into account the available data on the risk of lactic acidosis, and to refer the matter to the Committee for Medicinal Products for Human Use (CHMP). An overview of the relevant information for the discussion is presented hereinafter, including clinical data submitted by marketing authorisation holders.

2.2. Data on pharmacokinetics

Metformin is exclusively eliminated unchanged in the urine. About 90% of absorbed metformin is eliminated via the renal route within the first 24 hours. In healthy subjects (GFR >90 mL/min) the plasma elimination half-life ($t_{1/2}$) of metformin is approximately 5 hours, and there is minimal

accumulation of metformin with multiple dosing (Graham et al. 2011). At usual clinical doses and schedules, metformin steady-state plasma concentrations are generally <1.5 µg/ml. Maximum metformin plasma levels during controlled clinical trials do not generally exceed 5µg/ml (Frid et al. 2010).

In subjects with renal impairment, metformin renal clearance is decreased leading to an increase in metformin systemic exposure. Table 1 shows systemic exposure of metformin in patients with T2DM and moderate renal insufficiency compared with normal renal function (Sambol et al. 1995). There are higher plasma C_{max} and AUC of metformin in subjects with renal impairment compared to the healthy subjects. Mean plasma metformin C_{max} was approximately 3-fold higher in subjects with moderate or severe renal impairment. Similarly, mean metformin AUC was up to 5.8 times higher in subjects with moderate or severe renal impairment.

Table 1 Effects of age and stage of RI following a single oral dose of 850 mg metformin

Subject	n	Age (yrs)	CL_{CR} (ml/min)[a]	C_{max} (µg/ml)	AUC_{inf} (µg/ml.h)	CL_R (ml/min)	CL/F (ml/min)	$t_{1/2}$ (h)
Healthy young (HV)	6	18-40	>90	1.4±0.3	10±2	636	1155	7
Healthy middle-age	3	>40-<60	102±1	1.6±0.5	11±3	395	1032	11
Healthy elderly	12	≥65	>60	2.5±0.7	16±4	412	728	11
Mild RI	5	[b]	61-90	1.9±0.5	13±2	384	852	17
Moderate RI	4	[b]	31-60	4.1±1.8	58±37	108	238	16
Severe RI	6	[b]	10-30	3.9±0.9	53±30	130	259	17

In addition, a summary of the systemic exposure of metformin at steady state following repeated treatment with metformin in T2DM patients is shown in Table 2.

Table 2 Steady state concentrations of metformin in T2DM patients

Subject	Age (yrs)	CL_{CR} (ml/min)	Dose mg/day	C_{trough} (µg/ml)	Reference
Pat	70-88	>60	1700	1.1±0.3	(Lalau et al. 1990)
		30-60	850	0.9±0.2	
Pat	-	>60[a]	1500 (500-3000)	0.6 [0.01-2.7]	(Frid et al. 2010)
		30-60[a]	1500 (500-3000)	1.0 [0.01-1.9]	
		<30[a]	1500 (500-300)	1.1 [0.7-2.5]	

[a] mi/min/1.73 m^2

The expected systemic exposure of metformin in patients with different stages of renal function, has been simulated using a population PK (PPK) model based on pooled data from three studies with a

total of 4,895 metformin plasma concentrations from both T2DM patients and healthy subjects (Duong, Kumar, et al. 2013). The simulations aimed for a $C_{ss,av}$ of 1.5 µg/ml and was restricted not to exceed 5 µg/ml as upper therapeutic limit. The study concluded that metformin plasma concentrations are kept below 5 µg/ml when used at a daily dose of 1000mg/day for GFR of 30ml/min and 2000mg/day for GFR up to 60 ml/min.

Another pharmacokinetic model (Adam and O'Brien 2014) is based on linear regression analysis between metformin CL and CLCR and assuming a bioavailability of 60%. This study suggested a threshold of the metformin plasma concentration of <10 mg/l, no dose limitation at an GFR≥ 40ml/min, with a maximum of 2000mg/day in the remaining renal impairment stage 3b.

Relationship between plasma exposure of metformin and plasma levels of lactate

Metformin decreases clearance of lactic acid, by inhibiting the mitochondrial oxidation, and thereby resulting in an increase in plasma levels of lactate. Lactic acidosis is defined as blood lactate concentrations above 5 mmol/l and arterial pH < 7.35 (de Groot et al. 2011).

Samples taken arbitrarily (i.e. at random points in time) for determination of metformin exposure in 16 patients reported with metformin associated lactic acidosis (MALA showed a range of plasma concentrations between 0.4-44 µg/ml following treatment with in average of 1744 mg/day metformin (range 850-2550 mg/day). The mean GFR was calculated to 20 ml/min (range 3-56 ml/min) at the time for admission (compared to 44 ml/min (range 5-98 ml/min) estimated at an earlier time point pre-admission (van Berlo-van de Laar, Vermeij, and Doorenbos 2011).

Three cases of MALA, in patients with renal impairment, reported lactate levels of 14-25 mM and determined plasma concentrations of metformin of 42-85 µg/ml following daily doses of 1700-2000 mg. As no data or information on time for administration in relationship to time for determination of the plasma levels, of lactate and metformin are available, no conclusions can be drawn on potential relationships (Runge et al. 2008).

In addition, in the PPK model by (Duong, Kumar, et al. 2013) no correlation was found between metformin $C_{av,as}$ and lactate. In the few subjects with elevated plasma lactate levels lactic acidosis was ruled out. Moreover, according to (DeFronzo et al. 2016), whether systemic plasma levels of metformin can help in predicting the risk of lactic acidosis remains unclear.

Study EMR200084-622: Pharmacokinetics, efficacy and safety of metformin in CKD

In a non-comparative, open-label pilot phase II study (EMR200084-622) submitted by Merck, T2DM patients with different stages of CKD (stages 1-5), not treated with metformin before, were included to receive repeated dosing with different dosing regimens and the systemic exposure of metformin was determined 12h after the last dose.

Other inclusion criteria included a renal function control at least 3 months before start of study to ensure a stable renal function (less than 30% of fluctuation in the last three months), age 18-80 years. Exclusion criteria were severe hepatic failure, other liver function impairment, unstable or missing renal function control, need for X-ray with contrast medium injection during study, pregnancy, lactation, hypersensitivity to metformin or any acute systemic illness with lactate concentration > 2.5 mmol/l. All patients underwent at least 3 one week-blocks of metformin treatment at an increasing dosage.

Metformin was administered to 76 patients, including 14 in renal impairment stage 3a and 16 in 3b, respectively, and was effective in lowering blood glucose in a dose dependent-way in the different stages of renal impairment, with a maximum at 2000 mg for stage 1 and 4; and 1000 mg in stage 5. Metformin levels were not exceeding the threshold of 5mg/l in all patients except three patients with 2000mg/day in CKD stage 4 and 5, respectively (see Table 3). Of note the metformin plasma concentrations in phase II (the maximum proposed dose of 1000mg/day) only rose significantly in CKD stage 4, but not in 3a or 3b.

Table 3. Steady state trough data following repeated metformin dosing with 500 mg qpm, 500 mg bid, 1000 mg bid and 1000 mg qam + 2000 mg qpm during one week, with a wash-out period of one week between each regimen.

CKD Stage		1	2	3A	3B	4	5
Phase1 (after 500 mg/day for a week)	No.	17	11	14	16	12	6
	eGFR (ml/min)	121.2±20.1 (90-150)	77.7±9.7 (59-96)	55.9±6 (41-65)	37.8±5.4 (30-47)	22.6±4.7 (16-29)	12.7±1 (11-14)
	Blood glucose (mmol/l)	9.56±3.35 (3-16.3)	8.84±2.86 (5.6-16)	9.86±3.28 (5.2-16)	8.75±2.89 (4.8-16.7)	8.55±3.82 (3.9-16)	8.96±2.11 (6.2-12)
	Lactate (mmol/l)	–	–	1.34±0.55 (0.62-2.66)	1.12±0.37 (0.5-1.6)	1.18±0.43 (0.7-1.97)	0.73±0.52 (0.16-1.7)
	Plasma metformin (mg/l)	0.23±0.11 (0.10-0.44)	0.46±0.26 (0.10-1.03)	0.86±0.54* (0.10-2.11)	0.97±0.52 (0.33-2.0)	1.44±1.13‡ (0.29-4.17)	1.38±0.57 (0.83-2.44)
	Erythrocyte metformin (mg/l)	0.23±0.11 (0.10-0.57)	0.54±0.31 (0.12-1.16)	0.65±0.23* (0.40-1.09)	0.96±0.76 (0.10-3.12)	1.02±0.64‡ (0.46-2.82)	1.43±0.24 (0.80-1.38)
Phase 2 (after 1000 mg/day for a week)	No.	17	11	14	15	12	5
	GFR (ml/min)	123.3±18 (91-150)	78.5±11.9 (62-96)	53.5±6.2 (39-61)	35.7±6.3 (30-44)	22.3±5.5 (11-32)	11.8±2.6 (8-15)
	Glycemia (mmol/l)	9.17±2.96 (4.7-14.4)	8.32±3.73 (5.6-18.7)	8.42±1.97 (5.5-12.2)	9.03±2.64 (5-14.6)	6.75±3.89 (2-15.9)	7.74±1 (6.3-8.7)
	Lactate (mmol/l)	–	–	1.34±0.68 (0.53-3)	1.31±0.56 (0.54-2.4)	1.16±0.38 (0.5-1.67)	0.44±0.17 (0.2-0.61)
	Plasma metformin (mg/l)	0.50±0.51 (0.10-2.18)	0.66±0.36 (0.32-1.45)	1.09±0.51 (0.31 -1.82)	1.24±0.50 (0.5 -2.07)	2.28±1.16 (0.89-4.9)	1.92±0.95 (1.03-3.53)
	Erythrocyte metformin (mg/l)	0.55±0.40 (0.10-1.86)	0.76±0.43 (0.24-1.84)	0.96±0.30 (0.59-1.49)	1.47±0.68 (0.73-3.12)	1.63±0.58 (0.62-2.47)	1.20±0.90 (0.10-2.44)
Phase 3 (after 2000 mg/day for a week)	No.	15	11	13	13	11	5
	GFR (ml/min)	121.7±22.3 (85-150)	80.3±7.5 (69-96)	55.3±8.1 (42-76)	37.3±5.5 (30-45)	22.5±3.3 (17-27)	12±1.2 (10-13)
	Glycemia (mmol/l)	8.59±2.95 (4.4-14.9)	7.92±1.59 (5.1-10)	8.72±2.73 (4.2-13.2)	7.85±1.67 (5.7-11.3)	7.11±3.40 (2.7-14.5)	9.62±4.16 (6.7-16.6)
	Lactate (mmol/l)	–	–	1. 4±0.56 (0.64-2.45)	1.21±0.64 (0.1-2.7)	1.47±0.67 (0.74-2.7)	0.63±0.14 (0.43 -0.79)
	Plasma metformin (mg/l)	0.49±0.30 (0.10-1.1)	0.84±0.62 (0.11 -2.0)	1.31±0.90 (0.48-3.04)	2.07±1.03 (0.76-4.06)	3.09±1.58 (1.55-7.2)	4.37±1.73 (3.07-7.19)
	Erythrocyte metformin (mg/l)	0.73±0.27 (0.10-1.15)	1.19±0.42 (0.49-1.88)	1.48±0.70 (0.83-3.34)	2.32±0.90 (0.82-4.18)	2.68±0.64 (1.61-3.57)	4.54±2.03 (1.56-6.74)
Phase 4 (after 3000 mg/day for a week)	No.	10	–	–	–	–	–
	GFR (ml/min)	123.8±19 (94-150)	–	–	–	–	–
	Glycemia (mmol/l)	8.77±2.88 (5.6-14.7)	–	–	–	–	–
	Lactate (mmol/l)	–	–	–	–	–	–
	Plasma metformin (mg/l)	0.82±1.09 (0.17 -3.88)	–	–	–	–	–
	Erythrocyte metformin (mg/l)	0.90±0.50 (0.25-1.83)	–	–	–	–	–

*: No.=13 ‡: No.=10 ◊: No.=11

None of the patients experienced critical lactate levels as per definition (>5mmol/l) (de Groot et al. 2011). A total of four patients experienced a lactate level above the criterion of metformin withdrawal (>2.5mmol/l). However, in those patients, the increase in lactate level was only modest. The maximal value was 3mmol/l in one single CKD 3a patient at the end of the phase 2 (1000mg metformin/day). The investigator nevertheless decided to continue metformin therapy in the latter cases because of intolerance to other antidiabetic agents, and of the absence of metformin accumulation (plasma metformin level of 1.8 mg/l). In the following phase with double metformin daily dose, lactate value (phase 3, 2000mg/day) in the same patient was not below 2.5 mmol/l, thus indicating other causes of

lactate elevation. Moreover, lactate values were not increased in the patients having the highest metformin levels (> 5mg/l).

The increase in metformin levels was only more pronounced in CKD 4 to 5 patients, and even more, plasma metformin levels only exceptionally exceeded 5mg/l, which was not accompanied by hyperlactemia (lactate >2.5mg/dl). In parallel, the hyperlactemia observed in four patients was not accompanied by high metformin plasma levels, demonstrating that there was no relation between the highest metformin values and the highest lactate values.

Dose recommendations in moderate renal impairment

In the literature the use of metformin in patients with renal impairment it has been widely reported using a decreased dosing regimen. However there are no clear and univocal recommendations on metformin dosages in patients with renal impairment. A summary of the main references is included in Table 4 below.

Table 4 Metformin dosages recommendations in patients with renal impairment

	CKD stage 0-1 GFR ≥90 mL/min	CKD stage 2 GFR ≥60 mL/min	CKD stage 3a GFR ≥45 mL/min	CKD stage 3b GFR ≥ 30 mL/min	CKD stage 4-5 GFR <30 mL/min
(Lipska, Bailey, and Inzucchi 2011)			Normal dose Monitor renal function every 3-6 months	Reduce 50% or to half-maximal dose Monitor renal function every 3 months	Stop
(Klachko and Whaley-Connell 2011)	Maximum 2,500 mg daily	1,000 mg twice daily	500 mg twice daily	500 mg daily	
(Arnouts et al. 2014)			Maximum 1.5 g per day	Maximum 850 mg/day	
(Inzucchi et al. 2014)	2550 mg daily	2550 mg daily	2000 mg daily Consider more cautious follow-up renal function	1000 mg daily Consider more cautious follow-up renal function	Do not use

In addition, the majority of European and international treatment guidelines recommend the use of metformin in moderate renal impairment:

- Boden Institute National Evidence Based Guideline for Blood Glucose Control in T2DM (Colagiuri S 2009): contraindicated in patients with severe renal impairment (GFR<30ml/min) and should be used with caution in people with moderate renal impairment (GFR of 30-45ml/min).

- National Institute for Health and Care Excellence (NICE 2015): recommends using metformin with caution in patients, in whom the serum creatinine exceeds 130µmol/l or GFR is less than 45ml/min. Doses should be lower and prescribed with increased frequency of monitoring. In patients already taking metformin, the drug should be discontinued if the serum creatinine exceeds 150µmol/L or GFR falls below 30ml/min.
- The Expert Consensus on Management of Diabetic Patients with Impairment on Renal Function (Bonnet et al. 2011): recommended to reduce the metformin dosage when the creatinine clearance is between 60 and 30ml/min. Metformin must be withdrawn in a creatinine clearance below 30ml/min.
- Italian Diabetes societies AMD and SID (Bruno et al. 2011): allow using metformin with caution up to an GFR of 30ml/min; metformin should not be used below these values.
- American Diabetes Association (ADA) (Tuttle et al. 2014): increased monitoring of renal function in CKD stage 3 is recommended. A lower dose, together with close monitoring of renal function, are recommended in CKD stage 3b. In the latter case, namely CKD 3b, patients should not be initiated on metformin. This precaution is made in order to give patients the possibility of a beneficial treatment that has been safely used at less severe CKD, without putting patients at this stage at risk of intolerance.
- American Association of Clinical Endocrinologists (Handelsman et al. 2011) : in the Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan, metformin is contraindicated in severe renal impairment (stage IV and 5, GFR<30ml/min). Otherwise, metformin should be used with caution in renal impairment.
- Norwegian National Diabetes Guidelines (Claudi T 2009). Prevention, Diagnostics and Treatment: contraindicates metformin at GFR <40ml/min, with no dose adjustment in stage IIIa.
- French HAS / ANSM diabetes treatment guideline (ANSM 2013): contraindicates metformin in GFR below 30 ml/min (stage 4 and 5), recommends daily doses below 1500mg metformin in 30 to 60 ml/min (stage 3), together with frequent control of renal function.
- The clinical practice guideline in the management of patients with diabetes and chronic kidney disease stage 3b or higher (GFR <45ml/min) was published by the ERA-EDTA (European Renal Association / European Dialysis and Transplant Association) (ERA 2015). Metformin is recommended as first line agent in a dose adapted to the renal function, when lifestyle measures alone are insufficient to lower HbA1c to the desired range. The committee has based their recommendation on the most positive benefit amongst all treatment classes. A maximum daily dose of 850 to 1500 mg/day for CKD stage 3b is suggested. In CKD stage 4, 500mg/day should not be exceeded.
- For the KDIGO (Kidney Disease: Improving Global Outcomes), the available evidence suggest that the dose of metformin should be reduced to a maximum of 1000 mg per day when the GFR reaches 45 ml/min, and should generally be discontinued when the GFR reaches 30 ml/min. The use of metformin may be appropriate in patients with even more advanced CKD (GFR 15–29 ml/min) if the kidney disease is stable and if alternative treatments to manage glycemia are unavailable or produce significant side effects. The work group proposed that

pharmacokinetic studies should be performed in patients with diabetes and CKD to provide the evidence to support the proposed change in usage (Molitch et al. 2015). The KDIGO guideline has also proposed to change the FDA guidelines.

Conclusions on pharmacokinetics and dosing recommendation in moderate renal impairment

In literature the therapeutic plasma concentration of metformin is reported to be <2 µg/ml. Patients with renal impairment are expected to have lower clearance and a higher systemic exposure compared to patients with normal renal function. Data are consistent across publications, for subjects with moderate renal impairment a 2 to 2.5 fold higher systemic exposure and for subjects with moderate to severe renal impairment, a 2 to 4 fold higher systemic exposure are reported. Other potential sources of PK variability are age or polymorphisms of metformin transporters. Population PK modelling has been performed and these models confirm that metformin exposure increases with decreasing renal function.

Although there are no clear and univocal recommendations on metformin dosages in patients with renal impairment, based on the observed increase of exposure with decreasing renal function and the results of the PPK modelling studies, it has been shown that metformin plasma concentrations remain within the expected therapeutic range when administered at 2000 mg/day and 1000 mg/day doses in patients with moderate renal impairment Stage 3a (GFR 45 - 59 ml/min) and Stage 3b (GFR 30 - 45 ml/min), respectively.

Study EMR200084-622 has also demonstrated a gradual increase of metformin mean plasma increase parallel to the metformin dose, with metformin plasma concentrations using a dose of 1000mg/day only increasing significantly in CKD stage 4, but not in stages 3a or 3b. In this study plasma lactate values in the T2DM patients, with different degrees of renal impairment, were determined at the same time points as the steady state concentrations of metformin. Daily doses of 1000 mg/day in patients with moderate renal impairment (CKD grade 3a and 3b) did not increase lactate levels.

The assessment of the overall data presented has shown that there is no clear relationship between metformin concentration and the occurrence of lactic acidosis. Lactic acidosis seems to occur more frequently with higher exposure, however other conditions (e.g., severe infection, respiratory disease, liver disease) increase the risk of lactic acidosis. No information is available on dosing regimen or on time for administration in relation to time for plasma sampling, therefore no conclusions can be drawn on potential relationship systemic exposure of metformin and the risk of lactic acidosis.

In conclusion, metformin has been used regularly in patients with moderate renal impairment at maximum daily doses that were not causing significant metformin or lactate plasma elevations. In addition, recent literature and clinical guidelines in the treatment of T2DM recommend the use of metformin in moderate renal impairment. As there is a clear relationship between renal function and metformin exposure, a recommendation for a daily dose of 2000 mg/day and 1000 mg/day dose in patients with moderate renal impairment stages 3a and 3b, respectively, can be concluded from the data provided.

2.3. Data on efficacy

Metformin is a first-line therapy for patients with T2DM (Inzucchi et al. 2012). Metformin reduces the risk of cardiovascular disease and all-cause mortality in patients with normal or mildly reduced renal function (UKPDS 1998; Ekstrom et al. 2012; Holman et al. 2008; Roussel et al. 2010).

Metformin is a biguanid agent which lowers both basal and postprandial plasma glucose. Metformin inhibits the production of hepatic glucose (gluconeogenesis), reduces intestinal glucose absorption and improves cellular glucose uptake and utilization. Lowering blood glucose with metformin in T2DM does not cause hypoglycaemia (Arnouts et al. 2014). The efficacy of metformin in the treatment of T2DM has been extensively studied. Besides lowering the blood glucose level metformin may have additional beneficial effects such as weight reduction (Malin and Kashyap 2014), lowering of plasma lipid levels (Xu et al. 2015) and prevention of vascular complications.

The achievement of a good glycaemic control is of great importance for preventing and delaying progression of microvascular and macrovascular complications in patients with both T2DM and chronic kidney disease (CKD). T2DM is the leading cause of chronic kidney disease (CKD) worldwide (National Kidney 2012).

There are data from clinical studies investigating the use of metformin in patients with CKD, however, long term follow up is based on observational studies from large patient cohorts with specified subgroup evaluations in patients with CKD. The pharmacodynamics of metformin are independent of the kidney and there is no reason to assume that the benefits of metformin would be reduced in patients with renal impairment.

Impact on blood glucose

In a small prospective study, 11 elderly patients with GFR<60 ml/min were treated with 850 mg metformin for two months, resulting in good glycemic control and metformin and lactate blood levels remaining in the therapeutic range (Lalau et al. 1990).

Another prospective study on direct effectiveness of metformin involved 35 patients with CKD stage 5 on peritoneal dialysis (PD), with median time on PD of 31 months, and median HbA1c of 6.8%. All study patients were using insulin. Metformin was introduced at a daily oral dose in the range 0.5 – 1.0g (0.5g daily being the minimum recommended therapeutic dose). Throughout the study period, median blood sugar median HbA1c were stable. Metformin introduction demonstrated efficacy by sparing approximately 30% of insulin. Furthermore, the overweight patients lost weight (Al-Hwiesh et al. 2014).

Impact on all-cause and cardiovascular mortality

In the REACH study evaluating 19 691 patients with T2DM and established atherothrombosis treated with or without metformin, the adjusted hazard ratio for 2-years mortality was 0.76 (95% CI, 0.65-0.89;p<0.01) overall, and 0.64 (95% CI, 0.48-0.86; P = .003) in the subgroup of patients with an estimated GFR of 30 to 60 ml/min/1.73 m^2 (Roussel et al. 2010).

Furthermore, in a large retrospective study with 51,675 men and women with T2DM registered in the Swedish National Diabetes Register, metformin compared to other oral antidiabetic agents or insulin, was associated with reduced risks of acidosis/serious infection (adjusted HR 0.85, 95% CI 0.74 to 0.97) and all-cause mortality (HR 0.87, 95% CI 0.77 to 0.99), in patients with GFR 45-60 ml/min, and no increased risks of all-cause mortality, acidosis/serious infection or cardiovascular disease were found in patients with GFR 30-45 ml/ min (Ekstrom et al. 2012).

In the Renal Insufficiency and Cardiovascular Events (RIACE) Italian Multicenter Study, evaluating 15,773 patients with T2DM, metformin was independently associated with lower prevalence of cardiovascular disease for any age quartile and GFR category (1 = GFR≥90; 2 = 60–89; 3 = 30–59; and 4 ≤30ml/min) than all other treatments (Solini et al. 2013).

It has been stated that it may be important to take into consideration that stopping metformin in moderate CKD may deprive patients of metformin's macrovascular benefits at the very time cardiovascular risk begins to substantially rise and that using metformin, in doses adapted to GFR in stable CKD, is safer than switching to other glycaemia-lowering drugs such as insulin, which might increase the risk of hypoglycaemia (Inzucchi et al. 2012; Herrington, Nye, and Aung 2013).

There are several data showing that metformin is already widely used in T2DM patients with CKD stage 3, despite current prescribing restrictions. The use has increased since 2008. In OREDIA (Observation of patients with renal disease and diabetes) a multi-centric study in France which analyzed the therapeutic management of 2.472 CKD versus 1.232 non-CKD patients (GFR > 60 ml/min) it was found that 63% of patients with CKD stage 3 (GFR 59-30ml/min) used metformin, and 33% with CKD stage 4 or 5 (GFR <30ml/min), with 31% of patients in stage 3 treated with >2000mg metformin/day (Penfornis et al. 2014).

The trend of prevalence use in different CKD stages in USA has been extracted from the NHANES survey data. With increasing CKD, serum bicarbonate fell and serum anion gap was increased. Within the stages, metformin use was associated with a higher CVD risk than the comparison group, but the influence of renal impairment was stronger than the one of the medication. The authors did not see any increased risk of severe acidosis (Kuo et al. 2015).

Conclusions on efficacy

The number of clinical studies performed with metformin in patients with renal impairment is small, however several studies have confirmed that the benefits of metformin in subjects with normal renal function are maintained in this patient population. Metformin has been shown effective in lowering hyperglycemia in patient with moderate renal impairment stages 3a and 3b and in reducing the overall mortality. Moreover, it slows the further deterioration of renal function and provides additional significant micro-and macrovascular benefits. In addition, long-term epidemiological data support the benefits of metformin in patients with moderate renal insufficiency.

In conclusion, the data provided together with the well-established use of metformin in patients with GFR 30-59 ml/min supports the clinical efficacy of metformin on blood glucose lowering for patients with moderate renal impairment.

2.4. Data on safety

2.4.1. Risk of lactic acidosis in patients with moderate renal impairment

Clinical safety data

In the large, updated Cochrane meta-analysis on metformin-associated lactic acidosis (Salpeter et al. 2010) pooled data from 347 comparative trials and cohort studies in diabetic patients treated with different hypoglycemic drugs, with 70,490 patient-years of metformin use and 55,451 patient years in the non-metformin group no cases of lactic acidosis were found. In this analysis, 53% of prospective studies allowed for inclusion of renal insufficiency, but patient-level serum creatinine concentrations were not always available for review. Based on statistical inference, the estimated upper limit of true incidence was 4.3 and 5.4 cases per 100,000 patient-years in the metformin and non-metformin groups, respectively. This investigation suggests that "lactic acidosis is extremely rare and its incidence does not differ in those treated with metformin compared to other agents".

A second meta-analysis (Inzucchi et al. 2014) was performed on all published studies in Medline and Cochrane databases pertaining to metformin, kidney disease, and lactic acidosis between 1950 and

June 2014. Sixty five articles were included which were pharmacokinetic / metabolic studies, large case series, retrospective studies, meta-analyses, and a clinical trial. The authors found that metformin plasma levels generally remain within the therapeutic range and lactate concentrations are not substantially increased when used in patients with moderate chronic kidney disease (CKD stage 3). The overall incidence of lactic acidosis in metformin users varied across studies from approximately 3/100.000 to 10/100.000 person-years and was generally indistinguishable from the background rate in the overall population with diabetes. The authors suggest a maximum daily dose of 1000mg metformin in CKD stage 3b patients and concluded that, as long as the renal function is stable and the patient is closely observed, metformin is unlikely to increase the risk of lactic acidosis, even in patients with moderate CKD (GFR 30-59ml/min). However, there is indirect evidence that a rapid drop of GFR can lead to a sudden accumulation of metformin. Therefore, patients should be instructed to reduce or stop metformin in conditions with enhanced risk of acute kidney injury, e.g. severe bouts of diarrhoea, or dehydration or fever. The author´s concluded also that "there have been no randomized clinical trials to test the specific hypothesis that metformin is safe in patients with mild to moderate CKD. Randomized trials would help to better inform evidence based guidelines. However, given the rarity of lactic acidosis in the setting of metformin therapy, a study would need to examine hundreds of thousands of patients for many years to demonstrate non-inferiority compared with other agents, which might not be feasible."

Data on the impact of renal insufficiency on metformin clearance during long-term use was collected by another study (Lalau et al. 1990). In this investigation, 24 older patients (11 in CKD stage 3, 13 in stage 2 or higher) were administered metformin 850 mg/day or 1,700 mg/day. After 2 months, metformin plasma levels remained in the therapeutic range and lactate within the reference limits in all participants, and both were not statistically different between those with and without renal impairment.

In addition, another study (Frid et al. 2010) measured trough levels of metformin in serum of 137 diabetic patients with varying renal function. There were few patients having metformin serum levels >20µmol/l (>~2.6µg/ml). Of the 20 patients in the 2 months follow-up group, 6 had a CKD stage 4, and 14 had a CKD stage 3. Median metformin level was 10µmol/l (IQR 5.3–16µmol/l). In combination with a previous evaluation on 7 cases of lactic acidosis with metformin levels between 33.1mg/l and 88.1 mg/l (median 42.6mg/l), the data suggest that very high metformin levels are needed to cause lactic acidosis. The authors concluded that metformin may be safely used at GFR above 30ml/min. Furthermore, they stated that patients above this GFR limit rarely had metformin levels above 20µmol/l, which for the authors seemed to be a safe level.

A cross-sectional study (Al Awadhi et al. 2008) in 106 diabetic patients revealed that 30 (28%) patients with moderately impaired renal function (GFR <60ml/min) and five with severely impaired renal function (GFR <30ml/min) were safely treated with metformin. No cases of lactic acidosis were observed.

Further investigations address metformin long-term safety in patients with moderate renal impairment (Connolly and Kesson 1996; Lim et al. 2007; Rachmani et al. 2002). These studies also found no increased risks in various degrees of renal insufficiency.

The study by Hung (Hung et al. 2015) conducted a retrospective observational cohort study on type 2 diabetic CKD stage 5 patients (defined by receiving erythropoiesis-stimulating agents), as documented in the Taiwan national health insurance research database between 2000 and 2009. Of these, 813 patients were using metformin despite contraindication, and were matched 1:3 with non-users by propensity score. Mean follow-up was 2.1 years. After multivariate adjustment, metformin use was associated with a higher, but non-significant risk of metabolic acidosis (1.6 vs. 1.3 events per 100 patient years, adjusted HR 1.3 (95%CI 0.88–1.93; p=0.19), which was not dose related (HR 1.8 in ≤

500mg/day, 1.4 in 500-1000mg/day and 1.5 in ≥ 1000mg/day). The number of patients proceeding to end-stage renal disease was significantly lower in metformin users (HR 0.76 (95%CI 0.69-0.84; p<0.0001). In contrast, metformin use was an independent risk factor for mortality (HR 1.35; 95%CI 1.2- 1.51; p<0.001). The risk was dose dependent and non-significantly increased with ≤ 500mg metformin/day (HR 1.14 (0.85-1.44); or 500-1000mg/day HR 1.30 (0.93-1.45); but significantly increased at daily doses of ≥1000mg HR 1.57 (1.29-1.83), consistently across all subgroup analyses.

A matched-case control study was carried out in the Grenoble Hospital University to evaluate the strength between the association between lactic acidosis and well-recognized risk factors, most importantly metformin (Lepelley et al. 2016). In this study 302 cases of lactic acidosis and 604 controls were included. Metformin was not associated with a higher risk of lactic acidosis, only in the case of acute kidney injury (OR=1.79; p=0.020), but not in those without acute kidney injury (OR=0.86; p=0.628). Mild-to moderate CKD (stage 2-3) was also not associated with an increased risk of lactic acidosis (OR=0.36; p=0.002); only severe to end-stage CKD (OR=1.62; 0.325). The intercurrent diseases acute kidney injury (OR=9.58; p<0.001); acute decompensated heart failure (OR=3.55;p<0.001) and sepsis (OR=8.28; p<0.001) were significantly associated with lactic acidosis.

Another study (Schernthaner and Schernthaner-Reiter 2015) calculated the HR of all-cause mortality for the use of metformin at different stages of CKD, taking into account the majority of the results presented previously, and gave respective dose recommendations (See Table 5)

Table 5. All-cause mortality HR and recommended daily dose for metformin during different stages of CKD (Schernthaner, 2015)

Use of metformin during different stages of CKD

CKD stage	eGFR (ml/min/1.73 m²)	Recommended dosage (mg daily)	All-cause mortality: HR (95% CI; *P*)
1 and 2	>60	1,700–3,000	0.87 (0.81–0.94; *P*<0.001)[6]
3A	45 to <60	1,700–2,000	0.87 (0.77–0.99; *P*<0.05)[6]*
3B	30 to <45	1,000	1.02‡ (0.84–1.24)[6]*
4	15 to <30	Cease use	n/a‡
5	<15	No use	1.35 (1.20–1.51; *P*<0.001)[2]‡

*Combined HR for stage 3A and 3B: 0.64 (0.48–0.86; *P*<0.01).[5] ‡Combined HR for stage 4 and stage 5: 1.06 (0.47–2.38; *P* not significant).[5] Data compiled from elsewhere.[2,5,6] Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; n/a, not available.

The study summarised that "premature cessation of metformin use in patients with renal disease might expose them to considerable harm. In clinical practice, we often see premature cessation of metformin use, which leads to poor glucose control, followed by increasing deterioration of renal function. Furthermore, a denial of metformin to patients with T2DM and CKD might further increase their already elevated risk of cardiovascular disease." Based on their meta-analysis and available data on efficacy and safety, they recommend the use of metformin CKD patients including stage 3b, up to 1000 mg/day, but not in stage 4.

In a large, nested, case-control analysis of the UK general practice research database (Bodmer et al. 2008), the crude incidence of lactic acidosis was 3.3 cases per 100,000 person-years among metformin users (with different stages of renal impairment). This study estimated the incidence in sulphonylurea users to be 4.8/100,000 patient-years. Relevant co-morbidities known as risk factors for lactic acidosis could be identified in all case subjects (Mani 2009).

By using electronic databases of hospital discharge diagnoses and laboratory results from over 41000 person-years of exposure in three diverse US populations with T2DM, another study (Brown et al. 1998) observed 9.7/100,000 patient-years in the time when metformin was not yet on the US market.

A retrospective propensity score matched cohort study was conducted using the Japanese Medical Data Vision claims database (Chang, Sakaguchi, and Dolin 2016). T2DM patients aged 18 or above who received diabetes drugs during January 2010 through August 2014 were identified. Poisson regression and Cox proportional hazard models were used to estimate the incidence and assess if metformin use was associated with increased risk of lactic acidosis. Thirty cases of lactic acidosis were identified among 283.491 treated T2DM patients with 504.169 patient-years of follow-up. Crude incidence of lactic acidosis was 5.95 per 100.000 patient-years. T2DM patients with chronic kidney disease (CKD) were seven-fold more likely to develop lactic acidosis than those without CKD (adjusted hazard ratio (aHR), 7.33, 95%CI, 3.17–16.96). Use of metformin was not associated with risk of lactic acidosis in the study population (aHR, 0.92, 95%CI, 0.33–2.55), and in the propensity score matched cohort (aHR, 0.90, 95%CI, 0.26–3.11). Similar findings were observed among diabetes patients with chronic liver disease (CLD) and CKD. The age-sex adjusted incidence rates in metformin users and non-users were 5.80 and 5.78 per 100.000 person-years, respectively (Incidence rate ratio, 1.00, p=0.99). The authors concluded that use of metformin was not associated with increased risk of lactic acidosis in diabetic patients including those with CKD or CLD.

A UK Clinical Practise Research Datalink (CPRD) analysis by the MAH for Glucophage was performed for and presented in FR/H/xxxx/WS/16, and was later published (Richy et al. 2014). In parallel, a second analysis from the same database was published on the same topic (Eppenga et al. 2014). Both investigations were carried out in a completely isolated manner, while using the same source data.

The study by Eppenga was performed in an independent, academic setting (Radboud University Medical Center, The Netherlands). This study examined whether treatment with metformin was associated with a higher risk of lactic acidosis or elevated lactate concentrations, compared to that of users of other noninsulin antidiabetic (NIAD) who had never used metformin. Patients were classified in four groups: current, recent, past and never metformin users.

Renal function was assessed as the mean GFR value one week to one year before exposure to metformin or comparators started, which might be biased by the onset of any acute renal impairment. The primary outcome was lactic acidosis, defined by either a CPRD Read code or a record of elevated plasma lactate concentrations (>5mmol/l). The study included 223,968 metformin patients who accounted for 743,151 person-years for current users. Overall, 68 lactic acidosis events were measured, 55 of which were in current metformin users (defined as at least one metformin prescription in the three months before the start of prescription coverage period). The crude incidence of lactic acidosis or elevated plasma lactate concentrations was 7.4 (95% CI: 5.6 - 9.63) per 100,000 person-years in current metformin users and 2.2 (95% CI: 0.36 - 7.24) in never users. Given the overlap in the confidence interval, no significant difference could be found. Within the group of current metformin users, the incidence rates were 5.29 (95% CI: 3.54-7.60), 14.45 (95% CI: 7.60-24.7) and 19.65 (95% CI: 6.38-45.80) cases per 100,000 patient-years in patients with GFR ≥ 60 (currently approved), 45-59 and 30-44 (moderate kidney impairment, off label) ml/min, respectively.

The study published by (Richy et al. 2014) examined whether the metformin users in T2DM had an increased risk of lactic acidosis at different levels of renal impairment, as compared to metformin users with normal renal function. Patients with T2DM and a continuous exposure to metformin between January 2007 and December 2012 were included. Renal function was assessed as the most recent GFR value or diagnostic code before study end or outcome was detected, in order to capture the most severe or deteriorated baseline renal function. The primary outcome of the study was defined as lactic

acidosis evaluated by CPRD read code. Fatal cases of lactic acidosis were also assessed. The incidence rate of lactic acidosis in metformin patients with T2DM was assessed by renal impairment category; normal kidney function was the reference category for comparisons. The study included 77,601 metformin-treated patients, accounting for 337,590 person-years. Overall, there were 35 lactic acidosis events with no fatal cases. The overall incidence rate of lactic acidosis in metformin users was 10.37 per 100,000 patients-years.

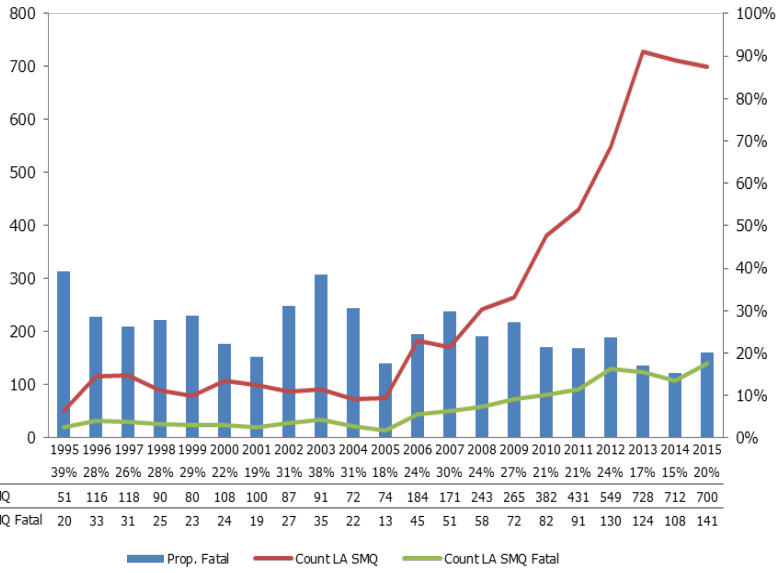
No significant difference in the incidence of lactic acidosis was observed in normal, mild (stage 2), moderate (stage 3), or severe renal (stage 4 and 5) impairment: 7.6 [0.9–27.5], 4.6 [2.00–9.15], 17 [10.89– 25.79], and 39 [4.72–140.89] cases per 100,000 patient-years, respectively. Despite the variety of methodologies applied to the data in the two studies, the estimates were very close in absolute value for each GFR category, the maximum difference between stage 2 and 4/5 being 0.12%.

In both studies, no significant difference between the rates of lactic acidosis in patients with normal, mild or moderate renal impairment were found, especially when taking into account the wide confidence intervals observed in both studies. Some trends for correlation between lactic acidosis rates and declining renal function could be noticed; however both studies did not adjust for comorbidities between the CKD stages, making it thus impossible to compensate for confounding effects. Accordingly in the study by Richy (2014), a clear increase of confounding conditions associated with lactic acidosis and declining renal function was found, which indicates that there might be other reasons unrelated to metformin in the increasing incidence of lactic acidosis in increasing renal impairment.

Spontaneous case reports of lactic acidosis

According to the EMA EudraVigilance report, there were 43,856 case reports of metformin containing medicinal products in EudraVigilance of which 5,476 (12.5%) referred to lactic acidosis (Standardised MedDRA Queries (SMQ) Broad, 1995 to 2015) (see Figure 1). The yearly trend of case reports of lactic acidosis showed an increase peaking in 2013, however the increase in total counts has not been followed by an increase in the proportion of fatal cases. Introduction of national pharmacovigilance regulations may have influenced the increasing reporting rates, which may also explain the decline of the incidence of fatality due to the additional monitoring performed.

Figure 1: Trend of reports of Lactic acidosis SMQ (Broad). Distribution of case reports (total and fatal) from 1995 to 2015



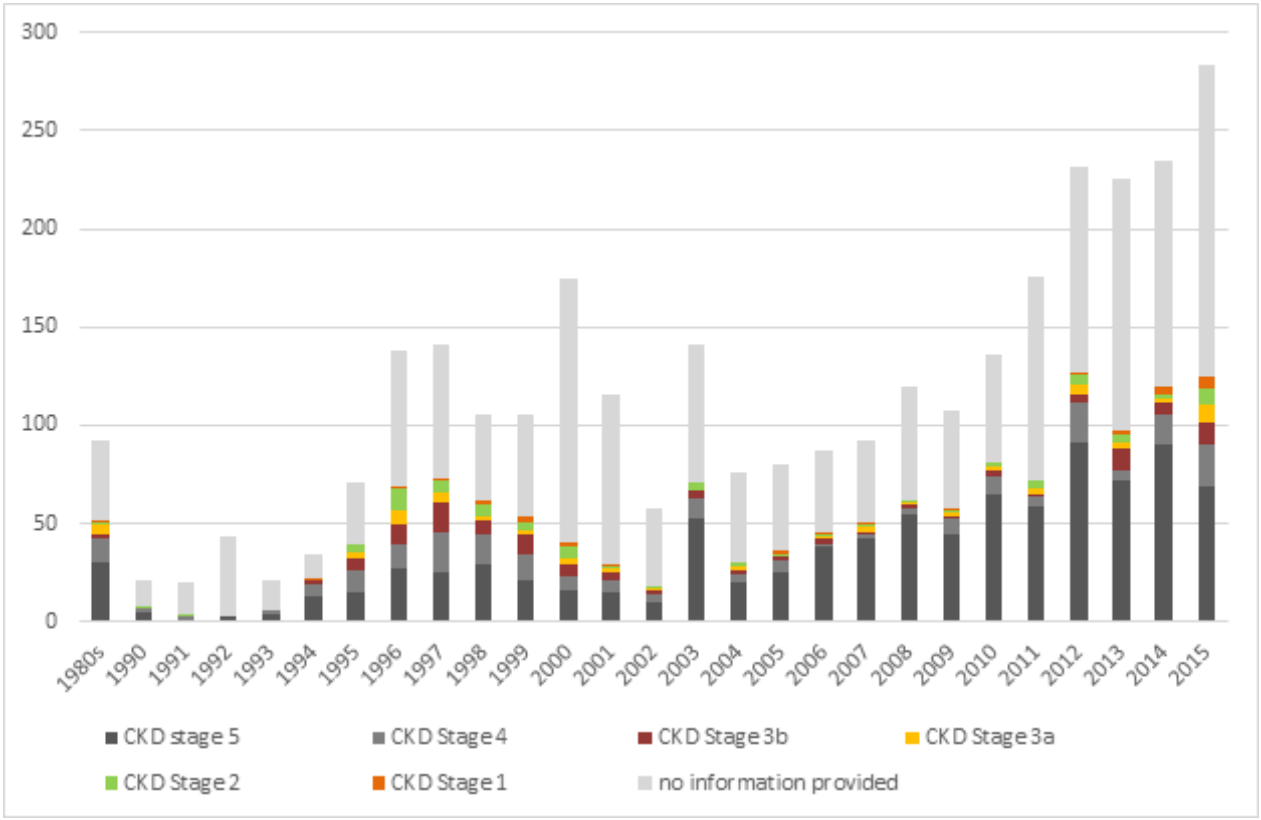
	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Prop. Fatal	39%	28%	26%	28%	29%	22%	19%	31%	38%	31%	18%	24%	30%	24%	27%	21%	21%	24%	17%	15%	20%
Count LA SMQ	51	116	118	90	80	108	100	87	91	72	74	184	171	243	265	382	431	549	728	712	700
Count LA SMQ Fatal	20	33	31	25	23	24	19	27	35	22	13	45	51	58	72	82	91	130	124	108	141

The report showed that in only 31 cases GFR was reported at the time of the adverse reaction, the majority of case reports (17 out of 31) reported GFR group <15 ml/min. The 60-89 GFR ml/ml group included four case reports (12.9% of the cases with GFR information) and none of them had a fatal outcome. About 10% of patients (549 out of 5476) developing lactic acidosis had a reported medical history of renal failure.

The MAH Merck has submitted cumulative searches of their safety databases on lactic acidosis from 1980 to 2015. The search retrieved 3132 single cases of SMQ (Standardised MedDRA Queries) lactic acidosis. Overall, of the 3132 cases of this analysis, 2453 (78%) of the cases recorded the event term lactic acidosis. In the SMQ set of lactic acidosis, a metformin dose was provided in 2028 cases (65% of 3132). The reported metformin dose (daily dose or intake dose in suicidal cases) ranked between 100 mg and 270,000mg. 1793 cases (57% of 3132) provided metformin plasma concentrations. Both metformin and lactate plasma values were recorded in 457 cases (15% of 3132 cases). The majority reported a lactate of 50 mmol/l or lower, and metformin plasma concentrations below 100 mg/l.

In 1454 cases (46% of 3132) a creatinine clearance was reported. Further analysis of the renal impairment was done based on 'modification of diet in renal disease' (MDRD) using the simplified equation (Levey et al. 1999; Levey et al. 2005) (See Figure 2). Around 80% (1162 of 1454) of all SMQ cases, in which a MDRD was deducible, were attributable to renal impairment stage 4 and 5, meaning severe renal impairment (GFR<30ml/min).

Figure 2. Renal impairment as per MDRD in SMQ lactic acidosis cases per year



Spontaneous reports of lactic acidosis have been published in the literature since the first marketing authorisation of metformin. In more recent times, the publications often group retrospective case report collections from toxicology units or Health Authority compilations.

A retrospective analysis by (Huang, Castelino, and Peterson 2015) was performed in lactic acidosis cases in metformin treated patients reported to the Australian Therapeutic Goods Administration. Of the 152 MALA cases, 17.4% (n=23) had a fatal outcome. Plasma lactate levels were higher in non-survivors. Around 75% of all cases were reported to have at least one additional condition, which may have caused lactic acidosis. Metformin dosage, plasma lactate and serum creatinine were not related.

An additional study (McNamara and Isbister 2015) published a retrospective case series of metformin overdose (n=36) cases admitted to a toxicology unit in Australia over 20 years. Median ingested dose was 10 g (IQR: 5– 16.1 g; range: 3.5–50 g). Blood pH and lactate levels were available in 25 of the 36 cases. Median lowest pH was 7.35 (IQR: 7.28 to 7.38; range: 7.16 to 7.43), acidosis (pH < 7.35) occurred only in 11/25. Median peak lactate was 3.9 mmol/l (IQR: 2.6–5.2 mmol/l). Only five presentations (5/36) met the criteria for lactic acidosis. The authors concluded that most metformin overdoses result in minor clinical effects and do not progress to lactic acidosis, and have hyperlactatemia with or without acidosis.

In a recent study (Boucaud-Maitre et al. 2016) 727 case reports were analysed from the pharmacovigilance database of the ANSM between 1985 and 2013 reporting lactic acidosis and associated with metformin. Metformin plasma concentration was presented in 260 patients, lactate in 556 patients and pH in 502 patients.

The authors stated that there were significant differences between surviving and deceased patients in lactate concentration (10.8 ± 9.5 mmol/l vs. 16.3 ±14.6 mmol/l). Whilst there was a good correlation between the severity of hyperlactemia or pH and fatal outcome, there was no respective increase in metformin concentrations >5mg/l. Consequently, the relationship of metformin, lactate and pH was based on 199 patients, where only lactate remained associated with mortality after adjustments of variables. Nevertheless, the authors deduce that metformin plasma accumulation due to acute renal failure may be considered the main cause of rise in lactate and fall in pH, as 30% of patients with supra-therapeutic metformin-concentrations of >5mg/l died, whilst 11% died with metformin <5mg/l.

Other important risk factors for renal impairment and lactic acidosis

Diarrhea, vomiting and dehydration

According to a study on MALA (Duong, Furlong, et al. 2013) , acute renal failure leads to a loss of renal clearance of lactic acid, which may lead to lactic acidosis. This model also illustrates that the circle can be initiated by acute renal impairment, diarrhea / vomiting or any direct cause of lactic acidosis. And indeed, in a matched-case control study by (Lepelley et al. 2016), acute kidney injury was the risk factor most dominantly associated with lactic acidosis (OR=9.58; p<0.001). In a multivariate analysis stratified by acute kidney injury, those patients with a mild-to moderate CKD (stage 2-3) had a lower odds ratio for lactic acidosis in both the acute kidney injury and the no-comparison arm. It was only in severe and end-stage CKD that the OR was increased.

Alcohol

There is a recent population-based cohort study (Koning et al. 2015) that found that alcohol consumption is inversely associated with the risk of developing CKD, where the hazard ratio for CKD risk was 0.85 (0.69– 1.04) for occasional (under 10 g/week), 0.82 (0.69–0.98) for light (10–69.9 g/week), 0.71 (0.58– 0.88) for moderate (70–210 g/week), and 0.60 (0.42–0.86) for heavier (over 210 g/week) alcohol consumers (significant trend). Alcohol consumption was also found to be inversely related to CKD stage 3 in Taiwanese men (Hsu et al. 2013).

In acute intoxication, alcohol dehydrates the consumer by inducing diuresis as well as volume depletion. Last but not least, alcohol induced gastritis causes nausea and vomiting (Jairam et al. 2014; Kaizu 1997; Garcia-Garcia, Jha, and World Kidney Day Steering 2015). Alcohol intoxication is therefore to be regarded as risk factor drug for acute renal failure. In addition, in a retrospective analysis on lactic acidosis, the authors found no link to alcoholism (Scale and Harvey 2011).

Iodinated contrast media

The number of cases that reported metformin in correlation with the administration of iodinated contrast media was also investigated. Iodinated contrast media were reported as co-suspect or concomitant drugs in 45 of 3132 cases of the SMQ lactic acidosis. In 42 cases this information is in the case report text, summing up to a total of 66 cases (2% of 3132), with 26 of them (39% of 66) being fatal.

Only 14 cases reported metformin plasma levels, with 7 cases in the supratherapeutic range (7.6 to 50 mg/l). Contrast-induced nephropathy (CIN) is a common complication of administration of iodinated contrast media. Metformin per se is not a risk factor for CIN (Benko et al. 2007), but the risk of acute renal function deterioration increases the risk of acute renal failure, the main risk factor for metformin accumulation (Tonolini, 2012). The incidence of CIN ranges from 0.1% to 13% without prior renal failure was 0%. In patients with previous renal failure, the incidence of CIN was 4.7%. In a very recent study by Li (2016), the incidence of CIN was not significantly different between patients with T2DM and

patients with insulin resistance, but about 3- to 4-fold higher than in insulin sensitive patients (8.7% vs 6.7% vs 2.2%, P < .05).

A retrospective cohort study (Shah et al. 2015) was conducted in patients at a San Francisco medical center to determine if there is a change in kidney function in patients on metformin with estimated glomerular filtration rate (GFR) < 60 ml/min who receive IV contrast. In the 35 patients, mean pre-contrast GFR was 54±6 ml/min/1.73m2 and post-contrast GFR was 59±19. The authors conclude that the current practice of holding metformin for two days after IV contrast should be re-evaluated as there was no significant change in kidney function. However, the number of subjects in this retrospective analysis may be considered relatively too small, as the number of cases received by the company corresponds to an incidence rate of 0,5 per 1,000,000 patient years (66 cases within an exposure of 127,593,915 patient years).

Based on the European Society of Urogenital Radiology (Stacul et al. 2011), patients receiving intravenous iodinated contrast medium should stop taking metformin 48h before contrast medium administration if their falls GFR<45ml/min. Renal function should be re-assessed 48h after contrast medium and metformin should only be restarted if it has not deteriorated further. The Canadian Association of Radiologists use a threshold of <60ml/min (Benko et al. 2007).

In the matched-case control study by (Lepelley et al. 2016), iodinated contrast media use demonstrated a higher Odds ratio for lactic acidosis (OR=8.58; 95%CI 3.77-19.52; p<0.001) compared to metformin (OR=1.79; 95%CI 1.09-2.93; p=0.020).

Other medicines

In literature, medicines known to potentially induce an acute renal failure include antihypertensive therapy (including ACE inhibitor, angiotensin II receptor blocker), diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, antibiotics, antiviral, antifungal, oncologic drugs, radiocontrast, calcineurin inhibitors, lithium, H2-blocker, statins, gout medication and SGLT2-inhibitors (Pazhayattil and Shirali 2014; McWilliam 2007; Markowitz and Perazella 2005). Health care professionals should be informed that other drugs may contribute to the development of lactic acidosis by acutely impairing the renal function.

Other causes of lactic acidosis

The most common associated factors with lactic acidosis include acute cardiorespiratory illnesses, sepsis and renal failure, and are significantly associated with mortality (Scale and Harvey 2011). It was therefore suggested (Lalau 2010) that the incidence of MALA could be reduced by assessing other associated risk factors. Indeed many of the cases of lactic acidosis report other drugs and conditions associated with lactic acidosis, and most cases of lactic acidosis in people taking metformin fail to provide adequate information to permit assessment of causation, including lactic acid concentrations and pH (Kajbaf and Lalau 2013). Another report (Stades et al. 2004) also showed that plasma concentrations of metformin were not correlated to increased lactic acid concentration. In addition, increased concentrations of neither lactic acid nor metformin were associated with increased mortality risk. In contrast, acute cardiovascular events, liver cirrhosis, and sepsis were all associated with an increased mortality risk. Interestingly, all but one of the cases in Stades' review had at least one risk factor (cardiovascular events, pulmonary failure, hepatic failure, alcohol excess, or sepsis) for the development of lactic acidosis, independent of metformin use. Most of the patients developed lactic acidosis in the presence of acute or worsening renal failure.

According to a retrospective analysis of 149 cases in a general hospital, lactic acidosis most often occurs in diabetic patients with acute renal or cardiorespiratory illness or sepsis (Scale and Harvey 2011). There is also a number of drugs known to cause LA (Adeva-Andany et al. 2014).

The lack of a relation between lactic acid/metformin concentrations and mortality and the absence of an association between metformin concentration and lactic acid concentration suggest that the association between lactic acidosis and metformin is coincidental, although causality cannot be ruled out completely (Lalau and Race 2000, 1999; Holstein and Stumvoll 2005). Physicians should be educated on the range of other risk factors that contribute to lactic acidosis in patients treated with metformin (Lalau and Race 2001).

In a matched-case control study by (Lepelley et al. 2016), the intercurrent diseases acute kidney injury (OR=9.58; p<0.001); acute decompensated heart failure (OR=3.55; p<0.001) and sepsis (OR=8.28; p<0.001) were significantly associated with lactic acidosis, but not metformin.

2.4.2. Other risks of metformin besides lactic acidosis in renal impairment

The most common side-effects observed in association with metformin use in diabetic individuals are mild to moderate gastrointestinal events including diarrhea, nausea, vomiting, abdominal pain, and decreased appetite, among others.

The majority of side-effects usually occur shortly after beginning of metformin treatment and the majority of patients (78%) who continue the use of metformin recover from these side-effects during the ongoing treatment (de Jong, Harmark, and van Puijenbroek 2016). These undesirable effects resolve spontaneously in most cases and can be minimised by slow up-titration or the use of the extended release formulation of metformin. However, vomiting and diarrhea which can occur during treatment start of metformin therapy may contribute to a worsening of the patients' renal function, especially if severe and prolonged enough to cause dehydration.

The gastrointestinal events might be related to the fact that metformin is a substrate of Organic Cation Transporter 1 (OCT1) which plays an important role in the transfer of cations from the gut lumen to the interstitium (McCreight, Bailey, and Pearson 2016). Metformin absorption through the enterocytes is in part mediated by OCT1(Han et al. 2015), and is discussed to be related with the gastrointestinal adverse effects of metformin (McCreight, Bailey, and Pearson 2016; Dujic et al. 2016). As OCT1 is probably apically expressed it is most likely to influence local concentrations of metformin in the gut (lumen and enterocytes), rather than its transfer into the blood.

Other well-known adverse reactions of metformin (e.g. taste disturbance, loss of appetite, skin reactions such as erythema, pruritus, or urticaria, decrease of vitamin B12 and liver function tests abnormalities or hepatitis) as well as the important potential risk leukocytoclastic vasculitis are not impacting the benefit-risk especially in patients with moderate renal impairment.

Conclusions on safety

The use of metformin is currently contraindicated in the EU in patients with various degrees of moderate renal impairment due to the risk of lactic acidosis. Lactic acidosis is a very rare and serious side effect that occurs most often in patients with acute renal or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis.

Based on the data provided in this referral procedure, the reporting rate of lactic acidosis among metformin users from post-marketing has been estimated between 1 and 10 per 100.000 patient years. In addition, the risk of fatal outcome of lactic acidosis cases has declined over time, from around 50% to less than 20% in recent years.

Recent studies have shown that it is unclear whether metformin per se is associated with an enhanced risk for lactic acidosis and data are conflicting. As per recent scientific survey (Kraut and Madias 2014), lactic acidosis is not primarily a condition caused by metformin treatment but the main causes of lactic acidosis are cardiogenic or hypovolemic shock, advanced heart failure, severe trauma or hypoxemia, sepsis, severe anemia, vigorous exercise, seizures, shivering, diabetes mellitus, cancer, liver disease, and other drugs that can acutely impair renal function. In addition, in the matched-case control study by Lepelley ((Lepelley et al. 2016)), acute kidney injury was the risk factor most dominantly associated with lactic acidosis (OR=9.58; p<0.001). Therefore, although causality cannot be ruled out completely, other causes than metformin are the most likely cause of lactic acidosis.

Apart from lactic acidosis, the overall safety profile of metformin in patients with chronic kidney disease is similar to the safety profile in patients with normal renal function.

In conclusion, the possible elevated risk of lactic acidosis could be sufficiently minimised in patients with GFR greater than 30 ml/min if a clear dosing recommendation, additional monitoring of GFR levels before and during treatment and updated warnings and precautions are described in the SmPC and package leaflet.

Warnings recommended include recommendations to discontinue prior to the administration of iodinated contract agents which may result in metformin accumulation and an increased risk of lactic acidosis, or at the time of surgery until the renal function has been evaluated and found to be stable. In addition, some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis as well, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. Therefore, when starting or using such products in combination with metformin, close monitoring of renal function is necessary.

In addition, the CHMP was of the opinion that in order to further characterize the risk of lactic acidosis in patients with moderate renal impairment using metformin, routine pharmacovigilance activities needed to be extended to include cumulative reviews of the events of the SMQ lactic acidosis and targeted follow-up questionnaires including medical data available regarding any potential occurrence of lactic acidosis for each individual case safety report.

2.5. Fixed dose combinations products containing metformin

Most of the fixed dose combinations (FDC) products have at present a contraindication in patients with moderate renal impairment GFR< 60 ml/min, which is related to the metformin component. The currently available efficacy and safety data for using these fixed combination products in patients with moderate to severe renal impairment is scarce. The available scientific evidence described for metformin as a single component is also applicable to the FDC, however several aspects need to be taken into account before giving a specific dose recommendation of using these combination products.

The main aspect to be considered is the restrictions regarding renal impairment for the other active substance in the combination. In addition recommending a suboptimal dose of the second active substance should be avoided, taking into consideration the available tablet strengths for the fixed dose combination product for both metformin and the other active substance. Moreover, the feasibility of using a fixed dose combination product in patients who may need frequent dose adjustments of one or

two of the components due to their changing renal function needs to be considered, as the need to stop taking metformin acutely may be especially important in these patients. Moreover, patients using a combination product might be automatically left without the second active substance. In all cases if no adequate strength of the product is available, individual monocomponents should be used instead of the fixed dose combination.

Information of dosing in moderately renally impaired patients has been reviewed and approved with respect to the second active substance in combination products in the context of previous procedures; based on these data, the following dose recommendation for fixed dose combination products containing metformin was agreed:

Saxagliptin/metformin

Saxagliptin as monocomponent may be used in patients with mild renal impairment without dose adjustment, whereas the dose should be reduced to 2.5 mg once daily in patients with moderate to severe renal impairment.

Sitagliptin/metformin

Sitagliptin as monocomponent may be used in patients with GFR ≥ 50 ml/min without dose adjustment, whereas the dose should be reduced to 50 mg once daily in patients with moderate to severe renal impairment.

Vildagliptin/metformin

Vildagliptin as monocomponent may be used in patients with GFR ≥ 50 ml/min without dose adjustment, whereas the dose should be reduced to 50 mg once daily in patients with moderate to severe renal impairment.

Linagliptin/metformin

Linagliptin as monocomponent may be used in patients with renal impairment without dose reduction, with the recommended dose being 5 mg daily.

Alogliptin/metformin

Alogliptin as monocomponent may be used in patients with renal impairment. For patients with mild renal impairment (GFR > 50 to ≤ 80 ml/min), no dose adjustment of alogliptin is necessary. In patients with moderate renal impairment (GFR ≥ 30 to ≤ 50 ml/min), one-half of the recommended dose of alogliptin should be administered (12.5 mg once daily).

Pioglitazone/metformin

Pioglitazone as monocomponent may be initiated at 15 mg or 30 mg once daily and the dose may be increased up to 45 mg once daily. No dose adjustment is necessary in patients with impaired renal function.

Glibenclamide/metformin

Glibenclamide may be used in patients with moderate renal impairment GFR > 30 ml/min. The recommended dose is 1.75 mg to 10.5 mg daily. Initiation is not recommended in patients with moderate renal impairment Stage 3b (GFR 30-44 ml/min) due to increased risk of hypoglycaemia. Glibenclamide is contraindicated in patients with severe renal impairment.

Dapagliflozin/metformin

The recommended dose is 10 mg daily. Dapagliflozin is not recommended in patients with GFR < 60 ml/min.

Canagliflozin/metformin

Canagliflozin as mono-component may be used in patients with GFR > 45 ml/min, although treatment should not be initiated in patients with GFR < 60 ml/min. In patients with GFR 45-60 ml/minute, it is recommended that the canagliflozin dose of 100 mg should be used. Canagliflozin should not be used in patients with GFR < 45 ml/min.

Empagliflozin/metformin

Empagliflozin as mono-component may be used in patients with GFR > 45 ml/min, although treatment should not be initiated in patients with GFR < 60 ml/minute. In patients with GFR 45-60 ml/min, it is recommended that the empagliflozin dose of 10 mg should be used. Empagliflozin is not recommended in patients with GFR < 45 ml/min.

3. Benefit-risk balance

Beneficial effects

Metformin is the first-line therapy in T2DM. For patients with T2DM overall, long-term beneficial effects of metformin have been demonstrated including reduction of cardiovascular risk and all-cause mortality. The mode of action of metformin is not dependent on kidney function and, therefore, a maintained efficacy is expected in patients with renal impairment provided an exposure within the therapeutic interval is achieved with the provided dose.

A benefit from metformin on macrovascular outcomes and mortality is reported in the literature in patients with renal impairment, which is a high risk patient group for these events. Moreover, it slows the further deterioration of renal function and provides additional significant micro-and macrovascular benefits in this patient population.

Most of the recent guidelines from learned societies based on the available literature recommend metformin in patients with moderate renal impairment (GFR 30-59 ml/min). Some propose dose reduction or use with caution. Most of the guidelines recommend to stop metformin as soon as the patients GFR falls <30 ml/min.

Uncertainty of beneficial effects

The therapeutic range of metformin plasma concentration is unclear, making it difficult to estimate the relative exposure in pharmacokinetic studies. There are no prospective randomised clinical studies on all-cause and cardiovascular mortality in patients with renal impairment. The use of metformin is, however, well-known and frequent in these patients. Consequently, efficacy data on large observational studies data exists in this patient group. The majority of the patients in these studies had GFR 45-60 ml/min and the data is somewhat more limited in patients with GFR 30-45 ml/min. Adjustment for important covariates and in some studies, propensity scoring have been used in these studies in order to minimize confounding by indication.

Unfavourable effects

The most common side-effects observed in association with metformin use in diabetic individuals are mild to moderate gastrointestinal events including diarrhea, nausea, vomiting, abdominal pain, and decreased appetite. In most cases, these events can be minimized by slow up-titration or the use of the extended release formulation of metformin. However, vomiting and diarrhea which can occur

during treatment start of metformin therapy may contribute to a worsening of the patients' renal function, especially if severe and prolonged enough to cause dehydration.

Metformin clearance is decreased in the setting of renal impairment. In small available studies, however, drug levels remain stable and within therapeutic range at reduced dose, when GFR is greater than 30 ml/min and do not significantly increase circulating lactate levels.

Lactic acidosis, a serious metabolic complication, most often occurs in diabetic patients with acute renal or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and likely lowers the threshold for developing lactic acidosis. In case of dehydration (severe diarrhoea or vomiting, fever, heat, reduced fluid intake) temporary discontinuation of metformin and contact with a health care professional is recommended. Other risk factors/ causes for lactic acidosis are drugs that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs), excessive alcohol intake, hepatic insufficiency, poorly controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia. Intravascular administration of iodinated contrast media may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. The frequency of lactic acidosis in the setting of metformin therapy as the only risk factor is very low.

Uncertainty of unfavourable effects

There have been no randomized clinical trials to test the specific hypothesis that metformin is safe in patients with GFR 30-60 ml/min. Available evidence include meta-analyses, retrospective studies and smaller mechanistic investigations.

There were 5,476 case reports of metformin containing medicinal products in EudraVigilance that referred to lactic acidosis. About 10% of patients had a reported medical history of renal failure. Only a very small number of reported cases contained information on GFR or laboratory values to support the lactic acidosis diagnosis. An increased risk of lactic acidosis may be related to renal impairment irrespectively of metformin use.

Based on the data provided a clear relationship between metformin concentration and the occurrence of lactic acidosis has not been shown. Metformin has been used regularly in patients with moderate renal impairment at maximum daily doses that were not causing significant metformin or lactate plasma elevations. Lactic acidosis seems to occur more frequently with higher exposures of metformin, however other conditions (e.g., severe infection, respiratory disease, liver disease) increase the risk of lactic acidosis. In addition, no conclusions could be drawn on potential relationship systemic exposure of metformin and the risk of lactic acidosis.

Overall benefit-risk assessment

The benefits of metformin in the treatment of T2DM in patients with moderate renal impairment have been demonstrated in terms of the reduction of cardiovascular risk and all-cause mortality. Moreover, metformin treatment slows the further deterioration of renal function and provides additional significant micro-and macrovascular benefits in this patient population.

The most common side-effects observed in association with metformin use in diabetic individuals are mild to moderate gastrointestinal events including diarrhea, nausea, vomiting, abdominal pain, and decreased appetite. Apart from lactic acidosis, the overall safety profile of metformin in patients with moderate renal impairment is similar to the safety profile in patients with normal renal function.

The risk of lactic acidosis is very rare in clinical practice and in the majority of cases only observed in emergency care. In addition, although causality cannot be ruled out, other factors rather than metformin are most likely the causes of lactic acidosis.

Overall, metformin has been used safely in patients with moderate renal impairment at reduced doses without causing significant metformin or lactate plasma elevations. Moreover, recent clinical guidelines in the treatment of T2DM recommend the use of metformin in moderate renal impairment. As there is a clear relationship between renal function and metformin exposure, a recommendation for a daily dose of 2000 mg/day and 1000 mg/day dose in patients with moderate renal impairment stages 3a and 3b, respectively, can be concluded from the data provided.

In conclusion, the possible elevated risk of lactic acidosis could be sufficiently minimised in patients with moderate renal impairment (GFR greater than 30 ml/min) with a clear dosing recommendation, additional monitoring of GFR levels before and during treatment, and updated warnings and precautions in the SmPC and package leaflet. In addition, routine risk minimisation will be extended to include cumulative review of lactic acidosis in the PSURs and a targeted questionnaire.

Based on the review of all available data on safety and efficacy, the benefit-risk balance of medicinal products containing metformin remains favourable and it is recommended that the marketing authorisations are varied regarding the use in renal impairment.

4. Risk management

The MAHs should update their risk management system described in a Risk Management Plan which shall be submitted to the National Competent Authorities for assessment within 3 months following adoption of the CHMP Opinion.

4.1. Pharmacovigilance plan

The following routine pharmacovigilance activity is to be implemented by all MAHs of products containing metformin:

- A targeted questionnaire should be implemented in order to request and obtain from the reporter all relevant follow-up information including medical data available regarding the condition lactic acidosis for each individual case safety report. These questionnaires will enable the MAH to further document the cases reported and recorded in the MAH's database with regards of the lactic acidosis risk. These cases will be subject to the routine signal detection performed by the MAH on the cases received.

  The following points should be included in the questionnaire:

  - metabolic acidosis: lactate level, blood pH (arterial our venous), anion gap, ketonuria and β-hydroxybutyrate
  - metformin: daily dose; date/time/value of last dose, plasma level, concentration in erythrocytes
  - renal function: known values before and during the event.
  - risk factors: alcohol use, exposure to contrast media, infection/sepsis, renal disease, dehydration, diarrhoea, vomiting, acute heart failure, acute myocardial infarction, other conditions with hypoxia

In addition, the following routine pharmacovigilance activity is to be implemented by the MAHs of products subject to the requirements to provide PSURs as per EURD List:

- A cumulative analysis of the events of the SMQ lactic acidosis including the information collected through the questionnaires should be provided within the next PSURs of the products, with a special focus on CKD stage 3.

4.2. Risk Minimisation activities

4.2.1. Amendments to the product information

The CHMP considered that amendments to sections 4.2, 4.3, 4.4, 4.5 of the SmPC were necessary to include the information of this review.

The use of metformin containing medicinal products was extended to patients with moderate renal impairment (GFR 30 to 59 ml/min), with the exception of the fixed-dose combination dapagliflozin/metformin, which is still not recommended this patient population. In addition the fixed-dose combinations canagliflozin/metformin and empagliflozin/metformin are not recommended in patients with GFR<45 ml/min.

Moreover these products should be used at a lower dose in patients with moderate renal impairment.

The CHMP however considered that metformin containing products should keep the contraindication in patients with severe renal impairment.

Further warnings and precautions of use related to the risk of lactic acidosis associated with the use of metformin containing products were also included and other important information harmonised.

The Package Leaflet was amended accordingly.

5. Grounds for Opinion

Whereas,

- The CHMP considered the procedure under Article 31 of Directive 2001/83/EC for metformin containing medicinal products.
- The CHMP reviewed the totality of the data submitted by the MAHs on the safety and efficacy of metformin containing medicinal products for the treatment of Type 2 diabetes mellitus in subjects with moderate renal impairment (GFR 30-59 ml/min) with a focus on the risk of lactic acidosis.
- The CHMP considered that there is evidence from clinical and epidemiological studies indicating the benefits of the use of metformin containing medicinal products in patients with moderate renal impairment (GFR 30-59 ml/min).
- The CHMP considered the evidence from epidemiological studies, which have shown that lactic acidosis is a very rare condition that occurs most often in patients with acute renal or cardiorespiratory illness or sepsis. Recent scientific data have concluded that the main causes of lactic acidosis are cardiogenic or hypovolemic shock, severe heart failure, severe trauma, and sepsis; therefore lactic acidosis is not primarily caused by metformin treatment.

- The CHMP considered that publications in the medical literature have shown that metformin at reduced dose may be safely used in patients with moderate renal impairment. In addition, published epidemiological studies indicate that metformin is often used in clinical practice in patients with moderate renal impairment as reflected in current clinical guidelines without a marked increase in risk of lactic acidosis or other serious side effects.
- The CHMP was of the view that the risk of lactic acidosis can be minimised in patients with moderate renal impairment with clear dosing recommendations, additional monitoring of GFR levels before and during treatment and updated warnings and precautions in the Summary of Product Characteristics (SmPC) and Package Leaflet (PL). In addition, routine pharmacovigilance activities will be extended to include a cumulative review and a targeted follow up questionnaire on lactic acidosis cases to be submitted in subsequent PSURs.

In view of the above, the Committee considers that the benefit-risk balance of metformin containing medicinal products remains favourable taking into account the agreed amendments to the product information.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for metformin containing medicinal products.