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METFORMIN

500MG & 1000MG POWDER FOR ORAL SOLUTION

2.5 Clinical Overview

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MODULE 2 OVERALL SUMMARIES

2.5 Clinical Overview

Contents

Abbreviations

µ	micro
^{14}C	radioactive isotope of carbon
ACE	angiotensin-converting-enzyme
ADA	American Diabetes Association
ADOPT	A Diabetes Outcomes Progression Trial
ADR	adverse drug reaction
A_e	cumulative amount excreted
AE	adverse event
AGE	advanced glycosylation end product
AMP	adenosine mono phosphate
AMPK	adenosine mono phosphate activated protein kinase
ANOVA	ANalysis Of VAriance
ATP	adenosine triphosphate
AUC	area under curve
AUCss	area under the curve at steady state
AVM	Avandamet® (rosiglitazone/metformin)
BID	twice daily (from the Latin 'bis in die')
BMI	body mass index
BMI-SDS	body mass index standard deviation score
CI	confidence interval
CKD	chronic kidney disease
CL	clearance
CLCR	creatinine clearance
CL_R	renal clearance
CMSC	Contrast Media Safety Committee
C_{max}	maximum plasma concentration
C_{min}	minimum concentration
CRC	colorectal cancer
CRD	Centre for Reviews and Dissemination Database
CVVH	continuous veno-venous haemofiltration
dL	decilitre
DDP-4	dipeptidyl peptidase 4
E_2	estradiol
EASD	European Association for the Study of Diabetes
ED	Emergency Department
eGFR	estimated glomerular filtration rate
ER	extended release
ERK	extracellular signal regulated kinases
ESFR	end-stage renal failure
ESRD	end stage renal disease
ESUR	European Society of Urogenital Radiology
EU	European Union

FA	fatty acids
FBG	fasting blood glucose
FBP1	fructose-1,6-bisphosphatase 1
FDA	Food and Drug Administration
FDC	fixed-dose combination
FFA	free fatty acids
FPG	fasting plasma glucose
FSH	follicle stimulating hormone
g	gram
G6Pase	glucose-6-phosphatase
GCK	glucokinase
GCP	Good Clinical Practice
GDM	gestational diabetes mellitus
GI	gastrointestinal
GITS	gastrointestinal therapeutic system
GLP	Good Laboratory Practice
GLP	glucagon-like peptide
GLUT	glucose transporter
GYS	glycogen synthase
h	hour
HbA1c	glycosylated hemoglobin
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HF	heart failure
HGP	hepatic glucose production
HR	hazard ratio
ICU	intensive care unit
IDF	International Diabetes Federation
IR	immediate release
IRS	insulin receptor substrate
IV	intravenous
K_{el}	elimination rate constant
kg	kilogram
L	litre
L/P	lactate/pyruvate
LC	lung cancer
M-ER	metformin extended-release
MAPK	mitogen activated protein kinases
MATE	multidrug and toxin extrusion protein
mg	milligram
min	minute
mL	millilitre
mM	milli mole
MODY	maturity onset diabetes of the young

NAFLD	non-alcoholic fatty liver disease
NHANES	National Health and Nutrition Examination Survey
NICE	National Institute for Health and Clinical Excellence
NIDDM	non-insulin-dependent diabetes mellitus
nmol	nanomole
NSAIDs	non-steroidal anti-inflammatory drugs
OCT	organic cation transporter
OR	odd ratio
OS	overall survival
PC-AKI	post-contrast acute kidney injury
PCOS	Polycystic Ovary Syndrome
PEPCK	phosphoenolpyruvate carboxykinase
PFKL	6-phosphofructokinase
pH	negative logarithm of hydrogen ion concentration
PK	pharmacokinetic
PM	placebo/metformin
PMAT	plasma membrane monoamine transporter hENT4
PO	per os
PTZ	pentylenetetrazol
PYGL	glycogen phosphorylase
QD	once daily (from the Latin 'quaque die')
SD	standard deviation
SLC22A	solute carrier family 22 members
SNP	single nucleotide polymorphism
SPC	Summary of Product Characteristics
SR	sustained release
$t_{½}$	half-life
T1D	Type 1 diabetes mellitus
T2D	Type 2 diabetes mellitus
TDD	total daily dose
TID	three times daily (from the Latin '*ter in die*')
T_{lag}	lag time
T_{max}	time to maximum plasma concentration
TZD	thiazolidinediones
UK	United Kingdom
UKPDS	UK Prospective Diabetes Study
Vd	volume of distribution
VM	vildagliptin/metformin
WHO	World Health Organisation
XR	extended-release

MODULE 2 OVERALL SUMMARIES

2.5 Clinical Overview

2.5.1 Product Development Rationale

Metformin 500mg & 1000mg Powder for Oral Solution of Morningside Healthcare Ltd, UK is indicated for the treatment of Type 2 diabetes mellitus (T2D) particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.

- In adults, Metformin may be used as monotherapy or in combination with other oral anti-diabetic agents or with insulin.
- In children from 10 years of age and adolescents, Metformin may be used as monotherapy or in combination with insulin.

The active ingredient in Metformin 500mg & 1000mg Powder for Oral Solution is metformin hydrochloride. Each sachet of Metformin 500mg Powder for Oral Solution contains 500 mg metformin hydrochloride corresponding to 390 mg metformin base, and that of Metformin 1000mg Powder for Oral Solution contains 1000 mg metformin hydrochloride corresponding to 780 mg metformin base.

Diabetes mellitus is a complex and heterogeneous metabolic disorder characterized by a chronic hyperglycaemia and disturbances of carbohydrate, lipid, and protein metabolism [redacted] It results from a deficiency of insulin secretion and/or of insulin action. Classification is based on the etiology of the disease and distinguishes between several types of diabetes: Type 1 (T1D), Type 2, gestational, and other types (e.g., genetic alterations of pancreatic β-cells, genetic deficiencies leading to a decrease in insulin activity, mitochondrial diabetes, and several diseases like endocrinopathies or pancreas disease). The majority of diabetes cases are Type 1 and Type 2, the rest being constituted by rarer forms [e.g., maturity onset diabetes of the young (MODY)] that represent less than 5% [redacted]).

A global epidemic of diabetes is occurring. In 2007, it was estimated that diabetes was affecting 246 million people worldwide, representing 5.9% of the adult (20-79 years old) population. The most recent estimates from the International Diabetes Federation (IDF) predict that by 2025, diabetes is expected to affect some 380 million people, representing 7.1% of the adult population. T2D has seen the greatest increase in prevalence, largely driven by lifestyle factors including changes in dietary patterns and habits, declining levels of physical activity, and increasing sedentary behaviours [redacted]).

The American Diabetes Association (ADA) / European Association for the Study of Diabetes (EASD) and the National Institute for Health and Clinical Excellence (NICE) guidelines

recommend lifestyle modifications and metformin as first-line treatment [redacted] .

T2D is a life-long metabolic disorder characterized by high blood sugar, insulin resistance, and relative lack of insulin ([redacted]). The IDF estimated that, in Europe 35 million adults had diabetes (both Type 1 and Type 2) in 2011. This is projected to increase by 23%, to 43 million in 2030, which is the lowest increase of any region in the world [redacted]). T2D accounts for about 90% of cases of diabetes, with the other 10% due primarily to T1D and gestational diabetes.

The sulfonylureas and the biguanides that includes metformin are the oldest and most commonly used classes of oral hypoglycaemic drugs that have different mechanisms of action. While sulfonylureas stimulate insulin secretion, biguanides predominantly decrease hepatic glucose output. They have similar hypoglycaemic effect both lowering the glycosylated hemoglobin (HbA1c) value by approximately 1.5% points. In appropriately selected patients, metformin may be the oral hypoglycaemic agent of first choice, since it achieves a level of glucose control similar to that of the sulfonylureas without the same risk of weight gain or hypoglycaemia ([redacted] .

Metformin has been extensively used in human therapy. The use of metformin to treat diabetes was first reported in 1957 [redacted]). Metformin was introduced to treat diabetes in the UK and other European countries in 1958. The first large prospective comparator trial of metformin was carried out in the UK in 1968 [redacted]). In 1994, metformin was approved in the US. Long-term cardiovascular benefits of metformin were recognised by the UK Prospective Diabetes Study (UKPDS) Group in 1998, providing a new rationale to adopt metformin as initial therapy to manage hyperglycaemia in T2D [redacted]). In 2011, metformin was included in World Health Organisation (WHO)'s Model List of Essential Medicines [redacted]).

Currently, metformin is the recommended first-line, glucose-lowering medication [redacted]). The pivotal trial underlying the recommendation of metformin as the first-line, glucose-lowering drug of choice was the UK Prospective Diabetes Study (UKPDS), which compared metformin as monotherapy with chlorpropamide, glyburide and insulin in a subgroup of overweight participants [redacted] . Intensive glycaemic control with metformin decreased the risk of diabetes-related outcomes compared with other glucose-lowering agents. Metformin is also the only oral antidiabetic agent described as providing protection from diabetic complications in its European labelling. Accordingly, current UK guidelines from NICE state that "In people who are overweight [body mass index (BMI) > 25.0 kg/m^2] and whose blood glucose is inadequately controlled using lifestyle interventions alone, metformin should normally be used as the first-line glucose-lowering therapy" [redacted] Metformin does not cause weight gain or hypoglycaemia; and is rarely

associated with lactic acidosis (0.03 cases per 1000 patient-years have been reported). Due to the relatively short half-life ($t_{½}$) of 1.5 to 4.7 hours, the recommended dosing regimen of metformin is 2 or 3 times per day[redacted]).

The Applicant, Morningside Healthcare Ltd., UK, is preparing an Article 10.1 Generic application in accordance with EU Directive 2001/83/EC for Metformin 500mg & 1000mg Powder for Oral Solution based on Glucophage 500mg and 1000mg Powder for Oral Solution in Sachet of Merck Serono Ltd., a product that was discontinued in 2014 due to unforeseen manufacturing issues ([redacted]). Metformin, the active substance, is of well-established use, recognized as safe and effective, has high therapeutic margin and no particular concerns in terms of toxicity. The excipients in Metformin 500mg & 1000mg Powder for Oral Solution of Morningside Healthcare Ltd, UK are approved and established agents in widespread use in the pharmaceutical manufacturing industry.

This clinical overview is based upon a systematic search through[redacted] to identify peer-reviewed articles evaluating human pharmacokinetic, efficacy and safety data of metformin. This systematic search using the keyword 'metformin' yielded over 18,000 publications that were narrowed by keywords such as[redacted]
Truncation was used for permitting identification of variables of the used terms.

The present report provides critical evaluation of clinical data on the efficacy and tolerability of metformin dem0onstrating that Metformin 500mg & 1000mg Powder for Oral Solution of Morningside Healthcare Ltd, UK is safe and efficacious. All efficacy and safety data discussed here were retrieved from publicly available literature.

2.5.2 Overview of Biopharmaceutics

According to the 'Guideline on the investigation of bioequivalence' (*CPMP/EWP/QWP/1401/98 Rev. 1/ Corr* **), "If the test product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an approved oral solution, bioequivalence studies may be waived. However, if the excipients may affect gastrointestinal transit (e.g. sorbitol, mannitol, etc.), absorption (e.g. surfactants or excipients that may affect transport proteins), *in* vivo solubility (e.g. co-solvents) or in vivo stability of the active substance, a bioequivalence study should be conducted, unless the differences in the amounts of these excipients can be adequately justified by reference to other data".

The qualitative composition of the Glucophage 500mg and 1000mg Powder for Oral Solution in Sachet of Merck Serono (Reference product discontinued now) and the Metformin 500mg & 1000mg Powder for Oral Solution of Morningside Healthcare Ltd, UK (Test product) is shown in Table 1.

Table 1 The qualitative composition of the Reference product and the Test product

Ingredients	Function	Reference Product		Proposed Generic Product	
		500mg	1000mg	500mg	1000mg
Acesulfame potassium	Sweetener	√	√	x	x
Aspartame (E951)	Sweetener	√	√	x	x
Citric acid anhydrous	pH modifier	√	√	√	√
Erythritol	Diluent/Sweetener	√	√	x	x
Maize starch	Binder	√	√	x	x
Pullulan PI-20	Binder	√	√	x	x
Povidone 30	Binder	x	x	√	√
Povidone 90	Binder	x	x	√	√
Sucralose	Sweetener	x	x	√	√
Monobasic sodium citrate	Buffering/ pH Modifier	x	x	√	√
Mannitol	Diluent	x	x	√	√

Metfromin has high solubility in water and low permeability to cell membranes. Therefore, it can be classified as a BCS Class III drug [redacted]). The Metformin 500mg and 1000mg Powder for Oral Solution of Morningside Healthcare Ltd, UK contains [redacted] and [redacted] mannitol, respectively. According to the method of administration, the powder should be poured into a glass and 150 ml water should be added to obtain a clear to opalescent solution. Therefore, the concentrations of mannitol in such solutions are [redacted] and [redacted] / 150 ml, respectively. The absorption of metformin is slow and incomplete following administration of an oral solution, and the solution dosage form is bioequivalent to an IR tablet that dissolved

completely within 1 h [redacted]). The usual dosage for metformin is 250–500 mg three times daily (TID), up to a maximal of 3 g/day. The absolute bioavailability of a 500 mg immediate-release tablet of metformin hydrochloride given under fasting conditions is 50 – 60%; with the maximal plasma concentration occuring at approximately 2.5 h following oral administration. Mannitol is known reduce the small intestinal transit (SIT) time when compared to a control formulation [redacted] . Increasing the rate of SIT reduces the time available for drug absorption and may contribute to impaired absorption of luminal contents. Therefore, the incorporation of an excipient like mannitol into a pharmaceutical formulation could lead to reduced bioavailability for drugs that are exclusively absorbed from the small intestine (SI). The dependence of SIT time on the concentration of mannitol has been investigated [redacted]). Eight, healthy male subjects each received 200 ml of radiolabelled purified water, or a 200 ml solution of mannitol at three different concentrations; 0.755 g/200 ml, 1.509 g/200 ml and SIT times for the 0.755 g/200 ml, 1.509 g/200 ml and 2.264 g/200 ml mannitol solutions was reduced by 11%, 23% and 34% respectively, which, however, only reached statistically significant rate at the highest mannitol concentration.

2.5.2.1 Overview of Reference Formulation and Similarity

2.5.2.2 Comparative *In Vitro* Release Characteristics

2.5.2.3 Comparative *In Vivo* Release Characteristics

2.5.2.4 Conclusions on Bioequivalence

Since the amount of mannitol in the Metformin 500mg and 1000mg Powder for Oral Solution of Morningside Healthcare Ltd, UK is only about [redacted] and [redacted] respectively of the [redacted] dose of mannitol tested in the above summarized trial, which did not have a significant effect on SIT time, it can be safely conluded that the amount of mannitol present as excipient in the The Metformin 500mg and 1000mg Powder for Oral Solution of Morningside Healthcare Ltd, UK would not significantly alter the bioavailability of metformin, the active substance.

2.5.3 Clinical Pharmacology

2.5.3.1 Pharmacokinetics

2.5.3.1.1. Absorption

Metformin has an absolute oral bioavailability of 40 to 60%, and gastrointestinal (GI) absorption is apparently complete within 6 hours of ingestion. An inverse relationship was observed between the dose ingested and the relative absorption with therapeutic doses ranging from 0.5 to 1.5 g, suggesting the involvement of an active, saturable absorption process [redacted] . The mean ± SD fractional oral bioavailability of metformin is 55 ± 16%. It is absorbed predominately from the small intestine [redacted]).

The kinetics of ^{14}C-metformin have been studied in five healthy subjects after oral administration. The concentration of metformin in saliva was considerably lower than in plasma and declined more slowly. The bioavailability averaged 50-60%. The rate of absorption was slower than that of elimination, which resulted in a plasma concentration profile of "flip-flop" type for oral metformin [redacted]).

In a randomized, three-way, crossover, open-label, fed study, metformin pharmacokinetics were determined at steady-state [redacted]). Metformin extended release (ER) 500 mg tablets were administered for 5 days as 2 tablets once daily or one tablet twice daily and compared to one metformin immediate release 500 mg tablet given twice daily to 24 healthy volunteers. Serial plasma samples were collected for 24 hour following each administration of the first dose on Day 5. The pharmacokinetic parameters for metformin ER are listed in Table 2.

Table 2 Steady state pharmacokinetics of metformin after two dosing regimens of metformin extended release 500 mg tablets versus metformin

Pharmacokinetic parameter	Metformin ER 500 mg tablets, BID 2 × 500 mg, QD (n = 24)	Metformin ER 500 mg, QD × 500 mg, BID (n = 24)	Metformin ER 500 mg tablets, QD × 500 mg, BID (n = 24)
$AUC_{0-\infty}$ (ng.h/mL)	12907 ± 2011*	13329 ± 2581	13930 ± 2565
C_{max} (ng/mL)	1249 ± 246	817 ± 175	986 ± 193
C_{min} (ng/mL)	97 ± 30	386 ± 151	240 ± 59
T_{max} (h)	3.89 ± 0.53	4.06 ± 0.54	3.92 ± 0.29

* Data are mean ± SD

When compared to metformin immediate release (IR), the once daily dosing of metformin ER tablets resulted in slightly lower means ratio of the $AUC_{0-\tau}$ values: 92.6% (90% CI: 89.1 – 96.3%), although the observed C_{max} values were greater with a means ratio of 126.2% (90% CI: 121.2 – 131.5%). The twice daily dosing of metformin ER tablets resulted in similar $AUC_{0-\tau}$ values to those of metformin IR with a means ratio of 95.6% (90% CI: 92.0 – 99.3%), whereas

the C_{max} values were lower with a means ratio of 82.9% (90% CI: 79.5 – 86.3%). C_{min} (minimum concentration) for twice daily dosing was high compared to metformin IR, whereas it was lower for metformin ER once daily.

The pharmacokinetics of an ER formulation of metformin was investigated in 24 healthy male volunteers in a randomized, single-dose, four-period crossover study [redacted]). During each study period, subjects received a randomly assigned dose containing 1000, 1500, 2000 or 2500 mg metformin. Blood samples were drawn 0-72 hour after dosing for pharmacokinetic assessment. The pharmacokinetic parameters are summarized in the Table 3.

Table 3 Metformin pharmacokinetic parameters (mean ± SD).

Parameter	1000 mg	1500 mg	2000 mg	2500 mg
C_{max} (mg/mL)	1.42 ± 0.32	1.78 ±0.37	2.11 ± 0.52	2.48 ± 0.53
$AUC_{0\text{-}72h}$ (mg.h/mL)	11.90 ± 2.76	16.68 ± 4.14	20.65 ± 3.82	24.18 ± 3.97
AUC_{∞} (mg.h/mL)	11.94 ± 2.71	16.70 ± 4.15	20.81 ± 3.87	24.26 ± 4.10
T_{max} (h)	6.3 ± 1.4	6.7 ± 1.6	7.8 ± 2.0	7.2 ± 2.1
T_{lag} (h)	0.4 ± 0.5	0.3 ± 0.6	0.2 ± 0.4	0.0 ± 0.0
$t_{½}$ (h)[a]	5.0	5.6	7.4	7.5

[a] Harmonic mean

To assess the steady-state pharmacokinetics of metformin extended release tablets, an open-label, multiple-dose, five-regimen, two-sequence clinical study lasting 5 weeks was conducted [redacted]. Sixteen healthy volunteers aged 18-40 years were included in the trial. Three 1-week regimens of metformin ER (500, 1000 and 1500 mg, QD) were administered sequentially. Subjects were alternately given either metformin ER 2000 mg, QD or metformin IR 1000 mg, BID during weeks 4 and 5. Absorption of metformin ER was slower than that of metformin IR (T_{max} = 7 and 3 hours, respectively). C_{max} following the administration of metformin ER 2000 mg, QD was 36% higher than that following the evening dose of metformin IR 1000 mg, BID. The extent of absorption, determined by area under the plasma concentration-time curve (AUC), was equivalent for both formulations. The mean accumulation ratio of metformin extended release was 1.0, indicating no accumulation with multiple-dose administration. Intrasubject variabilities in C_{max} and AUC of metformin were comparable between metformin ER and metformin IR.

The bioavailability of metformin from an aqueous solution (A), a rapidly dissolving tablet (B), and three sustained release products (D, C, and E) was compared[redacted]). A single oral dose (1.0 g) of these products was administered to six healthy volunteers in a randomized cross-over study. Plasma levels of metformin were followed up to 10 hour and excretion into urine up to 48 hour after the dose. The peak plasma levels after A and B were similar and significantly ($p < 0.05$) higher than after C, D and E. The AUC was significantly ($p < 0.05$) higher with A than with other products. The recovery of metformin in urine was 37%, 33%,

25%, 28% and 29% of the dose after A, B, C, D and E, respectively. The values of A and B were significantly ($p < 0.05$) higher than those of C, D and E. Thus, the bioavailability of metformin even from aqueous solution and rapidly dissolving tablets was relatively low and further deteriorated when metformin was administered as sustained release products. The bioavailability of the three sustained release products studied was similar.

The bioavailability and pharmacokinetic properties of 3 marketed product of metformin extended/sustained release formulation were tested in Indian male volunteers [redacted]). The study was designed as an open-label, randomized, 3-treatment, single-dose, crossover, bioavailability study comparing 3 marketed brands of 500 mg metformin extended/sustained release tablets in 18 healthy human male volunteers under fed condition. A single oral dose of 500 mg metformin sustained release products, Glycomet sustained release (metformin hydrochloride 500 mg sustained release tablets, USV Ltd.), Bigomet sustained release (metformin hydrochloride 500 mg sustained release tablets, Otsira Genetica) and extended release reference product was administered as per computer generated randomization schedule during 3 period of the study having 7 days of washout period. The predetermined regulatory range of 90% confidence intervals (CI) for bioequivalence was 0.80 to 1.25. The 90% CI for log transformed data for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Glycomet sustained release vs. reference were 82.11-98.91, 86.29-102.17 and 86.34-102.59 respectively whereas for Bigomet sustained release vs. reference were 104.39-125.76, 94.78-112.22 and 92.85-110.33 respectively. The results suggested that the Glycomet sustained release was bioequivalent to reference product, whereas Bigomet sustained release was not as per regulatory defined criteria.

The relative bioavailability and bioequivalence of a new tablet formulation of metformin hydrochloride with reference to a standard product was investigated in healthy Chinese adult male volunteers [redacted]). Two randomized, comparative, two-way crossover studies were therefore conducted. In Study 1, which was a single-dose study, 20 subjects received 1000 mg metformin hydrochloride ER tablets as test product followed by the same amount of metformin hydrochloride IR tablets as reference product with a 7-day washout period between the two doses. In Study 2, which was a multiple-dose study, 22 subjects received metformin hydrochloride ER 1000 mg/day for 9 consecutive days followed by metformin hydrochloride IR 1000 mg/day with a 14-day washout period between the doses of the test and reference product. A significant difference was found in the ANOVA for C_{max} in the single-dose study, while this was not the case in the multiple-dose study. Two one-sided t-tests showed that there were no significant differences in the AUC values between the two formulations. It was indicated that the test preparation was bioequivalent to the reference preparation when both metformin hydrochloride extended-release and metformin hydrochloride immediate-release were investigated in healthy Chinese adult male volunteers. And on the basis of the mean

AUC_{0-t}, $AUC_{0-\infty}$ and AUC_{ss}, the relative bioavailability of the metformin hydrochloride ER was found to be 107.80%, 111.89% and 110.61% respectively compared with metformin hydrochloride IR.

The single-dose pharmacokinetics of two gastric-retentive ER tablet formulations of metformin hydrochloride in fed, healthy volunteers were compared with those of the currently marketed immediate-release metformin hydrochloride product [redacted]). The plasma concentration-time profiles demonstrated extended-release characteristics from the gastric-retentive tablets. The mean bioavailability from each gastric-retentive tablet was approximately 115%, relative to the immediate-release product. Cmax values were lower and t max values were greater for the gastric-retentive tablets compared with the immediate release product. In contrast to conventional extended-release metformin tablets reported in the literature, these gastric-retentive tablets showed extended-release plasma concentration profiles of metformin hydrochloride and increased bioavailability compared with the immediate-release tablet.

Dose proportionality

To determine if metformin ER could improve the dose proportionality of metformin, a dose-escalating study was conducted in 35 healthy male and female subjects [redacted]). This was a four-way, single-dose, open-label study, in which metformin extended release 500-mg tablets were dosed at 1, 2, 3 or 5 tablets as a single dose. There was a minimum of 7 days between study arms. The dose-normalized PK parameters are listed in Table 4.

Table 4 Dose proportionality of metformin extended release tablets: 500 – 2500 mg dose range (dose–normalized data)

Pharmacokinetic parameter	Metformin ER 500 mg tablets 1 × 500 mg (n = 35)	Metformin ER - 500 mg tablets 2 × 500 mg (n = 35)	Metformin ER 500 mg tablets 3 × 500 mg (n = 35)	Metformin ER 500 mg tablets 1 × 500 mg (n= 35)
$AUC_{0-\infty}$ (ng.h/mL)	3501 ± 796	3351 ± 959	3097 ± 946	2831 ± 887
C_{max} (ng/mL)	473 ± 145	434 ± 112	390 ± 99	326 ± 80
T_{max}(h)	3.89 ± 0.53	4.06 ± 0.54	3.92 ± 0.29	3.80 ± 0.41

* Data are mean ± SD

The results suggested a somewhat less than proportional increase in exposure, as assessed by $AUC_{0-\infty}$ and C_{max} of metformin with increasing dose, whereas T_{max} was relatively constant. However, in comparison to metformin immediate release where the relative bio-availability of the highest dose (2550 mg) was only 58% compared to the lowest dose (500 mg) the relative bioavailability of the metformin extended release highest dose (2500 mg) was 80% compared to the lowest dose (500 mg). Linear regression analysis demonstrated a near linear increase in $AUC_{0-\infty}$ and C_{max} with metformin extended release dose ($r^2 = 0.98$ and 0.90, respectively). This

improvement in dose proportionality was probably owing to the slower input rate form the metformin extended release tablets and implied that bioavailability was not compromised at higher doses with metformin extended release tablets.

Effect of food

Pharmacokinetics of metformin ER formulation were studied under fasting and fed conditions and compared to those of IR under fasting conditions in humans [redacted]). 78 healthy human volunteers participated in 3 independent studies (26 subjects per study) were given either 1000 mg, PO metformin IR or 750 mg metformin ER. Results showed the increased ER bioavailability and delayed time to reach C_{max} in the fed state as compared to fasted state, with no significant difference in C_{max} and half-life values. On the other hand, the IR formulation showed significant differences in all parameters as compared to extended release formulation, yet the half-life was similar. C_{max} mean value of 1956 ng/mL (Table 5) of IR formulation is close to the upper limit of 2000 ng/mL and hence prone to increase above the upper limit at steady state.

Table 5 Metformin mean (SD) plasma pharmacokinetic parameters after 1000 mg immediate release oral dose/ 750 mg extended release oral doses to 78 healthy volunteers under different states.

Formulation / Pharmacokinetic parameter	ER-Fed	ER-Fasted	IR-Fasted	p
$AUC_{0\rightarrow t}$ (ng.mL/h)	7143 (1671)	5795 (2279)	12459 (3553)	< 0.05
$AUC_{0\rightarrow\infty}$ (ng.mL /h)	7448 (1585)	6167 (2236)	12884 (3450)	< 0.05
C_{max} (ng/mL)	794 (143)	832 (300)	1956 (476)	< 0.05
$T_{½}$ (h)	3.66 (0.8)	3.8 (1.2)	3.39 (0.7)	> 0.05
K_{el} /(h)	0.2 (0.1)	0.19 (0.1)	0.22 (0.1)	> 0.05
T_{max} (h)	6.35 (1.1)	4.3 (1.0)	2.58 (1.0)	< 0.05

* > 0.05 for extended release - Fed vs extended release - Fast C_{max} comparison

Indeed, 10 subjects had C_{max} values above 2000 ng/ml. However, C_{max} mean values are close to the effective level of 1000 ng/mL and prone to fall within 1000-2000 ng/mL at steady state.

In an open-label, three-period, six-sequence crossover study, 30 healthy males, aged 18 to 43 (mean 29) years were randomly assigned to a single tablet of treatment metformin hydrochloride sustained release (SR) 1000 mg; fasted condition: metformin hydrochloride SR 1000 mg, fed state or metformin hydrochloride SR 1000 mg/glimepiride 2 mg, fed state with a one week washout between treatments [redacted]). Following a high fat meal, C_{max} from treatments metformin hydrochloride SR 1000 mg, fed state and metformin hydrochloride SR 1000 mg/glimepiride 2 mg, fed state increased by 9% and 7%, respectively; AUC increased by 17% and 7% respectively compared to treatment metformin hydrochloride SR 1000 mg, fasted condition. The mean C_{max} of metformin with metformin hydrochloride sustained release 1000 mg, fasted condition, metformin hydrochloride SR 1000 mg, fed state and metformin

hydrochloride SR 1000 mg/glimepiride 2 mg, fed state were 915.98 ng/mL, 994.82 ng/mL and 975.77 ng/mL respectively; mean $AUC_{0-\infty}$ was 10602.92 ng.h/mL, 12073.31 ng.h/mL and 11164.76 ng.h/mL respectively; median T_{max} was eight hours for each treatment; mean $t_{½}$ was 4.58 h, 4.12 h and 4.22 h, respectively. Food slightly increased the bioavailability of metformin from metformin hydrochloride 1000 mg SR tablet and from a fixed dose combination of metformin hydrochloride 1000 mg SRrelease /glimepiride 2 mg, with no evidence of dose-dumping of metformin from either formulation

2.5.3.1.2. Distribution

Distribution of metform in is rapid, but a slow transfer to a deep compartment seems to occur [redacted] . Metformin accumulates in the oesophagus, stomach, duodenum, salivary glands and kidneys [redacted]). Binding to plasma proteins does not occur ([redacted] ,but an increase in the blood:plasma metformin concentration ratio over 24 hours has been observed afte single oral doses of 1.5g, indicating a slow association of the drug with blood cells [redacted]). The mean apparent volume of distribution (Vd) ranges from 63 to 276L [redacted]). Metformin is accumulated by liver above the plasma concentration and distributes mainly in the cytosol [redacted]).

2.5.3.1.3. Metabolism

Based on early studies was considered that metformin does not undergo metabolism in either animals or humans [redacted]). The fact that metformin is excreted unmetabolised was confirmed by a study with radiolabelled metformin in humans [redacted]). However, the data from another study [redacted] showed incomplete recovery of metformin in the urine after IV administration, in accordance with a further study [redacted] in which 20% of the dose was not accounted for. It is therefore possible that some metabolic transformation may occur in humans, but no metabolites or conjugates have been identified. The negligible hepatic metabolism of metformin contrasts with the extensive aromatic hydroxylation of phenformin in the liver, a condition which may favour phenformin accumulation and lactic acidosis in patients with a low hydroxylation capacity [redacted]).

2.5.3.1.4. Elimination

Metformin undergoes rapid renal excretion. It has a plasma elimination half-life ($t_{½ß}$) ranging from 1.5 to 4.5 h after IV injection and from 2.0 to 6.0 h after PO administration in healthy volunteers [redacted]). Urinary data have indicated a further terminal elimination phase with a half-life of 8 to about 20 hours involving only a small fraction (< 5%) of the administered dose [redacted]). Ranges of values for renal and total clearance are reported to be 20.1 to 36.9 L/h and 26.5 to 42.4 L/h, respectively, indicating active tubular secretion of metformin. Renal clearance of metformin is correlated with creatinine clearance, but total clearance is a more appropriate (inverse) predictor of accumulation [redacted]).

Following IV administration of metformin, the majority of the dose was excreted in urine within 8 hours, while after oral administration of 0.5g metformin, 50% was recovered in urine and 27% in faeces. No metformin seems to be exhaled by the lungs, The concentration of metformin in saliva was reported to be considerably lower than in plasma (about 10% of plasma concentration) and to decline more slowly [redacted]). Although metformin has been administered to some pregnant diabetic women ([redacted]), no published data are available regarding transfer of the drug across the placenta or excretion in breast milk. Prescribing advice for metformin in pregnancy is inconsistent and often reflects historical safety concerns based on uncertainty rather than evidence [redacted].

Genetic polymorphism

The oral absorption, hepatic uptake and renal excretion of metformin are mediated very largely by organic cation transporters (OCTs) [redacted] . An intron variant of OCT1 (single nucleotide polymorphism [SNP] rs622342) has been associated with a decreased effect on blood glucose in heterozygotes and a lack of effect of metformin on plasma glucose in homozygotes. An intron variant of multidrug and toxin extrusion transporter [MATE1] (G>A, SNP rs2289669) has also been associated with a small increase in anti-hyperglycaemic effect of metformin. Overall, the effect of structural variants of OCTs and other cation transporters on the pharmacokinetics of metformin appears small and the subsequent effects on clinical response are also limited. However, intersubject differences in the levels of expression of OCT1 and OCT3 in the liver are very large and may contribute more to the variations in the hepatic uptake and clinical effect of metformin.

Metformin pharmacokinetics was studied in relation to genetic variations in OCT1, OCT2, OCT3, OCTN1, and MATE1 in 103 healthy male Caucasians [redacted]). Renal clearance varied 3.8-fold and was significantly dependent on creatinine clearance ($r^2 = 0.42$, $p < 0.0001$), age ($r^2 = 0.09$, $P = 0.002$), and OCT1 polymorphisms. Carriers of zero, one, and two low-activity OCT1 alleles (Arg61Cys, Gly401Ser, 420del, or Gly465Arg) had mean renal clearances of 30.6, 33.1, and 37.1 L/h, respectively ($P = 0.04$), after adjustment for creatinine clearance and age). Immunohistochemical staining of human kidneys demonstrated OCT1 expression on the apical side of proximal and distal tubules

2.5.3.2 Pharmacokinetics in Special Populations

2.5.3.2.1 Renal Impairment

In a clinical study, 30 subjects were allocated into 3 groups, based on their renal functions as assessed by creatinine clearance (CL_{Cr}): subjects with normal renal function (CL_{Cr} of > 80 mL/min, eight males, two females), patients with mild renal impairment (CL_{Cr} of 51 – 80 mL/min, nine males, one female), and patients with moderate renal impairment (CL_{Cr} of 30 –

50 mL/min, six males, four females)[redacted]). Metformin extended release was administered 5 min after a high fat meal had been consumed. Plasma samples were collected out to 36-hour post dose. Urine was collected during the following time-intervals: 0 – 2, 2 – 4, 4 – 8, 8 – 12, and 12 – 24 and 24 – 36 hour. The pharmacokinetic parameters based on the plasma and urine concentrations are shown in Table 6 for each group.

Table 6 Metformin plasma and urine pharmacokinetics in renally-impaired patients compared to normal subjects administered metformin extended release tablets

PK parameter	Group 1 (mild renal impairment) (n = 10)	p-value for comparison to Group 3	Group 2 (mod. renal impairment) (n = 10)	p-value for comparison to Group 3	Group 3 (normal renal function) (n = 10)
Plasma					
$AUC_{0-\infty}$ (ng hour/mL)	6732 (41.9) [*, ‡]	0.044	9537 (48.3) [*]	0.0002	4379 (22.1) [*, §]
C_{max} (ng/mL)	601 (35.2) [*]	0.443	874 (24.6) [*]	0.002	511 (15.1) [*]
T_{max} (hour)	4.51 ± 1.09 [*]	0.695	5.02 ± 1.45	0.999	5.00 ±1.94 [*]
Urine					
A_e (mg)	84.1 (39.0) [*]	0.734	79.7 (40.5) [*]	0.949	77.0 (33.0) [*]
% Dose (%)	18.0 ± 7.0	0.734	16.9 ± 6.9	0.949	16.2 ± 5.4
CL_R (mL/min)	278 ± 93	0.401	157 ± 55	< 0.0001	332 ± 126

[*] Geometric mean; [‡] n = 8; [§] n = 9.
A_e: cumulative amount excreted; CL_R: renal clearance; % Dose: percentage of dose excreted; M-ER: metformin extended-release.

Maximum plasma concentrations were achieved in about 4 – 5 hour in all three groups, indicating no effect of the renal function on the gastric retention or release properties of the extended-release formulation. Patients with moderate renal impairment had approximately a two-fold increase in total exposure, based on $AUC_{0-\infty}$, to metformin when compared to those with normal renal function ($p < 0.001$). Similarly, those in the mild renal impairment groups showed increased exposure, although the increase, 1.5-fold, was less pronounced ($p = 0.0448$). Maximum observed concentrations were about 80% higher in the moderate impaired group ($p= 0.002$) and ~ 27% greater in the mild renal impaired group ($p = 0.443$) compared to the healthy subjects. The renal clearance of metformin decreased with decreasing renal function. In the mild group it was decreased by 16% ($p=0.4$) and in the moderate group by 53% ($p=< 0.001$).

Kinetic parameters of metformin were determined in volunteers with normal renal function and in patients with different degrees of renal impairment [redacted]. After oral administration of metformin tablets, drug recovery in urines was only 37.6%, possibly not as a consequence of low bioavailability (a similar low recovery was found after oral administration of the metformin solution used for the intravenous studies), but of binding to

the intestinal wall, as shown in animal and clinical studies with metformin and other biguanides. Metformin was rapidly eliminated through active secretion by the kidney (mean renal clearance, 440.8 mL/min) Metformin was neither metabolized nor protein bound in plasma. The very brief plasma t 1/2 made significant accumulation, with a standard thrice daily regimen, unlikely

Factors influencing the pharmacokinetic variability, including variant transporters were investigating to compare healthy subjects and patients with T2D and to simulate doses of metformin at varying stages of renal function [redacted]). Plasma concentrations of metformin were pooled from three studies: patients with T2D (study A; n = 120), healthy Caucasian subjects (study B; n = 16) and healthy Malaysian subjects (study C; n = 169). Creatinine clearance and total body weight were clinically and statistically significant covariates with the apparent clearance and volume of distribution of metformin, respectively. None of the 57 single-nucleotide polymorphisms (SNPs) in transporters of metformin were significant covariates. In contrast to previous studies, there was no effect on the pharmacokinetics of metformin in patients carrying the reduced function OCT1 allele (R61C, G401S, 420del or G465R). Dosing simulations revealed that the maximum daily doses in relation to creatinine clearance to prescribe to patients are 500 mg (15 mL/min), 1,000 mg (30 mL/min), 2,000 mg (60 mL/min) and 3,000 mg (120 mL/min), for both the immediate-release and extended-release formulations. The population model enabled doses of metformin to be simulated for each stage of renal function, to ensure the concentrations of metformin do not exceed 5 mg/L. However, the plasma concentrations of metformin at these dosage levels were still quite variable and monitoring metformin concentrations may be of value in individualising dosage. Thus it was concluded that metformin could be used, with appropriate dosage adjustment, in patients with renal impairment.

2.5.3.2.2 Hepatic Impairment

An observational prospective cohort of 100 consecutive diabetic patients with ongoing hepatitis C virus (HCV) cirrhosis and no contraindication to metformin were included in a screening programme for hepatocellular carcinoma ([redacted]). After a median follow-up of 5.7 years, the use of metformin was independently associated with reduced incidences of hepatocellular carcinoma [hazard ratio (HR): 0.19; 0.04–0.79)] and liver-related death/transplantation (HR: 0.22; 0.05–0.99. Thus, metformin may not be contraindicated in patients with compensated HCV cirrhosis, but may instead provide benefits [redacted]. Mild- to-moderate steatosis is a common finding in overweight/obese patients with T2D, and metformin may be prescribed in such a population with no harmful effects [redacted] In particular, no increased risk of lactic acidosis has been reported. Metformin may also have potentially beneficial effects in patients with non-alcoholic fatty liver disease (NAFLD), although the evidence is rather scanty [redacted]). Conflicting results have been

reported in young people with fatty liver, with a reduction in prevalence and severity after 6 months of metformin in one study [redacted]), but no better results compared with lifestyle after 24 months of metformin in another [redacted]). In participants in the Edinburgh Type 2 Diabetes Study, the use of metformin was unexpectedly associated with the presence of hepatic steatosis (compared with those classed as normal/probable normal) on ultrasound scans independent of BMI and glycaemic control [odds ratio (OR): 2.19; 1.59–3.00] [redacted]). Metformin has no significant effect on liver histology [redacted] [redacted]).

2.5.3.2.3 Pregnancy

Pharmacokinetics of metformin was evaluated during pregnancy [redacted] . Serial blood and urine samples were collected over one steady-state dosing interval in women treated with metformin during early to late pregnancy (n = 35) and postpartum (n = 16). Maternal and umbilical cord blood samples were obtained at delivery from 12 women. Metformin concentrations were also determined in breast milk samples obtained over one dosing interval in 6 women. Metformin renal clearance increased significantly in mid (723 ± 243 mL/min, $p < 0.01$) and late pregnancy (625 ± 130 mL/min, $p < 0.01$) compared with postpartum (477 ± 132 mL/min). These changes reflected significant increase in creatinine clearance (240 ± 70 mL/min, $p < 0.01$ and 207 ± 56 mL/min, $p < 0.05$ versus 165 ± 44 mL/min) and in metformin net secretion clearance (480 ± 190 mL/min, $p < 0.01$ and 419 ± 78 mL/min, $p < 0.01$ versus 313 ± 98 mL/min) in mid and late pregnancy versus postpartum, respectively. Metformin concentrations at the time of delivery in umbilical cord plasma ranged between non-detectable (<5 ng/mL) and 1263 ng/mL. The daily infant intake of metformin through breast milk was 0.13 to 0.28 mg, and the relative infant dose was less than 0.5% of the mother's weight-adjusted dose. The results indicate that metformin pharmacokinetics are affected by pregnancy-related changes in renal filtration and net tubular transport and can be roughly estimated by the use of creatinine clearance. At the time of delivery, the foetus was exposed to metformin concentrations from negligible to as high as maternal concentrations. In contrast, infant exposure to metformin through the breast milk was found to be low.

The effects of pregnancy on metformin pharmacokinetics were determined [redacted]). Seven women with T2D taking metformin throughout pregnancy were studied on two occasions, once at 28-36 weeks gestation and once at least 8 weeks postpartum. Serum metformin concentrations were determined across a dosing interval using high-performance liquid chromatography. The areas under the serum concentration-time curve from 0 to 4 hour post-dose (AUC_{0-4}) and 0 to 8 hour post-dose (AUC_{0-8}) where possible, were compared in the pregnant and non-pregnant state. Metformin concentrations were lower in pregnancy in six subjects, with a mean (95% CI) AUC_{0-4} that was 69% (53.6, 84.8) of the postpartum value.

The AUC_{0-4} of one subject was higher in pregnancy at 142% of the postpartum value. Overall, the mean (95% CI) AUC_{0-4} during pregnancy for all seven subjects was 80% (51.3, 107.8) of the postpartum value ($p = 0.053$, two-tailed t-test; $p = 0.027$, one-tailed t-test). These results were consistent with the hypothesis that the clearance of metformin increased in pregnancy as a result of enhanced renal elimination.

2.5.3.2.4 Breastfeeding

In order to determine whether metformin is excreted into breast milk, seven women were started on metformin 500 mg, BID on the first day after caesarean delivery ([redacted]). Breastfeeding was started at the same time. Peak and trough serum and milk samples were drawn between postoperative days 4 and 17. In 3 infants, blood was drawn for glucose determination at the same time as the maternal samples. The mean peak and trough serum metformin concentrations were 1.06 µg/mL (range 0.68 –1.90 µg/mL) and 0.42 µg/mL (range 0.26–0.51 µg/mL), respectively, whereas the mean peak and trough metformin concentrations in breast milk were 0.42 µg/mL (range 0.38–0.46 µg/mL) and 0.39 µg/mL (range 0.31– 0.52 µg/mL), respectively. The mean milk : serum ratio was 0.63 (range 0.36 –1.00) and the mean estimated infant dose as a percentage of the mother's weight-adjusted dose was 0.65% (range 0.43–1.08%). In 3 infants, the blood glucose concentrations 4 hours after a feeding were within the normal limit, ranging from 47–77 mg/dL. It was concluded that metformin was excreted into breast milk, but the amounts seem to be clinically insignificant.

Two studies were performed to evaluate transfer of metformin into human milk [redacted] In Study 1, 3 nursing mothers taking metformin were studied throughout a dosing interval at steady state. Blood samples were obtained from 2 suckling infants. In Study 2, 5 healthy lactating women who volunteered to express milk after weaning were given metformin, 500 mg, at weaning and were studied for up to 72 hours. In Study 1, the milk-to-plasma concentration ratios based on area under the concentration-time curve analysis were 0.37, 0.50, and 0.71. The estimated "doses" of metformin that would be ingested by the breast-fed infants were 0.18%, 0.20%, and 0.21% of the maternal doses, adjusted for weight. In the breast-fed infants, no metformin was detected ($n = 2$). In study 2, the milk-to-plasma concentration ratio based on area under the concentration-time curve analysis was unable to be calculated for 3 subjects because of the unexpected persistence of metformin in milk beyond the study period. For the 2 subjects studied for 72 hours, the milk-to-plasma concentration ratios based on area under the concentration-time curve analysis were 0.27 and 0.47 and the infant doses were 0.11% and 0.25%. The concentration-time profile for metformin in milk in all subjects was unexpectedly flat. The unusual concentration-time profile for metformin in milk suggested that the transfer of metformin into milk was not solely dependent on passive diffusion.

2.5.3.2.4 Age

The most important change interfering with the pharmacokinetic profile is the progressive decrease of renal function with aging ([redacted]). Indeed, a positive correlation has been reported between fasting plasma metformin concentrations and both age and serum creatinine in a diabetic population treated long term with the biguanide compound. Because most cases of lactic acidosis have been reported in elderly patients (over half the patients were over 60 years and a substantial proportion were over 75 years of age) [redacted], metformin is usually not recommended in elderly individuals over the age of 65 or 70 years [redacted] .

2.5.3.2.5 Gender

No specific gender related information could be retrieved about the pharmacokinetics of metformin.

2.5.3.2.6 Race

No specific race related information could be retrieved about the pharmacokinetics of metformin.

2.5.3.3 Clinically Relevant Pharmacokinetic Interactions

The low or absent protein binding (in contrast with sulphonylureas) and the lack of hepatic metabolism (in contrast with phenformin) of metformin reduce the possibility of drug interactions with metformin through pharmacokinetic mechanisms [redacted]).

Acarbose

The α-glucosidase inhibitor acarbose significantlyredu ced the bioavailability of metformin 1.0g for the first 9 hours after oral coadministration in 6 healthy volunteers [redacted]). Acarbose 100mg reduced the mean plasma C_{max} of metformin by 35% without affecting T_{max} Furthermore, it induced a significant reduction (by 35%) in metformin AUC_{540min}, but did not diminish the 24-hour urinary excretion of the drug.

Furosemide

A single-dose study, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration [redacted]). Furosemide increased metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine

A single-dose, metformin-nifedipine drug interaction study in healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine [redacted] T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic drugs

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion, theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems [redacted]). Such an interaction has been observed between metformin and oral cimetidine in normal healthy volunteers. In both single and multiple-dose metformin-cimetidine drug interaction studies, there was a 60% increase in peak metformin plasma and whole blood concentrations, as well as a 40% increase in plasma and whole blood metformin AUC.

2.5.3.4 Pharmacodynamics

2.5.3.4.1 Pharmacology and Mode of Action (Primary Pharmacodynamics)

The antihyperglycaemic action of biguanides is mainly a consequence of reduced glucose output owing to inhibition of liver gluconeogenesis and, possibly to a lesser extent, increased insulin-mediated glucose uptake in the skeletal muscle. Metformin has little effect on glucose absorption through the gastrointestinal tract but slightly delays the absorption process [redacted]). The polarity of metformin makes it dependent on membrane transporters for cellular uptake and secretion. The main metformin transporters are solute carrier family 22 members (SLC22A) 1 and 4 (also known as OCT1 and OCTN1, respectively) [redacted]), multidrug and toxin extrusion protein (MATE) 1 and 2, and the plasma membrane monoamine transporter hENT4 (also known as PMAT) [redacted]).

Inhibiting gluconeogenesis in the liver

The liver expresses high levels of SLC22A1, and is considered to be the main site of action of metformin. In addition, metformin concentration is higher in the portal circulation than elsewhere in the body, which might contribute to metformin accumulation in the liver. In the live, metformin is suggested to have an effect on the regulation of glucose uptake, gluconeogenesis, glycolysis and glycogen synthesis (Fig. 1; [redacted]).

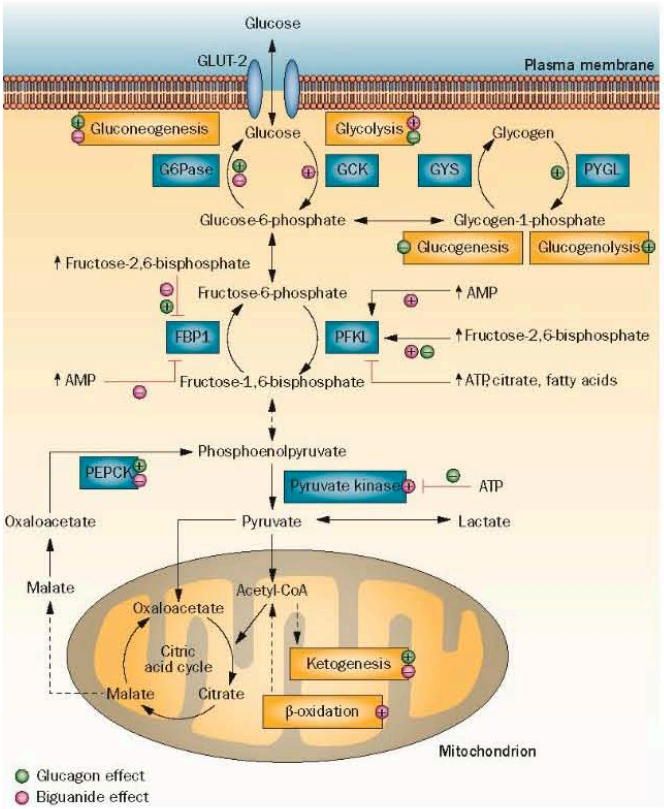

Figure 1 The effects of glucagon and biguanides on gluconeogenic and glycolytic fluxes. The role of glucagon signalling on the expression and activity of various enzymes and its opposition by biguanides is illustrated in a simplified scheme of hepatic glucose metabolism. Glycolysis is a pathway that converts glucose into pyruvate whilst generating adenosine triphosphate (ATP); gluconeogenesis is an energy-consuming process of glucose synthesis from non-carbohydrate precursors such as lactate or pyruvate. Many of the metabolic steps of gluconeogenesis are the reverse of the glycolytic pathway. Both glucagon and biguanides can regulate these pathways. A rise in fructose-2,6-bisphosphate, induced by metformin, inhibits fructose-1,6-bisphosphatase 1 (FBP1) and activates 6-phosphofructokinase (PFKL). Biguanides abrogate glucagon's effect on the gluconeogenic flux and influence fatty acid metabolism. AMP and ATP have modulatory effects on several metabolic steps. The rate of glycolysis and gluconeogenesis is also determined by the concentration of glucose and lactate (and other precursors of glucose). The stimulatory (+) and inhibitory (–) effects are highlighted in green for glucagon and in red for biguanide signalling. G6Pase, glucose-6-phosphatase; GCK, glucokinase; GLUT-2, glucose transporter 2; GYS, glycogen synthase; PEPCK, phosphoenolpyruvate carboxykinase; PYGL, glycogen phosphorylase [redacted]).

Metformin increases the activity of the insulin receptor and of insulin receptor substrate 2 (IRS-2) and enhances glucose uptake via increased translocation of glucose transporters, such as GLUT-1 (also known as SLC2A1), to the plasma membrane. As a result, metformin enhances the insulin-mediated suppression of gluconeogenesis. Furthermore, and possibly of greater importance, metformin opposes the gluconeogenic action of the peptide hormone glucagon. Gluconeogenesis accounts for 28–97% of overall hepatic glucose output depending on the feeding status in nondiabetic individuals, the rate being higher in patients with advanced T2D mellitus. In this patient population, metformin was reported to reduce hepatic glucose output by up to 75% [redacted]).

Increasing glucose uptake in skeletal muscle

Metformin improves insulin sensitivity and insulin-mediated glucose uptake in skeletal muscle [redacted]). This effect is mediated through an increase in the tyrosine kinase activity of the insulin receptor and through enhanced activity and translocation of glucose transporters, such as GLUT-4 (also known as SLC2A4), to the plasma membrane. Increased insulin receptor expression and an enhanced ability to restore enzymatic pathways involved in insulin signalling have also been attributed to metformin.

Altering endocrine function in the pancreas

The antidiabetic action of metformin has been associated with reduced insulin concentrations in the circulation [redacted]). Consequently, metformin monotherapy is associated with only a minimal risk of hypoglycaemia. Metformin seems to interact with the incretin axis, as an enhancer and sensitizer for the actions of glucagon-like peptide 1 (GLP-1). GLP-1 increases secretion of insulin and reduces secretion of glucagon in response to glucose and has widespread tissue-specific metabolic effects. Metformin stimulates expression of GLP-1 receptor in the pancreas and increases plasma GLP-1 levels. Moreover, circulating levels of dipeptidyl peptidase 4 (DDP-4), which is known to degrade incretins, were reported to be lower in patients treated with metformin than in untreated individuals [redacted]).

Antilipolytic action

Metformin may inhibit agonist-induced lipolysis in adipocytes via inhibition of ERK1/2 phosphorylation, but it may counteract adipose tissue expansion through 5'-AMP-activated protein kinase (AMPK) dependent stimulation of FA (fatty acids) oxidation and inhibition of lipogenesis in subcutaneous fat depot [redacted]). This antiadipogenic effect may contribute to reduced fat mass. The antilipolytic action of metformin could contribute to insulin sensitization through the decrease of systemic free fatty acids (FFA) levels. The contribution of metformin to the attenuation of glucotoxicity and lipotoxicity may further improve insulin sensitivity in adipose tissue. An AMPK-dependent mechanism may also enhance glucose uptake by visceral adipose tissue. Metformin may also modulate

adipokine secretion through molecular pathways, which appear to differ between individual adipokines and may involve either p44/p42 mitogen-activated protein kinase (MAPK) or AMPK.

Clinical trials exploring pharmacodynamics

T2D patients (n = 7) with fasting hyperglycaemia (15.5 ± 1.3 mM) were studied 3 months before and after metformin treatment to examine the mechanism by which metformin lowers endogenous glucose production[redacted]). Seven healthy subjects matched for sex, age, and BMI, served as control subjects. The rate of glucose production was twice as high in the diabetic subjects as in control subjects (0.70 ± 0.05 vs. 0.36 ± 0.03 mM/m^2/min, p < 0.0001). Metformin reduced that rate by 24% (to 0.53 ± 0.03 mM/m^2/min, p = 0.0009) and fasting plasma glucose concentration by 30% (to 10.8 ± 0.9 mM, p = 0.0002). The rate of gluconeogenesis was three times higher in the diabetic subjects than in the control subjects (0.59 ± 0.03 vs. 0.18 ± 0.03 mM/m^2/min) and metformin reduced that rate by 36% (to 0.38 ± 0.03 mM/m^2/min, p = 0.01). By the 2H2O method, there was a twofold increase in rates of gluconeogenesis in diabetic subjects (0.42 ± 0.04 mM/m^2/min), which decreased by 33% after metformin treatment (0.28 ± 0.03 mM/m^2/min, p = 0.0002). There was no glycogen cycling in the control subjects, but in the diabetic subjects, glycogen cycling contributed to 25% of glucose production and explains the differences between the two methods used. In conclusion, metformin lowered the rate of glucose production in T2D patients through a reduction in gluconeogenesis.

The effect of metformin on glucose metabolism was examined in eight obese (% ideal body weight, 151 ± 9%) and six lean (% ideal body weight, 104 ± 4%) NIDDM subjects before and after 3 months of metformin treatment (2.5 g/day)[redacted]). Fasting plasma glucose (11.5-8.8 mM), HbA1c (9.8-7.7%), oral glucose tolerance test response (20.0-17.0 mM; peak glucose), total cholesterol (5.67-4.71 mM), and triglycerides (2.77-1.52 mM) uniformly decreased (p < 0.05-0.001) after metformin treatment; fasting plasma lactate increased slightly from baseline (1.4 to 1.7 mM; p = NS). Body weight decreased by 5 kg in obese NIDDM subjects, but remained constant in lean NIDDM. Basal hepatic glucose production declined in all diabetics from 83 to 61 mg/m^2.min (p < 0.01), and the decrease correlated (r = 0.80; p < 0.01) closely with the fall in fasting glucose concentration. Fasting insulin (115 to 79 pmol/L) declined (p < 0.05) after metformin. During a 6.9 mM hyperglycaemic clamp, glucose uptake increased in every NIDDM subject (113 ± 15 to 141 ± 12 mM/m2/min; p < 0.001) without a change in the plasma insulin response. During a euglycemic insulin clamp, total glucose uptake rose in obese NIDDM subjects (121 ± 10 to 146 ± 9 mM/m^2/min; p < 0.05), but decreased slightly in lean NIDDM (121 ± 10 to 146 ± 0.5; p = NS). Hepatic glucose production was suppressed by more than 80-90% in all insulin clamp studies before and after metformin treatment. In conclusion, metformin i) lowered the fasting

plasma glucose and insulin concentrations; ii) improved oral glucose tolerance; and iii) decreased plasma lipid levels independent of changes in body weight. The improvement in fasting glucose resulted from a reduction in basal hepatic glucose production. Metformin per se does not enhance tissue sensitivity to insulin in NIDDM subjects. The improvement in glucose metabolism under hyperglycaemic, but not euglycaemic conditions suggests that metformin augments glucose-mediated glucose uptake. Metformin had no stimulatory effect on insulin secretion.

In a double-blind cross-over study, nine obese T2D patients were treated with metformin 0.5 g, TID, PO or placebo for 4 weeks [redacted]). Metformin treatment significantly reduced mean day-time plasma glucose levels (10.2 ± 1.2 vs 11.4 ± 1.2 mM, $p < 0.01$) without enhancing mean day-time plasma insulin (43 ± 4 vs 50 ± 7 mU/L, NS) or C-peptide levels (1.26 ± 0.12 vs 1.38 ± 0.18 nmol/L, NS). Fasting plasma lactate was unchanged (1.57 ± 0.16 vs 1.44 ± 0.11 mM, NS), whereas mean day-time plasma lactate concentrations were slightly increased (1.78 ± 0.11 vs 1.38 ± 0.11 mM, $p < 0.01$). The clamp study revealed that metformin treatment was associated with an enhanced insulin-mediated glucose utilization (370 ± 38 vs 313 ± 33 mg/m^2/min, $p < 0.01$), whereas insulin-mediated suppression of hepatic glucose production was unchanged. Also basal glucose clearance was improved (61.0 ± 5.8 vs 50.6 ± 2.8 mg/m^2/min, $p < 0.05$), whereas basal hepatic glucose production was unchanged (81 ± 6 vs 77 ± 4 mg/m^2/min, NS). It was concluded that metformin treatment in obese Type II diabetic patients reduces hyperglycaemia without changing the insulin secretion

To establish the anti-hyperglycaemic mechanisms of metformin in NIDDM independently of the long-term, aspecific effects of removal of glucotoxicity, 21 NIDDM subjects (14 obese, 7 non-obese) were studied on two separate occasions, with an isoglycaemic (plasma glucose ~ 9 mM) hyperinsulinemic (two-step insulin infusion, 2 hour each, at the rate of 4 and 40 mU/m^2/min) clamp combined with [3-^{3}H]glucose infusion and indirect calorimetry, after administration of either metformin (500 mg/os before the clamp) or placebo [redacted]). Compared with placebo, hepatic glucose production (HGP) decreased approximately 30% more after metformin treatment (from 469 ± 50 to 330 ± 54 mM/min), but glucose uptake did not increase. Metformin suppressed FFAs by approximately 17% (from 0.42 ± 0.04 to 0.35 ± 0.04 mM) and lipid oxidation by approximately 25% (from 4.5 ± 0.4 to 3.4 ± 0.4 mM/kg/min) and increased glucose oxidation by approximately 16% (from 16.2 ± 1.4 to 19.3 ± 1.3 mM/kg/min) compared with placebo ($p < 0.05$). Metformin did not affect non-oxidative glucose metabolism, protein oxidation, or total energy expenditure. Suppression of FFAs and lipid oxidation after metformin correlated with suppression of HGP ($r = 0.70$ and $r = 0.51$, $p < 0.001$). The effects of metformin in obese and non-obese subjects were no different. Thus, it was concluded that the specific, anti-hyperglycaemic effects of metformin in the clinical condition of hyperglycaemia in NIDDM are primarily due to suppression of HGP, not

stimulation of glucose uptake, and are mediated, at least in part, by suppression of FFA and lipid oxidation.

2.5.3.4.2 Secondary Pharmacodynamics

Polycystic Ovary Syndrome (PCOS)

PCOS is a set of symptoms due to elevated androgens in females [redacted]). A metabolic syndrome of obesity-related and/or intrinsic insulin resistance occurs in about half of PCOS patients, and the compensatory hyperinsulinism has tissue-selective effects, which include aggravation of hyperandrogenism. The effectiveness of metformin in improving clinical and biochemical features of PCOS was assessed in a systematic review and meta-analysis ([redacted] . Thirteen randomised controlled trials investigating the effect of metformin compared with either placebo or no treatment or with ovulation induction agent were evaluated. The results confirm that metformin is effective in achieving ovulation in women with polycystic ovary syndrome with odds ratios of 3.88 (95% CI 2.25 to 6.69) for metformin compared with placebo and 4.41 (2.37 to 8.22) for metformin and clomifene compared with clomifene alone. An analysis of pregnancy rates shows a significant treatment effect for metformin and clomifene (odds ratio 4.40, 1.96 to 9.85). Metformin is an effective treatment for anovulation in women with PCOS.

The effect of metformin pretreatment to improve follicle stimulating hormone (FSH)-induced ovulation was evaluated in 21 women with clomiphene-resistant PCOS in a randomized prospective trial [redacted]). The patients were divided randomly into groups A and B (10 subjects each). Group A underwent two cycles of FSH stimulation and then received metformin for a month before undergoing a third cycle. Group B received 1,500 mg of metformin for at least a month before a single cycle of FSH stimulation. The number of follicles > 15 mm in diameter on the day of human chorionic gonadotropin (hCG) administration was significantly lower in cycles performed after metformin treatment. The percentage of cycles with hCG was withheld because of excessive follicular development was significantly lower in cycles treated with metformin. Plasma levels of estradiol (E_2) were significantly higher in cycles treated with FSH alone than in those treated with FSH and metformin. By reducing hyper-insulinism, metformin determines a reduction in intraovarian androgens which leads to a reduction in E_2 levels and favours orderly follicular growth in response to exogenous gonadotropins.

The effect of metformin on spontaneous and clomiphene-induced ovulation was studied in 61 obese women with PCOS [redacted]). Women who did not ovulate spontaneously were given clomiphene (50 mg, QD) for five days while continuing to take metformin or placebo. Twenty-one women in the metformin group and 25 women in the placebo group were given clomiphene because they did not ovulate spontaneously during the first phase of the study. Overall, 31 of the 35 women (89%) treated with metformin ovulated spontaneously or

in response to clomiphene, as compared with 3 of the 26 women (12%) treated with placebo. The ovulatory response to clomiphene can be increased in obese women with the PCOS by decreasing insulin secretion with metformin.

Cancer

Diabetes mellitus has been associated with a 1.2–2.0-fold increase in cancer incidence [redacted] . It was first suggested in 2005 that metformin use was associated with a reduced incidence of cancer [redacted]). Recently, epidemiological studies and meta-analyses have revealed that patients with T2DM have a lower incidence of tumor development than healthy controls and that patients diagnosed with cancer have a lower risk of mortality when treated with metformin, demonstrating an association between metformin and tumorigenesis [redacted] . *In vivo* and *in vitro* studies have revealed that metformin has a direct antitumor effect, which may depress tumor proliferation and induce the apoptosis, autophagy and cell cycle arrest of tumor cells. The mechanism underpinning the antitumor effect of metformin has not been well established. Studies have demonstrated that reducing insulin and insulin-like growth factor levels in the peripheral blood circulation may lead to the inhibition of phosphoinositide 3-kinase/Akt/mechanistic target of rapamycin (mTOR) signaling or activation of AMP-activated protein kinase, which inhibits mTOR signaling, a process that may be associated with the antitumor effect of metformin.

A systematic search of PubMed, EMBASE, the Cochrane Library, and the Web of Science was conducted for related articles up to August 2016 [redacted]). Of 81 articles identified, 8 retrospective cohort studies, representing 6098 cases of colorectal cancer (CRC) patients with T2D who used metformin and 4954 cases of CRC patients with T2D who did not use metformin, were included in this meta-analysis. There was no significant heterogeneity and quality difference between studies. Metformin users had significantly improved overall survival (OS) (HR = 0.82, 95% CI: 0.77-0.87, p = 0.000). However, metformin use cannot affect CRC-specific survival (HR = 0.84, 95% CI: 0.69-1.02, p = 0.079) compared to non-users. This meta-analysis suggests that metformin use may improve survival among CRC patients with T2D. However, prospective controlled studies are still needed to rigorously evaluate the efficacy of metformin as an anti-tumor agent.

In another meta-analysis, PubMed, EMBASE, and Cochrane Library were searched till July 1, 2016 and cohort studies were included [redacted] . Seven cohort studies with a medium heterogeneity (I2 = 56.1% and p = 0.033) were included in the meta-analysis. An improved OS for metformin users over nonusers among colorectal cancers with diabetes was noted (HR 0.75; 95% CI 0.65 to 0.87). However, metformin revealed no benefits for cancer-specific survival (HR 0.79, 95%, CI 0.58 to 1.08). In conclusion, metformin prolongs the OS of diabetic CRC patients, but it does not affect the CRC-specific survival.

Survival, recurrences and metastasis in patients with T2D along with CRC or lung cancer (LC) (CRC, n = 202; LC, n = 180) taking metformin were investigated using the electronic medical record in Memphis Veterans Affairs Medical Center [redacted]). Patients with CRC or LC and T2D on metformin were compared to controls taking any medication except metformin. For CRC, the metformin group noted fewer deaths (48% versus 76%, $p < 0.001$), recurrences (4% versus 19%, $p = 0.002$), metastases (23% versus 46%, $P = 0.001$), better 5-year survival rates (57% versus 37%, $p = 0.004$), overall survival years (5.7 versus 4.1, $p = 0.007$) and greater carcinoembryonic antigen decrease (72% versus 47%, $P = 0.015$). Metformin was associated with improved 5-year survival rates (29% versus 15%, $p = 0.023$) and overall survival years (3.4 versus 1.8, $P < 0.001$) in LC. In conclusion, metformin therapy is associated with significantly better prognosis in patients with CRC and improved survival in LC. Patients with CRC on metformin had fewer recurrences and metastases.

2.5.3.4.3 Safety Pharmacology

No formal safety pharmacological studies can be retrieved. Some studies suggest that metformin possesses cardioprotective and neuroprotective properties. Metformin attenuate pentylenetetrazol (PTZ)-induced apoptotic neurodegeneration in human cortical neuronal cells. Diabetic neuronal damage results from hyperglycemia followed by increased formation of advanced glycosylation end products (AGEs), which leads to neurodegeneration. Metformin has a neuroprotective effect in advanced glycation end product treated human neural stem cells via activation of AMPK [redacted]).

Metformin improves dyslipidaemia and reduces concentrations of inflammatory and haemostatic biomarkers in non-diabetic individuals, suggesting possible cardiovascular benefit. The effect of metformin on cardiovascular outcomes of patients with T2D has been studied in two randomised controlled trials. In the UKPDS, overweight patients taking metformin had a 39% lower risk of myocardial infarction over 10 years than did patients on conventional dietary therapy, and post-trial observational data showed continuing benefit [redacted]). In the HOME trial, which included 390 patients with T2D on insulin, metformin reduced the composite cardiovascular endpoint by 40% [redacted]).

2.5.3.5 Clinically Relevant Pharmacodynamic Interactions

Hyperglycemic drugs

Drugs that tend to produce hyperglycemia may lead to a derailed blood sugar control. These include thiazide and other diuretics, corticosteroids, phenothiazines, thyroid hormone replacement drugs, e.g., levothyroxine, estrogens, estrogen plus progestogen, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, isoniazid, and $ß_2$-agonists ([redacted]). ACE-inhibitors may decrease the blood glucose levels. When such drugs are administered to patients receiving

metformin, the patient should be closely observed to maintain adequate glycemic control. More frequent blood glucose monitoring may be required, especially at the beginning of treatment

Alcohol

Ethanol administration to biguanide-treated diabetics resulted in identical increases in blood lactate and lactate/pyruvate (L/P) ratio during phenformin and metformin treatment obese diabetics [redacted]). Alcohol can potentiate the effects of metformin on lactate metabolism, which may rarely result in lactic acidosis, particularly in acute alcohol intoxication [redacted]). Metformin may cause increased levels of lactic acid in the blood after alcohol consumption [redacted] .

Glucocorticoids

Diabetics treated with metformin in equipotent dosages exhibited the highest blood lactate, L/P ratio, and beta-hydroxybutyrate levels during, both before and during glucocorticoid administration [redacted]).

2.5.4 Overview of Efficacy

The efficacy of metformin, both in monotherapy and in combination therapy, has been documented by a large number of studies. Overall, metformin monotherapy has been estimated to lower HbA1c by approximately 1.5% [redacted]). In combination, metformin can also significantly lower HbA1c, and the magnitude of the effect depends on the therapeutic combination, the follow-up of the study and the type of subjects included.

2.5.4.1 Dose-finding trials

In a multicenter, double-blind, 14-week study, 451 patients were randomized to placebo or metformin with doses of 500, 1000, 1500, 2000, or 2500 mg daily over 11 weeks [redacted]). HbA1c dropped by -0.6% to -2.0% with increasing daily metformin dose (500 to 2000 mg), and differences between dosage groups were significant ($p < 0.05$).

The dose-response relationship has been confirmed by two double-blind, randomized, placebo-controlled studies of 24 and 16 weeks' duration [redacted] . In Protocol 1, 240 patients were randomized to receive metformin extended-release (XR) 1000 mg formulation once daily or placebo in a 2:1 ratio for 12 weeks. In Protocol 2, 742 patients were randomized to receive metformin XR 500 mg, QD, 1000 mg, QD, 1500 mg, QD, 2000 mg, QDy, 1000 mg, BID or placebo for 16 weeks. The primary endpoint in each study was the change from baseline in HbA1C at 12 weeks (Protocol 1) or 16 weeks (Protocol 2). In comparison with placebo, treatment differences amounted to -0.6% (500 mg, QD), -0.7% (1000 mg, QD), -1.0% (1500 mg, QD) and -1.0% (2000 mg, QD). It appears that 1500 mg and 2000 mg per day represent the optimal metformin dosages for most patients.

2.5.4.2 Monotherapy

The therapeutic potential of acarbose and metformin was tested in a randomized three-arm (placebo, acarbose, metformin) group comparison that was double-blind with respect to acarbose/placebo treatment and single-blind with respect to metformin treatment ([redacted] . Both drugs were equally active compared with placebo ($p < 0.05$ for the comparisons with placebo): HbA1c dropped to 9.8% with placebo, 8.5% with acarbose, and 8.7% with metformin.

In a double-blind clinical trial, 205 patients with recently diagnosed T2D were randomized to either 30 mg pioglitazone or 850 mg metformin daily with titrations upward to 45 mg and 2550 mg, respectively [redacted]). Specifically, HbA1c and fasting plasma glucose were comparable at the end of the study (pioglitazone: -1.3% reduction of HbA1c, $p < 0.0001$ vs. baseline; metformin: -1.5% reduction of HbA1c, $p < 0.0001$ vs. baseline; pioglitazone vs. metformin: $p = 0.280$).

The ADOPT (A Diabetes Outcomes Progression Trial) Study group evaluated rosiglitazone (4–8 mg), metformin (850–1700 mg), and glyburide (5–10 mg) as initial treatment for patients with newly diagnosed T2D in a double-blind, randomized, trial of 4360 patients with a median treatment duration of 4 years [redacted]). The primary outcome was the time to monotherapy failure, defined as fasting plasma glucose exceeding 180 mg/dL. Incidence of monotherapy failure at 5 years was 15% with rosiglitazone, 21% with metformin and 34% with glyburide. Thus, rosiglitazone was associated with 32% lower failure risk as compared with metformin ($p < 0.001$) and 63% lower failure risk as compared with glyburide ($p < 0.001$). There was no difference in the proportion of patients reaching a glycemic target of HbA1c lower than 7%. Metformin-treated patients had more gastrointestinal (GI) untoward effects, but lower body weight (mean difference: 6.9 kg) than those receiving rosiglitazone.

A 24-week, randomized, double-blind, placebo-controlled trial allocated 1091 patients with T2D to sitagliptin 100 mg/metformin 1000 mg, sitagliptin 100 mg/metformin 2000 mg, metformin 1000 mg, metformin 2000 mg, sitagliptin 100 mg, or placebo [redacted]). In monotherapy, both agents accomplished significant reductions in HbA1c, which were slightly more pronounced with metformin (-1.30% with metformin 2000 mg, -0.99% with metformin 1000 mg and -0.83% with sitagliptin 100 mg).

The efficacy of vildagliptin (100 mgdaily, n = 526), a dipeptidyl peptidase-4 (DPP-4) inhibitor and metformin (up to 2000 mg daily, n = 254) was compared in a double-blind, randomized, study of one-year treatment in drug-naïve patients [redacted]). Both agents achieved significant reductions in HbA1c that were slightly more pronounced with metformin (-1.4% with metformin and -1.0% with vildagliptin). Thus, the statistical non-inferiority of 50 mg, BID vildagliptin to 1000 mg, BID metformin could not be established. Body weight was unchanged with vildagliptin ($p = 0.17$), but was lowered with metformin ($p < 0.001$).

The efficacy of metformin monotherapy has been evaluated in a very comprehensive Cochrane review ([redacted]). In the review, 29 trials with 5259 participants were included. Metformin was compared with sulphonylureas (13 trials), glitazones (3 trials), meglitindes (2 trials), α-glucosidase inhibitors (2 trials), placebo (12 trials), diet (3 trials) and insulin (2 trials). Metformin monotherapy produced a significant benefit in glycemic control, weight reduction, lipidemic profile and diastolic blood pressure. In terms of glycemic control, metformin was significantly superior to placebo or diet and modestly better than sulphonylureas. Serum lipids and body weight were also improved with metformin than with sulphonylureas. It was concluded that placebo, sulphonylureas, α-glucosidase inhibitors, glitazones, meglitinides, insulin and diet could not produce a more favourable effect on glycemic control, body weight, or serum lipids than metformin.

The effects of ER metformin was compared with IR metformin on post-prandial glycaemic excursion, chronic glycaemia, lipid profiles, insulin resistance and islet function in T2D in a

randomised, open-labelled, positive-controlled multicentre study including 150 Chinese patients [redacted]). Both metformin IR and ER metformin modestly but significantly decreased HbA1c levels and BMI after 12 weeks of treatment, however, there were no significant differences between the two groups. The post-prandial glycaemia at 120 min after a standard meal in ER metformin group was higher than in metformin IR group (11.02 ± 3.08 mM vs. 9.74 ± 2.61 mM, $p < 0.05$).

In a prospective, randomized, double-blind study, 55 T2D patients were randomly assigned to receive either ER metformin or IR metformin (at a maximal dosage of 2000 mg/day for 12 weeks) [redacted]). Significant decreases ($p < 0.001$) in mean HbA1c and fasting plasma glucose (FPG) levels were observed in each group. However, the mean changes in HbA1c from baseline to end point in the 2 groups were not significantly different.

2.5.4.3 Combination therapy

Combination with sulphonylureas

The combination of metformin (500–1500 mg) and glibenclamide (5–10 mg) was assessed in a double-blind study including 165 unselected T2D patients [redacted] . The dose was titrated with a fasting blood glucose (FBG) concentration of < 6.7 mM as the target, using at most six dose levels, the first three comprising increasing monotherapy (M or G) or low-dose primary combination (MGL), and the second three add-on therapies (M/G and G/M) and primary combination therapy escalated to high dose (MGH). Success rates were higher on MGL than on monotherapy. The difference in achieving acceptable control (FBG ≤ 7.8 mM) was 70% versus 51% (95% confidence interval 3–36%, $p = 0.032$). When the drugs were combined, a slightly greater FBG reduction ($p = 0.026$) was observed, at lower dosage ($p = 0.013$). The response could not be predicted from body weight, but depended upon initial FBG ($p = 0.019$) and meal-stimulated C-peptide ($p = 0.007$). FBG declined progressively with increasing doses of metformin, whereas glibenclamide exerted most of its effect at low dose.

In a randomized, multicentre study, 372 patients were treated for 5 months with metformin (850 mg three times per day), glimepiride (starting dose 1 mg and titration up to 6 mg) or metformin and glimepiride [redacted]). Combination treatment produced significantly greater reductions of HbA1c (changes: +0.07% ± 1.20% for metformin, +0.27% ± 1.10% for glimepiride, -0.74% ± 0.96% for combination treatment, $p < 0.001$), fasting blood glucose (changes: +14.4 ± 7.2 mg/dL for metformin, +12.6 ± 55.8 mg/dL for glimepiride and -32.4 ± 39.6 mg/dL for combination treatment, $p < 0.001$) and post-prandial blood glucose (changes: +19.8 ± 106.2 mg/dL for metformin, +1.8 ± 91.8 mg/dL for glimepiride and -46.8 ± 70.2 mg/dL for combination treatment, $p < 0.001$) than either agent alone. Improved efficacy was accompanied by significantly ($p = 0.039$) more frequent symptomatic hypoglycemia in the combination group.

A 4-month double-blind, multicenter trial, 411 patients were allocated to metformin 500 mg, glibenclamide 5 mg, metformin-glibenclamide 500 mg/2.5 mg or metformin-glibenclamide 500 mg/5 mg [redacted]). The reductions in HbA1c and fasting plasma glucose was significantly ($p < 0.05$) more pronounced for metformin-glibenclamide 500 mg/2.5 mg (-1.20% and -47.16 mg/dl) and 500 mg/5 mg (-0.91% and -42.12 mg/dl), compared with metformin (-0.19% and -10.26 mg/dl) or glibenclamide (-0.33% and -13.14 mg/dl). The glycemic endpoint of HbA1c < 7% was accomplished significantly ($p = 0.001$) more frequently by patients receiving metformin- glibenclamide 500 mg/2.5 mg and 500 mg/5 mg (75% and 64%, respectively) than those receiving glibenclamide (42%) and metformin (38%) alone. These favorable effects were obtained with lower metformin and glibenclamide doses in the combined treatment group than in patients receiving either drug alone.

In a 16-week, randomized, double-blind trial, 639 patients inadequately controlled on at least half-maximal dose of sulphonylurea were assigned to glyburide 10 mg, metformin 500 mg, glyburide/metformin 2.5 mg/500 mg, or glyburide/metformin 5 mg/500 mg [redacted]). Glyburide/metformin combination succeeded in reducing HbA1c by -1.7% more than glyburide alone ($p < 0.001$) and by -1.9% more than metformin alone ($p < 0.001$), ultimately leading to lower fasting plasma glucose levels than glyburide ($p < 0.001$) or metformin groups ($p < 0.001$).49

The additive effect of glipizide/metformin combination was assessed in a randomized a multicenter, parallel-group, active-controlled trial recruiting 247 patients ([redacted]). Patients were randomized to glipizide 30 mg, metformin 500 mg, or glipizide/ metformin 5/500 mg tablets for 18 weeks. Maximum total daily doses were glipizide 30 mg, metformin 2000 mg, and glipizide/metformin 20/2000 mg. Glipizide/metformin combination exerted a superior effect in terms of HbA1c reduction ($p < 0.001$), as well as improvement ($p < 0.05$) of fasting glucose levels and 3-hour postprandial glucose levels than did either drug in single therapy. Four times more patients attained HbA1c < 7.0% with glipizide/metformin (36.3%) than either glipizide (8.9%) or metformin (9.9%) alone.

In a multicenter, double-blind, placebo-controlled study, 122 patients T2Ds inadequately controlled on a stable metformin dose of at least 1000 mg were randomized to add-on 2.5 mg glipizide gastrointestinal therapeutic system (GITS) or add-on placebo ([redacted]). Glipizide significantly improved glucose control. In patients receiving metformin plus glipizide, HbA1c was reduced from 7.45% ± 0.1% to 6.8% ± 0.1%, compared with a change from 7.64% ± 0.1% to 7.46% ± 0.1%, in the placebo group ($p < 0.0002$). In the metformin plus glipizide group, fasting glucose was reduced from 154 ± 4 mg/dL to 132 ± 4 mg/dL, compared with a change from 156 ± 4 mg/dL to 153 ± 5 mg/dL in the placebo group ($p < 0.0002$).

In a multicentre, double-blind, randomized, controlled trial, 99 T2D patients on a stable metformin dose of 1500 mg/day were compared with add-on glimepiride (2 mg/day) to add-

on rosiglitazone (4 mg/day) [redacted]). Both treatments significantly ($p < 0.05$ vs. baseline) reduced BMI, HbA1c, fasting and post-prandial glucose. In patients receiving metformin plus glimepiride, BMI was reduced from 26.5 ± 1.3 kg/m^2 to 25.2 ± 1.4 kg/m^2, HbA1c was reduced from 7.7% ± 0.5% to 7.0% ± 0.7%, fasting glucose was reduced from 164 ± 20 mg/dL to 152 ± 20 mg/dL and postprandial glucose was reduced from 185 ± 18 mg/dL to 171 ± 21 mg/dL.

Combination with meglitindes

In 467 patients on high-dose metformin, add-on nateglinide led to significant reductions of HbA1c (-0.36%, $p = 0.003$, with nateglinide 60 mg; -0.59%, $p < 0.001$, with nateglinide 120 mg), linked with a modest decrease of fasting glucose levels ([redacted] .

In a double-blind randomized trial of 262 patients suboptimally controlled on maximal metformin doses, nateglinide plus metformin and gliclazide plus metformin combinations proved equally efficacious in terms of final HbA1c (-0.14% for nateglinide vs. -0.27% for gliclazide; $p = 0.396$) and proportion of patients (40% vs. 47.4%) achieving an endpoint HbA1c < 7%.53. Fasting plasma glucose changed from baseline to 52 weeks by -3.6 mg/dL with nateglinide and -12.6 mg/dLwith gliclazide ($p = 0.096$)[redacted] .

In a 26-week, multicentre, open-label parallel trial subjects poorly controlled with mono- or dual-oral antidiabetic therapy were randomized 1:1: 1 to receive repaglinide/metformin fixed-dose combination (FDC) either BID or TID or a rosiglitazone/metformin FDC, BID. A total of 561 subjects were randomized; 383 completed the study [redacted]). Repaglinide/metformin FDC, BID was non-inferior to repaglinide/metformin FDC, TID with respect to HbA1c. Additionally, changes in mean fasting plasma glucose values from baseline to end of study were not significantly different between the BID and the TID dose groups. There were no major hypoglycaemic episodes reported in either group during the trial, and overall adverse event profiles were similar.

In the 16-week multicenter, placebo-controlled, randomized, double-blind, parallel-group trial, the efficacy and safety of repaglinide were investigated as an add-on therapy for Japanese patients with T2D receiving metformin monotherapy (at a dose of 1,500 mg/day, mainly) in addition to diet and exercise [redacted] . After 16 weeks, mean reductions in HbA1c were significantly greater for the repaglinide group than for the placebo group (-0.98 ± 0.72% vs 0.13 ± 0.63%, $p < 0.001$). In the long-term study, the mean change in HbA1c was -0.76 ± 0.83%. Hypoglycemia was reported in 11.7, 0 and 13.3% of patients in the repaglinide group, placebo group and long-term study, respectively.

A prospective, randomized, multicenter trial was carried out to assess the efficacy and safety of combined treatment with mitiglinide and metformin for T2D patients who showed inadequate glycemic control with metformin monotherapy [redacted]). Subjects with

HbA1c >7.0% after an 8-week metformin run-in phase were randomized to a 16-week trial phase with metformin + mitiglinide or metformin + placebo. Compared with the metformin + placebo group, the metformin + mitiglinide group showed a greater reduction in HbA1c (-0.7 ± 0.6%vs-0.4 ± 0.7%, p = 0.002), fasting plasma glucose (-0.77 ± 1.76 mM vs -0.05 ± 1.60 mM, P = 0.015) and 2-h postprandial glucose (-3.76 ± 3.57 mM vs -0.84 ± 3.07 mM, P < 0.0001). The proportion of the patients who achieved the target HbA1c value of <7% at the end of the study was also higher in the metformin + mitiglinide group than the metformin + placebo group (49.3%vs 28.8%, p = 0.016). There were no differences in the adverse event rates between groups.

Combination with alpha-glucosidase inhibitors

In a 12-month, multicenter, randomized, double-blind, placebo-controlled study, 354 patients were assigned to placebo or acarbose (initial dose 50 mg, titration to 100 mg, and finally to a maximum of 200 mg) in addition to their usual diet/metformin/sulfonylurea/insulin regimen [redacted]. Compared with placebo, acarbose significantly lowered postprandial glucose from 318.6 mg/dL to 237.6 mg/dL for the diet alone group, from 347.4 mg/dL to 284.4 mg/dL for the metformin group, from 372.6 mg/dL to 298.8 mg/dL for the sulfonylurea group, and from 331.2 mg/dL to 282.6 mg/dL for the insulin group (p < 0.01 vs. placebo). Initially, mean HbA1c amounted to 6.7% ± 0.2% for the diet alone group, 7.8% ± 0.2% for the metformin group, 8.0% ± 0.2% for the sulfonylurea group, and 7.7% ± 0.2% for the insulin group. At the end of the trial period, HbA1c was lower in patients receiving acarbose than in patients receiving placebo; the difference was -0.9% for the diet alone group (p = 0.005), -0.8% for the metformin group (p = 0.011), -0.9% for the sulfonylurea group (p < 0.002), and -0.4% for the insulin group (p = 0.077).

The efficacy of metformin plus acarbose combination has been confirmed in a multicenter, randomized, double-blind, placebo-controlled trial enrolling 89 overweight patients inadequately controlled by metformin [redacted]). They were randomized to acarbose (titrated up to 100 mg, TID) or placebo. Metformin plus acarbose yielded a significant reduction of both mean HbA1c by -1.02% (p = 0.0001) and mean fasting glucose by -20.38 mg/dL (p = 0.0395).

In a multicenter, double-blind, placebo-controlled study, 324 patients were allocated to either placebo, miglitol alone (titrated to 100 mg, TID), metformin alone (500 mg, TID, or miglitol plus metformin for 36 week [redacted]. Metformin plus miglitol demonstrated a reduction in HbA1c of -1.78% (p = 0.002). Fasting plasma glucose (-44.8 vs. -20.4 mg/dL; p = 0.0025) and postprandial glucose (-59.0 vs. -18.0 mg/dL; p = 0.0001) were also significantly improved.

In a multicentre, double-blind, randomized, placebo-controlled and parallel group study, miglitol (titrated to 100, TID) added to metformin (1500–2250 mg/day) was compared to

placebo added to metformin in 152 patients [redacted]. Miglitol plus metformin led to a significant reduction of HbA1c (-0.21% with miglitol vs. +0.22% with placebo, p = 0.011) and a significant reduction of post-meal glucose (final values: 248.4 mg/dL for miglitol vs. 284.4 mg/dL for placebo, p = 0.0007).

Combination with glitazones

In a randomized, double-blind, placebo-controlled 26-week trial recruited 348 patients with a HbA1c of 8.8%, were allocated to 2.5 g metformin plus placebo, 2.5 g metformin plus 4 mg rosiglitazone, or 2.5 g metformin plus 8 mg rosiglitazone [redacted]). Compared with the metformin-placebo group, HbA1c decreased by -1.0% in the 4 mg metformin-rosiglitazone group and by -1.2% in the 8 mg metformin-rosiglitazone group ($p < 0.001$). Likewise, fasting plasma glucose decreased by -39.8 mg/dL and -52.9 mg/dL compared placebo group ($p < 0.001$).

In a double-blind, placebo-controlled study conducted in Mexico, 116 patients were randomized to metformin 2.5 g/day plus placebo (n=39), metformin 2.5 g/day plus rosiglitazone 2 mg bd (n = 37), or metformin 2.5 g/day plus rosiglitazone 4 mg bd (n = 40) for 26 weeks ([redacted]). Mean HbA1c levels decreased significantly from baseline to Week 26 in the rosiglitazone 2 mg, BID (-0.7%; p = 0.0052) and 4 mg, BID (-1.2%; p=0.0008) groups, but increased in the placebo group (+0.3%; p = 0.2651). Mean fasting plasma glucose and fructosamine levels also improved significantly with metformin plus rosiglitazone therapy in a dose-ordered manner compared with placebo ($p < 0.0019$ and p=0.0006, respectively).

In a phase IV, randomized, double-blind, multi-centre study in 688, drug naÏve, male and female T2D patients glycaemic control achieved with Avandamet® (rosiglitazone/metformin) (AVM) compared with metformin monotherapy was evaluated [redacted]. As initial therapy, AVM was superior to metformin in achieving statistically significant reductions in HbA1c ($p < 0.0001$) and FPG ($p < 0.001$), with more patients reaching recommended HbA1c and FPG targets for intensive glycaemic control. The glycaemic effects attained with AVM compared to metformin monotherapy were durable over 18 months of treatment. In conclusion, superior glycaemic control was achieved with AVM compared with metformin monotherapy that was durable over 18 months of treatment.

In a double-blind study, 318 patients were randomized to metformin-glibenclamide (1000/5 mg per day) or metformin 500 mg plus rosiglitazone 4 mg (1000–2000 mg/4 mg per day) for 24 weeks ([redacted]). Metformin-glibenclamide-treated patients had significantly greater reductions of HbA1c (-1.5%) and fasting glucose (-46 mg/dL) than metformin-rosiglitazone-treated patients (-1.1%, $p < 0.001$; -36 mg/dL, p = 0.03). At the end of the study, HbA1c was lower than 7% in more patients receiving metformin-glibenclamide than in those on metformin plus rosiglitazone (60 vs. 47%, $p < 0.05$).

In a 16-week, double-blind trial 328 patients were randomized to once-daily pioglitazone 30 mg + 1000 mg metformin or placebo + 1000 mg metformin[redacted]). Pioglitazone plus metformin therapy led to significant decreases in HbA1c (-0.83%) and fasting plasma glucose (-37.7 mg/dL) compared with placebo + metformin ($p < 0.05$), which were accompanied by significant ($p < 0.05$) improvements in triglycerides (-18.2%) and HDL-cholesterol (+8.7%).

Two 2-year, randomised, multicentre trials were performed in patients with inadequately controlled T2D (HbA1c 7.5-11% inclusive), who were receiving either metformin or a sulphonylurea at ≥ 50% of the maximum recommended dose or at the maximum tolerated dose [redacted]). In the first study, patients on metformin received add-on therapy with pioglitazone (15-45 mg/day, n = 317) or gliclazide (80-320 mg/day, n = 313). In the second study, patients on sulphonylurea therapy were randomised to receive add-on therapy with either pioglitazone (15-45 mg/day, n = 319) or metformin (850-2,550 mg/day, n = 320). HbA1c, fasting plasma glucose, insulin and lipids were investigated. At week 104, the mean reduction from baseline in HbA1c was 0.89% for pioglitazone and 0.77% for gliclazide addition to metformin ($p = 0.200$). There was a statistically significant between-group difference for the change in mean fasting plasma glucose at week 104 (-1.8 mM for pioglitazone vs -1.1 mM for gliclazide, $p < 0.001$). There were no significant differences in changes from baseline in glycaemic parameters for pioglitazone compared with metformin addition to sulphonylurea therapy.

Combination with DPP-4 inhibitors

The efficacy and safety of sitagliptin, added to metformin therapy was assessed in a randomized, single-blind, placebo controlled trial recruiting 701 patients poorly controlled on metformin ≥ 1500 mg per day[redacted] . The trial confirmed the superiority of add-on sitagliptin (100 mg per day) over placebo in HbA1c and fasting glucose. HbA1c was reduced from 7.96% ± 0.81% to 7.26% ± 0.97% with sitagliptin and from 8.03% ± 0.82% to 7.95% ± 1.10% with placebo ($p < 0.001$). Fasting glucose was reduced from 169.2 ± 41.4 mg/dL to 151.2 ± 39.6 mg/dL with sitagliptin and increased from 172.8 ± 41.4 mg/dL to 178.2 ± 50.4 with placebo ($p < 0.001$). Significantly ($p < 0.05$) more patients arrived at an HbA1c < 7% with sitagliptin (47%) than with placebo (18.3%), and this was accomplished without any increase in hypoglycemias and other side-effects.

In a 12-week core study, placebo (n = 51) or vildagliptin (n = 56; 50 mg) was added to metformin treatment (1.5–3.0 mg/day)[redacted]). A 40-week extension followed in 71 patients. Meal tests were performed at 0, 12, 24, and 52 weeks; glucose, insulin, and C-peptide were evaluated. In subjects completing 52 weeks with participation in all meal tests (n = 57), HbA1c decreased in the vildagliptin/metformin group (VM group, n = 31) but increased in the placebo/metformin group (PM group, n = 26; between-group difference -1.0 ± 0.2%; p

< 0.001; baseline of all subjects combined 7.7 ± 0.1%). Also, fasting glucose decreased in the VM group but increased in the PM group (difference -0.9 ± 0.3 mM, p = 0.016; baseline 9.8 ± 0.3 mM). Insulin secretion (postmeal suprabasal area under the 0- to 30-min C-peptide curve divided by the 30-min increase in glucose) was increased in the VM group but was reduced in the PM group (difference +0.011 ± 0.03 pmol/l 30 min/mM, p = 0.018; baseline 0.036 ± 0.02).

In a randomized, double-blind, placebo-controlled study, the effect saxagliptin (2.5, 5, or 10 mg, QD) or placebo plus a stable dose of metformin (1,500-2,500 mg) was investigated in 743 patients (A1C ≥ 7.0 and ≤ 10.0%) [redacted]). HbA1c was reduced (-0.59%, -0.69%, and -0.58% vs. +0.13% with placebo; p < 0.0001) in a dose-dependent fashion. Fasting glucose showed the same decrease (-14.31 mg/dL, -22.03 mg/dL, and -20.50 mg/dL vs. +1.24 mg/dL with placebo; p < 0.0001).

Combination with GLP-1 analogues

The ability of the incretin mimetic exenatide to improve glycaemic control and reduce body weight was assessed over 82 weeks in patients with T2D failing to achieve glycaemic control with maximally effective doses of metformin [redacted]). At the end of the placebo-controlled trial, exenatide resulted in an HbA1c reduction from baseline of −1.0 ± 0.1% (mean ± SE) (exenatide treatment arms), with durable HbA1c reductions after 82 weeks of −1.3 ± 0.1%. The percent of patients who achieved HbA1c ≤ 7% at weeks 30 and 82 was 46 and 59% respectively. After 30 weeks, exenatide caused a reduction in weight from baseline of −3.0 ± 0.6 kg, with a progressive reduction in weight of −5.3 ± 0.8 kg after 82 weeks.

In a triple-blind, placebo-controlled, 30-week study of 336 patients uncontrolled by maximal dose of metformin, it was found that adding 5 or 10 µg exenatide reduced HbA1c by 0.78% ± 0.10% (10 µg) or 0.40% ± 0.11% (5 µg) (p < 0.002 vs. placebo) [redacted] . Overall, 46% (10 µg), 32% (5 µg), and 13% (placebo) achieved HbA1c ≤ 7% (p < 0.01 vs. placebo).

Drug-naive, recently diagnosed subjects with T2D were randomized in an open-fashion design in a single-centre study to metformin/pioglitazone/exenatide (triple therapy; n = 106) or an escalating dose of metformin followed by sequential addition of sulfonylurea and glargine insulin (conventional therapy; n = 115) to maintain HbA1c levels at <6.5% for 2 years [redacted]). Participants receiving triple therapy experienced a significantly greater reduction in HbA1c level than those receiving conventional therapy (5.95 vs. 6.50%; p < 0.001). Despite lower HbA1c values, participants receiving triple therapy experienced a 7.5-fold lower rate of hypoglycaemia compared with participants receiving conventional therapy. Participants receiving triple therapy experienced a mean weight loss of 1.2 kg versus a mean weight gain of 4.1 kg (p < 0.01) in those receiving conventional therapy.

A 26-week, multi-country, randomized, double-blind, placebo-controlled study compared exenatide twice-daily vs. placebo in 165 subjects suboptimally controlled with thiazolidinediones (TZDs) with or without metformin HbA1c 8.2% ± 0.9 (mean ± SD), fasting serum glucose 9.1 ± 2.6 mM body weight 93.9 ± 17.8 kg, diabetes duration 6.4 ± 4.3 years [redacted]). After a 2-week, single-blind, lead-in period, subjects were randomly assigned (2 : 1) to add exenatide or placebo to current regimens. Exenatide reduced HbA1c significantly more than placebo [-0.84% ± 0.20) vs. -0.10% ± 0.23), treatment difference -0.74% ± 0.16), p < 0.001)]. Mean reductions in body weight were similar in both treatments at endpoint [exenatide, -1.4 ± 0.6) kg vs. placebo, -0.8 ± 0.7) kg, p = 0.176)]. Nearly 71% of subjects had both a reduction in HbA1c and body weight with exenatide compared with 54% with placebo.

Combination with insulin

In a randomised, double blind, double dummy, parallel trial the effect of insulin treatment in combination with metformin or an insulin secretagogue, repaglinide, was studied in non-obese patients with T2D [redacted]). Of the 459 patients who were eligible, 102 were randomised, and 97 completed the trial. Patients had had T2D for approximately 10 years. At the end of treatment, HbA_{1c} concentration was reduced by a similar amount in the two treatment groups (insulin plus metformin: mean (standard deviation) HbA_{1c} 8.15% (1.32) *v* 6.72% (0.66); insulin plus repaglinide: 8.07% (1.49) *v* 6.90% (0.68); p = 0.177). Total daily insulin dose and risk of hypoglycaemia were also similar in the two treatment groups. Weight gain was less with metformin plus biphasic insulin aspart 70/30 than with repaglinide plus biphasic insulin aspart 70/30 (difference in mean body weight between treatments −2.51 kg, 95% confidence interval −4.07 to −0.95).

Metformin can effectively be combined with insulin. The aim of using metformin in insulin-treated patients is to offset insulin resistance, reduce insulin requirements and minimize weight gain [redacted]). In a randomized, controlled trial, partially blinded study, 96 patients (mean age, 58 ± 1 years; mean BMI, 29 ± 1 kg/m^2) whose T2D was poorly controlled with sulfonylurea therapy (mean HbA_{1c}, 9.9% ± 0.2%; mean fasting plasma glucose level, 11.9 ± 0.3 mM [214 ± 5 mg/dL]) were randomly assigned to 1 year of treatment with bedtime intermediate-acting insulin plus glyburide (10.5 mg) and placebo, metformin (2 g) and placebo, glyburide and metformin, or a second injection of intermediate-acting insulin in the morning.

The greatest reduction of HbA1c was accomplished in the bedtime insulin and metformin group (from 9.7% ± 0.4% to 7.2% ± 0.2%; p < 0.001, compared with baseline and p < 0.05 compared with other groups). This therapeutic combination also succeeded in the lowest hypoglycemia rates (p < 0.05) compared with other groups) and in absence of weight gain (p < 0.001 compared with all other groups).

In a 24-week, open-label, parallel-group trial, 315 patients who were on metformin and/or a sulfonylurea with a stable dose of 0 to 2 daily insulin injections were randomized to receive insulin lispromix 50 (50% insulin lispro-protamine suspension and 50% lispro, TID) plus metformin or bedtime insulin glargine plus metformin for 24 weeks [redacted]). Both combinations managed to improve metabolic control. Metformin was better with lispromix50 than glargine in terms of HbA1c, post-prandial hyperglycemia and glycemic variability, whereas metformin plus glargine was superior in lowering fasting plasma glucose.

2.5.5 Overview of Safety

2.5.5.1 Adverse Events Characteristic of Pharmacological Class

Metformin belongs to the biguanide class together with two other bioactive drugs, phenformin and buformin. All three possess antihyperglycemic properties, however, phenformin and buformin have been withdrawn from the market in most countries due to toxic effects. Biguanides affect lactate metabolism causing lactic acidosis [redacted]). Lactic acidosis in the advanced stages can lead to severe tissue hypoperfusion and hypoxia causing multiorgan failure. Adverse drug reactions (ADRs) to phenformin and metformin reported to the Swedish Adverse Drug Reaction Committee during 1965-77 were analysed in relation to sales and prescription data [redacted]). The biguanides accounted for 0-6% of all reported adverse drug reactions but for 6% of the fatal cases (all phenformin). Sixty-four ADRs to phenformin and eight to metformin were classified as causal relation "probable" or "not excluded." Fifty-one of these reactions (71%) were lactic acidosis, all but one being reactions to phenformin. Adverse reactions to phenformin included hypoglycaemia (5%), liver reactions (3%), pulmonary hypertension (2%), thrombocytopaenia (2%), and other AEs (5%). By 1976, the association between lactic acidosis and administration of phenformin was established when a report described the treatment of 38 patients who presented with lactic acidosis, of which 15 were undergoing treatment with phenformin. Another contraindication to the use of phenformin was cardiovascular disease. In the 1976 report on severe adverse events due to the biguanide drug, 11 of the 15 lactic acidosis patients taking phenformin were hypertensive. Of the 11 hypertensive patients, five were hypertensive prior to initiating phenformin treatment, whereas the others experienced an elevation of blood pressure upon receiving treatment. In 1978, based on the number of contraindications to phenformin, the impracticality of monitoring the patients for changes in serum parameters, and the severity of developing lactic acidosis—which can often be fatal—the U.S. Food and Drug Administration (FDA) ordered the withdrawal of this antidiabetic drug from the U.S. market. The use of buformin has also been associated with often fatal lactic acidosis ([redacted]). Buformin was used to treat diabetes for nearly 20 years but together with phenformin was withdrawn from the market in most countries by 1978 because of an association with fatal lactic acidosis [redacted]). Other side effect includes stomach upset such as, gas, diarrhea, and/or constipation.

2.5.5.2 Adverse Events of Metformin

Metformin is considered one of the safest oral hypoglycemic agents. It reduces insulin resistance, but does not promote insulin secretion from β-cells, and thus it is not associated with increased risk of hypoglycemia.

GI disturbances

The most common adverse reactions resulting in discontinuation of metformin treatment are GI disturbances described as diarrhoea, nausea, vomiting, abdominal pain, and dyspepsia ([redacted]). They are usually mild and wane over the first days of treatment; nonetheless, they may be dose-limiting and reduce patient compliance. [redacted]). GI side effects may be minimized by using the sustained-release metformin formulation, which has been shown to be much better tolerated[redacted]). Taking the drug with meals t also reduces GI side effects. In addition, initially the drug should be taken low dose and titrated up the dose slowly ([redacted]). Insufficient nourishment, alcohol intake and co-administration with anti-diabetic drugs such as insulin, sulfonylureas and meglitinides may bring about to hypoglycemia[redacted]).

Lactic acidosis

Lactic acidosis is a rare, but serious, metabolic complication that occurs due to metformin accumulation during treatment [redacted]). The onset of lactic acidosis is often subtle, and accompanied only by nonspecific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence and non-specific abdominal distress. There may be associated hypothermia, hypotension and resistance bradyarrhythmias with more marked acidosis. The reported incidence of lactic acidosis in clinical practice has proved to be very low (< 10 cases per 100,000 patient-years). When it occurs, however, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (> 5 mM), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels > 5 μg/mL are generally found.

Lactic acidosis occurs when there is renal insufficiency. Hence, metformin is contraindicated in patients who have substantial renal dysfunction. This condition still has a mortality up to 50% [redacted]). However, it is now extremely rare, its incidence ranging between 0.01 and 0.15 per 1000 patient-years [redacted]). More importantly, it virtually only occurs in patients with obvious contra-indications to metformin use [redacted]). Contraindications are related to conditions predisposing to tissue hypoxia (congestive heart failure, chronic obstructive pulmonary disease, severe infection or gangrene), to liver disease, as well as to intrinsic or functional reduction of renal function (chronic renal failure, congestive heart failure, advanced age) [redacted]). This is explicable on the basis that metformin is cleared by the kidneys and that elevated serum lactic acid concentration may result either from severe tissue hypoxia or from reduced hepatic clearance owing to liver disease [redacted]). Age itself is a much questioned contraindication, but most cases

of lactic acidosis have been described in elderly patients, and several authors suggest avoidance of metformin in patients aged at least 80 [redacted]). Even in patients with contra-indications, metformin-associated lactic acidosis is very rare and occurs due to a superimposed medical condition. Mortality is then closely related with the degree of hypoxia, rather than serum metformin levels, casting doubt on the causal role of metformin. Several studies have shown that a considerable proportion of patients receiving metformin have formal contraindications to its use and yet never develop lactic acidosis ([redacted]). As long as contraindications and warnings are respected, metformin may be safely administered with almost no lactic acidosis[redacted] .

Vitamin B12 levels

A decrease to subnormal levels of previously normal serum vitamin B12 levels, without clinical manifestations, is observed in approximately 7% of patients receiving metformin in controlled clinical trials of 28 weeks duration [redacted]). Such decrease, possibly due to interference with B12 absorption from B12-intrinsic factor complex is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. The reduction of vitamin B12 is induced by metformin in a dose dependent manner. The effects of metformin on vitamin B12 concentration were analyzed in a systematic review [redacted] . Six randomized controlled trials met the inclusion criteria. Serum vitamin B12 concentrations were significantly lower in patients treated with metformin than in those who received placebo or rosiglitazone (mean difference [MD], -53.93 pM/L; 95% confidence interval [CI], -81.44 to -26.42 pM/L, p = 0.0001). Subgroup analysis identified four trials in which patients received a lower dose of metformin (< 2000 mg/day) and two in which they received a higher dose (≥ 2000 mg/day), with MDs in vitamin B12 concentration after metformin treatment of -37.99 pM/L (95% CI, -57.44 to -18.54 pM/L, p = 0.0001) and -78.62 pM/L (95% CI, -106.37 to -50.86 pM/L, p < 0.00001), respectively. The prevalence of biochemical B12 deficiency was described in adults with T2D taking metformin compared with those not taking metformin and those without diabetes [redacted]). Data on U.S. adults ≥ 50 years of age with (n = 1,621) or without T2D (n = 6,867) from the National Health and Nutrition Examination Survey (NHANES), 1999–2006 was analyzed. Biochemical B12 deficiency was present in 5.8% of those with diabetes using metformin compared with 2.4% of those not using metformin (p = 0.0026) and 3.3% of those without diabetes (p = 0.0002). Among those with diabetes, metformin use was associated with biochemical B12 deficiency (adjusted odds ratio 2.92; 95% CI 1.26–6.78). Vitamin-B12 malabsorption has been found in 21 (30%) of 71 diabetic patients taking long-term metformin therapy in addition to dietary management. Stopping metformin therapy resulted in reversion of B12 absorption to normal in most patients examined. Four patients with B12 malabsorption were found to have pathologically low serum B12 levels [redacted]).

Haemolytic anemia

Serious cases of metformin-induced hemolytic anemia, some with a fatal outcome, have been reported [redacted]). Two mechanisms were described for the metformin-induced immune hemolytic anemia; formation of an antibody against the erythrocyte-metformin complex and autoantibody formation [redacted] . Monitoring of hematologic parameters is recommended.

Metformin-induced encephalopathy

Serious cases of metformin-induced encephalopathy have been reported. Metformin-induced encephalopathy is a rare condition typically described in patients with end-stage renal failure (ESRF) patients [redacted] . Reported findings in metformin encephalopathy include Parkinsonism and vasogenic oedema with T2 hyperintensity in the basal ganglia. Symptoms and signs improve on withdrawal of metformin [redacted]). Some of these cases were reported without association with lactic acidosis, hypoglycemia, or renal impairment [redacted]).

Peri-operative considerations

Perioperative treatment of T2D with metformin is thought to increase the risk of life-threatening postoperative lactic acidosis. However, in a study, postoperative complications were identical whatever the treatment used, either metformin or other [redacted]).

Although, the incidence of lactic acidosis, whose main cause is renal failure, is 2–9/100,000 patients/year, its mortality rate ranges from 30– 50%. It is therefore important to look for risk factors before carrying out surgery [redacted]):

- renal failure (creatinine clearance < 60 mL/min);
- administration of iodinated contrast agents;
- situations that could alter renal function: dehydration, fasting or medical treatments [angiotensin-converting-enzyme (ACE) inhibitors and sartans, diuretics, non-steroidal anti-inflammatory drugs (NSAIDs)];
- severe heart failure (HF) (left ventricular ejection fraction < 30%);

The presence of these risk factors also means that metformin should not be restarted too quickly in the postoperative period. In practice, it is recommended to [redacted]:

- stop metformin the night before;
- not to restart before 48 h for major surgery and after assuring adequate renal function;
- not to stop in case of minor or ambulatory surgery except if there is severe renal failure.

Metformine in renal failure

Lactic acidosis appears either as part of a number of clinical syndromes (i.e., unrelated to metformin), induced by metformin (involving an analysis of the drug's pharmacokinetics and mechanisms of action), or associated with metformin (a more complex situation, as lactic acidosis in a metformin-treated patient is not necessarily accompanied by metformin accumulation, nor does metformin accumulation necessarily lead to lactic acidosis). Upon a critical analysis of guidelines and literature data on metformin therapy in patients with chronic kidney disease (CKD) the following conclusions has been drawn [redacted]): (i) metformin is rarely the sole cause of lactic acidosis; (ii) lactic acidosis in patients receiving metformin therapy is erroneously still considered a single medical entity, as several different scenarios can be defined, with contrasting prognoses. The prognosis for severe lactic acidosis seems even better in metformin-treated patients than in non-metformin users.

Contrast agents

Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. The Contrast Media Safety Committee (CMSC) of the European Society of Urogenital Radiology (ESUR) has updated its 2011 guidelines on the prevention of post-contrast acute kidney injury (PC-AKI)[redacted] . Key points are as follows:

- In CKD, hydration reduces the PC-AKI risk;
- Intravenous normal saline and intravenous sodium bicarbonate provide equally effective prophylaxis;
- No drugs have been consistently shown to reduce the risk of PC-AKI;
- Stop metformin from the time of contrast medium administration if estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m^2;
- Dialysis schedules need not change when intravascular contrast medium is given.

2.5.5.3 Effects in Population Sub-Groups

2.5.5.3.1 Pregnancy

Although, metformin is generally considered a non-teratogenic drug, safety of metformin hydrochloride in pregnant women has not been established. According to a systematic review, metformin appears to be effective and safe for the treatment of gestational diabetes mellitus (GDM), particularly for overweight or obese women[redacted]). However, patients with multiple risk factors for insulin resistance may not meet their treatment goals with metformin alone and may require supplementary insulin. Evidence suggests that there are potential advantages for the use of metformin over insulin in GDM with respect to maternal weight gain and neonatal outcomes. Furthermore, patients are more accepting of metformin than insulin. The use of metformin throughout pregnancy in women with polycystic ovary

syndrome reduces the rates of early pregnancy loss and preterm labor and protects against fetal growth restriction. There have been no demonstrable teratogenic effects, intra-uterine deaths or developmental delays with the use of metformin [redacted] .

2.5.5.3.2 Lactation

The effect of metformin during lactation as compared to formula feeding was studied to detect potential adverse effects on infants' growth, motor-social development, or intercurrent illness [redacted] . Growth, motor-social development, and illness requiring a paediatrician visit were assessed in 61 nursing infants (21 male, 40 female) and 50 formula-fed infants (19 male, 31 female) born to 92 mothers with PCOS taking a median of 2.55 g metformin per day throughout pregnancy and lactation. Within sex, at 3 and 6 months of age, weight, height, and motor-social development did not differ ($p > 0.06$) between breast- and formula-fed infants. No infants had retardation of growth, motor, or social development. Intercurrent illnesses did not differ. Metformin during lactation appears to be safe and effective in the first 6 months of infancy.

To determine whether metformin is excreted into breast milk and whether this exposure adversely affects the blood glucose of nursing infants, seven women were started on metformin 500 mg, BID on the first day after caesarean delivery [redacted]). Breastfeeding was started at the same time. The authors conclude that metformin is excreted into breast milk, but the amounts seem to be clinically insignificant. No adverse effects on the blood glucose of the 3 nursing infants were measured.

2.5.5.3.3 Paediatric

The effect of metformin vs. placebo was compared on HbA1c, total daily dose (TDD) of insulin, and other parameters in overweight/obese youth with T1D [redacted]). Minor hypoglycemia was reported in 3 subjects (20.0%) in the metformin arm, and 2 subjects (15.4%) in the placebo arm ($p = 1.00$). Nocturnal hypoglycemia was reported in 2 subjects (13.3%) in the metformin group, and 2 subjects (15.4%) in the placebo group ($p = 1.00$). One instance of major hypoglycemic event occurred in a subject in the metformin arm following a period of reduced caloric intake. The patient recovered fully without sequalae.

In a prospective, randomized, double-blind, placebo-controlled trial, the effect of metformin was assessed on body mass index standard deviation score (BMI-SDS), metabolic risk factors, and adipokines in obese children and young people with hyperinsulinemia and/or impaired fasting glucose or impaired glucose tolerance (metformin: 74, placebo: 77) [redacted]). The study was conducted at six pediatric endocrine centers in the UK and was comprised of 67.5% females, 65.6% postpubertal individuals, and 23.8% British Asian or Afro-Caribbean participants. The age range was 8–18 yr, the mean age was 13.7y (SD 2.3), and the mean BMI-SDS was +3.4 (SD 0.5). There were no suspected unexpected serious

adverse reactions, serious adverse events, or serious adverse reactions. There were 28 adverse events (20 in the metformin group and eight in the placebo group). The most common adverse events (diarrhea, nausea, and abdominal pain) were related to the gastrointestinal tract (known side effects of metformin). Good adherence to therapy was reported and observed in most participants. There were no significant changes in lactate concentrations in either group during the course of the trial, and there were no episodes of lactate acidosis.

2.5.5.3.4 Geriatric

Due to the potential for decreased renal function in elderly subjects, the metformin dosage should be adjusted based on renal function. Metformin use by elderly patients with mild to moderate chronic kidney disease should feature appropriate dose reductions and careful follow-up of kidney function [redacted]).

Clinical data were retrospectively studied for the safety (n = 1132) and efficacy (n = 568) of newly prescribed metformin treatment [redacted]). Among 1132 patients whose lactic acid level was measured before or after metformin therapy, 144 patients had a lactic acid level above the upper limit of reference values (2.28 mmol/L) at least once before or after administration of the drug. Among 144 patients, 57 were elderly and 87 were non-elderly. The frequency of patients with elevated lactic acid levels was slightly, but significantly, higher in elderly than in non-elderly patients (31.7% vs 22.4%, p = 0.02). Serum creatinine level was slightly, but significantly, higher in elderly patients than in non-elderly patients (71.6 ± 21.2 vs 65.4 ± 17.7 mM, P < 0.05). No significant difference, however, was observed in elevated lactic acid level between elderly and non-elderly patients (2.95 1 0.89 vs 2.90 ± 1.00 mmol/L). No case of lactic acidosis was observed in the study.

Cases has been reported of an elderly woman, a younger woman and a man who developed serious metformin-induced lactic acidosis in the absence of chronic renal impairment [redacted]). Laboratory results showed acute renal failure in all patients. The pH was 6.77, 6.98 and 6.7, respectively, and lactate levels were 18.2, 18.4 and 11.7 mM, respectively. Metformin plasma levels were 58, 57 and 39 mg/L. All patients received continuous veno-venous haemofiltration (CVVH), using bicarbonate as a buffer solution shortly after arrival on in the intensive care unit (ICU). In the subsequent hours, a steep decline in the plasma levels was observed, with a concomitant increase in pH.

2.5.5.3.5 Gender

Metformin is involved in lactate generation, which elevates the levels of blood lactate. Plasma lactate levels in female patients are significantly higher than those in male patients, with the highest level of lactate in premenopausal women [redacted]). Indeed, the SLC22A2 gene that encodes OCT2 polymorphisms may affect blood lactate levels in a sex-

gender-specific manner. Thus, women with diabetes who receive metformin should use caution to prevent the occurrence of lactic acidosis.

2.5.5.3.6 Racial

Electronic health records were used to identify adults who had a diagnosis of diabetes, two or more fills of metformin, and two or more HbA1c measurements [redacted]). In all, 19 672 patients with diabetes taking metformin were identified; 7429 were African American and 8783 were European American. Baseline HbA1c values in these two groups were 7.81% (61.8 mmol/mol) and 7.38% (57.1 mmol/mol), respectively. Compared with no use, metformin was associated with a 0.62% (6.8 mmol/mol) reduction in HbA1c; however, there was a significant difference by race-ethnicity ($p < 0.001$). Among African American individuals, metformin use was associated with a 0.90% (9.8 mmol/mol) reduction in HbA1c levels, whereas among European Americans, metformin was associated with a 0.42% (4.6 mmol/mol) reduction. Irrespective of baseline HbA1c, metformin use was associated with lower HbA1c levels in African American individuals.

2.5.5.4 Overview of Adverse Events of Metformin

Adverse events (a combination of clinical trials and post-marketing data) reported for Glucophage are summarized in Table 7 [redacted]):

Table 7 Adverse Event of Glucophage		
	Adverse Drug Reactions	Frequency
Gastrointestinal Disorders	GI symptoms (diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorexia).	Very common (>1/10)
Special Senses	Taste disturbance.	Common (≥1/100)
Hematologic Disorders	Decrease of vitamin B12 absorption.	Rare (≥1/10,000 and <1/1,000).
Metabolism and Nutrition Disorders	Lactic Acidosis	Very rare (<1/10,000)
Skin and Subcutaneous Tissue Disorders	Incidence of rash/dermatitis. Skin reactions such as erythema, pruritus, and urticarial.	Very rare (<1/10,000)
Hepatobiliary Disorders	Liver function tests abnormalities or hepatitis.	Very rare (<1/10,000)

2.5.5.5 Overdose

2.5.5.5.1 Experience and Symptoms

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases.

The case of a 40-year-old woman has been reported who claimed to have ingested between 75 and 100 g of metformin and subsequently developed severe lactic acidosis [redacted]). She eventually developed a peak serum lactate level of 40.0 mM and a serum pH nadir of 6.59 and became obtunded, hypotensive, and hypothermic. After aggressive supportive therapy with mechanical ventilation, vasopressor agents, sodium bicarbonate, and haemodialysis, her metabolic derangements steadily improved and she made a complete recovery without any residual sequelae. Her admission serum metformin concentration was later determined to be 160 µg/mL (therapeutic range is 1-2 µg/mL).

Three cases of metformin overdose with profound lactic acidosis have been reported [redacted]). Case 1: a 40-year-old woman presented after a polysubstance overdose. Within 8 h, vomiting and lethargy developed; a profound acidosis, pH 6.95, pCO_2 26, pO_2 195, and elevated serum lactate 21 mmol/L (ref 0.5-1.6 mmol/L) were noted. She was intubated; bicarbonate therapy and hemodialysis were initiated; however, she became hypotensive and died. A metformin level was 150 µg/mL (therapeutic 1-2 µg/mL). Case 2: a 69-year-old woman with NIDDM and end-stage renal disease (ESRD) presented to the Emergency Department (ED), having missed dialysis. She was sluggish and complained of abdominal pain; an acidosis, pH 7.37, pCO_2 20, pO_2 171; anion gap 38, and elevated serum lactate 18.9 mmol/L were noted. Hemodialysis was initiated when it was revealed that she took metformin daily. She improved rapidly and a metformin level was 27.4 µg/mL. Case 3: a 57-year-old woman with a history of NIDDM and ESRD presented with dyspnea. Laboratory studies showed pH 7.03, pCO_2 21, pO_2 99; anion gap 36, and lactate 16 mmol/L. Bicarbonate therapy and hemodialysis were initiated after discovering that she had recently been prescribed metformin. She had a fatal cardiac arrest after dialysis was completed.

A healthy 14-yr-old female was found following a seizure of unknown duration, thought to be secondary to hypoglycemia as a consequence of a self-ingestion of metformin, atenolol, and diclofenac [redacted]). She responded well to advanced resuscitation but progressively developed severe lactic acidosis, bradycardia, and hypotension in addition to persistent hypoglycemia. The peak lactate level was 37.5 mmol/L with an albumin corrected anion gap of 65 mmol/L. She was treated with high-volume venovenous hemofiltration and aggressive alkalinization therapy. The latter facilitated control of severe acidosis, whereas the

hemofiltration removed the ingested drugs in addition to endogenously produced lactate precipitated by metformin. In this case, early and aggressive treatment of the acidosis and cardiovascular compromise with inotropes, venovenous hemofiltration, and large doses of sodium bicarbonate in metformin overdose resulted in a successful outcome even in the presence of severe acidosis and very high lactate levels.

2.5.5.5.2 Treatment

Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions; therefore, hemodialysis may be useful for the removal of accumulated drug from patients in whom metformin overdosage is suspected ([redacted] .

2.5.5.6 World Wide Marketing Experience

Post-market adverse drug reactions are presented below in Table 8 [redacted]).

Table 8 Post-Market Adverse Drug Reactions of Metformin

Adverse Reaction System Organ Class	Metformin
Blood and Lymphatic System Disorders	Hemolytic anemia, some with a fatal outcome.
Gastrointestinal Disorders	Abdominal discomfort, abdominal distension, abdominal pain, abdominal pain upper, constipation, diarrhea, dry mouth, dyspepsia, flatulence, gastric disorder, gastric ulcer, gastrointestinal disorder, nausea, vomiting.
Hepatobiliary Disorders	Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation, autoimmune hepatitis, drug-induced liver injury, hepatitis, and pancreatitis.
Investigations	Blood lactic acid increased. Reduction of thyrotropin level in patients with treated or untreated hypothyroidism.
Nervous System Disorders	Encephalopathy.
Metabolism and Nutrition Disorders	Lactic acidosis, decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin, weight decreased, decreased appetite. Peripheral neuropathy in patients with vitamin B12 deficiency.
Endocrine and Metabolism	Hypomagnesemia in the context of diarrhea
Skin and Subcutaneous Tissue Disorders	Photosensitivity, erythema, pruritus, rash, skin lesion, and urticaria.

2.5.6 Benefits and Risks Conclusions

This clinical overview of the medicinal product candidate Metformin 500mg & 1000mg Powder for Oral Solution of Morningside Healthcare Ltd, UK has been compiled for evaluating literary data about the clinical efficacy and safety properties of metformin in preparation of an Application for Marketing Authorisation in Europe according to EU Directive 2001/83/EC Article 10(1).

2.5.6.1 Global Assessment of Efficacy

The biguanide metformin is an oral anti-hyperglycaemic agent used in the management of NIDDM. The indication of metformin therapy is treatment of T2D, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control. The ability of metformin to reduce circulating glucose levels in patients with T2D can be attributed to multiple mechanisms, such as increased glucose uptake in liver and muscle, reduced gluconeogenesis, improved GLP-1 and reduced glucagon functions. Nevertheless, the molecular principles of metformin action remain debated. Metformin also appears to have potentially beneficial effects on serum lipid levels and fibrinolytic activity. Unlike the sulphonylureas and insulin, metformin treatment is not associated with increased bodyweight. Addition of metformin to existing antidiabetic therapy confers enhanced anti-hyperglycaemic efficacy. This may be of particular use in improving glycaemic control in patients with NIDDM not adequately controlled with sulphonylurea monotherapy, and may serve to reduce or eliminate the need for daily insulin injections in patients with NIDDM who require this therapy. Metformin typically reduces basal and postprandial hyperglycaemia by approximately 25% in more than 90% of patients when given alone or with other therapies during a program of managed care. Unlike sulfonylureas, metformin does not produce hypoglycaemia in either T2D patients or normal subjects and does not cause hyperinsulinaemia. With metformin therapy, insulin secretion remains unchanged while fasting plasma insulin levels and day-long plasma insulin response may actually decrease.

Following an oral dose of metformin, T_{max} is reached in 2.5 hours. Pharmacokinetic studies of the conventional IR formulation demonstrate that metformin is absorbed into the upper GI tract, with only minimal absorption occurring in the colon. Absolute bioavailability is approximately 50-60% in healthy subjects. The pharmacokinetics of metformin absorption are non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 μg/mL. In controlled clinical trials, maximum metformin plasma levels did not exceed 4 μg/mL, even at maximum doses. Food decreases the extent and slightly delays the absorption of metformin. Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of

distribution ranged between 63 and 276 L. Metformin is excreted unchanged in the urine. No metabolites have been identified in humans. Renal clearance of metformin is >400 mL/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma. Metformin crosses the placenta and is distributed into breast milk in small amounts.

The effectiveness of metformin in T2D has been demonstrated in several clinical trials. The very first pivotal trial underlying the recommendation of metformin as the first-line, glucose-lowering drug of choice was the UKPD Study demonstrating that intensive blood glucose control with metformin reduces the risk of diabetic complications and death in overweight T2D patients. Metformin is also used with the thiazolidinediones, meglitindes, alpha-glucosidase inhibitors, glitazones, DPP-4 inhibitors, GLP-1 analogues or with insulin in patients requiring combined or more intensive therapy. Metformin has also been investigated for the prevention of T2D in patients at high risk. Although metformin treatment for an average 2.8 years reduced the incidence of T2D by 31% in a study of patients with impaired glucose tolerance, intensive lifestyle modification was actually more effective (58% reduction). Lifestyle modification was also more effective than metformin in reducing cardiovascular risk factors and the development of the metabolic syndrome. The durability of these effects is unknown but follow-up of this study is ongoing. There is some interest in using oral hypoglycaemics as adjuncts to insulin therapy in T1D patients. Short-term results from small studies have suggested that metformin may be beneficial, in this context, in adolescents with pubertal insulin resistance.

Recently, epidemiological studies and meta-analyses have revealed that T2D patients have a lower incidence of tumor development than healthy controls and that patients diagnosed with cancer have a lower risk of mortality when treated with metformin, demonstrating an association between metformin and tumorigenesis. Metformin is also an effective ovulation induction agent for non-obese women with PCOS and offers some advantages over other first line treatments for anovulatory infertility such as clomiphene.

2.5.6.2 Global Assessment of Safety

The most common adverse reactions resulting in discontinuation of metformin treatment are GI disturbances such as diarrhoea, nausea, vomiting, abdominal pain, and dyspepsia. The most serious metabolic complication that occurs due to metformin accumulation during treatment is lactic acidosis, which, however, is very rare. GI disturbances can occur at a frequency ranging up to 50%. Diarrhoea is the most prevalent and is unrelated to diabetic neuropathy. In combination with sulfonylureas, there is an increase in the occurrence of diarrhoea. Late onset diarrhoea can also occur and the differential diagnostic with diabetic diarrhoea is sometimes difficult to establish. The acute, reversible GI adverse effects seen with metformin may be

minimised by administration with or after food, and by using lower dosages, increased gradually as necessary. The risk of lactic acidosis due to metformin may be minimised by observance of prescribing precautions and contraindications intended to avoid accumulation of the drug or lactate in the body. Concomitant conditions characterized by hypotension or hypoxia can complicate the clinical picture and induce a mixed, type-B and type-A, anaerobic acidosis. Renal failure is a prerequisite for the development of metformin-induced lactic acidosis. The symptoms are nausea, vomiting, diarrhoea, somnolence and hyperpnoea. Importantly, the mortality seems more related to the concomitant clinical conditions than to the serum level of lactate and metformin.

The available data in mothers with PCOS do not indicate any harm to the foetus. However, when the patient plans to become pregnant and during pregnancy, diabetes should not be treated with metformin but insulin should be used to maintain blood glucose levels as close to normal as possible in order to lower the risk of foetal malformations associated with abnormal blood glucose levels. According to available data, metformin is excreted into breast milk, but the amounts seem to be clinically insignificant. A decision should be made whether to discontinue nursing or to discontinue metformin, taking into account the importance of the compound to the mother. Rare cases of cholestatic hepatitis characterized by severe cholestasis and mild portal inflammation are reported in the literature. Hypoglycaemia is rare but can occur when metformin is combined with NSAIDs or ACE inhibitors.

Cutaneous side effects occur sporadically and there are reports of psoriasiform eruption and erythema. Long-term treatment with metformin can decrease the serum levels of vitamin B12 inducing an increase of the homocysteine levels.

2.5.6.3 Overall Conclusion

In conclusion, metformin is a safe and effective anti-hyperglycaemic drug with well-established use for the treatment of T2D. Metformin has been in clinical use for over sixty years for the proposed indications and has a well-established side-effect profile. The outstanding scientific interest is best reflected by the over 18.000 publications about metformin at present. The EU Clinical Trials Register currently lists 756 registed trials with metformin.[1] The ClinicalTrials.gov lists 2120 metformin trials.[2] Although the nature of the cited scientific literature does not allow any comment on the Good Laboratory Practice (GLP) and the Good Clinical Practice (GCP) status, most of the cited experimental studies have been published in peer-reviewed journals; and monographs are published in reference textbooks of clinical

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pharmacology, and in formularies. These limitations are not considered as critical predominantly because of its over sixty year history of human clinical use.

The proposed pharmaceutical formulation of the drug products does not contain any novel excipients, or excipients being administered by a novel route, and, therefore, there is no unexpected toxicological potential.

The benefits of metformin and its place for the treatment of T2D and related conditions have been established in the several decades of clinical usage within the EU and in many other countries all over the world. Practical experience with metformin on the market in a large number of patients has also confirmed its safety and efficacy when used as directed.

The Summary of Product Characteristics (SPC) proposed by the Applicant takes the available pharmacodynamic, pharmacokinetic, toxicological, and clinical evidence into account, and is in accordance with the current knowledge with respect to the active moiety.

In conclusion, the assessment of available evidence on metformin and the widespread clinical use of such drug products favour the benefit from the availability of Metformin 500mg & 1000mg Powder for Oral Solution, the Applicant's drug product candidates.

2.5.7 Cited Literature References

Module	#	References
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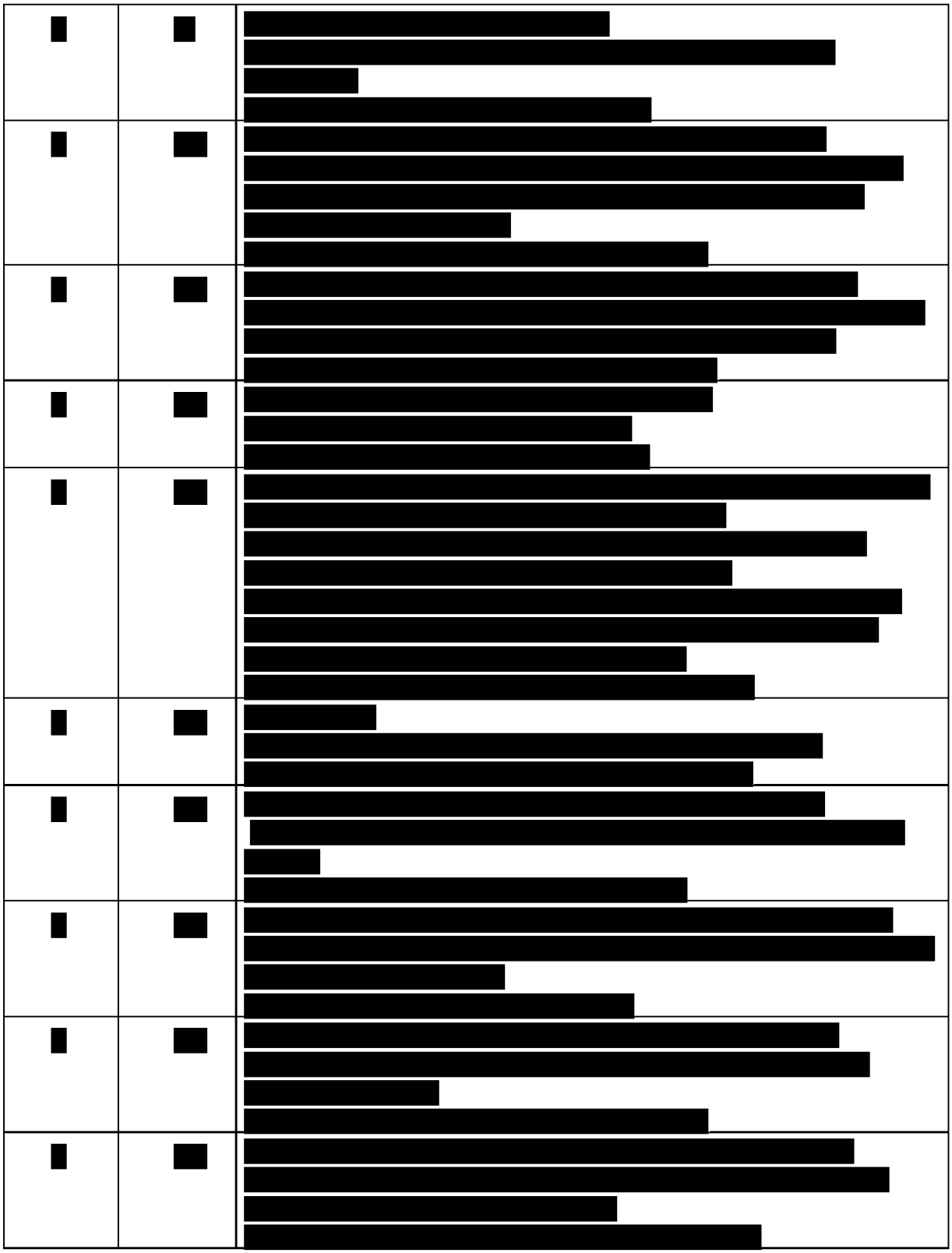

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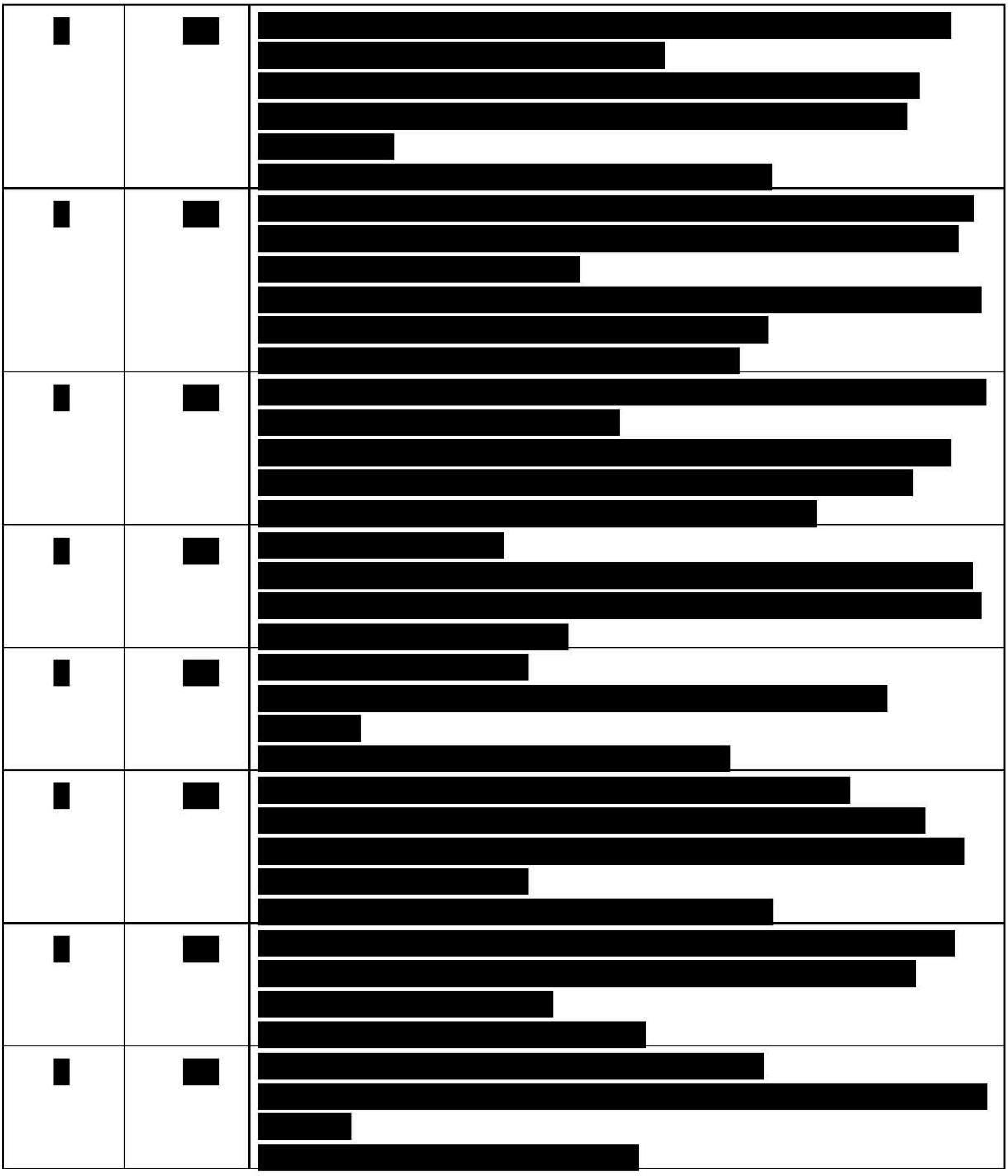

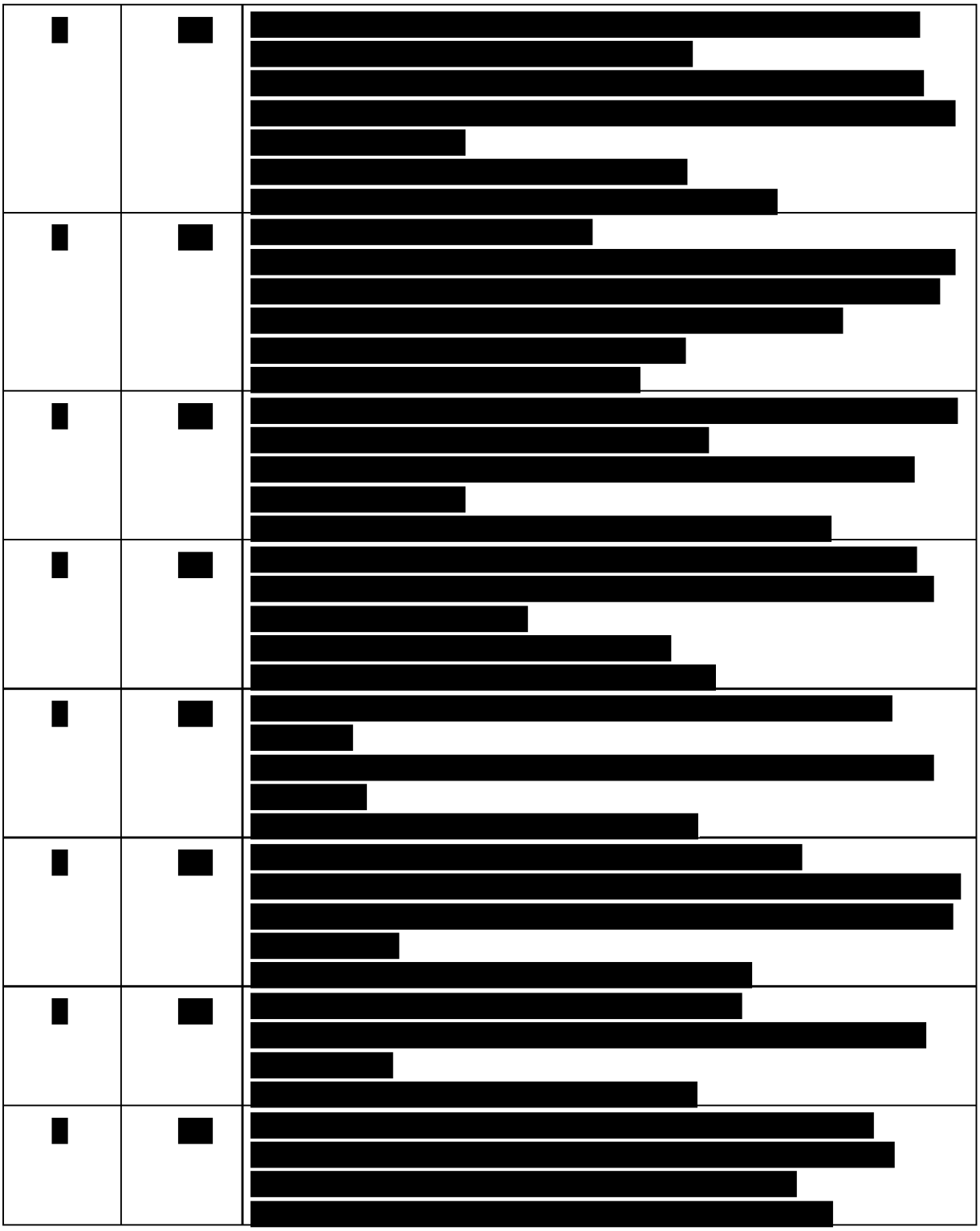

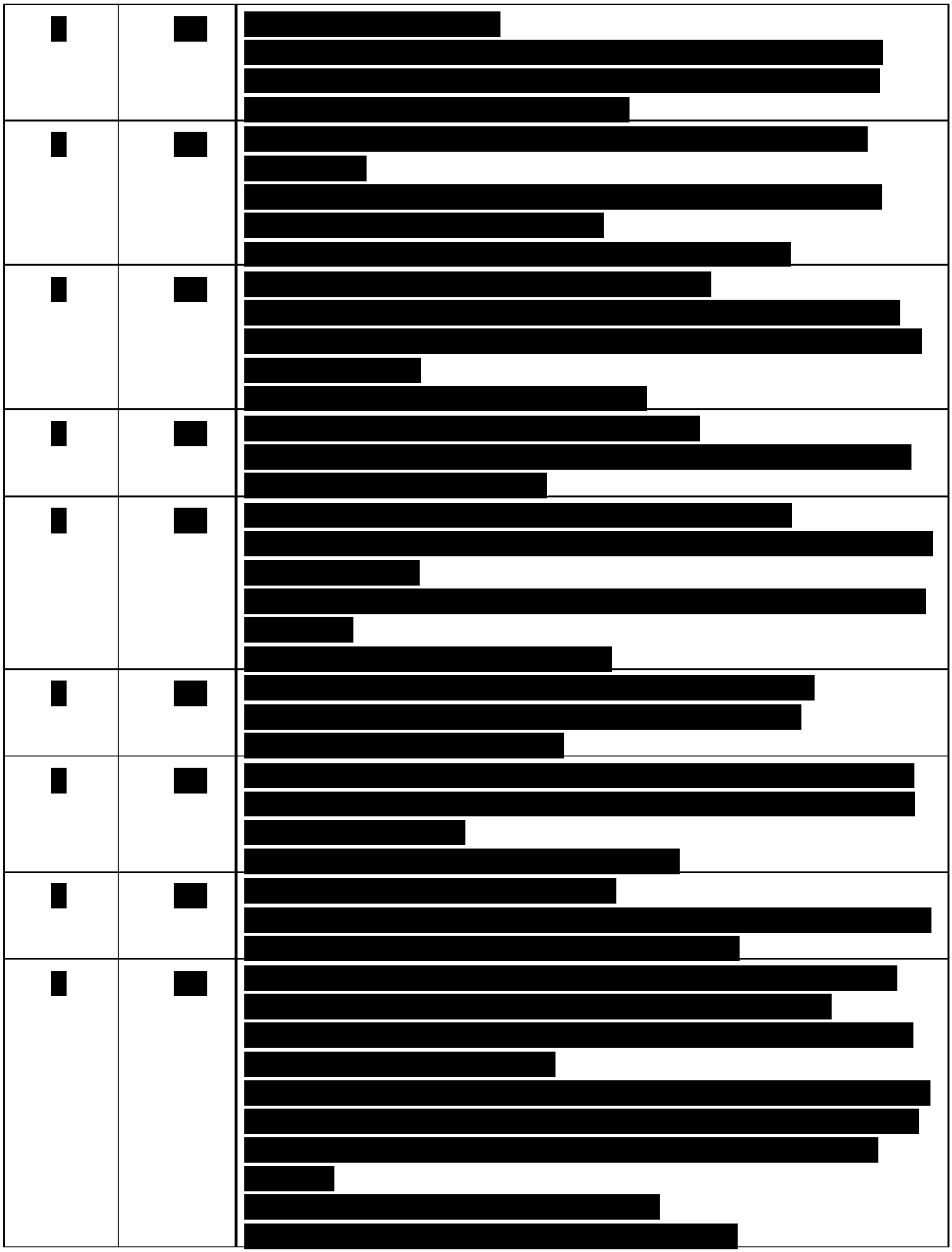

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