Safeguarding public health

MHRA

Metsol 500mg/5ml Oral Solution
PL 20249/0008

UK Public Assessment Report

The marketing authorisation for Metsol 500mg/5 ml Oral Solution was revoked on 23 January 2013.

This Public Assessment Report has been updated accordingly to explain the reasons for revocation.

The original Public Assessment report (17 July 2006) is appended to this report.

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Metsol 500mg/5ml Oral Solution
PL 20249/0008

Public Assessment Report: Revocation of a Marketing Authorisation

On 23 January 2013, the MHRA revoked a marketing authorisation ("product licence") for the medicinal product, Metsol 500mg/5ml Oral Solution (PL 20249/0008) meaning that this product could no longer be supplied to the market. This licence had been granted to Kappin Limited on 17th July 2006.

Information presented in the licence application supported the shelf-life and storage conditions that were approved. However, a Good Manufacturing Practice inspection performed by the MHRA in November 2011 cast doubt upon the reliability of this information. Subsequent monitoring identified significant quality concerns with product stability.

Kappin Limited ceased to market the product on 07 February 2012 at the request of the MHRA.

The MHRA asked advice from the Commission on Human Medicines (an independent panel of experts with whom the licensing authority consults regarding the safety, quality and efficacy of medicines). Having examined the evidence, the advice of the Commission in January 2012 was that the marketing authorisation for Metsol 500mg/5ml Oral Solution should be revoked.

Background to Licence Revocation

Metsol 500mg/5ml Oral Solution was granted a Marketing Authorisation on 17 July 2006 with a 24 month shelf-life when stored below 25^{o}C.

Stability data reviewed on 12 April 2012 identified analytical issues. Subsequent analysis of a stability sample highlighted levels of an individual related substance greater than the limit permitted by the current BP monograph for Metformin Oral Solution.

Owing to a failure to meet the registered control specification coupled with an absence of reliable stability data to assure the shelf-life, Kappin Limited complied with the MHRA's request to cease to market this product on 07 February 2012.

The licence was revoked by the MHRA on 23 January 2013.

REVISION HISTORY

Issue of UKPAR: Update 01	08 February 2013
Initial issue	17 July 2006

Annex 1 - UKPAR for initial grant of Marketing Authorisation:

METSOL 500MG/5ML ORAL SOLUTION

(METFORMIN HYDROCHLORIDE)

PL 20249/0008

UKPAR

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METSOL 500MG/5ML ORAL SOLUTION

(METFORMIN HYDROCHLORIDE)

PL 20249/0008

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) has granted Kappin Limited a Marketing Authorisation (licence) for the medicinal product Metsol 500mg/5ml Oral Solution (PL 20249/0008). This is a prescription only medicine [POM] used, alone or in combination with other medicines, to treat Type 2 diabetes not controlled by diet or exercise alone. (Type 2 diabetes is a form of diabetes that does not always require treatment with insulin.)

Metsol 500mg/5ml Oral Solution contains the active ingredient metformin hydrochloride. It is thought that metformin could act in three ways: (1) by reducing the production of glucose in the liver, (2) by increasing the sensitivity of the muscle to the actions of insulin, thereby improving the uptake and use of glucose, and (3) by delaying the absorption of glucose from the gut.

No new or unexpected safety concerns arose from this application and it was decided that the benefits of using Metsol 500mg/5ml Oral Solution outweigh the risks, hence a Marketing Authorisation has been granted.

METSOL 500MG/5ML ORAL SOLUTION

(METFORMIN HYDROCHLORIDE)

PL 20249/0008

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted a marketing authorisation for the medicinal product Metsol 500mg/5ml Oral Solution (PL 20249/0008) to Kappin Limited on 17 July 2006. The product is a prescription only medicine.

The application was submitted according to Article 10.1(a)(ii) of Directive 2001/83/EC, as amended, as a bibliographic application.

Metsol 500mg/5ml Oral Solution contains the active ingredient metformin hydrochloride. It is indicated for treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia. Metformin may act via 3 mechanisms: (1) reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis (2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation and (3) delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT).

PHARMACEUTICAL ASSESSMENT

PL NUMBER: **PL 20249/0008**
PRODUCT: **Metsol 500mg/5ml Oral Solution**
ACTIVE: **Metformin hydrochloride**
COMPANY: **Kappin Ltd.**
LEGAL STATUS: **POM**

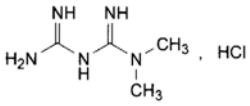
INTRODUCTION

This is an application for Marketing Authorisation in the UK submitted under Article 10.1(a)(ii) of Directive 2001/83/EC (as amended), a so-called "bibliographic application".

ACTIVE SUBSTANCE

Metformin hydrochloride

General information

Structure: 

Description: White crystals

Molecular formula: $C_4H_{11}N_5.HCl$

Manufacture

Manufacturer

The source of the drug substance has a Certificate of Suitability and this has been provided.

Manufacturing process

The manufacturing process is referenced to the Certificate of Suitability.

Control of active substance

Specification

A satisfactory drug substance specification has been provided.

Analytical procedures

The test methods used are those described in the European Pharmacopoeia and supplemented by the Certificate of Suitability.

Batch analysis

Satisfactory Certificates of Analysis are provided for three batches.

Container closure system

Relevant details, specifications and Certificates of Analysis have been provided for the packaging components. Suitable documentation has also been provided to demonstrate compliance of the primary packaging components with the food contact requirements of Directive 2002/72/EC and Ph.Eur.

Stability

Satisfactory stability data for storage under ICH conditions has been presented. All data and impurities remained well within specification.

An acceptable re-test period has been applied.

DRUG PRODUCT

Composition

The composition of the product is presented in the table below. The product is a sugar-free, colourless solution with orange flavouring and packed in 100ml amber glass bottles.

Product composition of Metsol 500mg/5ml Oral Solution

Name	Function	Reference
Metformin hydrochloride	Active ingredient	Ph.Eur.
Saccharin sodium	Sweetener	Ph.Eur.
Citirc acid monohydrate	Acidifying agent	Ph.Eur.
Sodium citrate	Acidifying agent	Ph.Eur.
Glycerol	Viscosity	Ph.Eur.
Sodium methyl parahydroxybenzoate	Preservative	Ph.Eur.
Sodium propyl parahydroxybenzoate	Preservative	Ph.Eur.
Orange Flavour (containing ethanol)	Flavouring	In-house
Purified water	Carrier	Ph.Eur.

Pharmaceutical development

Formulation development

The aim was to develop a liquid formulation that is sugar-free, alcohol-free and colour-free for use in children and in elderly patients who cannot swallow tablets.

Manufacturing development

A satisfactory summary is provided.

Microbiological attributes

The parahydroxybenzoate preservative system is used in the formulation to prevent spoilage. A satisfactory preservative efficacy test was performed.

Manufacture

Manufacturer

Batch release site: Orbis Consumer Products Ltd., Northfields Industrial Estate, Beresford Avenue, Wembley, Middlesex, UK.

A valid manufacturing authorisation has been supplied.

Manufacturing process and process controls

A flow diagram detailing the manufacturing process and in-process control testing has been provided. A satisfactory written summary of the process has been included.

Control of critical steps (in-process controls)

The in-process controls cover finished product and manufacturing specifications.

Process validation or evaluation

Satisfactory validation data has been presented.

The critical steps for validation have been identified and a relevant sampling schedule provided. The limits for the critical steps have been confirmed across the validation batches.

Control of excipients

Specification

All excipients except orange flavouring are controlled to the Ph.Eur. monographs. Satisfactory Certificates of Analysis are provided by the suppliers.

Declarations are provided from the manufacturer confirming that there are no excipients of animal or human origin in the product.

Control of drug product

Specification

An acceptable finished product specification has been provided.

Analytical procedures

All the details have been provided for the pharmacopoeial and non-pharmacopoeial methods.

Validation

Satisfactory validation data provided.

Reference standards

Certificates of Analysis on the reference standards have been provided. These are acceptable.

Batch analysis

Batch analysis details have been provided. These are all within specification and show a reasonable degree of comparability. Satisfactory Certificates of Analysis have been supplied.

Container closure system

The product will be packed in 100ml amber Type III glass bottles sealed with child resistant, tamper-evident screw caps. Specifications for the primary packaging components are provided.

A polyethylene double measuring spoon is also provided which is CE marked. Specifications and a certificate of CE marking are provided. Confirmation is provided that the polyethylene spoon conforms to the food contact requirements in 2002/72/EC and is controlled to the Ph.Eur. monograph.

Stability

Stability data was presented for representative batches at 25ºC/60%RH, 30^{o}C/60%RH and 40ºC/75%RH. The solutions are packed in 100ml amber Type III glass bottles as proposed for marketing.

Stability is assessed against the finished product specification.

There are no changes in the product specifications during the storage period. Based on these data, the applicant has proposed a shelf life of 24 months. This is acceptable.

Satisfactory in-use stability data has been provided. The product is stable under simulated in-use conditions over a period of five weeks. No indications of degradation of active or preservatives are observed. An additional in-use storage condition of use within 4 weeks of opening is proposed. This is acceptable.

SUMMARY OF PRODUCT CHARACTERISTICS
PATIENT INFORMATION LEAFLET
LABELLING

Satisfactory.

CONCLUSIONS AND ADVICE

A marketing authorisation can be granted.

PRECLINICAL ASSESSMENT

PL NUMBER: **PL 20249/0008**
PRODUCT: **Metsol 500mg/5ml Oral Solution**
ACTIVE: **Metformin hydrochloride**
COMPANY: **Kappin Ltd.**
LEGAL STATUS: **POM**

INTRODUCTION

This application for Metsol Oral Solution was made under Article 10.1(a)(ii) of Directive 2001/83/EC. A bibliographic application is acceptable since the product contains the active ingredient, metformin hydrochloride, which has been well established in therapeutic use. The proposed indication and dosing regimen are also well-established for this ingredient.

The Nonclinical Overview is an uncritical and superficial review of some clinical data with a brief review of some of the animal studies on reproduction. Examination of the literature references revealed that the provenance of the reports of the animal studies is the clinical literature in which brief reviews of animal studies are sometimes found.

NONCLINICAL ASPECTS

Metformin is a well established drug with over 30 years of clinical use as a first line hypoglycaemic agent. Therefore no further nonclinical studies have been conducted and none are required.

Metformin is a biguanide with antihypertensive effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

NONCLINICAL OVERVIEW

This was an overview mainly of some of the clinical data with some reference to the nonclinical data.

SUMMARY OF PRODUCT CHARACTERISTICS

Section 5.3 (Preclinical Safety Data) is acceptable.

CONCLUSIONS

There are no nonclinical objections to the grant of a Marketing Authorisation.

CLINICAL ASSESSMENT

PL NUMBER: **PL 20249/0008**
PRODUCT: **Metsol 500mg/5ml Oral Solution**
ACTIVE: **Metformin hydrochloride**
COMPANY: **Kappin Ltd.**
LEGAL STATUS: **POM**

INTRODUCTION

This is a national application for a UK Marketing Authorisation.

This application is submitted under Article 10.1(a)(ii), - so called "bibliographical application").

Metsol is an oral solution of metformin 500mg (as hydrochloride) in 5ml. It is indicated for treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone do not result in adequate glycaemic control. In adults, metformin oral solution 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 oral solution may be used as monotherapy or in combination with insulin.

The efficacy of metformin as an oral hypoglycaemic agent is well established.

Metformin is an orally administered biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via three mechanisms:

1. Reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
2. Increase of insulin sensitivity in muscle, thus improving peripheral glucose uptake and utilisation.
3. Delaying intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT).

It is available in the UK as 500mg and 850mg tablets and this high dosing regime makes the tablets large. Some patients, especially the elderly and the young, find it difficult to swallow. Although a liquid formulation is not available, hospitals and specials manufacturers have produced many different formulations, most commonly suspensions of crushed tablets, with varying degree of acceptability in terms of palatability and bioavailability. The applicant has therefore considered it prudent to develop a liquid formulation, ideally a solution, which is stable and palatable. Since metformin is freely soluble in water, this is possible.

Metformin has been available for clinical use in France since 1959, marketed by Lipha. It has been available for clinical use in the UK and the rest of Europe for well over 3 decades and

the FDA approved it in December 1994 on the basis of three clinical trials. It is now widely used. A bibliographic application is therefore appropriate and the applicant has supported this by submitting a number of excellent and comprehensive reviews. Its efficacy and safety are well known and need not be detailed in this assessment report. The applicant has provided a concise Clinical Overview. Pharmacology and efficacy of metformin have been well reviewed by Melchior WR and Jaber LA (1996) [*Metformin: an antihyperglycaemic agent for treatment of type II diabetes.* Ann Pharmacother *1996;30:158-64*] and by Klesper TB and Kelly MW (1997) [*Metformin hydrochloride: an antihyperglycaemic agent.* Am J Heath-Syst Pharm *1997;54:893-903*], two of the reviews submitted by the applicant.

Metformin has an absolute oral bioavailability of 32-61% (tablet or solution) with 20-30% being recovered in the faeces. According to Sambol NC *et al* (1996). [*Pharmacokinetics and pharmacodynamics of metformin in healthy subjects and patients with noninsulin-dependent diabetes mellitus.* J Clin Pharmacol *1996;36:1012-21*], the pharmacokinetics of metformin is significantly influenced by dose level but not by diabetes, gender or multiple dose administration. At higher doses or following administration of sustained release formulations, the % absorption is decreased. Administration with food may decrease bioavailability by as much as 25%. Metformin is excreted unchanged in the urine without any metabolic deactivation. There is a good correlation between metformin elimination and serum creatinine. The half-life of the drug is of the order of 5-6 hours.

No relationship between plasma concentration and drug response – therapeutic or the induction of lactic acidosis – has been established.

SUMMARY OF PRODUCT CHARACTERISTICS

This is satisfactory, being consistent with those of other metformin-containing products.

PATIENT INFORMATION LEAFLET

Satisfactory.

BIOEQUIVALENCE

The applicant has not provided a bioequivalence study. This is considered acceptable for the following reasons:

1. Absorption is rate-limited

2. Therapeutic efficacy or toxicity seem unrelated to plasma concentrations and therefore, minor differences in rates of absorption are not likely to be clinically relevant ("Note for Guidance on the investigation of bioavailability and bioequivalence", CPMP/EWP/QWP/1401/98, section 2.6).

3. *In vivo* bioequivalence studies are needed *(only)* when there is a risk that possible difference in bioavailability may result in therapeutic inequivalence ("Note for Guidance on the investigation of bioavailability and bioequivalence", CPMP/EWP/QWP/1401/98, section 5.1)

4. The drug is freely soluble in water

5. The product meets the criteria set out for an exemption in section 5.1.1 of the "Note for Guidance on the investigation of bioavailability and bioequivalence", CPMP/EWP/QWP/1401/98, notwithstanding section 5.1.2.

6. The following abstract and the conclusions from a study by Pentikainen PJ (1986) [*Bioavailability of metformin. Comparison of solution, rapidly dissolving tablet, and three sustained release products.* Int J Clin Pharmacol Ther Toxicol *1986;24:213-20*] justify why a bioequivalence study is not necessary:

"To study the bioavailability of metformin from aqueous solution (A), a rapidly dissolving tablet (B), and three sustained release products (D, C, E), 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 h and excretion into urine up to 48 h 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. The renal clearance of metformin was similar after all the products, averaging 518 +/- 16 (SE) ml/min. The terminal elimination half-life on the basis of urinary excretion rate data averaged 12.6 +/- 0.6 h with no significant difference between the products. The bioavailability on the basis of urinary excretion of metformin showed a significant ($p < 0.05$) positive correlation to the dissolution rate of the products *in vitro*. Thus, the bioavailability of metformin even from aqueous solution and rapidly dissolving tablets is relatively low and further deteriorates when metformin is administered as sustained release products. The bioavailability of the three sustained release products studied was similar."

7. The following abstract and the conclusions from a study by Sambol NC *et al* (1996). [*Pharmacokinetics and pharmacodynamics of metformin in healthy subjects and patients with noninsulin-dependent diabetes mellitus.* J Clin Pharmacol *1996;36:1012-21*] also justify why a bioequivalence study is not necessary:

"The pharmacokinetics of four single-dose treatments of the metformin administered orally (as the HCl salt) were compared in 24 healthy subjects: 500 mg and 850 mg tablets and 850 mg solution fasting and 850 mg tablet with food. Solution and tablet formulations are bioequivalent. Bioavailability of a 500 mg tablet is 14% greater than that of an 850 mg tablet. Compared with the fasting state, bioavailability is 24% lower, and the peak concentration delayed about 37 min when an 850 mg tablet is administered with food."

8. With regard to the BCS criteria, according to Cheng CL *et al* (2004) [*Biowaiver extension potential to BCS Class III high solubility-low permeability drugs: Bridging evidence for metformin immediate-release tablet.* Eur J Pharm Sci *2004;22:297-304*]:

"Metformin has high solubility in water [*Bretnall AS, Clarke GS. In: Metformin. Hydrochloride. In: Brittain HG, editor. Analytical. Profiles of Drug Substances and Excipients, Vol. 25.* London: Academic Press; 1998] and low permeability to cell membranes (Chou, 2000 [*Uptake and dispersion of metformin in the isolated perfused rat liver*. J Pharm Pharmacol *2000;52:1011-6*]; Nicklin *et al,* 1996 [*Transfer of metformin across monolayers of human intestinal Caco-2 cells and across rat intestine*. Int J Pharmaceutics 1996;128:155-62]). Therefore, it can be classified as a

BCS Class III drug. 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 (Sambol *et al* 1996a [*Pharmacokinetics and pharmacodynamics of metformin in healthy subjects and patients with noninsulin-dependent diabetes mellitus.* J Clin Pharmacol *1996;36:1012-21*]). Thus, it is evident that if the formulation of metformin IR product is rapid dissolving, dissolution will not affect availability of metformin. Using the rationale of the BCS, it can be argued that biowaivers can be granted for metformin IR products on the basis of *in vitro* dissolution profiles."

Therefore, since the product under assessment is a solution, an exemption is applicable even under the FDA Guidance.

RECOMMENDATION

There are no major clinical public health issues and the recommendation is to grant a marketing authorisation for this preparation.

OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Metsol 500mg/5ml Oral Solution are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

The active ingredient, metformin hydrochloride, is used for the treatment of type 2 diabetes mellitus. Its use is well established with recognised efficacy and acceptable safety.

No new or unexpected safety concerns arise from this application.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The efficacy of the active ingredient metformin is established and extensive clinical experience is considered to have demonstrated the therapeutic value of the compound. The risk-benefit assessment is therefore considered to be favourable.

METSOL 500MG/5ML ORAL SOLUTION

(METFORMIN HYDROCHLORIDE)

PL 20249/0008

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application for Metsol 500mg/5ml Oral Solution on 30 September 2005.
2	Following standard checks, the MHRA informed the applicant that its application was considered valid on 31 October 2005.
3	The MHRA's assessment of the submitted data was completed on 10 March 2006.
4	Further information was requested from the company on 10 April 2006.
5	The applicant submitted its response to further information request in a letter dated 2 June 2006.
6	The MHRA completed its assessment of the application on 3 July 2006.
7	The application was determined on 17 July 2006.

METSOL 500MG/5ML ORAL SOLUTION

(METFORMIN HYDROCHLORIDE)

PL 20249/0008

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Metsol 500mg/5ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Metformin (as hydrochloride)500 mg / 5ml

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Oral Solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Metformin Oral Soultion is indicated for treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.

- In adults, Metformin Oral Soultion 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 Oral Soultion may be used as monotherapy or in combination with insulin.

A reduction of diabetic complications has been shown in overweight type 2 diabetic adult patients treated with metformin as first-line therapy after diet failure (see 5.1. Pharmacodynamic properties).

4.2 Posology and method of administration

Adults:

Monotherapy and combination with other oral antidiabetic agents:

• The usual starting dose is 500mg 2 or 3 times daily given during or after meals.
• After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastrointestinal tolerability. The maximum recommended dose of metformin is 3 g daily.
• If transfer from another oral antidiabetic agent is intended: discontinue the other agent and initiate metformin at the dose indicated above.

Combination with insulin:

Metformin and insulin may be used in combination therapy to achieve better blood

glucose control. Metformin is given at the usual starting dose of 500mg 2-3 times daily, while insulin dosage is adjusted on the basis of blood glucose measurements.

Elderly: due to the potential for decreased renal function in elderly subjects, the metformin dosage should be adjusted based on renal function. Regular assessment of renal function is necessary (see section 4.4).

Children and adolescents:
Monotherapy and combination with insulin
• Metformin Oral Solution can be used in children from 10 years of age and adolescents.
• The usual starting dose is 500 mg or 850 mg once daily, given during meals or after meals.
• After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastrointestinal tolerability. The maximum recommended dose of metformin is 2 g daily, taken as 2 or 3 divided doses.

4.3 Contra-indications

• Hypersensitivity to metformin hydrochloride or to any of the excipients. May cause allergic reactions (possibly delayed).
• Diabetic ketoacidosis, diabetic pre-coma.
• Renal failure or renal dysfunction (creatinine clearance < 60 mL/min).
• Acute conditions with the potential to alter renal function such as:
  - dehydration
  - severe infection
  - shock
  - Intravascular administration of iodinated contrast agents (see 4.4 Warnings and special precautions for use).
• Acute or chronic disease which may cause tissue hypoxia such as:
  - cardiac or respiratory failure
  - recent myocardial infarction
  - shock
• Hepatic insufficiency, acute alcohol intoxication, alcoholism
• Lactation

4.4 Special warnings and precautions for use

Lactic acidosis.

Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing also other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.

Diagnosis:
Lactic acidosis is characterised by acidotic dyspnea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, metformin should be discontinued and the patient should be hospitalised immediately (see section 4.9).

Renal function:

As metformin is excreted by the kidney, serum creatinine levels should be determined before initiating treatment and regularly thereafter:
* at least annually in patients with normal renal function,
* at least two to four times a year in patients with serum creatinine levels at the upper limit of normal and in elderly subjects.
Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy or diuretic therapy and when starting therapy with an NSAID.

Administration of iodinated contrast agent

As the intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure, metformin should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Surgery

Metformin hydrochloride should be discontinued 48 hours before elective surgery with general anaesthesia and should not be usually resumed earlier than 48 hours afterwards.

Children and adolescents:

The diagnosis of type 2 diabetes mellitus should be confirmed before treatment with metformin is initiated.

No effect of metformin on growth and puberty has been detected during controlled clinical studies of one-year duration but no long-term data on these specific points are available. Therefore, a careful follow-up of the effect of metformin on these parameters in metformin-treated children, especially pre-pubescent children, is recommended.

Children aged between 10 and 12 years:
Only 15 subjects aged between 10 and 12 years were included in the controlled clinical studies conducted in children and adolescents. Although metformin efficacy and safety in children below 12 did not differ from efficacy and safety in older children, particular caution is recommended when prescribing to children aged between 10 and 12 years.

-Other precautions:

- All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.
- The usual laboratory tests for diabetes monitoring should be performed regularly.
- Metformin alone never causes hypoglycaemia, although caution is advised when it is used in combination with insulin or sulphonylureas.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended
Alcohol
Increased risk of lactic acidosis in acute alcohol intoxication, particularly in case of:
- fasting or malnutrition
- hepatic insufficiency
Avoid consumption of alcohol and alcohol-containing medications.

Iodinated contrast agents (see section 4.4)
Intravascular administration of iodinated contrast agents may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis.
Metformin should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Combinations requiring precautions for use
Glucocorticoids (systemic and local routes), beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. Inform the patient and perform more frequent blood glucose monitoring, especially at the beginning of treatment. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation.

ACE-inhibitors may decrease the blood glucose levels. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation.

4.6 Pregnancy and lactation

To date, no relevant epidemiological data are available. Animal studies do not indicate harmful effects with respect to pregnancy, embryonal or foetal development, parturition or postnatal development (see also section 5.3).
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.

Metformin is excreted into milk in lactating rats. Similar data are not available in humans and a decision should be made whether to discontinue nursing or to

discontinue metformin, taking into account the importance of the compound to the mother.

4.7 Effects on ability to drive and use machines

Metformin monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines.
However, patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with other antidiabetic agents (sulphonylureas, insulin, repaglinide).

4.8 Undesirable effects

The following undesirable effects may occur under treatment with metformin. Frequencies are defined as follows: very common:>1/10; common>1/100, <1/10; uncommon>1/1,000, <1/100; rare>1/10,000, <1/1,000; very rare <1/10,000 and isolated reports.

Metabolism and nutrition disorders:
Very rare: Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended if a patient presents with megaloplastic anaemia.
Very rare: Lactic acidosis (see 4.4. Special warnings and precautions for use).

Nervous system disorders:
Common: Taste disturbance

Gastrointestinal disorders:
Very common: Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that metformin be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.

Hepatobiliary disorders:
Isolated reports: Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders:
Very rare: Skin reactions such as erythema, pruritus, urticaria
In published and post marketing data and in controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year, adverse event reporting was similar in nature and severity to that reported in adults.

4.9 Overdose

Hypoglycaemia has not been seen with metformin doses of up to 85g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ORAL ANTI-DIABETICS
(A10BA02: Gastrointestinal tract and metabolism)

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via 3 mechanisms:
(1) reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
(2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation (3) and delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT).

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

Clinical efficacy:
The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes.

Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1000 patient-years) versus diet alone (43.3 events/1000 patient-years), p=0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1000 patient-years), p=0.0034.
- a significant reduction of the absolute risk of diabetes-related mortality: metformin 7.5 events/1000 patient-years, diet alone 12.7 events/1000 patient-years, p=0.017;
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1000 patient-years versus diet alone 20.6 events/1000 patient-

years (p=0.011), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1000 patient-years (p=0.021);
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1000 patient-years, diet alone 18 events/1000 patient-years (p=0.01)

For metformin used as second-line therapy, in combination with a sulphonylurea, benefit regarding clinical outcome has not been shown.

In type 1 diabetes, the combination of metformin and insulin has been used in selected patients, but the clinical benefit of this combination has not been formally established.

Controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year demonstrated a similar response in glycaemic control to that seen in adults.

5.2 Pharmacokinetic properties

Absorption:
After an oral dose of metformin, Tmax is reached in 2.5 hours. Absolute bioavailability of a 500mg or 850mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that 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 (Cmax) did not exceed 4 μg/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40% lower plasma peak concentration, a 25% decrease in AUC (area under the curve) and a 35 minute prolongation of time to peak plasma concentration were observed. The clinical relevance of these decreases is unknown.

Distribution:
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 Vd ranged between 63-276 L.
Metabolism:
Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination:
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.

Paediatrics:
Single dose study: After single doses of metformin 500 mg, paediatric patients have shown similar pharmacokinetic profile to that observed in healthy adults.

Multiple dose study: Data are restricted to one study. After repeated doses of 500 mg BID for 7 days in paediatric patients the peak plasma concentration (Cmax) and systemic exposure (AUC0-t) were reduced by approximately 33% and 40%, respectively compared to diabetic adults who received repeated doses of 500 mg BID for 14 days. As the dose is individually titratedbased on glycaemic control, this is of limited clinical relevance.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies on safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
Citric acid monohydrate
Sodium citrate
Saccharin sodium(E954)
Orange flavour
Sodium methyl parahydroxybenzoate (E219)
Sodium propylparahydroxybenzoate (E217)
Purified water.

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Do not store above 25ºC. Store in the original container. Discard one month after opening.
Keep out of the reach and sight of children.

6.5 Nature and contents of containers

Amber Type III Glass
Child Resistant Tamper Evident Cap- High density polypropylene cap with a polyethylene lining
5 ml polypropylene Spoon
Pack sizes available: 100ml

6.6 Special precautions for disposal

Not Applicable

7 MARKETING AUTHORISATION HOLDER

Kappin Limited
Unit 31, Northfields Industrial Estate
Beresford Avenue
Wembley, Middlesex
HA0 1NW

8 MARKETING AUTHORISATION NUMBER(S)

PL 20249/0008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/07/2006

10 DATE OF REVISION OF THE TEXT

17/07/2006

Patient Information Leaflet

METSOL 500MG/5ML ORAL SOLUTION

(METFORMIN HYDROCHLORIDE)

PL 20249/0008

Metsol 500mg/5ml Oral Solution

3083/1

Metformin hydrochloride

This leaflet contains important information about Metsol Oral Solution. Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you have any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet

1. What Metsol Oral Solution is and what is it used for

Metformin is one of a group of medicines called biguanide hypoglycaemic agents. These medicines work by lowering the amount of sugar in the blood.

Metsol Oral Solution may be used for the treatment of non-insulin dependent diabetes (type 2) not controlled by diet and exercise alone. Your doctor may prescribe Metformin for you or your child to take on its own or in combination with other oral antidiabetic medicines or insulin.

Your doctor or pharmacist will advice you how to take your medicine.

2. Before you take Metsol Oral Solution

Do not take Metsol Oral Solution if:
- you are pregnant, planning to become pregnant or breast-feeding.
- you have ever had an allergic reaction to Metformin or any of the ingredients in the solution. (An allergic reaction may include a rash, itching or difficulty breathing).
- you suffer from kidney or liver problems.
- you are a heavy drinker of alcohol.
- you have had heart failure or have recently had a heart attack, or have difficulty breathing.
- you have had serious complications with your diabetes (e.g. diabetic coma or ketonesin your urine).
- you are dehydrated (e.g. if you have suffered from diarrhoea or vomiting recently).
- you have had a serious infection or recently suffered trauma (shock).
- you have been told that the amount of oxygen in your blood is low.
- you need to have an X-ray.

Do not drink excessive alcohol or take medicines that contain alcohol whilst taking this oral solution.
If you have diabetes you should have your blood or urine tested for sugar regularly. Your doctor should check the function of your kidneys at least once a year (more often if you are elderly or have kidney problems). An annual check on vitamin B12 levels may be carried out.

You should continue to follow any dietary advice that your doctor has given you and should make sure that you eat carbohydrates regularly throughout the day. If you are over-weight, you should continue with your energy restricted diet.

If you see another doctor or go into hospital, let them know what medicines you are taking. Special care is needed (check with your doctor) if you are going into hospital for an operation under general anaesthetic or or certain X-ray tests. You will be given advice to stop Metsol Oral Solution for a while.

Driving and using machines

- When Metsol Oral Solution is taken on its own, it does not cause "hypos" (symptoms of low blood sugar or hypoglycaemia, such as faintness, confusion and increased sweating). Therefore, it should not affect your ability to drive or use machinery. However, Metsol Oral Solution can cause "hypos" when taken with other antidiabetic medicines, so in this case, you should take extra care when driving or operating machinery.

Pregnancy and Breast-feeding

- Do you think you may be pregnant? If so, you should not take Metformin, it may harm the baby.
- Are you breast-feeding? If so, you should not take Metformin, the active ingredient gets into mothers' milk.

Let your doctor know if you think you are pregnant. He or she can advise you on how to control your diabetes.

Important information about some of the ingredients of Metsol Oral Solution

- Sodium methyl parahydroxybenzoate (E219) and sodium propyl parahydroxybenzoate(E217): May cause allergic reactions (possibly delayed).
- This medicinal product contains small amounts of ethanol (alcohol), less than 100mg per10ml.

Taking other medicines

Please tell your doctor before you start to take Metsol Oral Solution if you:
- Are taking medicines such as steroids (e.g. hydrocortisone, prednisolone, betamethasone), medicines to treat asthma (e.g. salbutamol, terbutaline, salmeterol, formoterol), "water" tablets (diuretics), ACE inhibitors (medicines to lower blood pressure e.g. captopril).
- Are taking any medication you have bought yourself without a prescription.

Some medicines may not work very well when Metsol Oral Solution is also being taken. Does the doctor who pre-scribed Metsol Oral Solution know this? If not, tell your doc-tor before taking any solution. He or she will advice you how to take the medication.

3. How to take Metsol Oral Solution

Follow your doctor's instructions. Check the pharmacy label to see how much oral solution should be taken and how often to take it. If you are not sure how to take it ask your pharmacist or doctor.

The usual dosage(s) are described below:

The full effects may in some cases be delayed for up to two weeks.

Adults: Initially, one 5ml spoonful (500mg) 2 or 3 times daily with, or just after a meal. After you have been taking the medicine for about 2 weeks, your doctor may measure your blood sugar and adjust the dose. Any change in dosage must only be made on the advice of your doctor.

Elderly: Your doctor may prescribe a different dose.

Children: Not recommended in children under 10 years.

Metsol Oral Solution must be taken with or after food. The medicine should be taken for as long as your doctor tells you to as it may be dangerous to stop without their advice. If you are elderly or have reduced kidney function, it is particularly important to take this medicine exactly as directed by the doctor.

What to do if you take too much Metsol Oral Solution

Do not take more oral solution than your doctor tells you to. If you ever take too much go to the nearest hospital casualty department or tell your doctor immediately. Take the container and any remaining medicine with you to show to the doctor.

If you forget to take Metsol Oral Solution

If you forget to take a dose, take one as soon as you remember. Then go on as before. DO NOT take two doses at the same time. If you are worried ask your pharmacist or doctor for advice.

4. Possible side effects

This medicine sometimes causes unwanted effects in some people. These effects may include:

- *Effects on metabolism and nutrition:*
  Some patients, who have been taking Metsol Oral Solution for a long time, have experienced reduced levels of vitamin B12 in their blood. This would be detected by a blood test. If you start to loss weight unexpectedly, or suffer from severe nausea or vomiting, uncontrolled rapid breathing or abdominal pains, stop taking the medicine and contact a doctor immediately or go to the nearest A&E department. These symptoms can be severe, quick to appear and can be signs of serious problems with your diabetes (known as diabetic ketoacidosis and lactic acidosis).

- *Effects on the stomach and intestines:*
  More than 10% of patients experience diarrhoea, loss of appetite, nausea, stomach upset and vomiting especially at the start of treatment. Taking the medicine during or after meals usually helps to prevent these effects. When an increase in the dose of Metformin is prescribed, a gradual change to the higher dose lessens the likelihood of these symptoms occurring. 3% of patients suffer from a metallic taste.

- Effects on the skin:
  A mild red rash has been reported in some patients. However, this is very rare (less than 0.01 % of patients have experienced this effect).

You should consult your doctor if these effects are troublesome or continue.

If you get any other unusual effects, tell your doctor immediately.

5. Storing Metsol Oral Solution

As with all medicines, it is important to keep Metsol Oral Solution out of the reach and sight of children.

Do not store above 25^{O}C. Store in the original container. Discard after one month of opening.

Do not use Metsol Oral Solution after the expiry date printed on the carton or the bottle.

Do not keep outdated medicine or medicine that is no longer wanted. Take it to your pharmacist for safe disposal.

Always keep the medicine in the bottle in which it was originally given to you.

You may wish to read the leaflet again. Do not throw it away until you have finished your medicine.

6. Further Information

Metsol Oral Solution is a clear solution with a smell of Oranges.

Each 5ml of Metsol Oral Solution contains 500mg Metformin (as hydrochloride) as active ingredient.

Metsol Oral Solution also contains the following inactive ingredients: Glycerol, citric acid monohydrate, saccharin sodium (E954), sodium citrate, sodium methyl parahydroxybenzoate (E219), sodium propyl parahydroxybenzoate (E217), orange flavour (containing ethanol) and purified water.

Metsol Oral Solution is available in amber glass bottles fitted with child resistant closures and containing 100ml of the oral solution. A double ended 5ml and 2.5ml polypropylene spoon is also included to help measure the dose.

The Marketing Authorisation holder of Metsol Oral Solution (PL 20249/0008) is:

- Kappin Ltd., Northfield Industrial Estate, Middlesex. HA0 1NW
- Manufactured by Orbis Consumer Products Ltd, Northfield Industrial Estate, Middlesex HA0 1NW

REMEMBER
This medicine is for you or your child. Never give it to anybody else, even if their symptoms are the same as yours.

This leaflet does not tell you all about your medicine. If you have any questions or are not sure about anything then ask your doctor or pharmacist.

The information in this leaflet only applies to Metsol Oral Solution.

This leaflet was prepared in April 2006

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Labels/Packaging

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Bottle label