Public Assessment Report

Decentralised Procedure

Metformin hydrochloride 500 mg/5 ml Oral Solution

UK/H/1042/01/DC

Rosemont Pharmaceuticals Limited

Medicines and Healthcare Products Regulatory Agency

Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Rosemont Pharmaceuticals Limited a Marketing Authorisation (licence) for the medicinal product Metformin Hydrochloride 500 mg/5 ml Oral Solution (Product Licence number: 00427/0139). This medicine is available on prescription only.

Metformin is used to treat type 2 diabetes mellitus. Type 2 diabetics cannot make enough insulin, or the insulin they make does not work properly. Insulin is a hormone that allows body tissue to take glucose from the blood and use it for energy or for storage for future use. Metformin works by improving the body's sensitivity to insulin, allowing it to use glucose in the normal way.

The data submitted in support of the application for Metformin Hydrochloride 500 mg/5 ml Oral Solution raised no clinically significant safety concerns and it was therefore judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.

TABLE OF CONTENTS

Module 1

Information about the Decentralised Procedure

Name of the product in the Reference Member State	Metformin Hydrochloride 500 mg/5 ml Oral Solution
Type of application (Eudratrack details)	Level 1 Abridged Level 2 Initial Level 3 10.1 Level 4 Chemical substance Level 5 Prescription only
Name of the active substance	Metformin hydrochloride
Pharmacotherapeutic classification (ATC code)	Biguanides (A10BA02)
Pharmaceutical form and strength(s)	Oral solution, 500 mg/5 ml
Reference numbers for the Mutual Recognition Procedure	UK/H/1042/01/DC
Reference Member State	UK
Member States concerned	IE
Date of start of the procedure	06 December 2006
End date of decentralised procedure	10 July 2007
Marketing Authorisation Number(s)	PL 00427/0139
Name and address of the authorisation holder	Rosemont Pharmaceuticals Limited, Rosemont House, Yorkdale Industrial Park, Braithwaite Street, Leeds LS11 9XE, UK

Module 2

Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

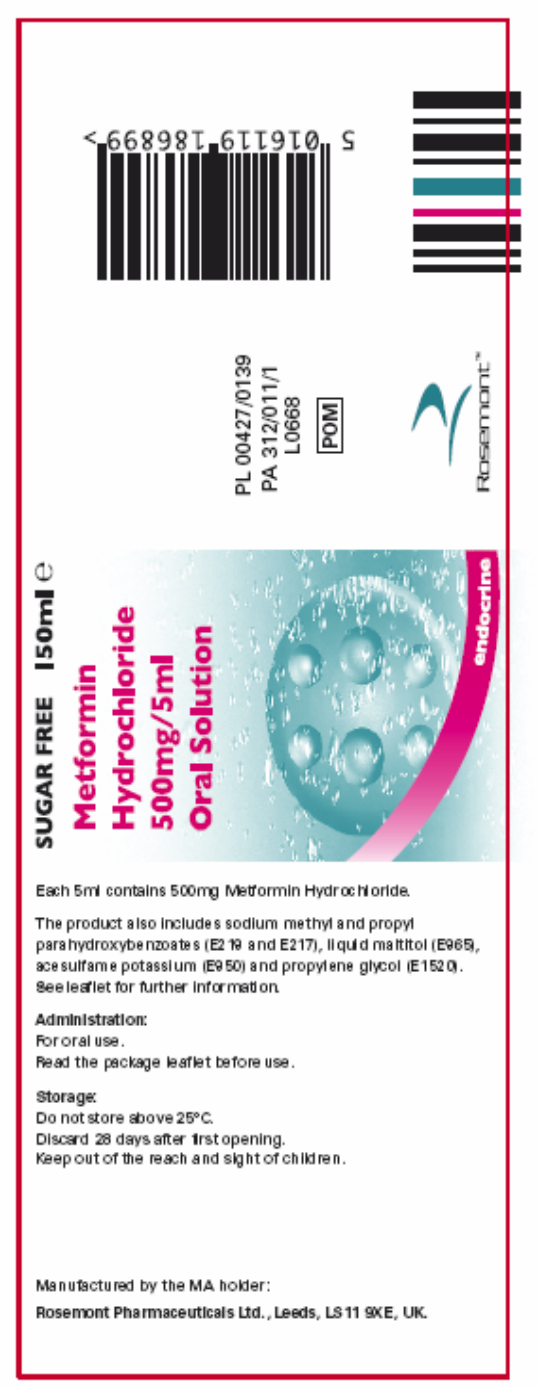
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

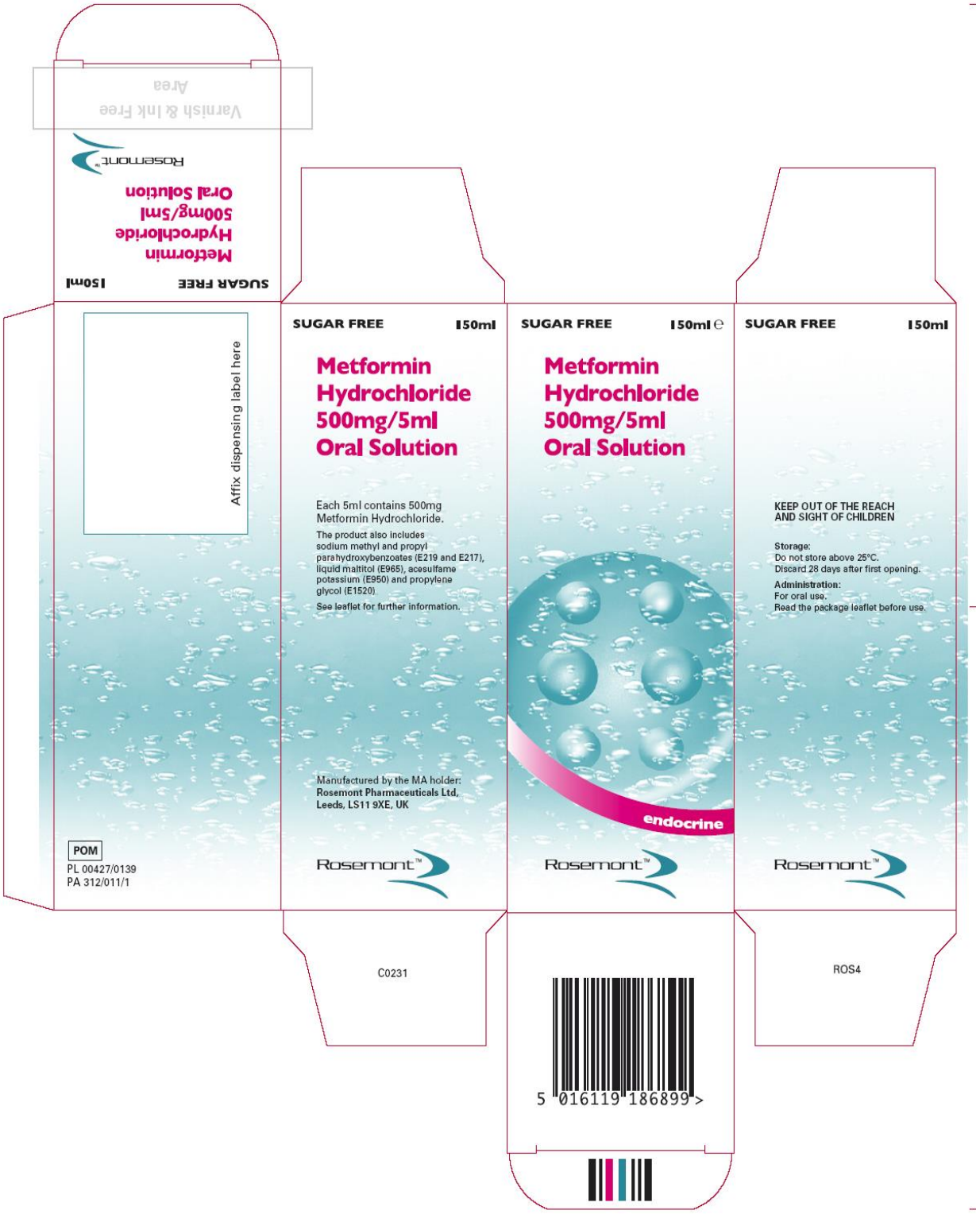
Module 4

Labelling

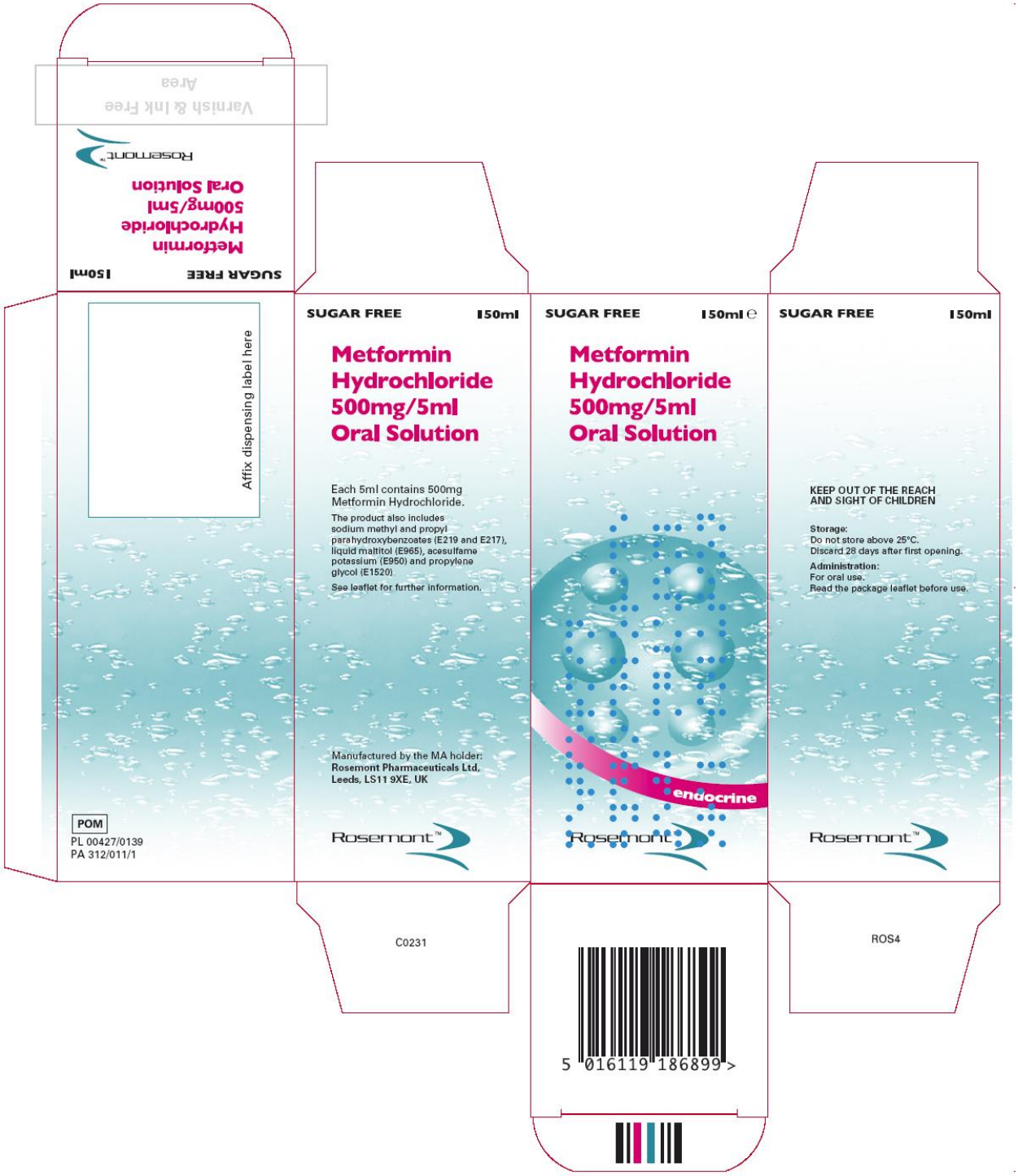
Bottle label :



Carton :


Varnish & Ink Free Area
Rosemont
Metformin Hydrochloride 500mg/5ml Oral Solution
SUGAR FREE 150ml
Affix dispensing label here
POM
PL 00427/0139
PA 312/011/1
SUGAR FREE 150ml
Metformin Hydrochloride 500mg/5ml Oral Solution
Each 5ml contains 500mg Metformin Hydrochloride.
The product also includes sodium methyl and propyl parahydroxybenzoates (E219 and E217), liquid maltitol (E965), acesulfame potassium (E950) and propylene glycol (E1520).
See leaflet for further information.
Manufactured by the MA holder:
Rosemont Pharmaceuticals Ltd,
Leeds, LS11 9XE, UK
Rosemont
C0231
SUGAR FREE 150ml
Metformin Hydrochloride 500mg/5ml Oral Solution
endocrine
Rosemont
5 016119 186899 >
SUGAR FREE 150ml
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
Storage:
Do not store above 25°C.
Discard 28 days after first opening.
Administration:
For oral use.
Read the package leaflet before use.
Rosemont
ROS4

Carton with Braille:



Module 5

Scientific discussion during initial procedure

I. RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Metformin Hydrochloride 500mg/5ml Oral Solution for treatment of type 2 diabetes mellitus is approvable.

II. EXECUTIVE SUMMARY

II.1 Problem statement

Not applicable.

II.2 About the product

Metformin is a biguanide with antihyperglycaemic effects. It lowers both basal and postprandial plasma glucose by inhibiting gluconeogenesis and glycogenolysis; by increasing insulin sensitivity, peripheral glucose uptake and utilisation; and delaying intestinal glucose absorption. It does not stimulate insulin secretion and is unlikely to produce hypoglycaemia.

Proposed indication:
Treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone do not result in adequate glycaemic control.

Proposed posology:
In adults the usual starting dose is one 5 ml spoonful (500 mg) two or three times daily given during or after meals. This can be increased up to 3 g daily after 10-15 days when used as monotherapy, or in combination with other oral antidiabetic agents. Dose adjustments are required for children, adolescents and the elderly.

Pharmacokinetics:
After an oral dose of metformin, T_{max} is reached in 2.5 hours and absolute bioavailability of a 500 mg or 850 mg metformin tablet is approximately 50-60% in healthy subjects. After oral administration, metformin absorption is saturable and incomplete and thus, non-linear. Food slightly delays and decreases the extent of metformin absorption. Plasma protein binding is negligible, but metformin partitions into erythrocytes. Metformin is excreted unchanged in urine. No metabolites have been identified in humans. 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. After single doses of metformin 500 mg, paediatric patients have shown similar pharmacokinetic profiles to those observed in healthy adults.

II.3 General comments on the submitted dossier

This is a standard abridged generic application for Metformin Hydrochloride 500mg/5ml Oral Solution submitted under Article 10.1 of Directive 2001/83/EC, as amended.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place at the sites of final product manufacture and batch release. Satisfactory evidence has been provided from the QP of the drug product manufacturer that the drug substance manufacturers adhere to the principles of GMP in the manufacture of metformin hydrochloride.

Regarding the submitted bioequivalence study, copies of ethical and local regulatory approval correspondence have been provided. Signed statements have been provided in respect of compliance with GCP and the Declaration of Helsinki.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
Copies of the current Certificates of Suitability from the drug substance manufacturer have been provided. The stability data provided support the re-test period of 5 years when stored in closed containers at 25ºC.

Drug Product
The development of the product has been extensively described, the choice of excipients justified and their functions explained. The applicant justified the concentrations of hydroxybenzoate-based preservatives and sweetener acesulfame potassium used in the product, these are based on the acceptable daily intake (ADI) limits set by the WHO. At end of shelf-life, the product remains adequately preserved. The amount of acesulfame is in line with that specified for foodstuffs in Directive 94/35/EC. The manufacturing process is simple and has been adequately described and validated.

The product specification covers appropriate parameters for this dosage form and impurity limits are in line with batch data provided. All analytical methods are either Ph Eur or appropriately validated.

The product will be stored in a Type III 150 ml glass, amber bottle with a child-resistant high-density polyethylene (HDPE), polyethylene (PE) -wadded, tamper-evident closure. Stability studies were performed in line with ICH guidelines in the proposed container. The stability data support the shelf-life of 12 months with the storage condition 'Do not store above 25 ºC.' In-use stability data to support the proposed in-use shelf-life of 1 month were also provided.

III.2 Non clinical aspects
The pharmacodynamic, pharmacokinetic and toxicological properties of metformin hydrochloride are well known. As metformin hydrochloride is a well known active substance, the applicant has not provided any additional studies and further studies are not required.

The non-clinical overview has been written by an independent consultant who is an appropriately qualified and experienced toxicologist. The overview, which is based on a literature review, is adequate. The data in this overview have not raised any new concerns.

There are no objections to the approval of Metformin Hydrochloride 500mg/5ml Oral Solution from the non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics
To support the application, the applicant has submitted a report detailing a single bioequivalence study. Although in some circumstances an exemption for oral solutions may be justified according to the note for guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the applicant has not sought to request an exemption.

The bioequivalence of Metformin Hydrochloride 500mg/5ml Oral Solution was evaluated in a single centre,

single dose, randomised, 2-period, 2-sequence, crossover, comparative study. The applicant's product was compared to Glucophage 500mg tablets (licensed to Merck UK) and the two products were shown to be bioequivalent.

Pharmacodynamics
No new data have been submitted and this is acceptable.

Clinical efficacy
No new data have been submitted and none are required. The efficacy of metformin is well established from its extensive use in clinical practice.

Clinical safety
No new data have been submitted and none are required for this type of application. The safety profile of metformin is well known.

IV. BENEFIT RISK ASSESSMENT

The application contains an adequate review of the published clinical data and bioequivalence has been demonstrated between the test and reference products. No major clinical concerns have been identified. The benefit-risk ratio is favourable. Approval of this marketing authorisation is recommended.

Overall conclusions

QUALITY

The important quality characteristics of Metformin Hydrochloride 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

The pharmacodynamic, pharmacokinetic and toxicological data submitted are satisfactory for an application of this type.

EFFICACY

Clinical studies have demonstrated the efficacy of metformin hydrochloride in the treatment of type 2 diabetes mellitus.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those of the innovator product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE – SUMMARY

The following table lists a non-safety update to the Marketing Authorisation for this product that has been approved by the MHRA since the product was first licensed. The table includes updates that have been incorporated into the text of this Public Assessment Report (PAR) or added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

Date submitted	Application type	Scope	Outcome
21 January 2013	Type IB	To change the invented name in Germany from Metformin hydrochloride 500 mg/5 ml Lösung zum Einnehmen to MetfoLiquid Geriasan 500 mg/5 ml Lösung zum Einnehmen. The common Summary of Product Characteristics (SmPC), label and leaflet text have also undergone minor formatting changes in line with Quality Review of Documents (QRD) guidelines.	Approved 06 September 2013

Annex 1

Reference:	PL 00427/0139, Application 20
Product:	Metformin Hydrochloride 500mg/5ml Oral Solution
Marketing Authorisation Holder:	Rosemont Pharmaceuticals Limited
Active Ingredient(s):	Metformin hydrochloride
Type of Procedure:	Mutual Recognition
Submission Type:	Variation
Submission Category:	Type IB
Submission Complexity:	Standard
EU Procedure Number (if applicable):	UK/H/1042/001/IB/012

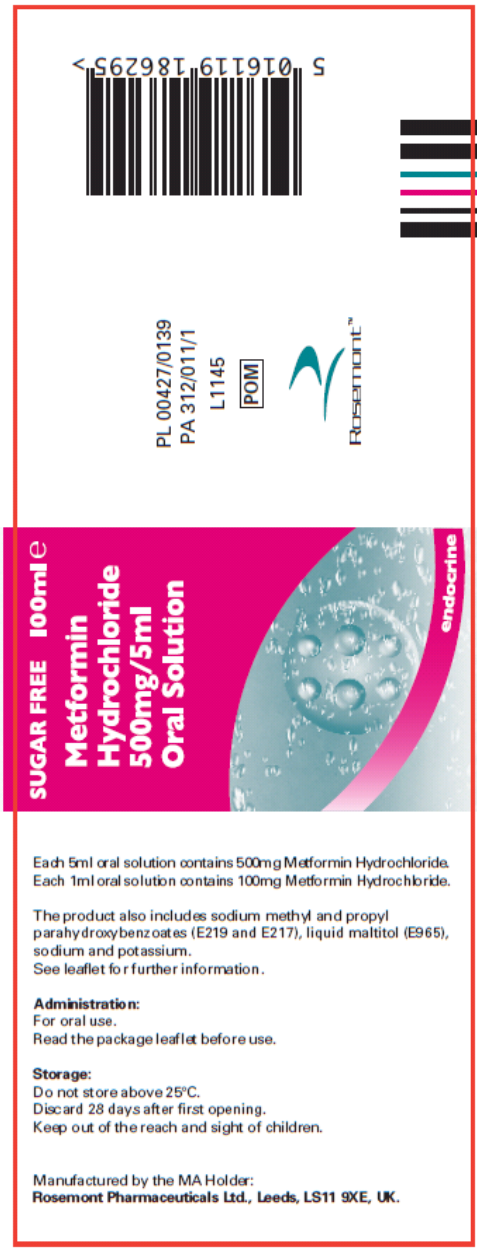
Reason:
To change the invented name in Germany from Metformin hydrochloride 500 mg/5 ml Lösung zum Einnehmen to MetfoLiquid Geriasan 500 mg/5 ml Lösung zum Einnehmen. The common Summary of Product Characteristics (SmPC), label and leaflet text have also undergone minor formatting changes in line with Quality Review of Documents (QRD) guidelines.

Supporting Evidence
Revised SmPC, labelling and leaflet have been provided.

Evaluation
The updated sections of the SmPC, the updated labelling and the leaflet are satisfactory.

Conclusion
The amendments to the SmPC, labelling and leaflet are acceptable and there are no objections to approval.

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website. The revised labelling is presented below.


PL 00427/0139
PA 312/011/1
L1145
POM
Rosemont™
SUGAR FREE 100ml e
Metformin Hydrochloride 500mg/5ml Oral Solution
endocrine
Each 5ml oral solution contains 500mg Metformin Hydrochloride.
Each 1ml oral solution contains 100mg Metformin Hydrochloride.
The product also includes sodium methyl and propyl parahydroxybenzoates (E219 and E217), liquid maltitol (E965), sodium and potassium.
See leaflet for further information.
Administration:
For oral use.
Read the package leaflet before use.
Storage:
Do not store above 25°C.
Discard 28 days after first opening.
Keep out of the reach and sight of children.
Manufactured by the MA Holder:
Rosemont Pharmaceuticals Ltd., Leeds, LS11 9XE, UK.


SUGAR FREE
100ml
Metformin
Hydrochloride
500mg/5ml
Oral Solution
Affix dispensing label here
POM
PL 00427/0139
PA 312/011/1
SUGAR FREE
100ml
Metformin
Hydrochloride
500mg/5ml
Oral Solution
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Rosemont
C0451
SUGAR FREE
100ml
Metformin
Hydrochloride
500mg/5ml
Oral Solution
endocrine
Rosemont
5 016119 186295
SUGAR FREE
100ml
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
Storage:
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Discard 28 days after first opening.
Administration:
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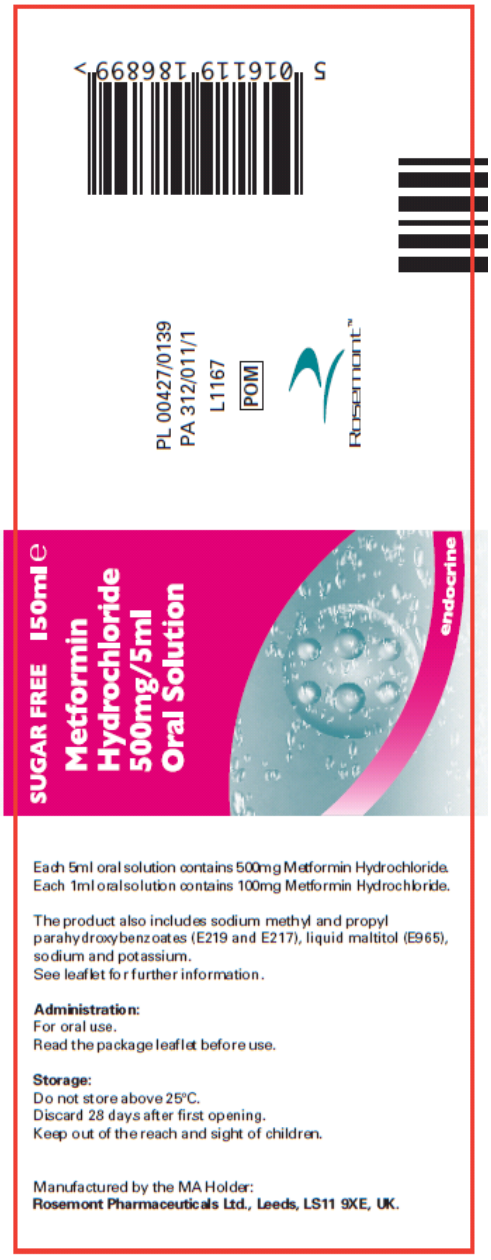
Rosemont
ROS43


PL 00427/0139
PA 312/011/1
L1167
POM
Rosemont
SUGAR FREE 150ml
Metformin Hydrochloride 500mg/5ml Oral Solution
endocrine
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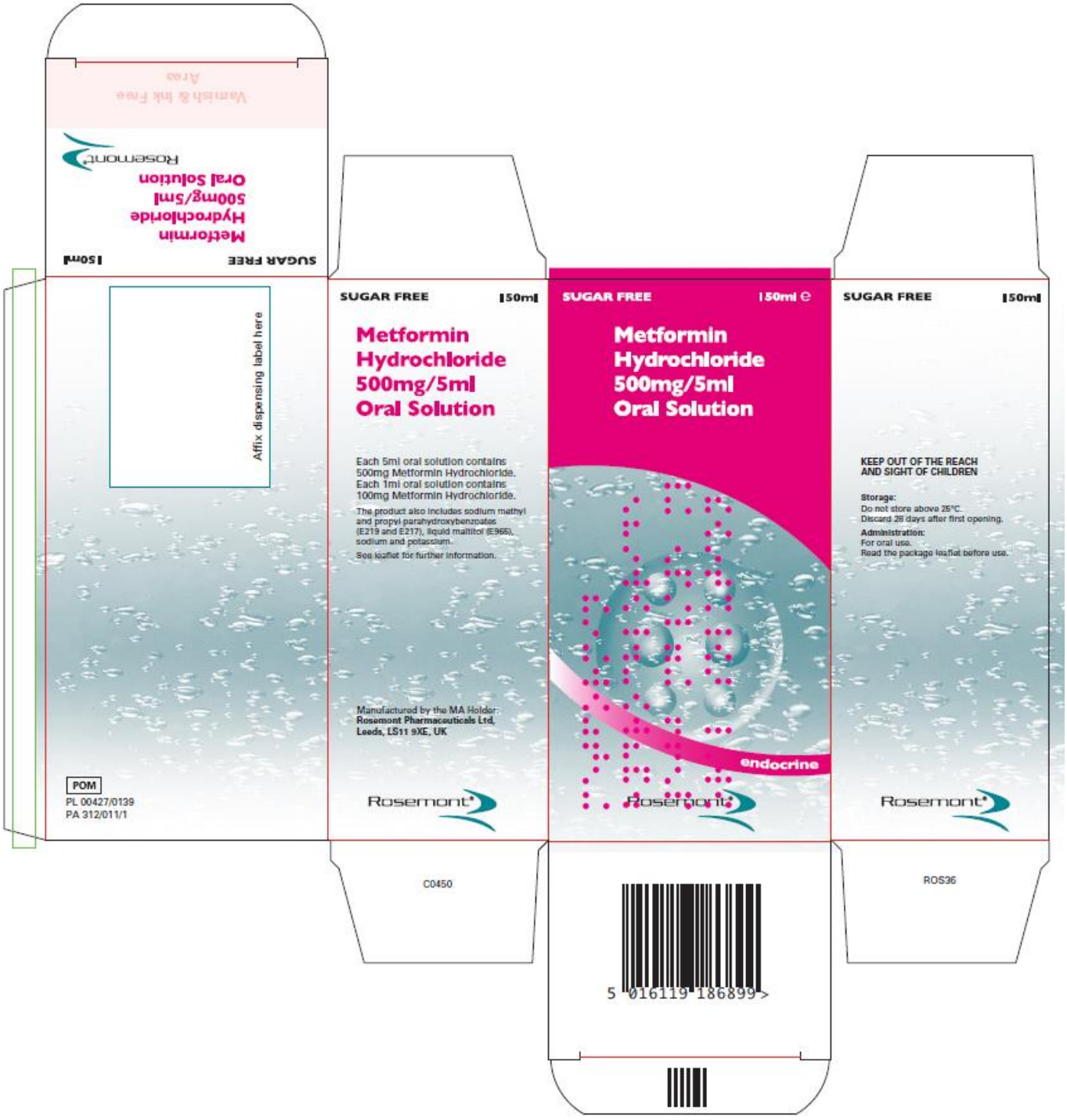

Decision – Approved 06 September 2013