Use of metformin to treat diabetes now expanded to patients with moderately reduced kidney function

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Information on metformin containing medicinal products

Metformin is a medicine used on its own or in combination with other medicines for the treatment of type 2 diabetes. Metformin is used together with diet and exercise to improve control of blood glucose (sugar) levels.

- Medicines containing metformin alone have been authorised nationally in Malta and are marketed as Glucophage and other trade names.
- Medicines containing combinations of metformin with other diabetes medicines in the same tablet e.g Janumet (sitagliptin / metformin hydrochloride) and Eucreas (vildagliptin / metformin hydrochloride) have been authorised centrally through the European Commision.

For more details on metformin containing medicinal products authorised in Malta refer to Annex 1 at the end of this document

New recommendations for patients with kidney impairment will be updated in the product information.

The European Medicines Agency (EMA) has concluded that metformin-containing medicines can now be used in patients with moderately reduced kidney function (GFR [glomerular filtration rate] = 30–59 ml/min) for the treatment of type 2 diabetes. The recommendations are the result of a review by EMA of metformin-containing medicines following concerns that current scientific evidence does not justify a contraindication in patients with moderate reduction of kidney function. Current product information also varies between countries and products within EU and is no longer consistent with clinical guidelines.

- Metformin may increase the risk of a rare but serious complication called lactic acidosis, which occurs when naturally produced lactic acid builds up in the blood faster than it can be removed. Currently, the product information states that metformin must not be used in patients with reduced kidney function because these patients are considered to be at a higher risk of developing lactic acidosis as their kidneys do not remove metformin efficiently enough.

- However, after considering the scientific literature, clinical data, epidemiological studies and clinical guidelines from medical bodies, EMA concluded that the large patient population with **moderately** reduced kidney function can benefit from use of metformin.

Sir Temi Żammit Buildings, Malta Life Sciences Park,
San Ġwann SĠN 3000, Malta
info.medicinesauthority@gov.mt | (+356) 23 439 000
www.medicinesauthority.gov.mt

- Clear dosing recommendations and monitoring before and during treatment aim to minimise any possible increased risk in these patients. The contraindication for patients with severely reduced kidney function will remain (GFR less than 30 ml/min).

- Companies marketing metformin-containing medicines will be requested to closely monitor and analyse future lactic acidosis cases and report these during upcoming periodic safety reviews in order to follow up on any changes in the frequency of this side effect.

- The product information for metformin-containing medicines will be updated (revised current contraindication, information about doses, monitoring and precautions in patients with reduced kidney function) to reflect the new recommendations and to ensure that the same advice is given to all patients across the EU.

The review has been carried out by the Committee for Medicinal Products for Human Use (CHMP). The CHMP opinion has been forwarded to the European Commission, which has issued a final legally binding decision applicable in all EU Member States.

In Malta

Information for Patients

- Metformin is used on its own or with other medicines, together with diet and exercise, for the treatment of type 2 diabetes.

- Up to now, metformin medicines were not recommended for patients with moderate to severe reduction of kidney function. This recommendation has now changed to allow their use in patients with moderately reduced kidney function (GFR=30–59 ml/min). The dose of metformin should be adapted depending on the patient's kidney function. These medicines should still not be used in patients with severely reduced kidney function (GFR less than 30 ml/min).

- Patients with reduced kidney function may be at higher risk of lactic acidosis, a rare but serious side effect of metformin medicines caused by build-up of lactic acid in the blood. However, for patients with only moderately reduced kidney function any risk can be minimised by careful checking of dose and monitoring, allowing these patients to get the benefits these medicines can provide.

- Dehydration (significant loss of body fluids) increases the risk of developing lactic acidosis. If you experience severe vomiting, diarrhoea or fever, are exposed to heat, or drink less fluid than normal, you could become dehydrated. In these cases, stop taking metformin for a short time and speak with your doctor for further instruction.

- If you have any question or concern about your diabetes treatment or your kidney function level, speak with your doctor, nurse or pharmacist.

For Healthcare Professionals

- The review of metformin-containing medicines concluded that they can now be used in patients with moderately reduced kidney function (GFR=30–59 ml/min). Use in patients with GFR<30 ml/min is still contraindicated. GFR should be assessed before initiation of treatment and at least annually thereafter.
- Reduced doses should be considered for patients with moderate reduction of kidney function according to dosage recommendations provided in the updated product information. The product information also details risk factors for lactic acidosis which should be reviewed prior to and during treatment.
- Several fixed-dose combination products containing metformin are available in Europe (see Annex 1). If these products are used in patients with reduced kidney function, restrictions and efficacy regarding the other active substance in the combination, the feasibility of dose adjustment and the alternative of using individual tablets should be considered.
- Some fixed-dose combination products are still not recommended in patients with moderately reduced kidney function because the other active substance in the combination should not be used in these patients. For example, dapagliflozin/metformin (Ebymect, Xigduo) is not recommended in patients with GFR<60 ml/min; canagliflozin/metformin (Vokanamet) and empagliflozin/metformin (Synjardy) are not recommended in patients with GFR<45 ml/min and should not be started in patients with GFR<60 ml/min. For more details on specific fixed-dose combination products see the latest product information which available from the EMA website.
- These latest recommendations will result in harmonisation of product information about the use of metformin in patients with reduced kidney function and the precautions for lactic acidosis across the EU.

For more information, including a list of references, please see the European Medicines Agency's press release

Reporting Adverse Drug Reactions

Healthcare professionals and patients are encouraged to maintain vigilance on metformin containing medicinal products. Suspected Adverse Drug Reactions (side effects) may be reported using the Medicines Authority ADR form, which can be downloaded from **www.medicinesauthority.gov.mt/adrportal** and sent by mail to Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 or by email to **postlicensing.medicinesauthority@gov.mt** or to the marketing authorisation holder or their local representatives.

Post-Licensing Directorate
Medicines Authority

Healthcare professionals and patients are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.

Annex 1: Tables of metformin containing medicinal products authorised in Malta

Nationally Authorised Products

Medicine Name	Active Ingredient(s) + Strength	Pharmaceutical Form	Authorisation Number	Marketing Authorisation Holder
Metformin 500 - 1A Pharma	Metformin hydrochloride 500 milligrams	Film-coated tablet	AA939/02301	1A Pharma GmbH
Metformin 500 - Actavis	Metformin hydrochloride 500 milligrams	Coated tablet	AA702/01301	Actavis UK Limited
Metformin 850 - Actavis	Metformin hydrochloride 850 milligrams	Tablet	AA702/01302	Actavis UK Limited
Metformin Oral Solution - Alapis	Metformin hydrochloride 100 milligrams/millilitre	Oral solution	MA828/00601	Alapis S.A.
Metformin 500 - Aurobindo	Metformin hydrochloride 500 milligrams	Coated tablet	AA807/01301	Aurobindo Pharma (Malta) Limited
Metformin 850 - Aurobindo	Metformin hydrochloride 850 milligrams	Coated tablet	AA807/01302	Aurobindo Pharma (Malta) Limited
Metformin 500 - Bristol	Metformin hydrochloride 500 milligrams	Film-coated tablet	AA737/01001	Bristol Laboratories Limited
Glibomet	Glibenclamide 2.5 milligrams / Metformin hydrochloride 400 milligrams	Film-coated tablet	MA203/00101	Laboratori Guidotti S.p.A.
Metforal 500	Metformin hydrochloride 500 milligrams	Film-coated tablet	AA203/00201	Laboratori Guidotti S.p.A.
Metforal 850	Metformin hydrochloride 850 milligrams	Film-coated tablet	AA203/00202	Laboratori Guidotti S.p.A.
Metformin Oral Solution Lamda	Metformin hydrochloride 1000 milligrams/5 millilitre	Oral solution	MA1072/00201	Lamda Laboratories SA
Glucophage 500	Metformin hydrochloride 500 milligrams	Film-coated tablet	PI521/05001A	Medicem Limited
Brot	Metformin hydrochloride 500 milligrams	Film-coated tablet	AA032/06901	Medochemie Limited
Glucophage 500	Metformin hydrochloride 500 milligrams	Film-coated tablet	MA165/00101	Merck Sante S.A.S.

Glucophage 850	Metformin hydrochloride 850 milligrams	Film-coated tablet	MA165/00102	Merck Sante S.A.S.
Glucophage 500	Metformin hydrochloride 500 milligrams	Film-coated tablet	PI908/02701A	NeoFarma Pharmaceuticals Limited
Glyformin 500	Metformin hydrochloride 500 milligrams	Film-coated tablet	MA084/00901	Remedica Limited
Sophamet 500	Metformin hydrochloride 500 milligrams	Film-coated tablet	AA1035/00201	Sopharma AD
Metformin 500 - Special Concept Development (UK)	Metformin hydrochloride 500 milligrams	Tablet	AA1160/00101	Special Concept Development (UK)
Metformin Oral Solution - Syri	Metformin hydrochloride 100 milligrams	Oral solution	MA1101/00601	Syri Limited
Metformin 500 - Wockhardt	Metformin hydrochloride 500 milligrams	Coated tablet	AA154/06501	Wockhardt UK Limited
Metformin 850 - Wockhardt	Metformin hydrochloride 850 milligrams	Coated tablet	AA154/06502	Wockhardt UK Limited

Centrally Authorised Products

Medicine Name	Active Ingredients	Pharmaceutical form	Agency product number	Marketing Authorisation Holder
Competact	Pioglitazone / metformin	Film-coated tablet	EMEA/H/C/655	Takeda Pharma A/S
Ebymect	Dapagliflozin propanediol monohydrate / Metformin hydrochloride	Film-coated tablet	EMEA/H/C/4162	AstraZeneca AB
Efficib	Sitagliptin / Metformin hydrochloride	Film-coated tablet	EMEA/H/C/896	Merck Sharp & Dohme Ltd
Eucreas	Vildagliptin / Metformin hydrochloride	Film-coated tablet	EMEA/H/C/807	Novartis Europharm Limited
Glubrava	Metformin hydrochloride / Pioglitazone hydrochloride	Film-coated tablet	EMEA/H/C/893	Takeda Pharma A/S
Icandra	Vildagliptin / Metformin hydrochloride	Film-coated tablet	EMEA/H/C/1050	Novartis Europharm Limited

Janumet	Sitagliptin / Metformin hydrochloride	Film-coated tablet	EMEA/H/C/861	Merck Sharp & Dohme Ltd
Jentadueto	Linagliptin / Metformin hydrochloride	Film-coated tablet	EMEA/H/C/2279	Boehringer Ingelheim International GmbH
Komboglyze	Saxagliptin / metformin hydrochloride	Film-coated tablet	EMEA/H/C/2059	AstraZeneca AB
Ristfor	Sitagliptin / Metformin hydrochloride	Film-coated tablet	EMEA/H/C/1235	Merck Sharp & Dohme Ltd
Synjardy	Empagliflozin / Metformin	Film-coated tablet	EMEA/H/C/3370	Boehringer Ingelheim GmbH
Velmetia	Sitagliptin / Metformin hydrochloride	Film-coated tablet	EMEA/H/C/862	Merck Sharp & Dohme Ltd
Vipdomet	Alogliptin / Metformin	Film-coated tablet	EMEA/H/C/2654	Takeda Pharma A/S
Vokanamet	Canagliflozin / Metformin hydrochloride	Film-coated tablet	EMEA/H/C/2656	Janssen-Cilag International N.V.
Xigduo	Dapagliflozin propanediol monohydrate / Metformin hydrochloride	Film-coated tablet	EMEA/H/C/2672	Bristol-Myers Squibb/AstraZeneca EEIG
Zomarist	Vildagliptin / Metformin hydrochloride	Film-coated tablet	EMEA/H/C/1049	Novartis Europharm Limited

Feedback Form

The Medicines Authority thanks you for the time taken to read this safety circular. The dissemination of safety circulars is an important process whereby Regulatory Authorities can communicate important issues with respect to the safety of medicines, in order to protect and enhance public health

The Medicines Authority kindly invites your anonymous feedback about the regulatory action being communicated. This may be returned by folding this form (address side up), stapling the ends and then posting (no stamp required).

Feedback:

We thank you for your interest and look forward to hearing your opinion.

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Pharmacovigilance Section

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Medicines Authority

Sir Temi Żammit Buildings

Malta Life Sciences Park

San Ġwann SĠN 3000