



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Gliclazide

Proprietary Product Name: Gliclazide Gppl MR 30;
Gliclazide Gxp MR 60; Gliclazide Genpar MR 60

Sponsor: Generic Partners Pty Ltd

July 2016

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<https://www.tga.gov.au>>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Common abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
AUC	Area under the concentration versus time curve
C _{max}	Peak plasma concentration
EU	European Union
ER	Extended release
IM	Immediate release
MR	Modified release
PBS	Pharmaceutical Benefit Scheme
T _{max}	Time to peak plasma concentration

I. Introduction to product submission

Submission details

Type of submission:	New generic medicine
Decision:	Withdrawn
Date of decision:	23 February 2016
Date of entry onto ARTG:	Not applicable
Active ingredient(s):	Gliclazide
Product name(s):	<i>30 mg tablet:</i> Gliclazide Gppl MR 30 <i>60 mg unscored tablet:</i> Gliclazide Gxp MR 60; Gliclazide Genpar MR 60
Sponsor's name and address:	Generic Partners Pty Ltd 313 Burwood Rd Hawthorn VIC 3122
Dose form(s):	Modified release tablet
Strength(s):	30 mg and 60 mg
Container(s):	Blister packs
Pack size(s):	14 or 100 tablets (30 mg) and 14 or 60 tablets (60 mg)
Approved therapeutic use:	Not applicable
Route(s) of administration:	Oral (PO)
Dosage:	60 mg/day
ARTG number (s):	Not applicable

Product background

This AusPAR describes the application by the Generic Partners Pty Ltd (the sponsor) to register a new generic for gliclazide with the following indication:

Type II Diabetes in association with dietary measures when dietary measures alone are inadequate to control blood glucose. During controlled clinical trials in patients with type II diabetes, a modified release formulation of gliclazide (30 mg-120 mg), taken as a single daily dose, was shown to be effective long term in controlling blood glucose levels, based on monitoring of HbA1c.

Gliclazide reduces blood glucose levels by stimulating insulin secretion from the beta (β) cells of the islets of Langerhans. Gliclazide shows high affinity, selectivity and reversible binding to the β cell adenosine triphosphate (ATP) gated potassium (K_{ATP}) channels with a low affinity for cardiac and vascular K_{ATP} channels. Increased postprandial insulin and C-

peptide secretion persists after two years of treatment. Gliclazide also has extra-pancreatic effects and haemovascular properties.

The proposed gliclazide modified release tablets have been developed as a generic equivalent to Diamicon 60 mg MR¹ (Servier) and Glyade MR 30 mg² (Servier, marketed by Alphapharm). The proposed indications are the same as those registered for Diamicon 60 mg MR and Glyade MR 30 mg.

Approvals have been granted in Europe and Canada for the 30 mg and scored 60 mg tablets. The application for the unscored 60 mg tablet is Australian specific. Specifications have been set based on those approved in the European Union (EU) as well as the results from testing of the 30 mg Bioequivalence (BE) batch at the time of commencement of the study.

The proposed dosages are different from those of the reference product Diamicon 60 mg MR (sponsor Servier) because this proposed generic does not have a score line, whereas the reference product (Diamicon) does. The proposed dosage changes are shown below using strikethrough (deletion) and yellow highlighting (addition):

For adult use only

~~APO-GLICLAZIDE MR 60 mg modified release tablets have a break bar and may be administered as whole or as half tablets (see Pharmacokinetics).~~

So that the modified release properties of the product can be maintained, tablets should not be chewed or crushed.

The tablet is not scored and should not be broken. If 30 mg doses are required, other brands are available.

~~Whole or half tablets of the 60 mg strength~~ **Gliclazide 60 mg modified release tablets** should be taken with food because there is an increased risk of hypoglycemia if a meal is taken late, if an inadequate amount of food is consumed or if the food is low in carbohydrate. It is recommended that the medication be taken at breakfast time. If a dose is forgotten, the dose taken on the next day should not be increased.

~~A single daily dose provides an effective blood glucose control. The daily dose may vary from half a 60 mg tablet to two 60 mg tablets per day i.e. 30 mg to 120 mg taken orally.~~

The initial recommended dose is 30 mg_z, even in elderly patients (≥ 65 years). As with all hypoglycaemic agents, the dose should be titrated according to the individual patient's response. Titration should be carried out in steps of 30 mg, according to the fasting blood glucose response. Each step should last for at least two weeks. A single daily dose provides an effective blood glucose control. The single daily dose may be between 30 mg and 120 mg. The daily dose should not exceed 120 mg.

Previously untreated patients should commence with a 30 mg dose and will benefit from dose titration until the appropriate dose is reached.

The sponsor withdrew the application for the proposed generic 30 mg MR tablet, during the current evaluation. The quality evaluator raised some concerns around the dissolution limits for the 30 mg MR tablet. It is unclear whether these could have been resolved.

¹ MR=modified release

² Gliclazide 30 mg modified release tablets are available in Australia in other brands.

Regulatory status

This is an application for a new generic. The originator product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 11 November 2009 (Diamicron) and 7 September 2007 (Glyade).

At the time the TGA considered this application, similar applications had been approved in the EU (decentralised procedure) and Canada (see Table 1).

Table 1: International regulatory status

Country	Status	Indications	Comments
EU Decentralised procedure	Approved 26 June 2014	[Product name] is indicated in adults for the treatment of non-insulin dependent diabetes (Type 2) when dietary measures, physical exercise and weight loss alone are not sufficient to control blood glucose.	
Canada	Patent hold April 2014 Approved May 2014 (30 mg)	Control of hyperglycaemia in gliclazide responsive diabetes mellitus of stable, mild, non-ketosis prone, maturity onset or adult type which cannot be controlled by proper dietary management and exercise, or when insulin therapy is not appropriate. <i>Geriatrics ≥ 65 years of age:</i> No significant differences in efficacy and tolerance were observed between patients over 65 years of age and younger patients; however greater sensitivity some older individuals cannot be ruled out (see Warnings and Precautions-Special Population, and Dosage and Administration). <i>Pediatrics (< 18 years of age):</i> Safety and effectiveness of gliclazide in children have not been established. TRADENAME is therefore not recommended for use in children and adolescents.	30 mg strength approved as split from 60 mg strength. Patent hold is on 60 mg strength.
	Patent hold August 2014 Approved 31 March 2015.		Patent hold is on 60 mg strength. Approved 31 March 2015.

Product Information

As this application was withdrawn before a decision had been made by the TGA there are no approved Product Information (PI) documents for the proposed products.

II. Quality findings

Introduction

Both of the proposed tablet strengths are unscored. The reference product Glyade MR 30 mg tablet is also unscored. However the reference product Diamicon 60 mg MR 60 mg tablet is scored.

The submission is a resubmission which proposed to register an unscored 30 mg tablet and a 60 mg scored tablet. A previous submission was rejected (principally) by the TGA due to the lack of bioavailability on the 30 mg tablet and the halved 60 mg tablet. The sponsor appealed this initial decision under section 60 of the Therapeutic Goods Act but the decision was not changed.

A different set of trade names are proposed for the two strengths (see *Submission details, Tradenames* above). Those for the 30 mg tablet were accepted previously. Those for the 60 mg tablet are new to distinguish them from the previous trade names for the scored 60 mg tablet. The clinical advice is that all these names are acceptable.

The 30 mg tablet described in this submission is the same as the 30 mg tablet described in the previous submission. The 60 mg tablet is the same formulation as described in the previous submission but it is unscored (previously scored).

- This lack of a score line on the 60 mg tablet when the reference product contains a score line is of clinical concern and there will be a separate clinical evaluation of this issue.

Both strengths of the tablet are packaged in blister packs (both polyvinyl chloride-Aluminium (PVC-Al) and PVC- Polyvinylidene chloride (PVDC)/Al). The proposed 30 mg tablet will be supplied in packs of 14 or 100 tablets as compared to the reference product which only has a 100 tablet pack. The 60 mg tablet will be supplied in packs of 14 or 60 tablets, compared to the reference product which only has a 60 tablet pack. It will be clarified that the 14 tablet pack is a sample pack.

The initial recommended dose is 30 mg per day and titrated according to the individual patient's response. The maximum daily dose is 120 mg.

There is a British Pharmacopeia (BP)/European Pharmacopeia (EP) monograph for Gliclazide drug substance and a BP monograph for Gliclazide (immediate release) tablets. However there are no United States Pharmacopeia (USP) monographs and no BP monograph for the proposed modified release tablets.

The sponsor has identified aspects of this submission that differ from aspects of the previous submission as shown below:

Quality changes are consistent with the previous application with the exception of:

- Updated Certificate of suitability (CEP) from the same active pharmaceutical ingredients (API) source (approved in the EU and Canada)
- Inclusion of commercial scale batch data for 30 mg strength tablet
- Inclusion of an unscored 60 mg tablet batch

- Updated stability data
- Comparative dissolution testing of unscored 60 mg tablet to the previously submitted scored 60 mg tablet
- Updates to specification-dissolution limits for the 30 mg strength have been determined based on the test product batch used for the BE study. Dissolution limits for the unscored 60 mg tablet have been determined based on the limits approved in the EU as the same bioequivalence studies were used.

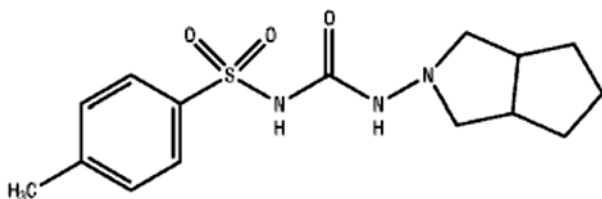
Where relevant, information which was identified as being the same as provided in the previous submission will be referenced in this report.

Note: This evaluation report covers the chemical, manufacture, quality control, stability and bioavailability aspects of the product. Where fermentation, sterilisation or microbiological testing is involved in its manufacture and quality control the relevant data have been referred to the TGA's Office of Laboratories and Scientific Services (OLSS) for assessment.

Drug substance (active ingredient)

Gliclazide has the following chemical name 1-(3-azabicyclo[3.3.0]oct-3-yl)-3-p-tolylsulphonylurea 1-(Hexahydrocyclopenta[c]pyrrol-2(1H)-yl)-3-[(4-methylphenyl)sulfonyl]urea (per EP monograph) and the following chemical structure, formula and molecular weight (Figure 1):

Figure 1: Chemical structure



Molecular Formula: C₁₅H₂₁N₃O₃S

Chirality: Achiral

Molecular Weight: 323.4

The drug substance is practically insoluble in water but freely soluble in dichloromethane, sparingly soluble in acetone and slightly soluble in ethanol 96%.

The Certificate of Suitability (CEP) provided with this submission is an update of that provided with the previous submission. It was dated 25 November 2013 and has no expiry date. The CEP has an additional test for related solvents.

The drug substance specification included the BP monograph parameters, plus additional tests for residual toluene and particle size distribution.

The specifications applied to the drug substance by the finished product manufacturer are unchanged from the previous submission (as are the test methods). The specifications have an additional test for microbial quality.

Newer batch analysis data have been provided. These show compliance with the specifications.

Drug product

The following drug products have been proposed:

- 30 mg modified release tablets: White biconvex capsule shaped tablet with 'GLI 30' on one side and plain on the other side.
- 60 mg modified tablets (unscored): White biconvex oval shaped tablet engraved with 'GLI' and '60' on both sides of the tablet.

The gliclazide extended release tablets contain the following ingredients gliclazide, lactose monohydrate, hypromellose (HPMC K100 LV), hypromellose (HPMC K4M CR, magnesium stearate.

Both strengths of the proposed product are direct scales. They are distinguished by the tablet shaped and engraving symbols. There has been no change in the composition of either tablet strengths.

The excipients are typical for this type of dosage form. These excipients were also used in the Australian innovator's product.

The formulation development section is assumed to remain unchanged compared to the data provided in an earlier submission.

However, the appearance of the 60 mg tablets has been changed to remove the score line.

Gliclazide is not hygroscopic. Solubility generated and permeability data (in PI) suggest that gliclazide belongs to Biopharmaceutics Classification System (BCS) Class II drug (high permeability/low solubility). Appropriate particle size control has been applied for the drug substance to be used in the proposed product.

Process validation has been performed with three production scale batches of the 30 mg modified release tablets. The results complied with the in-process and release specification limits and are consistent between batches.

Process validation was also performed for the one additional batch of 60 mg tablets which was unscored. The results complied with the in-process and release specification, apart from the deviation of thickness results. Given that this deviation does not significantly affect the dissolution profile, this issue will not be pursued.

Process validation batch results for the pilot scale batches (30 mg) and the scored tablet 60 mg were discussed in the previous submission and the results were deemed acceptable.

Control of drug product

There is no BP or USP monograph for gliclazide modified release tablets. Both strengths of the proposed product are controlled in accordance with in-house specifications.

These differ from those accepted previously in the following ways:

- The appearance of the 60 mg tablets has been changed to remove reference to the score line.
- The expiry limit for Impurity A in the 60 mg tablets has been increased. It is likely that the previous limit was a typographical error and the expiry limit was previously accepted for both strengths.
- The dissolution limits have been changed for both strengths.
- The currently proposed dissolution limits *differ from* those previously proposed, which were based on the dissolution results of the batch of 60 mg tablets used in the

bioequivalence studies and the same for both strengths (as only bioequivalence data was only provided for the 60 mg strength).

Certificates of Analysis for the pilot scale and production scale batches of the 30 mg tablet have been provided. The results complied with the release Finished Product Specification and are consistent between batches.

Certificates of Analysis for three batches of 60 mg scored tablet (former appearance) and one batch of the 60 mg unscored tablet (proposed appearance) have been provided. Apart from *Appearance and Dissolution*, all batches (scored or unscored) complied with the proposed finished product Specification for all parameters.

The stability of the proposed product under accelerated and normal storage conditions has been investigated.

The stability data supports the shelf-life assignment of *36 months, stored below 25°C* for batches packaged in PVC/Al and PVC/PVDC-Al blister pack.

Post approval stability protocol and stability commitment

A commitment was provided that the first three commercial batches of both strengths will be placed on long term conditions, and thereafter one batch per year of each strength in accordance with the protocol below. The sponsor should note that this is a critical dosage form and as such the maximum batch scale accepted for the 60 mg tablets is 120,000 tablets: a Category 3 Application will be required to increase this to 1.2 million tablets.

An assurance was provided that the authorities will be notified immediately in the event of any batch failures or unexpected trends becoming evident during the course of the trials.

Biopharmaceutics

Summary of bioavailability studies

A justification for the lack of a bioequivalence study using the proposed unscored 60 mg tablet based on comparative dissolution compared to the scored 60 mg tablets which was shown to be bioequivalent to the reference product Diamicron 60 mg MR tablet has been included.

Summary of human pharmacokinetics

Recommended dose

The initial recommended dose is 30 mg, even in elderly patients (≥ 65 years). The dosage should be titrated in 30 mg increment every two weeks according to the fasting blood glucose response. The daily dose should not exceed 120 mg.

Rate and extent of absorption

Hydration of the tablets induces formation of a gel to activate drug release. Plasma levels increase progressively, resulting in a plateau shaped curve from the sixth to the twelfth hour after administration. Intra-individual variability is low.

Gliclazide is completely absorbed and food intake does not affect the rate or degree of absorption. The relationship between the dose administered and the area under the concentration curve as a function of time is linear for doses of gliclazide up to 90 mg/day. At the highest evaluated dose (135 mg/day), the area under the concentration versus time curve (AUC) increases slightly more than proportionally to the dose.

Distribution

Gliclazide has a relatively low volume of distribution. It is strongly protein bound (approximately 94%).

Metabolism and elimination

Gliclazide is extensively metabolised in the liver via Phase I and Phase II routes, and only a small fraction of the drug is excreted in the urine unchanged. The metabolites have no significant pharmacodynamic effect and are primarily eliminated via the kidneys (60 to 70%) with 10 to 20% appearing in the faeces. The terminal elimination half-life of gliclazide is approximately 16 hours. The clearance of gliclazide has been found to be slightly reduced as a function of age.

Food effects

Food intake does not affect the rate or degree of absorption of gliclazide.

The tablets should be taken with food due to the increased risk of hypoglycaemia if a meal is taken late, if an inadequate amount of food is consumed or if the food is low in carbohydrate. It is recommended that the medication be taken at breakfast time.

Advisory committee considerations

See *Quality summary and conclusions* below.

Quality summary and conclusions

There are no further issues that require resolution and approval of registration of the proposed 60 mg products is recommended from a pharmaceutical chemistry and biopharmaceutics perspective.

However given the issues with larger batches, the TGA's Pharmaceutical Chemistry Subcommittee (PCS) of the Advisory Committee on Prescription Medicines (ACPM) recommends that it should be made a condition of registration that any future submission to increase the batch size of the 60 mg tablets above 120,000 tablets should be accompanied with stability data showing compliance with the accepted dissolution limits.

The sponsor has withdrawn the 30 mg strength from this application.

The following issues relate to this application:

- The proposed shelf life of 36 months when stored below 25 °C in PVC/Al and PVC/PVDC-Al blister packs is supported by the data for the unopened product.
- The PI is acceptable from a quality perspective.
- The sponsor has updated the colour mock-up blister and carton labels which are acceptable from a quality perspective.

Note: A statement '*The tablet is not scored and should not be broken. Swallow whole*' has been added to the revised carton labels for the 60 mg gliclazide tablets, in response to the clinical question. This issue is for the clinical evaluator to assess (also noting that the 30 mg strength is no longer proposed in this application).

- Acceptable Good Manufacturing Practice (GMP) evidence has been provided for all of the nominated overseas manufacturers listed.
- The evaluator has checked and made the appropriate changes to the Provisional ARTG Record (PARs). The sponsor should check and advise the TGA of any error or omission that requires amendment.

- The finished product specifications (release and expiry) are acceptable.
- The proposed trade names are acceptable from a clinical perspective.
- Summary of Biopharmaceutic data and/or justification is provided below:
 - The sponsor has provided justification for not performing bioequivalence studies on the unscored tablet 60 mg on the basis that bioequivalence was previously established for the proposed scored 60 mg against the Australian innovator product 60 mg tablet (Diamicron MR 60).
 - As the two tablets are the same formulation, manufactured by the same process and only differ in appearance, this justification relies on the ability to demonstrate that the dissolution profiles between the scored 60 mg tablet and the unscored 60 mg tablets are similar across the pH range. The information provided supported this justification and therefore the justification is acceptable from a quality perspective.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

The TGA sought the advice of two independent external clinical experts on the lack of the score line on the proposed generic 60 mg MR tablet see *Overall conclusion and risk/benefit assessment below for details*.

V. Pharmacovigilance findings

There was no Risk Management Plan evaluation conducted for this application.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Introduction

Key concern

Lack of a score line on the proposed generic tablet

The reference product (Diamicron 60 mg MR; sponsor: Servier) has a deep score line, allowing the 60 mg tablet to be broken into two (equal) 30 mg halves. In contrast, the proposed generic does not have a score line.

Lack of a score line on the proposed generic tablet is because of Australian specific patent issues.

The sponsor (Generic Partners) of the proposed generic 60 mg MR tablet has informed the TGA that they have not submitted a tablet with a score line because patent issues have emerged with the score line in Australia.

In a previous submission in Australia in 2013 (which was rejected because of pharmaceutical chemistry problems, see below) the (then) proposed Australian generic 60 mg MR tablet, from this particular sponsor, had a score line.

The sponsor's generic 60 mg MR tablet has a score line in various EU countries and Canada.

Score line for the reference product (Diamicron) is based on more evidence than the usual score line

Setting aside the issue of generics with or without score lines for a moment; to claim a functional score line, originator/reference products usually comply with the content and mass uniformity requirements of the EP or the FDA's 'Guidance for Industry: Tablet Scoring' (2013).

However, the sponsor of Diamicron (the reference product) was required to do more than just show that there is no loss of mass on breaking the tablet. More, specifically, the sponsor of Diamicron had to establish via pharmacokinetic studies that the two halves of the 60 mg MR scored tablet were bioequivalent to the whole 60 mg MR tablet. This is reflected in the PI:

Pharmacokinetics

Pharmacokinetic studies have demonstrated bioequivalence between a Diamicron 60 mg MR tablet and two halves (each half containing 30 mg gliclazide) of one Diamicron 60 mg MR tablet.

Score line is an integral part of the way the reference product is used in Australia

The TGA has been informed that, in Australia, the 30 mg tablet is infrequently dispensed by pharmacists. That is, the current practice is for pharmacists to typically dispense only the 60 mg tablet.

When patients start on gliclazide, they are up-titrated from 30 mg to 60 mg, then 90 mg and 120 mg (the maximum recommended dose). This up-titration is conveniently done by breaking the 60 mg tablet; otherwise the patient would need 2 lots of tablets: 30 mg and 60 mg (each step is typically for 2 weeks). Also, although the 120 mg dose is the most common final dose, a 90 mg final dose is not that uncommon. Further, some patients may need to be back-titrated from 120 mg to 90 mg, say.

In short, for the reference product (Diamicron), even when the medical practitioner has prescribed a 30 mg or 90 mg dose, the TGA has been told that current practice is for the pharmacist to dispense the 60 mg tablet; the patient is instructed to divide the scored 60 mg tablet into two 30 mg halves.

In keeping with this, the Australian approved PI for the reference product (Diamicron 60 mg MR) includes the following information.

Dosage and administration

For adult use only

Diamicron 60 mg MR tablets have a break bar and may be administered as whole or as half tablets (see Pharmacokinetics).

So that the modified release properties of the product can be maintained, tablets should not be chewed or crushed.

A single daily dose provides an effective blood glucose control. The daily dose may vary from half a tablet to two tablets per day i.e. 30 mg to 120 mg taken orally. The initial recommended dose is half a tablet (30 mg), even in elderly patients (≥ 65 years).

As with all hypoglycaemic agents, the dose should be titrated according to the individual patient's response. Titration should be carried out in steps of 30 mg, according to the fasting blood glucose response. Each step should last for at least two weeks. A single daily dose provides an effective blood glucose control. The single daily dose may be between half a tablet and two tablets (30 mg and 120 mg). The daily dose should not exceed two tablets (120 mg).

Previously untreated patients should commence with half a tablet of Diamicron 60mg MR (30 mg) dose and will benefit from dose titration until the appropriate dose is reached.

Data on Australian prescribing practices

The most recent data are from Pharmaceutical Benefits Branch (PBS), Commonwealth Department of Health. Australian Statistics in Medicines 2014, accessed December 2015 <<https://www.pbs.gov.au/info/browse/statistics>>

The following data are for the total of PBS scripts, Repatriation Pharmaceutical Benefits Scheme (RPBS)³ scripts and under-co-payments scripts.

- Gliclazide 60 mg MR (scored): 1,468,282 scripts
- Gliclazide 30 mg MR: 235,817 scripts

Based on these data, the 60 mg MR tablet represents 86% scripts written for MR gliclazide. This supports the view that the most common practice is for pharmacists to dispense the 60 mg MR tablet and for patients to use the deep score line to halve the 60 mg tablet should they require a 30 mg or 90 mg dose.

Of course, all doses can be obtained from the 30 mg MR tablets. The TGA's preferred approach is for the sponsor to register and market their generic 30 mg MR until such time as the patent on the score line expires in Australia. This is what happened in Canada.

Overseas regulatory status

The sponsor's/manufacture's proposed unscored 60 mg tablet is not currently registered in any comparable country. Scored versions are registered in various EU countries and Canada; see below.

EU

A (scored) 60 mg MR tablet was registered in various EU countries in 2014 (reference member state (RMS): Denmark; concerned member states (CMS): Austria, Belgium, Bulgaria, Estonia, France, Lithuania, Portugal, Slovenia, Slovakia and Hungary).

Canada

Both 30 mg and 60 mg (scored) MR tablets were approved in Canada in 2014 but only 30 mg MR tablet was initially marketed because of patent issues with score line for the 60 mg MR tablet. These appear to have resolved/expired and the (scored) 60 mg MR strength has been subsequently marketed in Canada.

³The Australian Repatriation system is based primarily on the principle of compensation to veterans and eligible dependants for injury or death related to war service. In certain cases, treatment is also provided for accepted injuries or conditions that are not service-related or have occurred as a result of other than war service. Through the *Veterans' Entitlements Act 1986* the Department of Veterans' Affairs provides programs of compensation, income support and treatment for eligible veterans and their dependants. One of the defined benefits for eligible veterans is the Repatriation Pharmaceutical Benefits Scheme. This range of medications and dressings is more comprehensive than is available through the Pharmaceutical Benefits Scheme.

Generics without score lines in Australia

The sponsor has provided a list of generics without score lines in Australia (where the reference product has a score line): lisinopril, enalapril, amlodipine, risperidone, metformin (immediate-release).

Generics without score lines in comparable overseas jurisdictions

In the US, if the reference product has a score line, then the generic product must have a score line to allow the patient to 'switch between manufacturers of the same product without encountering problems related to the dose'.⁴

Canada is similar to US.

Some EU countries allow generics not to have score lines.

As outlined above, in EU countries, the sponsor's 60 mg MR gliclazide tablet does have a score line.

Generic 60 mg modified-release tablets available in UK (registered by MHRA)

In the UK there is a 60 mg MR gliclazide generic without a score line (Laaglyda MR 60 mg; alternative trade name: Nazdol; sponsor: KRKA). Diaglyaran 60 mg (sponsor: Ranbaxy, UK), has a score line, but the SmPC states that the score line is not intended for breaking the tablet (that is, it is not a functional score line; see Table 3, below). It may be that pharmacist practice in United Kingdom (UK) is different from Australia and the 30 mg tablet is more commonly dispensed.

Table 3: Summary of other registered products

Brandname	Sponsor	Date of registration	Score line	Posology
Bilxona 60mg modified- release	Actavis Group (Iceland)	April 2015	Yes	The tablet can be divided into equal doses. The daily dose may vary from one half to 2 tablets per day, i.e. from 30 to 120 mg taken orally in a single intake at breakfast time. It is recommended that the tablet(s) (whole or half tablet) be swallowed in one piece without chewing or crushing.
Diaglyaran 60 mg modified- release	Ranbaxy (UK) Limited	March 2015	Yes	The score line is not intended to for breaking the tablet to provide a 30 mg dose. The tablets should be

⁴ FDA, MAPP 5223.2, Scoring configuration of generic drug products, updated 2012

Brandname	Sponsor	Date of registration	Score line	Posology
				swallowed whole and not crushed or chewed. A 30 mg dose cannot be obtained by dividing the tablet.
Laaglyda MR 60 mg (Nazdol)	KRKA (Slovenia)	January 2013	No	The tablets should be swallowed whole and not crushed or chewed.
Vamju 60 mg modified-release	Mercury Pharmaceuticals Limited (UK)	September 2014	Yes	The 60 mg tablet can be divided into equal doses. The daily dose may vary from 30 to 120 mg (that is, 1 to 4 tablets of 30 mg per day or one half to 2 tablets of 60 mg per day) taken orally in a single intake at breakfast time. It is recommended that the tablet(s) be swallowed whole, without crushing or chewing.

Other gliclazide generics in Australia

There are currently no 60 mg MR generics of gliclazide registered in Australia.

A generic 30 mg MR tablet is registered (sponsor Apotex).

The other currently registered generic gliclazide products are immediate release tablets.

Previous Australian regulatory history for this particular generic gliclazide sponsored by Generic Partners

A previous application for this product for 30 mg tablets and 60 mg (scored) tablets was submitted by Generic Partners in January 2013. The TGA rejected the application in February 2014 because of unresolved quality concerns, including:

- Lack of BE data on the proposed 30 mg tablets
- Lack of BE data on halved 60 mg (scored) tablets
- Lack of data to demonstrate comparable dissolution profiles between 60 mg tablets, 30 mg tablets and halved 60 mg tablets.

The sponsor submitted an appeal in April 2014. The appeal Delegate upheld the initial decision (June 2014) to reject the application.

The differences between this current application and that previous application include:

- The 60 mg tablet does not have a score line (as outlined above, the sponsor has stated that patent issues have emerged over the score line in Australia).

A bioequivalence study under fasting conditions was included for the 30 mg MR tablets (however, the sponsor withdrew the application to register the 30 mg MR tablet during the evaluation).

Quality

The quality evaluator has advised that the proposed generic 60 mg MR release tablet has met the quality requirements for registration.

Bioequivalence studies were not submitted for the new unscored 60 mg MR tablet, based on the argument from the sponsor that bioequivalence had been previously established to the reference product (Diamicron MR 60) for the originally proposed scored tablet. This justification was considered acceptable by the quality evaluator because:

- The dissolution profiles between the scored and unscored 60 mg MR tablets were similar across the pH range
- The scored and unscored tablets have the same formulation and are manufactured by the same process

The sponsor withdrew the application for the proposed generic 30 mg MR tablet, during this current evaluation. The quality evaluator raised some concerns around the dissolution limits for the 30 mg MR tablet. It is unclear whether these could have been resolved.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The TGA sought the advice of two independent external clinical experts on the lack of the score line on the proposed generic 60 mg MR tablet. The sponsor was consulted on the accuracy of the background information and wording of the questions before they were sent to the independent external clinical experts. The process was then an iterative one: the expert advice was sent to the sponsor, who responded. The sponsor responses were sent to the experts, who provided further advice, and this final round of advice was sent to the sponsor. This process is documented below.

Main issue

The key issue is that the reference product has a deep score line, allowing the 60 mg tablet to be broken into two (equal) 30 mg halves. The proposed Australian generic 60 mg tablet does not have a score line (the sponsor has informed the TGA that this is because of patent issues with the score line).

The TGA has been informed that the 30 mg tablet is uncommonly dispensed by pharmacists. That is, the current clinical practice in Australia is for pharmacists to typically dispense the 60 mg tablet even when the medical practitioner has prescribed a 30 mg dose; the pharmacist instructs the patient to divide the scored 60 mg tablet into two 30 mg halves. An unscored 60 mg gliclazide tablet is not currently registered in Australia or in any comparable country.

Delegate's request for expert advice

- With clear statements in the PI, Consumer Medicine Information (CMI) and on the pack labels that the tablet must not be broken, what is the possibility of dispensing errors, patient confusion or dosing errors if a 60 mg unscored generic tablet is registered?
- What are the clinical implications of the patient mistakenly breaking the unscored 60 mg tablet and taking one of the two resulting [likely unequal] portions?
- In addition to clear statements on the product PI/CMI and labels that the tablet must not be broken, could the risks be further mitigated by additional activities such as targeting of healthcare professionals by the sponsor or appropriate warnings in prescribing software?

Advice from external clinical experts on the unscored 60 mg gliclazide tablet***Advice from external expert 1****Issue to be addressed*

An application has been received for registration of a 60 mg gliclazide modified release tablet. Gliclazide is a member of the sulphonylurea drug family used to assist control of Type II diabetes mellitus. Unlike the only such product currently registered in Australia, Diamicon 60 mg MR, which is the reference product for the application, the proposed tablet has no score line enabling easy and accurate division into two 30 mg halves, enabling administration of doses of 30 or 90 mg which are in the recommended dose range for this medication.

A 30 mg modified release formulation is also proposed within the same application. A number of alternative 30 mg gliclazide modified release products are already registered and marketed in Australia.

The PI, CMI and pack labelling of the proposed 60 mg unscored tablet clearly states that the tablet should not be broken.

Expert 1 opinion

1. If it were quite clear in the mind of both prescriber and patient that the intention was to take the entire tablet as a 60 mg dose and under no circumstances to change this, then there would be no objection to registration.
2. Nevertheless there are a number of potential circumstances in which despite the above, patients might attempt division of the unscored tablet. For example they might, perhaps by another doctor, be advised to reduce the dose to 30 mg or increase it to 90 mg; or they might have been switched from the Diamicon MR preparation by a differential prescriber, who did not realise the distinction between the two preparations.
3. Breaking the unscored tablet, with or without the assistance of a tablet cutter, is likely to result in significant maldistribution of dose between the divided portions. In the case of a patient used to taking 30 mg which is the recommended starting dose of gliclazide MR, this might result in a dosing error in the order of 30%. In this expert's experience and knowledge of the experience of colleagues in the diabetes field, the 30 mg dose is relatively ineffective, so that a dosing error at this level would be unlikely to have serious consequences. Nevertheless it is a bad principle to deliberately use a preparation with the potential to result in such errors which might contribute to even low-level diabetes instability possibly over a long period of time.

4. It is possible for patients to be switched from original to generic products without the knowledge of the prescriber. Where this to happen in the instance of a patient who is used to breaking the original tablet in half, possibly without the knowledge of the dispensing pharmacist, there is the potential for errors to develop as described in the previous paragraph.
5. For patients needing a 30 mg dose, there is a perfectly satisfactory 30 mg formulation.
6. With regard to the question as to whether the risks of adverse consequences as described above might be mitigated by activity such as the targeting of healthcare professionals or warnings in prescribing software, this expert does not believe that such measures would provide sufficient protection. The types of error which are described above could occur without the knowledge of the original prescriber or dispensing pharmacist.
7. The information that the TGA has provided in this request makes it clear that the sponsor of the proposed generic 60 mg formulation would have included a score line facilitating division of the tablet were it not for patent issues relating to the original product. The product information for the original product makes it clear that the score line is there for the purpose of enabling intermediate dose levels as described above. Accordingly, the proposed unscored product is an incomplete and hence unsatisfactory substitute.

In summary, it is consider that the absence of the feature (the score line) which enables division of the tablet makes the proposed formulation an unsatisfactory alternative to the existing and long established original Diamicron 60 mg MR formulation and that it is therefore unsuitable for registration.

Cost factors have not been considered in forming this opinion.

Advice from external expert 2

A summary of products as indicated in brief from the TGA are shown in Table 4.

Table 4: Summary of products

30 mg tablet		60 mg tablet comment	Comment
Reference product Servier			
Australia	Glyade MR	Diamicron MR scored	Use of 30 mg tablet is uncommon even if prescribed, pharmacists dispense 60 mg, with instructions to break it in half
Proposed product generic gliclazide			
EU countries*	Gliclazide MR	Gliclazide MR scored	Scored tablets registered in EU countries, withdrawn from UK and Ireland for commercial reasons
Canada Approved marketed	Gliclazide MR	Gliclazide MR scored	Scored tablet is approved but not marketed due to patent issues with the score line

	30 mg tablet	60 mg tablet comment	Comment
Australia	Gliclazide MR	Gliclazide MR scored	Unscored Gliclazide 60 mg tablet is not currently registered in any comparable country

However, the expert noted that it appears there is an unscored gliclazide 60 mg tablet marketed in the UK Laaglyda MR, white, oval, biconvex tablet.⁵

General comments

From studies of splitting tablets, both scored and unscored, split tablets (scored or unscored) generally failed to meet expectations for weight variation⁶ (1:4 scored tablets passed the uniformity test versus 2:7 unscored tablets with at most 1/20 falling outside the range of 85 to 115% weight). These were split with a razor blade.

Poorly functioning score lines were perceived as a quality defect⁶ and could lead to reduced patient compliance with medication. This suggests there may be some advantage for some patients to have an unscored tablet available.

The effect of splitting a tablet, particularly a modified release tablet, on the release characteristics and pharmacokinetics of the active drug, will vary according to the technology used to obtain the modified release. Some may be suitable to split and some may not be. No specific information has been provided in the brief in relation to the effect on the pharmacokinetic profile of splitting the generic 60 mg gliclazide modified release tablet, so no further comment can be made on whether, if split, this product retains its pharmacokinetic profile or is subject to 'dumping'.

Other oral hypoglycaemic agents

There are other oral hypoglycaemic agents available to treat diabetes, one of these is metformin. Metformin is available in a number of forms including

- 500 mg unscored
- 500 mg scored
- 500 mg (controlled release) unscored
- 1000 mg scored, Diabex, Diaformin, Glucobete
- 1000 mg (controlled release) unscored

In relation to the specific request for advice

With clear statements in the PI, CMI and on the pack labels that the tablet must not be broken, what is the possibility of dispensing errors, patient confusion or dosing errors if a 60 mg unscored generic tablet is registered?

It is likely that a patient may be dispensed different forms of the tablet on different occasions (that is, may be dispensed a scored tablet on one occasion, and the unscored tablet on another occasion). This may not represent an error but may reflect differences in prescribing practices of individual doctors (that is, prescribing by brand name, versus generic prescribing) or differences in availability of specific products at particular pharmacies.

⁵ <https://www.medicines.org.uk/emc/medicine/28358>

⁶ <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeForPharmaceuticalScienceandClinicalPharmacology/UCM315770.pdf>

The different appearance of the tablets may contribute to patient confusion however, this is not unique to gliclazide but is already an issue with other products as indicated by the different metformin products as outlined above, where both scored and unscored tablets of the same dose are available.

It is difficult to anticipate the contribution to dosing errors, without more specific information on the effect on pharmacokinetics of splitting the 60 mg gliclazide modified release.

What are the clinical implications of the patient mistakenly breaking the unscored 60 mg tablet and taking one of the two resulting (likely unequal) portions?

As outlined above, the practice of splitting of tablets, both scored and unscored, generally fails to meet expectations for weight variation. Nonetheless, it is a relatively common practice in the community and seems to occur most frequently without any significant clinical implication.

However, there are additional considerations other than the effect of splitting on tablet size, these being the effects of splitting on the modified release characteristics of the tablet. Some modified release preparations, when split, no longer retain their modified release characteristics, altering the pharmacokinetic profile. Further information on the effect on the pharmacokinetic profile of splitting of the unscored 60 mg gliclazide tablet would be important to anticipate the potential clinical implications of the (unintended) splitting of the tablet.

In addition to clear statements on the product PI/CMI and labels that the tablet must not be broken, could the risks be further mitigated by additional activities such as targeting of healthcare professionals by the sponsor or appropriate warnings in prescribing software?

Appropriate advice re splitting or non-splitting of tablets is most likely to be useful if it is given as close to the interaction between the patient, and the tablets as possible. As such, it is most likely to be useful if it is given at the time of collection of the medicine, and on the medicine label.

Information given at the time of prescription is less likely to be useful, and specific warnings in prescribing software are not warranted in this expert's opinion. It is important that the prescriber can attend to other (potentially more significant) warnings, and to include a warning of this nature in prescribing software would distract from the capacity to attend to more significant warnings.

Delegate's summary and comments on the sponsor's response to the expert advice

As advised in correspondence during the evaluation phase, the TGA sought advice from clinical experts (specialists in community pharmacy, general practice, and/or endocrinology) on clinical safety issues associated with this application. A copy of the TGA request for advice and the advice obtained was provided to the sponsor. The sponsor's response to the clinical experts' concerns and comments detailed above are summarised below. The TGA's current position on the sponsor's response is also given below for the information of the sponsor and the ACPM.

Sponsor's response

The sponsor's proposed generic 60 mg unscored tablet has been shown to be bioequivalent to the innovator and therefore can be considered an acceptable alternative to the innovator where doses of 60 mg or 120 mg are required.

TGA's current position

The TGA agree that there is no problem for patients taking a 60 mg or 120 mg dose. However, 90 mg is a possible maintenance dose and patients could not achieve this dose

with the proposed generic 60 mg MR tablet because it cannot be split. Also, patients when initiating treatment with gliclazide are up-titrated from 30 mg and through 90 mg. The concern is that proposed generic can be used for some of the same doses that the reference product can be used for (60 mg, 120 mg) but not others (30 mg, 90 mg). This could create the risk of pharmacist and patient error. Note that this is a more complicated situation than a generic not being marketed with all the strengths of the reference product. More specifically, this is a case where the particular strength of the proposed generic cannot provide the same doses as the corresponding strength of the reference product; and that are recommended for use in clinical practice.

Sponsor's response

Approximately 70% of patients who are on Gliclazide require a dose of 120 mg Gliclazide before any clinical effect is seen (Diamicron 60 mg MR flyer), that is, there is no requirement to break the tablet.

TGA's current position

Yes, but most patients on initiating treatment are up-titrated from 30 mg and through 90 mg. It is not reassuring that there are likely to be no problems for 70% of patients.

Sponsor's response

The lack of scoring will be appropriately managed using PI/CMI, labelling statements, dispenser detailing, as well as promotion of already existing cautionary statements in the dispensing software to be printed on the dispensing label that the product should be swallowed whole and not crushed or chewed.

TGA's current position

It is well known that some patients break tablets even when the PI/CMI and statements on the pack instruct the patient not to (see 7). Suppose a pharmacist incorrectly dispensed the proposed (unscored) generic 60 mg R tablets to a patient who required a 90 mg daily dose. The patient would have the inconvenience of having to return to the pharmacy to obtain the reference (scored) 60 mg MR tablets or 30 mg MR tablets. The easiest (but concerning) option would be for the patient to (incorrectly) break the (unscored) generic 60 mg MR tablets; or take two of the (unscored) generic tablets.

Sponsor's response

A number of products are already approved (some PBS listed and 'a flagged') where the scoring differs between the innovator and generic brands where the lack of a score line is appropriately managed by similar statements in the PI and CMI to what we have included in our PI and CMI.

TGA's current position

Yes, but in these cases the score line of the reference product was supported by evidence that there was no undue loss of mass when the tablet was split; not by much stronger evidence of bioequivalence as is the case for Diamicron.

Sponsor's response

There are generic products approved in the EU of gliclazide unscored 60 mg tablets where the only instructions in the SmPC and PIL are to swallow the tablets whole. No specific instruction is provided that the tablets cannot or should not be broken in half.

⁷ Quinzler R, et al. The frequency of inappropriate tablet splitting in primary care. Eur J Clin Pharmacol. 2006;62(12):1065-73.

TGA's current position

The sponsor's generic 60 mg MR release tablet in various EU countries does have a score line. Australian specific patent laws seem to be the main reason for the sponsor not having a score line on the proposed Australian generic 60 mg MR tablet. The sponsor's Australian application in 2013 was for a proposed generic 60 mg MR tablet with a score line.

Laaglyda (also called Nazdol) is registered in the UK and it does not have a score line. The sponsor is a Slovenian company called KRKA. It is possible that, in the UK, pharmacists dispense 30 mg MR tablets for initiating gliclazide treatment; or if a 90 mg MR maintenance dose is required. This is not commonly the case in Australia. The sponsor of the proposed (unscored) generic in Australia (Generic Partners) would need to provide detailed documentation of the Medicines and Healthcare products Regulatory Agency (MHRA) reasoning in registering Laaglyda; the fact of registration is not enough. The sponsor should also note that providing the MHRA reasoning to the TGA would not necessarily trump TGA concerns that the presence of an unscored generic 60 mg MR tablet on the Australian market would increase the risk of pharmacist dispensing errors and patient dosing errors.

The sponsor should also note that the most recent report of the Australian Commission on Safety and Quality in Health Care on medication safety (2013) stated that 12% of medical admissions (that is 230,000 admissions per year) were attributable to medication/dosing errors; a (conservative) estimate of the cost of these admissions was \$1.2 billion per year.

Sponsor's response

There is a generic product approved in the EU of gliclazide scored 60 mg tablets, however there is specific advice in their SmPC and PIL that the tablet cannot be broken in half to make a 30 mg dose.

TGA's current position

The TGA assume the sponsor is referring to a product called Diaglyaran, which is registered in the UK, and has a score line, but the posology in the SmPC says that the tablet should not be broken. In other words, the score line is not functional.

The sponsor is referred to the comments for Laaglyda. MHRA reasoning would need to be provided and this would not necessarily trump Australian specific concerns about the unscored proposed generic tablet increasing the risk of medication errors.

Sponsor's response

There is no requirement in the EU or TGA guidelines for generic products to be able to match all uses of the innovator and they are not required to match exactly all attributes of the innovator product, provided the differences can be appropriately managed, as is already the case for unscored generic products currently listed on the PBS.

TGA's current position

Yes, this is correct. The issue is that the TGA does not think the differences can be appropriately managed in this particular circumstance. More specifically, for the 60 mg MR reference (innovator) product, the deep score line is supported by evidence of bioequivalence; not just evidence of no loss of mass on breaking. Further, given the inconvenience of having to return to that pharmacy in the case of a dispensing error, there is a material risk that patients will break the unscored generic tablet, despite instructions on the pack and in the PI/CMI not too.

Risk management plan

There was no RMP evaluation conducted for this application.

Risk-benefit analysis

Delegate's considerations

Summary of issues

The key issue is that the proposed generic 60 mg MR tablet does not have a score line; whereas the reference tablet (Diamicron) does. The sponsor's 60 mg MR tablet, marketed in similar overseas countries, does have a score line. The sponsor has stated that the reason for not having a score line in Australia is related to (presumably, Australian specific) patent issues. The score line on the reference product is supported by evidence showing that two halves of the 60 mg MR tablet are bioequivalent to the whole 60 mg MR tablet. This is more than the standard evidence for a score line, which is (typically) in vitro data showing that there is only limited loss of mass on breaking the tablet.

For the information of the sponsor and the ACPM, the reasons for rejection, at this point in time, are given below. The sponsor should specifically address these reasons in their pre-ACPM response.

In Canada, where there were similar patent issues on the score line, the sponsor marketed the 30 mg MR tablet, until the patent issues were resolved. The same approach would be preferable approach Australia, rather than introducing an unscored 60 mg MR tablet onto the market which will increase the risk of pharmacist and patient medication errors.

In contrast to the Canadian approach, the sponsor's Australian approach means that there is no guarantee that, when the patent on the score line expires in Australia, that the sponsor's/manufacture's generic scored 60 mg MR tablet (marketed in similar countries overseas) will be marketed in Australia.

Proposed action

At this point in time, the Delegate's view is that safety and efficacy have not been satisfactorily established for the proposed generic 60 mg MR tablet which does not have a score line.

Reasons for proposed action

- It is accepted that for most patients, the lack of a score line on the proposed generic tablet will not raise any major clinical concerns. This is especially the case for patients on the 120 mg dose, which is the most common dose.
- However, when gliclazide therapy is started, patients typically up-titrate from a starting dose of 30 mg; and through 90 mg (typically each dose-level lasts two weeks). Also, for some patients, 90 mg is the appropriate long term/maintenance dose; and, other patients might, at some point in time, require back-titration from 120 mg to 90 mg.
- For patient convenience, current practice in Australia is for pharmacists to dispense the 60 mg MR (scored) reference tablet, allowing patients to make up 30 mg and 90 mg doses by halving the 60 mg (scored) tablet. This should not be done with the proposed unscored 60 mg generic tablet; although patients used to breaking the scored reference tablet might break the unscored proposed generic tablet, despite warnings on the pack and in the PI/CMI.
- It is agreed that pharmacists should not dispense the proposed generic 60 mg MR tablet if a 30 mg or 90 mg dose is prescribed. Statements on the pack and in the PI/CMI could warn against this. However, in quality engineering terms, the presence of an unscored 60 mg MR generic tablet on the Australian market would create a system problem: an increased risk of pharmacist error (and subsequent patient error).

- The clinical effect of taking part of the proposed generic unscored MR 60 mg tablet (should the patient incorrectly try to break it, because he/she is accustomed to doing this with the reference scored tablet) is uncertain. Too high a dose can lead to hypoglycaemia; too low a dose to hyperglycaemia.
- It is accepted that these problems might only occur uncommonly (10^3 to 10^2 patient-years exposure) or rarely (10^4 to 10^3 patient-years exposure).
- However, even if these problems are uncommon or rare, it means that efficacy and safety of the unscored generic tablet is not equivalent to efficacy and safety of the scored reference tablet. That is, at a population-level the efficacy and safety of Generic Partners proposed (unscored) 60 mg MR generic tablet have not been satisfactorily established (the quality section have advised that the quality of the proposed [unscored] generic 60 mg MR tablet is acceptable).
- In general, the efficacy and safety of a generic tablet is established by showing bioequivalence to the reference product; then, all the efficacy and safety data for the reference product can be bridged across to the generic product. However, in this particular circumstance, the lack of a score line increases the risk of pharmacist or patient error, leading to possible over or under dosing. As listing in the immediately preceding dot-point, even if the increased risk of dosing error is small, it means that, at a population-level, the efficacy and safety of the proposed generic 60 mg MR is not equivalent to the efficacy and safety of the reference tablet.
- The most recent report of the Australian Commission on Safety and Quality in Health Care on medication safety (2013) stated that 12% of medical admissions (that is, 230,000 admissions per year) were attributable to medication/dosing errors; a (conservative) estimate of cost was \$1.2 billion per year. Introducing an avoidable system problem (that is, registering an unscored generic 60 mg MR tablet) into the Australian healthcare system, that will likely lead to more dosing/medication errors, is not prudent.
- Spontaneous pharmacovigilance is unlikely to detect any increased rate of hypoglycaemia associated with introduction of the proposed unscored generic 60 mg MR tablet onto the Australian market.
- The sponsor's argument that there are other generics without score lines registered in Australia is not convincing. The evidence for the functionality of most score lines is based on limited loss of mass on breaking the tablet. In contrast the evidence for the functionality of the deep score line for Diamicron is a bioequivalence study.
- The sponsor's argument that there are other gliclazide 60 mg MR generics without score lines registered in UK is not convincing. For patient convenience, current practice in Australia is for pharmacists to dispense the 60 mg MR (scored) reference tablet, allowing patients to make up 30 mg and 90 mg doses by halving the 60 mg (scored) tablet. Also, the sponsor's 60 mg MR generic tablet, which is marketed in the EU, has a score line.
- The sponsor's argument that the increased risk of pharmacist/patient error with the proposed unscored generic tablet can be adequately mitigated by statements on the pack and in the PI/CMI is not convincing. It is well known that some patients break tablets even when the PI/CMI and statements on the pack instruct the patient not to (see for example⁸).

⁸ Quinzler R, et al. The frequency of inappropriate tablet splitting in primary care. *Eur J Clin Pharmacol.* 2006;62(12):1065-73

- A better strategy would be for the sponsor/manufacturer to register and market their 30 mg MR generic tablet in Australia, until the patent issues have been resolved with the score line on 60 mg MR tablet. This is what happened in Canada.

Request for Advisory Committee on Prescription Medicines (ACPM) advice

1. *Has the sponsor satisfactorily established that the efficacy and safety of the proposed generic 60 mg MR tablet is the same as that of the reference 60 mg MR tablet (Diamicron)?*

Response from sponsor

The Delegate has requested the advice of the ACPM as to whether Generic Partners, the sponsor of a generic version of Gliclazide MR 60 mg tablets, has satisfactorily established the efficacy and safety of this formulation, compared to the reference 60 mg MR tablet (Diamicron brand).

While the quality evaluator has advised that the proposed generic 60 mg MR tablet has met the requirements of equivalence to the 60 mg Diamicron MR reference tablet, the TGA is concerned that the lack of a score line on the generic formulation could create the risk of pharmacist and patient error.

The TGA suggest that, because the reference 60 mg Diamicron MR tablet has a score line, the pharmacist is likely to dispense a 60 mg Diamicron MR tablet, rather than a 30 mg MR tablet, when a 30 mg or 90 mg is prescribed. If this was the case the patient is therefore likely to take HALF a 60 mg Diamicron MR tablet to administer these doses.

Furthermore the TGA suggests that if the unscored generic 60 mg MR tablet becomes available for substitution at the pharmacy level, any patient prescribed a 30 mg or 90 mg dose, may also use the unscored 60 mg MR tablet to administer the prescribed dose. If this was the case, the TGA suggest that it could potentially result in maldistribution of dose between the split portions of the unscored tablet. The TGA suggest that the clinical consequence of taking part of an unscored tablet could be hypoglycaemia, if the split portion was too large; or hyperglycaemia if the split proportion was too small.

The sponsor requests that the following information, which supports the sponsor's position that the TGA view will not be the case in practice, should also be fully considered by the Committee:

Proposed use of the generic unscored 60 mg MR tablet

The sponsor's generic 60 mg unscored gliclazide tablet is to be used for maintenance doses of 60 mg or 120 mg gliclazide (and not for the 30 mg or 90 mg). The PI, CMI and labels reflect this use.

TGA's position: Agree that there is no problem for patients taking a 60 mg or 120 mg dose.

Can differential scoring be successfully managed?

The sponsor has shown examples of approved products on the ARTG as well as approved products in the UK and across the EU, that any potential safety risks concerning prescriber/patient errors between innovator and generic products can and has been successfully managed for over 10 years through statements in the PI/CMI/PIL/SPC (see our Section 31 response to TGA, Attachment 2 to DOV).

TGA mention that the innovator product had to submit a BE study to successfully demonstrate that the score line was functional and could be used to produce a 30 mg dose. Any other approved product with a functional score line has demonstrated that halving the tablet can acceptably produce a half dose of that product, regardless of the data they

were required to submit. The fact remains that innovator products with proven, functioning score lines were approved and subsequently, corresponding generics without score lines were approved (which by definition have been proven to be bioequivalent to the innovator) with only statements in their PI and CMI highlighting the differences. All these products were approved based on their quality, safety and efficacy and can be used for their intended use stated in their product information. The sponsor's product should not be treated any differently.

The examples the sponsor provided demonstrate that there are a significant number of generic products out there with no score line, where the same lowest strength of the innovator has a score. There is therefore no way to break the generic product in the same way as the innovator in these cases, which have been TGA approved and in some cases PBS a flagged for years, with no clinical safety issues. The sponsor's proposed generic is of the higher strength available and therefore the lower strength can be obtained by other brands available in the market.

TGA's concern that our examples of unscored or non-functional score line gliclazide products approved in the EU is not convincing as the clinical practise is not known, nor the agency's reasoning for approval. The fact remains that these products have been approved by regulatory authorities, which by TGA's definition are comparable to the TGA and, whilst our specific unscored generic product has not been approved in these markets, the examples of products approved by other sponsor's should be considered. Our application proved that the EU innovator was the same as the Australian innovator product and that our generic was bioequivalent to the innovator. Regardless of prescribing practises in UK/EU, the MHRA and other referred EU authorities, comparable regulatory authorities to Australia, have found these alternatives to the gliclazide innovator to be of acceptable safety, efficacy and quality despite the differences and any risks to prescribing/patient errors are effectively managed by statements in the PIL/SPC.

The unscored 60 mg gliclazide MR tablet will be used to administer a 30 mg or 90 mg dose

The sponsor does not agree with the TGA assumption that the unscored generic 60 mg MR tablet will be dispensed to patients prescribed a 30 mg or 90 mg dose of gliclazide.

The following information relevant to general precautions provided to health professionals and consumers associated with breaking or splitting modified release tablets, the professional standards and expectations of pharmacists, and past dispensing history relating to the 30 mg MR tablet, has lead the sponsor to an alternative conclusion:

- Quinzler (2006)⁹ to which the TGA refer makes the following conclusion regarding tablet splitting: 'The splitting of tablets in primary care is a frequent habit likely driven by medical and economic considerations. Almost 1% of all tablets are split that must not be fragmented. However, the SmPC and PL provide only limited information on divisibility stressing the need to improve this information promptly to avoid medication errors.'

The study's conclusion states that almost 1% of all tablets are split which should not be split. This percentage is made up of immediate release, enteric coated and modified release tablets. It states that current Summary of Product Characteristics (SmPC)/ patient information leaflet (PIL) provide only limited information and that this should be improved to avoid medication errors and no mention was made of labelling.

- Since this paper was written in 2006, significant improvements have been made for specific advice to be included in PIL/SmPC/PI/CMI across EU and Australia for

⁹Quinzler R, et al. The frequency of inappropriate tablet splitting in primary care. Eur J Clin Pharmacol. 2006; 62(12):1065-73.).

- all products and our product is no exception. The sponsor is doing more than putting specific statements in the PI and CMI for their product. The sponsor is also adding text on the carton as well as specific dispensing labels and are providing pharmacist training highlighting that the product does not have a score line compared with the innovator, and so is not to be dispensed for a 30 mg or 90 mg dose.
- Only a fraction of the 1% mentioned in this study is made up of modified release tablets. Specific product advice on PI/CMI as well as carton labelling and specific dispensing labels and pharmacist training will remove the risk that even this fraction will split our product.
 - The generic products mentioned in the sponsor’s response, where they either had no score line, or a non-functional score line, compared to the innovator, were all approved by TGA and registered on the ARTG post 2006, that is, post the Quinzler paper:
 - Unscored: Apotex Lisinopril 5 mg (2008); Scored: APO-Lisinopril 5 mg (2013)
 - Unscored: Enalapril Generic Health 5 mg (2008)
 - Unscored: Auro-amlodipine 5 mg (2009)
 - Unscored: Risperidone Actavis (now Risperidone Amneal) 0.5 mg (2010)
 - Unscored: Formet Aspen 500 (2012), Metformin Ranbaxy (2008), Metformin Generic Health (2008), Glucobete 500 (2011), Metformin AN (2011)
 - Examples provided of gliclazide products registered in the EU where the generic does not have a score line, or a functional score line were all also approved and registered after 2006:
 - Unscored: Laaglyda MR 60 mg (2013), Diacronal MR 60 mg (2013)
 - Scored but cannot be broken: Diagylaran 60 mg MR (2015)
 - The safety risks for the above products are all successfully managed with statements in their PI/CMI to the correct and proper use of their medicine.
 - Not all generics have the same excipients as the innovator, some which may be allergenic to some patients. The safety risk to the patient exists in these circumstances and the risk is removed by listing all excipients in the PI and CMI, with excipients of concern also included on the carton label. The safety risk for this medicine will be successfully managed in this manner.
 - Not all generic medicines are approved for the same indications as the innovator, while this may not pose a safety risk, it does highlight the importance of each medicine’s PI and CMI to highlight any differences between the innovator and the generic product. It cannot be assumed by the TGA that doctors and pharmacists do not check the brand specific information prior to prescribing/dispensing to a patient. In fact, it should be assumed that they do.
 - Advice in the Diamicon 60 mg MR Product Information (PI) that a 30 mg dose may be administered as half a 60 mg tablet is inconsistent with advice provided in the PI of the 30 mg gliclazide MR formulation (Glyade) supplied by the same manufacturer of Diamicon 60 mg (Servier Laboratories (Australia)), and the advice given for many other widely prescribed and dispensed medicines formulated as modified release formulations (Table 4). In all cases, the advice is that the tablet *should not* be broken, divided, crushed or chewed.

Table 4: Dosage and Administration advice from PI or CMI of modified release tablets

Product	Advice
Ceclor CD	Should not be cut, crushed or chewed.
Concerta Extended Release	Must be swallowed whole...and must not be chewed, divided or crushed.
Diabex XR	Swallow the tablets whole...do not break, crush or chew the tablets.
Glyade MR 30 mg	Glyade MR tablets are modified release and therefore should be neither broken nor chewed.
Imdur Durules	Should not be chewed or crushed, and should be swallowed whole.
MS Contin	Should be swallowed whole, not chewed, crushed or broken.
Naprosyn SR	Should be taken whole and not chewed.
OxyContin	Are to be swallowed whole, and not to be cut, broken, chewed, crushed or dissolved.
Plendil ER	Should be swallowed whole...and must not be divided, crushed or chewed.
Pristiq	Must be swallowed whole...and not divided, crushed, chewed, or dissolved.
Seroquel XR	The tablets should be swallowed whole and not split, chewed or crushed.

As a general rule, pharmacy best practice specifies that any dose of a medicine should be administered as a whole dosage form wherever possible, rather than a divided or broken tablet:

- It is therefore the exception rather than the rule, that modified release tablets should be broken to deliver half doses, when acceptable whole dose alternatives are available. Consequently it is unlikely that a pharmacist would routinely assume that a modified release oral formulation can or should be broken or divided, and therefore unlikely to be their default position when considering how a half dose of a modified release medicine is best dispensed and administered (Table 4).
- The 30 mg dose of gliclazide is the recommended starting dose and acknowledged by a TGA external clinical expert to be relatively ineffective.
- The sponsor has previously supplied advice to the TGA that 70% of patients receive a 120 mg dose of gliclazide MR daily. It is therefore also unlikely that a significant proportion of patients are stabilised on 90 mg daily.
- Even though the 30 mg dose is the starting dose, and unlikely to be effective in the majority of patients, and that a relatively small proportion of patients take a 90 mg

daily dose, 14% of prescriptions issued in 2014 were for the 30 mg MR tablet, as provided in the Delegates 'request for ACPM Advice' (see above Overall conclusions and risk-benefit analysis). This suggests that most patients stabilised on a 30 mg or 90 mg do in fact receive a 30 mg MR tablet.

- The Australian Pharmaceutical Formulary and Handbook (APF) provides a guide to the type of counselling and cautionary advisory labels for medicines (CAL), to assist in the safe and efficacious use of specific treatments.
- For gliclazide MR tablets it is recommended that label A is added to this product: 'SWALLOW WHOLE Do not crush or chew'
- This advice is consistent with information provided in the PI for two formulations of gliclazide 30 mg MR tablets; Oziclade (Ranbaxy) and Glyade MR (Servier). '... MR tablets are modified release tablets and therefore should be neither broken nor chewed.'
- The Pharmaceutical Society of Australia (PSA) Professional Practice Standards version 4 2010, endorsed by the Pharmacy Board of Australia, proscribe a range of professional activities consistent with current pharmacy best practice¹⁰:
 - Standard 5: Dispensing, provides advice on the appropriate use of CAL, under criterion 7.6: Uses cautionary advisory labels to indicate specific usage instructions. The APF advice is to add label A to gliclazide MR products.
 - Standard 3: Counselling; Criterion 5.2 requires CMI to be offered to consumers, with the pharmacist explaining the information contained in the CMI, and its relevance to the medicine supplied. In the case of supplying the generic gliclazide 60 mg MR tablet, the pharmacist should clearly explain that the 60 mg MR tablet should not be broken, crushed or chewed, and if the dose prescribed relies on a 30 mg component, then a specific 30 mg MR tablet should be dispensed.
- The PSA Dispensing Practice Guidelines advise that "The medication is labelled with adequate directions, ancillary labels and additional instructions as applicable"¹¹. The APF advice is to add label A to gliclazide MR products:
 - Standard 5: Dispensing; Criterion 8 advises that the pharmacist should ensure that the consumer has adequate dosing instructions and fully understands how to safely use the dispensed medicine. This includes provision of a CMI where required, use of appropriate CAL as recommended in the APF, and verbal counselling.
 - 'Counselling and verification of patient understanding of medication use occurs, incorporating the use of written drug information where appropriate.' In the case of supplying the generic gliclazide 60 mg MR tablet, the pharmacist should clearly explain that the 60 mg MR tablet should not be broken, crushed or chewed, and if the dose prescribed relies on a 30 mg component, then a specific 30 mg MR tablet should be dispensed.
- The proposed generic unscored 60 mg MR tablet PI and CMI advice that the 60 mg MR tablet should not be broken, chewed or crushed. If a 30 mg or 90 mg dose is required, other brands are available.

¹⁰The Pharmaceutical Society of Australia (PSA) Professional Practice Standards version 4 2010. <https://www.psa.org.au/download/standards/professional-practice-standards-v4.pdf>. Accessed 14 January 2016.

¹¹The Pharmaceutical Society of Australia Dispensing Practice Guidelines. <https://www.psa.org.au/download/guidelines/member-only-guidelines/dispensing-practice-guidelines.pdf>. Accessed 14 January 2016.

- The proposed generic unscored 60 mg MR tablet carton label states 'the tablet is not scored and should not be broken'.

Conclusion

The TGA conclusion that an unscored generic 60 mg MR tablet will invariably be used by the pharmacist to administer a 30 mg or 90 mg dose is not supported by:

- The number of prescriptions issued for the 30 mg MR tablet.
- The exception rather than the rule that a modified release tablet may be broken to provide a 'half dose'.
- Professional Pharmacy Practice standards which emphasise the need to appropriately counsel patients, and provide written and labelling advice which reinforces a best practice of not halving the generic unscored 60 mg MR tablet, and more appropriately dispense a 30 mg gliclazide MR tablet for 30 and 90 mg doses.
- Previously provided examples of TGA approved unscored generics where the innovator is scored.
- The information contained in our products' PI, CMI, carton labelling as well as the training which will be provided to Pharmacists.

The negative clinical consequences of taking a split, unscored tablet

As set out above, the sponsor does not accept that any patient will split our 60 mg MR tablet. However, the sponsor considers that the clinical consequences of an administered 'half dose' using our unscored generic 60 mg MR tablet, if it did occur, will not impact on safety or efficacy of the medicine. The following information is provided in support of this conclusion:

- Dose dumping does not occur if the unscored version of the tablet were to be inadvertently split, which the sponsor does not accept would occur, as the product was originally formulated to be split.
- The sponsor has previously supplied advice to the TGA that 70% of patients receive a 120 mg dose of gliclazide MR daily. It is therefore unlikely that a significant proportion of patients are stabilised on 90 mg daily.
- Advice from a TGA external clinical expert concludes that the 30 mg dose is relatively ineffective, so that a dosing error due to maldistribution of dose following splitting of the unscored 60 mg MR tablet which the sponsor does not accept would occur, would be unlikely to have serious consequences.
- While Frey (2003)¹² were able to establish a relationship between the pharmacokinetics of gliclazide and its long term pharmacodynamics in 634 type 2 diabetic patients, the average AUC producing maximum effect on fasting plasma glucose was 20 µg.h/mL. However, the intersubject variability in both maximum effect, and the AUC of gliclazide inducing 50% of maximal effect were large (30% and 60% respectively).¹²
- Furthermore, Davis (2000)¹³ found that the rate and extent of gliclazide absorption had a limited impact on glycaemia in 19 type 2 diabetics, with no significant

¹²Frey N, Laveille C, Paraire M et al. Population PKPD modelling of the long-term hypoglycaemic effect of gliclazide given as a once-a-day modified release (MR) formulation. *British Journal of Clinical Pharmacology* 2003; 55: 147-157.

¹³Davis TME, Daly F, Walsh JP et al. Pharmacokinetics and pharmacodynamics of gliclazide in Caucasians and Australian Aborigines with type 2 diabetes. *British Journal of Clinical Pharmacology* 2000; 49: 223-230.

correlation established between gliclazide peak plasma concentration (C_{max}) and time to glucose C_{max} (T_{max}).

- In addition, Shiba (1986)¹⁴ showed that the mean and 95% confidence interval of steady state gliclazide concentrations, two hours after oral administration of 40 mg gliclazide per m² was 5.86; 3.40 to 7.72 µg/mL.

Conclusion

- While the sponsor does not accept that patients will split our tablet, any small differences in the daily dose of gliclazide which may occur if an unscored generic 60 mg MR tablet was used against pharmacy best practice, or the manufacturer's advice, to provide a 'half dose', will not impact the clinical outcome, given the inherent variability in pharmacokinetics and pharmacodynamics of gliclazide and relatively poor correlation between concentration and effect on glucose.
- The sponsor has demonstrated that the unscored 60 mg tablet is safe and efficacious when taken in line with the proposed PI and is therefore approvable:
 - Dose titration can be done using other brands where a patient requires a 30 mg or 90 mg dose.
 - TGA agree that the unscored 60 mg tablet is acceptable for 60 mg and 120 mg doses.
 - Dose dumping does not occur if the tablet were to be inadvertently split.
 - TGA clinical expert concludes that the 30 mg dose is relatively ineffective, so that a dosing error due to maldistribution of dose following splitting of the unscored 60 mg MR tablet (which the sponsor do not accept would occur) would not have serious consequences.

Advisory committee considerations

The ACPM resolved to recommend to the TGA Delegate of the Minister and Secretary that:

The ACPM, taking into account the submitted evidence of pharmaceutical efficacy, safety and quality considered LIZIDIC MR (+ other tradenames) tablet containing 60 mg of gliclazide to have an overall negative benefit–risk profile.

In making this recommendation the ACPM;

- noted that the manufacturing quality requirements have been met and bioequivalence of the whole 60 mg tablet to the reference product, Diamicon 60 mg is accepted. This generic can be considered an acceptable alternative to the innovator where doses of 60 mg or 120 mg are required
- noted the main issue is the absence of a score line, which is an integral part of the way the reference product is dispensed and used in Australia
- expressed concern that although the proposed generic can be used for some of the same doses that the reference product can be used for (60 mg, 120 mg); other dose (30 mg, 90 mg) carry a risk of pharmacist and patient error
- noted the mitigation measures proposed by the sponsor to lower the identified risk, however remained concerned that patients may continue to break the tablets risking dosing errors

¹⁴Shiba T, Kajinuma H, Suzuki K et al. Serum gliclazide concentration in diabetic patients. *Diabetes Research and Clinical Practice* 1986; 2: 301-306.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

- *Has the sponsor satisfactorily established that the efficacy and safety of the proposed generic 60 mg MR tablet is the same as that of the reference 60 mg MR tablet (Diamicron)?*

The ACPM advised that although manufacturing quality requirements have been met and bioequivalence is accepted, the committee considered the proposed unscored tablet 'an incomplete and unsatisfactory substitute' for the reference product.

The ACPM was of the view that;

- this is a quality use of medicines issue
- by failing to provide an identical product this ultimately puts the onus of distinguishing medicines, at a very detailed level, on the patient rather than supplying an inherently safe product
- the mitigation strategies are all potentially useful but will not prevent some patients from breaking the tablets, and without data on bioequivalence of halved tablets and potential dose dumping, there are unanswered safety questions.

The ACPM agreed with the TGA's preferred approach; for the sponsor to register and market their generic 30 mg MR, until such time as the patent issues on the score line expires in Australia thus mirroring the events in Canada. This is the most reasonable approach.

The ACPM also advised that the US approach, if the reference product has a score line, then the generic product must have a score line to allow the patient to 'switch between manufacturers of the same product without encountering problems related to the dose' is clearly a sensible approach and is recommended to the TGA, for adoption of a similar policy.

Outcome

The sponsor withdrew this application before the TGA had reached a decision.

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