***Public Assessment Report***
**XIGDUO XR**

## INFORMASI PRODUK

| | | |
|---|---|---|
| Nama obat | : | XIGDUO XR |
| Bentuk sediaan | : | Tablet salut selaput |
| Zat aktif | : | Dapagliflozin / Metformin : 5/500 mg; 5/1000 mg; 10/500 mg dan 10/1000 mg |
| Kemasan | : | Dus, 4 blister @ 7 tablet salut selaput |
| Pendaftar | : | PT AstraZeneca Indonesia |
| Produsen | : | AstraZeneca Pharmaceuticals LP, USA |
| Kategori Registrasi | : | Registrasi obat baru yang sudah terdaftar dengan indikasi baru |
| Indikasi yang diajukan | : | *XIGDUO XR (dapagliflozin and metformin HCl extended-release) is indicated as substitution therapy for treatment of type 2 diabetes mellitus in adjunct to diet and exercise to improve glycemic control in adult patients already controlled with dapagliflozin and metformin XR given concurrently at the same dose level (see section Clinical trials and Special warning and precautions for use for available data on combination therapy)*<br><br>*For study results with respect to combination of therapies, effects on glycaemic control and cardiovascular events, and the populations studied, see sections Special warnings and special precautions for use, Undesirable effects, dan Pharmacodynamic properties* |
| Posologi yang diajukan | : | Lampiran I<br>Tidak terdapat perubahan pada posologi yang telah disetujui |

## PENGANTAR

Xigduo XR merupakan obat yang mengandung dua zat aktif berbeda yaitu dapagliflozin dan metformin, dua obat anti-hiperglikemik dengan mekanisme kerja yang berbeda dan saling melengkapi untuk meningkatkan kontrol glikemik pada pasien diabetes tipe 2.

Dapagliflozin adalah penghambat SGLT2 yang sangat kuat, selektif dan reversible. SGLT2 adalah transporter utama yang bertanggung jawab untuk reabsorpsi glukosa dari filtrat glomerulus kembali ke sirkulasi. Dapagliflozin meningkatkan kadar glukosa plasma puasa dan pasca-prandial dengan mengurangi reabsorpsi glukosa ginjal yang menyebabkan ekskresi glukosa urin.

Metformin adalah biguanida dengan efek anti-hiperglikemik, menurunkan glukosa plasma basal dan postprandial. Ini tidak merangsang sekresi insulin dan karena itu tidak menghasilkan hipoglikemia. Metformin merangsang sintesis glikogen intraseluler dengan bekerja pada sintase glikogen. Metformin meningkatkan kapasitas transpor jenis transporter membran glukosa tertentu (GLUT-1 dan GLUT-4)

Xigduo XR telah disetujui di Indonesia dengan indikasi " *XIGDUO XR (dapagliflozin and metformin HCl extended-release) is indicated as a substitution therapy for treatment of type 2 diabetes mellitus in adjunct to diet and exercise to improve glycemic control in adult patients already controlled with dapagliflozin and metformin XR given concurrently at the same dose level.*"

Evaluasi saat ini difokuskan pada data klinik yang mendukung penambahan klim pada bagian indikasi yaitu terkait efek penggunaan Xigduo XR pada kardiovaskular.

## ASPEK MUTU

NA

Pengajuan registrasi berupa penambahan klim indikasi pada produk obat yang sudah terdaftar. Tidak terdapat perubahan terhadap mutu obat, sehingga tidak dilakukan evaluasi pada aspek mutu.

## ASPEK KHASIAT DAN KEAMANAN

### Studi Non Klinik
NA
Tidak terdapat dapat non klinik yang diserahkan untuk mendukung pengajuan ini

### Studi Klinik
Evaluasi dilakukan pada 1 studi klinik, yaitu studi DECLARE (D1693C00001). Studi ini bertujuan untuk menentukan efek dapagliflozin dibandingkan plasebo pada *cardiovascular* (CV) *outcome* ketika ditambahkan ke terapi yang digunakan saat ini (*current therapy*) pada pasien Diabetes Mellitus Tipe 2 (DMT2) dengan penyakit kardiovaskular atau setidaknya 2 faktor risiko kardiovaskular. Studi dilakukan pada 16.906 pasien dengan median waktu *follow-up* selama 4,2 tahun.

Pada studi ini, sebagian besar pasien terus menerima metformin sebagai terapi rutin selama penelitian; penggunaan metformin bersamaan setelah studi pengacakan adalah 85.6% dan 87.5%, masing masing pada kelompok dapagliflozin dan plasebo.

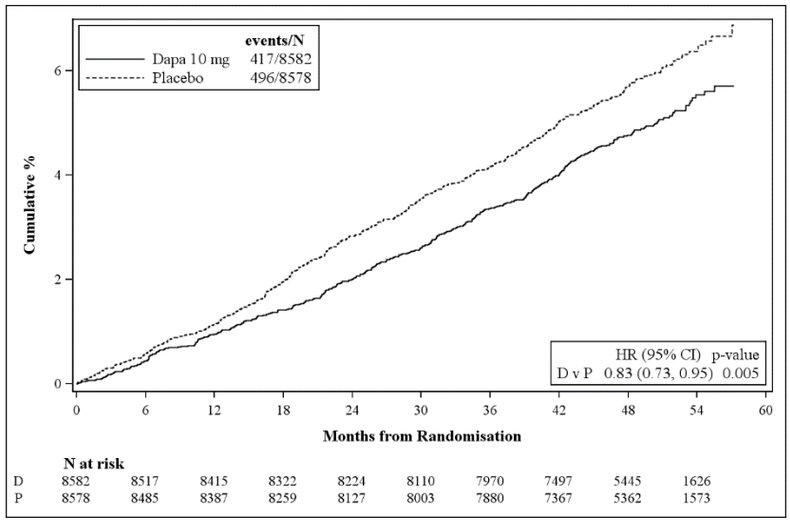
Hasil evaluasi menunjukkan bahwa :
1. Dapagliflozin secara signifikan (secara statistik dan klinis) dapat menurunkan kejadian *composite of hospitalization for heart failure* (HF) and CV *death*, dengan *Hazard Ratio* (HR) 0,83 ([95% CI 0,73, 0,95] p=0,005).

**Table 1 Time from randomisation to first occurrence of any event of hospitalisation for heart failure and CV death (FAS)**

| Efficacy variable | Dapa 10 mg (N=8582) | | Placebo (N=8578) | | Hazard ratio (CI) | p-value |
|---|---|---|---|---|---|---|
| | Patients with events n (%) | Event rate | Patients with events n (%) | Event rate | | |
| Composite endpoint hospitalisation for heart failure/CV death | 417 (4.9) | 12.2 | 496 (5.8) | 14.7 | 0.83 (0.73, 0.95) | 0.005[a] |
| Hospitalisation for heart failure | 212 (2.5) | | 286 (3.3) | | | |
| CV death | 205 (2.4) | | 210 (2.4) | | | |
| Single components[c] | | | | | | |
| Hospitalisation for heart failure | 212 (2.5) | 6.2 | 286 (3.3) | 8.5 | 0.73 (0.61, 0.88) | <0.001[b] |
| CV death | 245 (2.9) | 7.0 | 249 (2.9) | 7.1 | 0.98 (0.82, 1.17) | 0.830[b] |

*Source: Table 11.2.1.1*
[a] *Two-sided p-value.*
[b] *Nominal p-values.*
[c] *Single components were analysed as exploratory variables. The number of first events for the single components are the actual number of first events for each component and do not add up to the number of events in the composite endpoint.*
*All events were adjudicated and confirmed by CEC. Hazard ratio, CI andp-value calculated from Cox proportional hazards model (Wald test) stratified by baseline CV risk and haematuria with treatment as a model term. 95% CIs were calculated for the composite endpoints. Event rate displayed as event rate per 1000 subject years.*
*CI Confidence interval; Dapa Dapagliflozin; FAS Full analysis set; N Number of patients per treatment group; n Number of patients with events; CEC Clinical Event Adjudication Committee; CV Cardiovascular*

**Figure 1. Kaplan-Meier plot of adjudicated event of the composite of hospitalisation for heart failure and cardiovascular death (FAS)**




*Source: Figure 11.2.9*
*N at risk is the number of patients at risk at the beginning of the period. 1 month corresponds to 30 days. 2-sided p-value is displayed. Analysis of time from randomisation to first occurrence of event or censoring.*
*CI Confidence interval; Dapa Dapagliflozin; D Dapa 10 mg; FAS Full analysis set; HR Hazard ratio; N Number of patients per treatment group; P Placebo; v Versus*

2. Dapagliflozin non-inferior dibandingkan plasebo untuk analisa *major adverse cardiovascular events* (MACE) dengan nilai *non-inferiority margin* 1.3 (HR 0,93 [95% CI 0,84, 1,03], p=0,172).

**Table 2 Time from randomisation to first occurrence of any event of the composite of CV death, myocardial infarction, and ischaemic stroke (FAS)**

| Efficacy variable | Dapa 10 mg (N=8582) | | Placebo (N=8578) | | Hazard ratio (CI) | p-value |
|---|---|---|---|---|---|---|
| | Patients with events n (%) | Event rate | Patients with events n (%) | Event rate | | |
| Composite endpoint CV death/myocardial infarction/ischaemic stroke (MACE) | 756 (8.8) | 22.6 | 803 (9.4) | 24.2 | 0.93 (0.84, 1.03) | 0.172[a] |
| CV death | 166 (1.9) | | 167 (1.9) | | | |
| Myocardial infarction | 377 (4.4) | | 428 (5.0) | | | |
| Ischaemic stroke | 213 (2.5) | | 208 (2.4) | | | |
| Single components[c] | | | | | | |
| CV death | 245 (2.9) | 7.0 | 249 (2.9) | 7.1 | 0.98 (0.82, 1.17) | 0.830[b] |
| Myocardial infarction | 393 (4.6) | 11.7 | 441 (5.1) | 13.2 | 0.89 (0.77, 1.01) | 0.080[b] |
| Ischaemic stroke | 235 (2.7) | 6.9 | 231 (2.7) | 6.8 | 1.01 (0.84, 1.21) | 0.916[b] |

*Source: Table 11.2.1.1*
[a] *Two-sided p-value.*
[b] *Nominal p-values.*
[c] *Single components were analysed as exploratory variables. The number of first events for the single components are the actual number of first events for each component and do not add up to the number of events in the composite endpoint.*
*All events were adjudicated and confirmed by CEC. Hazard ratio, CI and p-value calculated from Cox proportional hazards model (Wald test) stratified by baseline CV risk and haematuria with treatment as a model term. 95% CIs were calculated for the composite endpoints. Event rate displayed as event rate per 1000 subject years.*
*CI Confidence interval; Dapa Dapagliflozin; FAS Full analysis set; MACE Major adverse cardiovascular event (cardiovascular death, ischaemic stroke, and myocardial infarction); CV cardiovascular; CEC Clinical Event Adjudication Committee; N Number of patients per treatment group; n Number of patients with events*

Keamanan

1. Pengobatan dengan dapagliflozin tidak terkait dengan efek samping yang serius, kecuali untuk kejadian *diabetic ketoacidosis* (DKA) yang jarang terjadi.
2. Pada pasien yang menggunakan metformin sebagai terapi awal, kejadian hipoglikemik mayor terjadi pada 43 (0.6%) dan 59 (0.8%), berturut-turut merupakan pasien dalam kelompok dapagliflozin dan plasebo.
3. Tidak ditemukan efek samping baru.

**KEPUTUSAN**

Mempertimbangkan data khasiat dan keamanan tersebut di atas, diputuskan registrasi obat baru yang sudah terdaftar dengan penambahan klim terkait resiko kardiovaskular pada bagian indikasi dari Xigduo XR tablet salut selaput dapat disetujui dengan perbaikan redaksional sebagai berikut :

*Therapeutic indication*
*XIGDUO XR (dapagliflozin and metformin HCl extended-release) is indicated as substitution therapy for treatment of type 2 diabetes mellitus in adjunct to diet and exercise to improve glycemic control in adult patients already controlled with dapaglifozin and metformin XR given concurrently at the same dose level (see section Clinical trials and Special warning and precautions for use for available data on combination therapy).*

***For study results with respect to combination of therapies, effects on glycaemic control and cardiovascular events, and the populations studied, see sections Special warnings and special precautions for use, Undesirable effects, dan Pharmacodynamic properties***

**Lampiran I**
**Posologi**
***Recommended Dosing***

- *Healthcare providers should individualize the starting dose of XIGDUO XR based on the patient's current treatment. [See Dosage Forms and Strengths (3).]*
- *XIGDUO XR should generally be taken orally, once daily with the evening meal*
- *XIGDUO XR tablets must be swallowed whole and never crushed, cut, or chewed. Occasionally, the inactive ingredients of XIGDUO XR will be eliminated in the feces as a soft, hydrated mass that may resemble the original tablet.*
- *Dosing may be adjusted based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 10 mg dapagliflozin and 2000 mg metformin HCl.*

***Patients with Renal Impairment***
*No dosage adjustment for XIGDUO XR is indicated in patients with an eGFR greater than or equal to 45 mL/min/1.73m2*
*Assessment of renal function is recommended prior to initiation of XIGDUO XR therapy and periodically thereafter.*
*XIGDUO XR is not recommended in patients with an eGFR below 45 mL/min/1.73 m2.*
*XIGDUO XR is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m2 [see Contraindications, Warnings and Precautions, Adverse Reactions, and Use in Specific Populations].*

***Hepatic Impairment***
*This medicinal product must not be used in patients with hepatic impairment*

***Public Assessment Report***
**XIGDUO XR**

## PRODUCT INFORMATION

| | | |
|---|---|---|
| Name of the drug | : | XIGDUO XR |
| Dosage form | : | Film-coated tablets |
| Active substances | : | Dapagliflozin/Metformin: 5/500 mg; 5/1000 mg; 10/500 mg and 10/1000 mg |
| Packaging | : | Box, 4 blisters @ 7 film-coated tablets |
| Applicant | : | PT AstraZeneca Indonesia |
| Manufacturer | : | AstraZeneca Pharmaceuticals LP, United States |
| Category Registration | : | Registration of a new indication of registered product |
| Indication Proposed | : | *XIGDUO XR (dapagliflozin and metformin HCl extended-release) is indicated as substitution therapy for treatment of type 2 diabetes mellitus in adjunct to diet and exercise to improve glycemic control in adult patients already controlled with dapagliflozin and metformin XR given concurrently at the same dose level (see section Clinical trials and Special warning and precautions for use for available data on combination therapy)*<br><br>*For study results with respect to combination of therapies, effects on glycaemic control and cardiovascular events, and the populations studied, see sections Special warnings and special precautions for use, Undesirable effects, dan Pharmacodynamic properties* |
| Posology proposed | : | Appendix I<br>No changes to the approved posology |

## INTRODUCTION

Xigduo XR is a medicine containing two different active substances, dapagliflozin and metformin, two anti-hyperglycemic drugs with different and complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes.

Dapagliflozin is a very potent, selective and reversible inhibitor of SGLT2. SGLT2 is the primary transporter responsible for the reabsorption of glucose from glomerular filtrate back into the circulation. Dapagliflozin increases fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion.

Metformin is a biguanide with anti-hyperglycemic effect, lowering basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycemia. Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of certain types of glucose membrane transporters (GLUT-1 and GLUT-4)

Xigduo XR has been approved in Indonesia with the indication "*XIGDUO XR (dapagliflozin and metformin HCl extended-release) is indicated as a substitution therapy for treatment of type 2 diabetes mellitus in adjunct to diet and exercise to improve glycemic control in adult patients already controlled with dapagliflozin and metformin XR given concurrently at the same dose level."*

The current evaluation is focused on clinical data that support the addition of claim indication section that is related to the cardiovascular effects of Xigduo XR use.

## QUALITY ASPECTS

NA

Submission of registration in the form of the addition of an indication of registered pharmaceutical product. There was no change in the quality of the drug, so no evaluation was made on the quality aspect.

## EFFICACY AND SAFETY ASPECTS

### Non Clinical Studies

NA

There are no non clinics submitted to support this submission

### Clinical Studies

The evaluation was conducted in 1 clinical study, the DECLARE study (D1693C00001). This study aimed to determine the effect of dapagliflozin versus placebo on cardiovascular (CV) outcomes when added to current therapy in Type 2 Diabetes Mellitus (DMT2) patients with cardiovascular disease or at least 2 cardiovascular risk factors. The study was conducted in 16,906 patients with a median follow-up of 4.2 years.

In this study, the majority of patients continued to receive metformin as routine therapy during the study; concomitant metformin use after randomization studies was 85.6% and 87.5%, respectively in the dapagliflozin and placebo groups.

The results of the evaluation showed that:

1. Dapagliflozin significantly (statistically and clinically) decreased the composite incidence of hospitalization for heart failure (HF) and CV death, with a Hazard Ratio (HR) of 0.83 ([95% CI 0.73, 0.95] p=0.005 ).

**Table 1 Time from randomisation to first occurrence of any event of hospitalisation for heart failure and CV death (FAS)**

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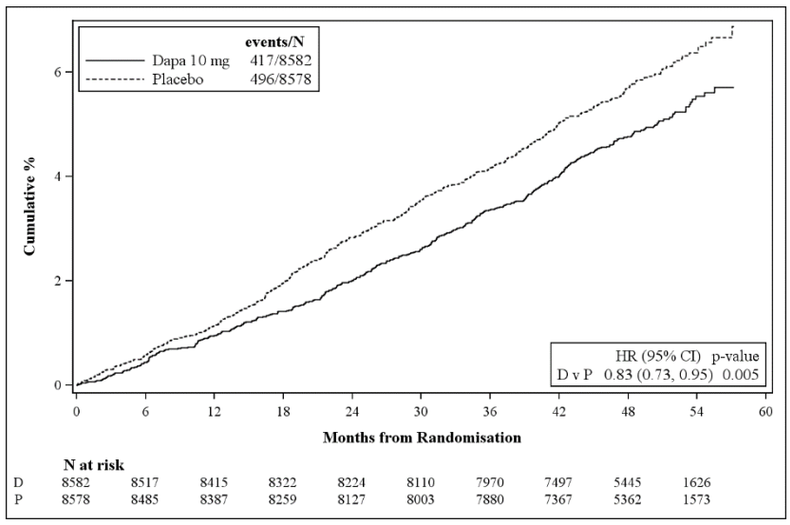


*Source: Figure 11.2.9*
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*CI Confidence interval; Dapa Dapagliflozin; D Dapa 10 mg; FAS Full analysis set; HR Hazard ratio; N Number of patients per treatment group; P Placebo; v Versus*

2. Dapagliflozin was non-inferior to placebo for the analysis of major adverse cardiovascular events (MACE) with a non-inferiority margin of 1.3 ( HR 0.93 [95% CI 0.84, 1.03], p=0.172 ).

**Tabel 2 Time from randomisation to first occurrence of any event of the composite of CV death, myocardial infarction, and ischaemic stroke (FAS)**

| Efficacy variable | Dapa 10 mg (N=8582) | | Placebo (N=8578) | | Hazard ratio (CI) | p-value |
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| Single components[c] | | | | | | |
| CV death | 245 (2.9) | 7.0 | 249 (2.9) | 7.1 | 0.98 (0.82, 1.17) | 0.830b |
| Myocardial infarction | 393 (4.6) | 11.7 | 441 (5.1) | 13.2 | 0.89 (0.77, 1.01) | 0.080b |
| Ischaemic stroke | 235 (2.7) | 6.9 | 231 (2.7) | 6.8 | 1.01 (0.84, 1.21) | 0.916b |

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**Safety**

1. Treatment with dapagliflozin was not associated with serious side effects, except for the rare occurrence of diabetic ketoacidosis (DKA).
2. In patients taking metformin as initial therapy, major hypoglycemic events occurred in 43 (0.6%) and 59 (0.8%), respectively patients in the dapagliflozin and placebo groups.
3. No new side effects were found.

**DECISION**

Taking into account the above efficacy and safety data, it was decided that the registration of a new drug already registered with the addition of a cardiovascular risk related to the indication section of Xigduo XR film-coated tablets could be approved with the following editorial improvements:

*Therapeutic indication*
*XIGDUO XR (dapagliflozin and metformin HCl extended-release) is indicated as substitution therapy for treatment of type 2 diabetes mellitus in adjunct to diet and exercise to improve glycemic control in adult patients already controlled with dapagliflozin and metformin XR given concurrently at the same dose level (see section Clinical trials and Special warning and precautions for use for available data on combination therapy).*

***For study results with respect to combination of therapies, effects on glycaemic control and cardiovascular events, and the populations studied, see sections Special warnings and special precautions for use, Undesirable effects, dan Pharmacodynamic properties***

**Appendix I**
**Posology**
***Recommended Dosing***

- *Healthcare providers should individualize the starting dose of XIGDUO XR based on the patient's current treatment. [See Dosage Forms and Strengths (3).]*
- *XIGDUO XR should generally be taken orally, once daily with the evening meal*
- *XIGDUO XR tablets must be swallowed whole and never crushed, cut, or chewed. Occasionally, the inactive ingredients of XIGDUO XR will be eliminated in the feces as a soft, hydrated mass that may resemble the original tablet.*
- *Dosing may be adjusted based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 10 mg dapagliflozin and 2000 mg metformin HCl*

***Patients with Renal Impairment***
*No dosage adjustment for XIGDUO XR is indicated in patients with an eGFR greater than or equal to 45 mL/min/1.73m$^2$*
*Assessment of renal function is recommended prior to initiation of XIGDUO XR therapy and periodically thereafter.*
*XIGDUO XR is not recommended in patients with an eGFR below 45 mL/min/1.73 m$^2$.*
*XIGDUO XR is contraindicated in patients with an estimated glomerular filtration rate (eGFR) Below 30 mL/min/1.73 m$^2$ [see Contraindications, Warnings and Precautions, Adverse Reactions, and Use in Specific Populations]*

***Hepatic Impairment***
*This medicinal product must not be used in patients with hepatic impairment*