Public Assessment Report
XIGDUO XR

INFORMASI PRODUK

Nama obat	:	**XIGDUO XR**
Zat Aktif	:	Tiap tablet salut selaput mengandung: - Metformin hydrochloride 502.61 mg ~ Metformin 500 mg - Dapagliflozin propanediol 12.30 mg ~ Dapagliflozin 10 mg
Bentuk sediaan	:	Tablet Salut Selaput
Kemasan	:	Dus, 4 blister @ 7 tablet salut selaput
Pendaftar	:	PT. ASTRAZENECA INDONESIA
Produsen	:	ASTRAZENECA PHARMACEUTICALS LP, MOUNT VERNON, USA
Kategori Registrasi	:	Registrasi obat baru yang sudah terdaftar dengan indikasi dan posologi baru
Indikasi yang diajukan:	:	*XIGDUO XR (dapagliflozin and metformin HCl extended-release) is indicated in adult patient type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control when treatment with both dapagliflozin and metformin is appropriate.* *(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, and Pharmacodynamic properties*
Posologi yang diajukan	:	***Posology and method of administration*** ***Recommended Dosing*** • *The dosage of antihyperglycaemic therapy with XIGDUO XR should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended dose of dapagliflozin 10 mg and metformin extended-release 2000 mg.* • *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* • ***Initial therapy**: If therapy with a combination tablet containing dapagliflozin and metformin is considered appropriate, the recommended dose of dapagliflozin is 10 mg once daily. The recommended starting dose of metformin extended-release is 500 mg once daily, which can be titrated to 2000 mg once daily. The maximum dose of XIGDUO XR is dapagliflozin 10 mg/metformin extended-release 2000 mg taken as two 5 mg/1000 mg tablets once daily.* ***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.* *Discontinuation for Iodinated Contrast Imaging Procedures* *Xigduo XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart Xigduo XR if renal function is stable (see Warnings and Precautions).*

PENGANTAR

Data dari International Diabetes Federation (IDF) menunjukan jumlah penderita diabetes di dunia pada tahun 2021 mencapai 537 juta. Angka ini diprediksi akan terus meningkat mencapai 643 juta di tahun 2030 dan 783 juta pada tahun 2045. Menurut IDF, Indonesia menduduki peringkat kelima negara dengan jumlah diabetes terbanyak dengan 19,5 juta penderita di tahun 2021 dan diprediksi akan menjadi 28,6 juta pada 2045.

Penatalaksanaan diabetes melitus (DM) dimulai dengan menerapkan pola hidup sehat (terapi nutrisi medis dan aktivitas fisik) bersamaan dengan intercensi farmakologis dengan obat anti hiperglikemia secara oral dan/atau suntikan. Obat anti hiperglikemia oral dapat diberikan sebagai terapo tunggal atau kombinasi.

XIGDUO XR merupakan obat dengan zat aktif kombinasi dua agen antihiperglikemik yaitu Dapagliflozin dan Metformin. Kombinasi tersebut memiliki mekanisme aksi komplementer untuk menurunkan glukosa plasma puasa (*fasting plasma glucose*; FPG) dan glukosa plasma pasca makan (*postprandial plasma glucose*;PPG) pada pasien diabetes tipe-2. Dapagliflozin termasuk ke dalam obat golongan penghambat SGLT-2 dengan bekerja mengurangi penyerapan kembali glukosa ginjal yang dapat menyebabkan ekskresi glukosa berlebih melalui urin (*glucuresis)*. Metformin merupakan obat golongan biguanida yang bekerja dengan menurunkan produksi glukosa hati, menurunkan penyerapan glukosa di usus dan meningkatkan sensitivitas insulin dengan meningkatkan penyerapan dan penggunaan glukosa perifer.

XIGDUO XR telah disetujui sejak tahun 2018 untuk indikasi terapi subtitusi pada pasien diabetes tipe-2 untuk dewasa. Saat ini pendaftar mengajukan penambahan klim "*when treatment with both dapagliflozin and metformin is appropriate*" pada bagian indikasi dan posologi. Pendaftar menyerahkan studi klinik berupa studi klinik untuk mendukung perubahan indikasi dan posologi tersebut. Evaluasi akan difokuskan pada studi klinik terkait perubahan tersebut.

ASPEK MUTU

Pengajuan registrasi berupa perubahan posologi baru 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

Tidak ada studi non klinik baru untuk pengajuan indikasi dan posologi baru.

Studi Klinik

Studi yang diserahkan dalam pengajuan registrasi obat ini adalah:

1. MB102021 (n=598): *A Multicenter, Randomized, Double-Blind, Active Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin in Combination with Metformin as Initial Therapy as Compared with Dapagliflozin Monotherapy and Metformin Monotherapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control*
2. MB102034 (n=638): *A Multicenter, Randomized, Double-Blind, Active Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin 10 mg in Combination with Metformin as Initial Therapy as Compared with Dapagliflozin 10 mg Monotherapy and Metformin Monotherapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control*

Hasil evaluasi efikasi berdasarkan studi klinik di atas adalah sebagai berikut:

1. Hasil studi MB102021 (n=598) yang mengevaluasi efikasi dan keamanan kombinasi dapagliflozin 5 mg dengan metformin sebagai terapi awal dibandingkan dengan monoterapi dapagliflozin dan monoterapi

metformin pada pasien Diabetes tipe 2 dengan kontrol glikemik yang tidak adekuat (HbA1c lebih besar sama dengan 7,5% dan kurang dari atau sama dengan 12,0%) menunjukkan bahwa :

- Penurunan kadar HbA1c dari *baseline* pada minggu ke-24 lebih besar signifikan pada kelompok kombinasi dapagliflozin + metformin dibandingkan dengan kelompok monoterapi dapagliflozin 2.05% vs 1.19%, p< 0.0001) maupun kelompok monoterapi metformin (2.05% vs 1.35% , p<0.0001)
- Penurunan kadar glukosa plasma puasa (FPG) dari *baseline* pada minggu ke-24 lebih besar pada kelompok kombinasi dapagliflozin + metformin dibandingkan dengan kelompok monoterapi dapagliflozin maupun kelompok monoterapi metformin (61 mg/dL vs 42 mg/dL vs 33.6 mg/dL, p < 0.0001)Persentase subjek yang mencapai kadar HbA1c <7% pada minggu ke-24 lebih tinggi pada
- kelompok kombinasi dapagliflozin + metformin dibandingkan dengan kelompok dapagliflozin (52.4% vs 22.5%, p <0.0001) maupun kelompok monoterapi metformin (52.4% vs 34.6%, dan p=0.003)
- Pada subjek dengan HbA1c lebih besar sama dengan 9% saat *baseline,* persentase subjek yang mengalami penurunan HbA1C pada minggu ke-24 lebih besar pada kelompok kombinasi dapagliflozin + metformin dibandingkan dengan kelompok monoterapi dapagliflozin (3.01% vs 1.67%, p <0.0001) maupun kelompok monoterapi metformin (3.01% vs 1.82%, p <0.0001). Kombinasi dapagliflozin 5 mg dan metformin XR umumnya aman dan dapat ditoleransi dengan baik.

3. Hasil studi MB102034 (n= 638) yang mengevaluasi keamanan dan efikasi kombinasi dapagliflozin 10 mg + metformin sebagai terapi awal dibandingkan monoterapi dapagliflozin 10 mg dan monoterapi metformin pada pasien diabetes tipe 2 dengan kontrol glikemik yang tidak adekuat (HbA1c ≥ 7,5% dan ≤ 12,0%) menunjukkan bahwa :
   - Penurunan kadar HbA1c dari baseline pada minggu ke-24 lebih besar pada kelompok kombinasi dapagliflozin + metformin dibandingkan kelompok monoterapi dapagliflozin (1.98% vs 1.45 % ,p <0.0001) maupun kelompok monoterapi metformin (1.98% vs 1.45 % ,p <0.0001).
   - Penurunan kadar glukosa plasma puasa (FPG) dari baseline pada minggu ke-24 lebih besar pada kelompok kombinasi dapagliflozin + metformin dibandingkan kelompok monoterapi dapagliflozin (60.4 mg/dL vs 46.4 mg/dL, p <0.0001) maupun kelompok monoterapi metformin (60.4 mg/dL vs 34.8 mg/dL, p <0.0001)
   - Persentasi subjek yang mencapai nilai HbA1c <7% pada minggu ke-24 lebih tinggi signifikan pada kelompok kombinasi dapagliflozin + metformin dibandingkan dengan kelompok dapagliflozin (46.6% vs 31.7%, p= 0.0012) maupun kelompok monoterapi metformin (46.6% vs 35.2%, p=0.0165)
   - Penurunan HbA1c pada subjek dengan HbA1c ≥ 9% saat baseline pada minggu ke- 24 lebih besar signifikan pada kelompok dapagliflozin + metformin dibandingkan dengan kelompok monoterapi dapagliflozin (2.59% vs 2.14% , p = 0.0122) dan monoterapi metformin (2.59% vs 2.05%, p = 0.0036)
   - Kombinasi dapagliflozin 10 mg dan metformin XR dapat ditoleransi dengan baik.

3. *Periodic Benefit-Risk Evaluation Report* (16 January 2022 hingga 15 Januari 2023) menunjukkan jumlah subjek yang terpapar hingga *data lock poin* sebanyak 7.782.754, tidak teridentifikasi adanya risiko baru yang terkait dengan penggunaan produk
4. Berdasarkan informasi produk yang diserahkan, indikasi yang diajukan yaitu "*when treatment with both dapagliflozin and metformin is appropriate*" menunjukkan bahwa sediaan *fixed-dose combination* digunakan sebagai terapi substitusi untuk pasien yang sebelumnya telah menerima kedua obat secara terpisah, sebagai *add-on therapy* pada pasien yang belum terkontrol dengan monoterapi atau pada pasien dengan kadar HbA1C ≥ 7,5%.

Evaluasi

Penilaian Manfaat-Risiko

Berdasarkan data khasiat dan keamanan yang diperoleh dari hasil studi klinik, obat XIGDUO XR memiliki efek yang menguntungkan dan efek yang tidak menguntungkan sebagai berikut:

a. Aspek yang menguntungkan:
   i. Studi MB102021 dan MB102034 menunjukkan penggunaan kombinasi dapagliflozin + metformin menurunkan HbA1c secara signifikan (2.05% dan 1.98%) dibandingkan pemberian tunggal - tunggalnya pada pasien diabetes tipe II naïve yang tidak memiliki kontrol glikemik yang memadai setelah pemberian obat selama 24 minggu.
   ii. Data keamanan penggunaan dapagliflozin dengan metformin menunjukkan tidak ada kematian selama

studi dan proporsi SAE yang similar dibandingkan dengan tunggal-tunggalnya hingga minggu ke- 24.

b. Aspek yang tidak menguntungkan:
   i. Important identified risk adalah Lactic acidosis (metformin) dan Diabetic Ketoacidosis (dapagliflozin).

Kesimpulan Manfaat-Risiko

Secara keseluruhan obat ini menunjukkan kemanfaatan sebagai *add-on therapy* pada pasien yang belum terkontrol dengan monoterapi atau pada pasien dengan kadar HbA1C ≥ 7,5%. Tidak teridentifikasi adanya risiko baru yang terkait dengan penggunaan produk. Pendaftar wajib melakukan pemantauan farmakovigilans dan pelaporan efek samping obat ke Badan POM.
Dengan demikian, XIGDUO DR dipertimbangkan memiliki manfaat yang lebih besar dibanding risikonya.

KEPUTUSAN

Berdasarkan hal-hal tersebut di atas, Rapat Komite Nasional Penilai Obat merekomendasikan bahwa registrasi obat dengan indikasi dan posologi baru XIGDUO XR Tablet Salut Selaput diterima dengan perbaikan indikasi dan posologi sebagai berikut:

INDIKASI

XIGDUO XR (dapagliflozin and metformin HCl extended-release) is indicated in adult patient type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control when treatment with both dapagliflozin and metformin is appropriate.

POSOLOGI

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If therapy with a combination tablet containing dapagliflozin and metformin is considered appropriate, the recommended dose of dapagliflozin is 10 mg once daily. The recommended starting dose of metformin extended-release is 500 mg once daily, which can be titrated to 2000 mg once daily. The maximum dose of XIGDUO XR is dapagliflozin 10 mg/metformin extended-release 2000 mg taken as two 5 mg/1000 mg tablets once daily.

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XIGDUO XR

PRODUCT INFORMATION

Drug Name	:	**XIGDUO XR**
Active Pharmaceutical Ingredients	:	Each film-coated tablets contains: - Metformin hydrochloride 502.61 mg ~ Metformin 500 mg - Dapagliflozin propanediol 12.30 mg ~ Dapagliflozin 10 mg
Dosage form	:	Film-coated tablet
Packaging	:	Box of 4 blisters @ 7 film-coated tablets
Applicant	:	PT. ASTRAZENECA INDONESIA
Manufacturer	:	ASTRAZENECA PHARMACEUTICALS LP, MOUNT VERNON, USA
Registration Category	:	New drug registration of a registered drug with new indication and posology
Proposed Indication	:	*XIGDUO XR (dapagliflozin and metformin HCl extended-release) is indicated in adult patient type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control when treatment with both dapagliflozin and metformin is appropriate.* *(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, and Pharmacodynamic properties*
Proposed Posology	:	***Posology and method of administration*** ***Recommended Dosing*** • *The dosage of antihyperglycaemic therapy with XIGDUO XR should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended dose of dapagliflozin 10 mg and metformin extended-release 2000 mg.* • *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 faeces as a soft, hydrated mass that may resemble the original tablet* • ***Initial therapy**: If therapy with a combination tablet containing dapagliflozin and metformin is considered appropriate, the recommended dose of dapagliflozin is 10 mg once daily. The recommended starting dose of metformin extended-release is 500 mg once daily, which can be titrated to 2000 mg once daily. The maximum dose of XIGDUO XR is dapagliflozin 10 mg/metformin extended-release 2000 mg taken as two 5 mg/1000 mg tablets once daily.* ***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.* ***Discontinuation for Iodinated Contrast Imaging Procedures*** *Xigduo XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart Xigduo XR if renal function is stable (see Warnings and Precautions).*

BACKGROUND

Data from International Diabetes Federation (IDF) show that per 2021, there are 537 million people with diabetes in the world. This figure projected to reach 643 million in 2030 and 783 million in 2045. Based on IDF, Indonesia is ranked at the fifth place with the highest number of people with diabetes, 19.5 million in 2021 and projected to reach 28.6 million in 2045.

Type 2 diabetes mellitus (DM) standard of care mainly focused on living a healthy lifestyle (medical nutrition therapy and physical activity) together with pharmacological intervention with anti-hyperglycemic drug orally and/or by injection. Anti-hyperglycemic drugs can be given as a monotherapy or combination.

XIGDUO XR is a drug with a combination of two anti-hyperglycemic agents, Dapagliflozin and Metformin. This combination have complementary mechanisms of action to improve both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) in patients with type-2 diabetes. Dapagliflozin is an SGLT-2 inhibitor that improves glycaemic control by reducing glucose reabsorption in the kidneys, leading to urinary excretion of excess glucose (glucosuria). Metformin is a biguanide that acts through lowering liver glucose production, glucose absorption in the small intestine, and improving insulin sensitivity by increasing peripheral glucose uptake and utilization.

XIGDUO XR has been approved since 2018 indicated as a substitution therapy for adult patients with type-2 diabetes. The applicant is proposing claim addition "*when treatment with both dapagliflozin and metformin is appropriate*" in the Indication and Posology. Applicant submitted clinical study reports to support the proposed change of indication and posology. Evaluation was focused on clinical studies regarding the change as mentioned before.

QUALITY ASPECT

The registration submission involved a change in posology of a registered drug. There is no change regarding to the quality of drug, thus no evaluation was conducted on quality aspect.

SAFETY AND EFFICACY ASPECT

Non Clinical Study

There is no new non clinical study to be submitted for new indication and posology.

Clinical Study

Studies submitted for this drug registration are:

1. MB102021 (n=598): *A Multicenter, Randomized, Double-Blind, Active Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin in Combination with Metformin as Initial Therapy as Compared with Dapagliflozin Monotherapy and Metformin Monotherapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control*
2. MB102034 (n=638): *A Multicenter, Randomized, Double-Blind, Active Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin 10 mg in Combination with Metformin as Initial Therapy as Compared with Dapagliflozin 10 mg Monotherapy and Metformin Monotherapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control*

Efficacy evaluation report based on clinical studies mentioned above are presented below:

1. MB102021 study report (n=598) on efficacy and safety evaluation of the dapagliflozin 5 mg and metformin combination as initiation therapy compared to dapagliflozin monotherapy and metformin monotherapy in

patients with type-2 diabetes patients with inadequate glycaemic control (characterized by HbA1c more than or equal to 7.5% and lower than or equal to 12.0%) shows that:

- HbA1c level reduction from baseline at week 24 is significantly greater in the dapagliflozin + metformin combination group compared to both dapagliflozin monotherapy (2.05% vs 1.19%, p<0.0001) and metformin monotherapy group (2.05% vs 1.35%, p<0.0001)
- Fasting plasma glucose reduction from baseline at week 24 is greater in dapagliflozin + metformin combination group compared to both dapagliflozin monotherapy and metformin monotherapy group (61 mg/dL vs 42 mg/dL vs 33.6 mg/dL, p<0.0001)
- Number of subjects who reached HbA1c level <7% at week 24 is higher in the dapagliflozin + metformin combination group compared to both dapagliflozin monotherapy (52.4% vs 22.5%, p<0.0001) and metformin monotherapy group (52.4% vs 34.6%, p=0.003)
- In subjects with HbA1c level greater than or equal to 9% at the baseline, number of patients who experienced lowered HbA1c level at week 24 is greater in the dapagliflozin + metformin combination compared to dapagliflozin monotherapy (3.01% vs 1.67%, p<0.0001) and metformin monotherapy group (3.01% vs 1.82%, p<0.0001).
- Combination of dapagliflozin 5 mg and metformin XR is generally safe and well tolerated.

2. MB102034 study report (n=638) on efficacy and safety evaluation of dapagliflozin 10 mg and metformin combination as initiation therapy compared to dapagliflozin 10 mg and metformin monotherapy in patients with type-2 diabetes with inadequate glycaemic control (HbA1c ≥ 7.5% and ≤ 12.0%) shows that:
   - HbA1c level reduction from baseline at week 24 is greater in the dapagliflozin + metformin combination group compared to dapagliflozin monotherapy (1.98% vs 1.45%, p<0.0001) and metformin monotherapy group (1.98% vs 1.44%, p<0.0001).
   - Fasted plasma glucose level reduction from baseline at week 24 is greater in dapagliflozin + metformin combination group compared to dapagliflozin monotherapy (60.4 mg/dL vs 46.4 mg/dL, p<0.0001) and metformin monotherapy group (60.4 mg/dL vs 34.8 mg/dL, p<0.0001)
   - Number of subjects who reached HbA1c level <7% at week 24 is higher in the dapagliflozin + metformin combination group compared to both dapagliflozin monotherapy (46.6% vs 31.7%, p=0.0012) and metformin monotherapy group (46.6% vs 35.2%, p=0.0165)
   - In subjects with HbA1c level greater than or equal to 9% at the baseline, number of patients who experienced lowered HbA1c level at week 24 is greater in the dapagliflozin + metformin combination compared to dapagliflozin monotherapy (2.59% vs 2.14%, p=0.0133) and metformin monotherapy group (2.59% vs 2.05%, p=0.0036).
   - Combination of dapagliflozin 10 mg and metformin XR is well tolerated.

3. Periodic Benefit-Risk Evaluation Report (16 January 2022 until 15 January 2023) shows that total number of subjects who were exposed until data lock point are 7,782,754. There is no identified new risk regarding to product usage.
4. Based on submitted information, the proposed indication "*when treatment with both dapagliflozin and metformin is appropriate*" shows that the fixed-dose combination dosage form can be used as a substitution therapy for patients who received two drugs separately, as an add-on therapy for patients who have not reached glycaemic control with monotherapy or in patients whose HbA1c level ≥ 7.5%.

Evaluation

Risk-Benefit Assessment

Based on efficacy and safety data obtained from clinical studies, XIGDUO XR has the following risks and benefits:

a. Beneficial aspects:
   i. MB102021 and MB102034 studies have shown that the use of dapagliflozin + metformin combination significantly reduce HbA1c levels (2.05% and 1.98%) compared to the monotherapies of each active substances after 24 weeks of treatment in drug naive patients with type-2 diabetes who have inadequate glycaemic control.
   ii. Safety data on concurrent use of dapagliflozin and metformin shows no death during the study period and similar SAE proportion to each active substances until week 24
b. Risk aspect:
   i. Important identified risks are Lactic acidosis (metformin) and Diabetic ketoacidosis including events with atypical presentation (dapagliflozin).

Risk-Benefit Conclusion

Overall, this drug shows benefit as an add-on therapy in patients who have not reached glycaemic control with monotherapies or in patients whose HbA1c level ≥ 7.5%. There is no new risk identified regarding the product usage. Applicant should do pharmacovigilance monitoring and report adverse drug reaction report to Indonesian FDA (Badan POM).

Therefore, XIGDUO XR is considered to have benefits that outweigh its risks.

Decision:

Based on the above considerations, the National Drug Evaluation Committee meeting recommended that the registration of XIGDUO XR Film-Coated Tablets for its new indication and dosage be accepted, with the following revisions to the indication and dosage:

Indication

XIGDUO XR (dapagliflozin and metformin HCl extended-release) is indicated in adult patient type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control when treatment with both dapagliflozin and metformin is appropriate.

Posology

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If therapy with a combination tablet containing dapagliflozin and metformin is considered appropriate, the recommended dose of dapagliflozin is 10 mg once daily. The recommended starting dose of metformin extended-release is 500 mg once daily, which can be titrated to 2000 mg once daily. The maximum dose of XIGDUO XR is dapagliflozin 10 mg/metformin extended-release 2000 mg taken as two 5 mg/1000 mg tablets once daily.