Public Assessment Report
QTERN

INFORMASI PRODUK

Nama obat	:	QTERN
Bentuk sediaan	:	Tablet salut selaput
Zat aktif	:	Tiap tablet salut selaput mengandung - Dapagliflozin propanediol 12.3 mg ~ Dapagliflozin 10 mg - Saxagliptin 5 mg
Kemasan	:	Dus, 2 blister @ 14 tablet salut selaput
Pendaftar	:	PT. AstraZeneca Indonesia
Produsen	:	• ASTRAZENECA PHARMACEUTICALS LP Mount Vernon, United States of America, (Manufacturer, Qc Testing) • ASTRAZENECA AB Sodertalje, Sweden, (Releaser, Primary Packaging)
Kategori Registrasi	:	Registrasi obat baru yang sudah terdaftar dengan kombinasi baru
Indikasi yang diajukan:	:	*QTERN is indicated as an adjunct to diet and exercise, in combination with metformin, to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and dapagliflozin is appropriate*.
Posologi yang diajukan	:	*The recommended dose of QTERN is one saxagliptin 5 mg/dapagliflozin 10 mg tablet taken once daily at any time of the day, with or without food. Tablet is to be swallowed whole.* *Please refer to Section Special Warnings and Precautions for Use for information regarding combinations not studied.* *Optimal medical management of patients with diabetes also involves attention to diet, exercise, blood glucose monitoring, assessment of complications and co-morbidities. Regular assessment and review of the compliance and benefit/risk of all therapies is recommended.* *Special populations* *<u>Patients with renal impairment</u>* *Assess renal function prior to initiation of QTERN and periodically thereafter. No dose adjustment is required for patients with eGFR ≥ 45 mL/min/1.73 m2.* *The glycaemic efficacy of dapagliflozin is dependent on renal function. QTERN should not be used in patients with an estimated glomerular filtration rate (eGFR) persistently <45 mL/min/1.73 m2 as calculated by the Modification of Diet in Renal Disease [MDRD] formula or in patients with end-stage renal disease (ESRD) or patients on dialysis (see Section Special Warnings and Precautions for Use and Section Adverse Effects (Undesirable Effects)).* *<u>Patients with hepatic Impairment</u>* *QTERN may be used in patients with mild or moderate hepatic impairment. QTERN should not be used in patients with severe hepatic impairment (see Section Special Warnings and Precautions for Use).* *<u>Paediatric and adolescent patients</u>* *Safety and effectiveness of QTERN in paediatric and adolescent patients (<18 years of age) have not been established.* *<u>Elderly patients</u>* *In general, no dosage adjustment is recommended based on age. Caution should be exercised due to the risk of hypovolaemia.*

Because elderly patients are more likely to have decreased renal function, care should be taken in the elderly based on renal function. (see Section Special Warnings and Precautions for Use and Section Pharmacological Properties).

Patients at risk for volume depletion
In patients with volume depletion, correcting this condition prior to initiation of QTERN is recommended (see Section Special Warnings and Precautions for Use).

PENGANTAR

QTERN merupakan obat dengan kombinasi baru Saxagliptin dan Dapagliflozin. Saxagliptin merupakan penghambat enzim DPP4, sehingga memperlama inaktivasi dari hormon increatin yaitu *Glucagon-like peptide* (GLP-1) dan *Glucose dependent insulinotropic popypeptide* (GIP). Dapagliflozin merupakan penghambat SGLT2 yang mengurangi reabsorpsi glukosa di tubulus proksimal ginjal sehingga menyebabkan peningkatan ekskresi glukosa melalui urin. Kombinasi keduanya dapat memberikan penurunan HbA1c untuk meningkatkan kontrol glikemik pada pasien DM tipe 2. Mengingat kombinasi Saxagliptin dan Dapagliflozin merupakan kombinasi baru, saat ini evaluasi difokuskan pada data uji klinik dan mutu obat untuk pembuktian efikasi, keamanan, dan mutu obat lebih lanjut.

ASPEK MUTU
QTERN (Saxagliptin/Dapagliflozin) tersedia dalam bentuk tablet salut selaput, mengandung Dapagliflozin 10 mg dan Saxagliptin 5 mg. Obat jadi mengandung eksipien yang terdiri dari *microcrystalline cellulose, Lactose anhydrous, Croscarmellose sodium, Silicon dioxide, Magnesiun stearate, Opary II White, Hydrochloric acid, Sodium hydroxide, Opadry II red, Opadry II purple, Opadry II yellow, Opadry II butterscotch, Opacode ink Blue dan Isopropyl Alcohol.*

Zat Aktif
Kedua zat aktif Saxagliptin dan Dapagliflozin yang digunakan dalam QTERN telah digunakan dalam sediaan lain yang telah disetujui beredar di Indonesia yaitu zat aktif dapagliflozin pada sediaan obat Forxiga 5 mg dan 10 mg tablet salut selaput dan Xigduo XR tablet salut selaput. Sedangkan zat aktif Saxagliptin pada sediaan obat Onglyza tablet salut selaput dan Kombiglyze XR tablet salut selaput. Evaluasi mutu kedua zat aktif tersebut mengacu pada produk-produk tersebut.

Obat jadi

Obat jadi diproduksi dalam bentuk tablet salut selaput berbentuk bulat dan berwarna coklat muda.

Saxagliptin/Dapagliflozin *fixed dose combination* (FDC) merupakan sediaan dengan gabungan dari formulasi dapagliflozin *core tablet* (similar dengan Forxiga), dengan 3 *layer film coating* yang berisi saxagliptin (similar dengan Onglyza).

Uraian proses produksi diserahkan dengan rincian dan memadai. Tahapan kritis proses telah diidentifikasi dan kontrol beserta rentang penerimaannya telah ditetapkan. Validasi proses telah dilakukan terhadap 3 bets skala produksi. Hasil validasi proses menunjukan kemampuan proses menghasilkan obat jadi yang memenuhi kriteria penerimaan yang ditetapkan.

Spesifikasi obat yang ditetapkan yakni pemerian (visual), identifikasi (UHPLC dan UV), Assay (UHPLC), *impurities (UHPLC), uniformity of dosage units (UHPLC), tablet disintegration,* kadar air, dan pemeriksaan mikrobiologi. Parameter dalam spesifikasi dipilih berdasarkan karakterisitik fisikokima dan sifat kritikal zat aktif dengan mempertimbangkan antara lain hasil uji bets yang digunakan dalam uji klinik, data stabilitas jangka panjang. Metode analisa yang digunakan telah divalidasi. Hasil analisa bets memberikan hasil yang memenuhi spesifikasi yang dipersyaratkan.

Data stabilitas dari 3 bets obat skala produksi telah dilakukan, yaitu pada suhu 30°C/75% RH selama 36 bulan dan suhu 40°C/75% RH selama 6 bulan serta dilakukan pemeriksaan stabilita bulk selama 12 bulan pada suhu suhu 30°C/65% RH dengan hasil yang memenuhi spesifikasi yang dipersyaratkan.

Kesimpulan
Dari aspek mutu, QTERN tablet salut selaput dapat dipertimbangkan untuk diterima.

ASPEK KHASIAT DAN KEAMANAN

Studi Non Klinik
Tidak ada studi non klinik baru untuk pengajuan kombinasi baru

Studi Klinik
Evaluasi dilakukan pada 4 studi klinik untuk mendukung khasiat dan keamananan Qtern tablet salut selaput yang diajukan, terdiri atas 1 studi fase I (CV181191, n=42), dan 3 studi fase III (studi CV181168, n=315; studi MB102129, n=301; studi CV181169, n=490).

1. Studi klinik fase 1 (Studi CV181191, n=42), dengan desain *open label, randomized, crossover, 3-priod, 3-treatment*, pada subjek sehat menunjukkan pemberian secara bersama saxagliptin 5 mg + dapagliflozin 10 mg tidak mempengaruhi profil farmakokinetik masing-masing zat aktif tunggalnya berdasarkan *90%CI geometric mean change ratio Cmax dan AuC(inf)* terhadap dapagliflozin 10 mg (0,943 dan 0,984) dan saxagliptin 5 mg (0,994 dan 1,046). Pemberian tunggal saxagliptin 5 mg, dapagliflozin 10 mg maupun kombinasi saxagliptin 5 mg + dapagliflozin 10 mg (*co-administered*) aman dan dapat ditoleransi dengan baik selama studi.
2. Studi klinik fase 3 (studi CV181168, n=315), dengan desain *multicenter, randomized, double blind, placebo-controlled, parallel group*, selama 24 bulan pada pasien DM tipe 2 yang sebelumnya mendapatkan terapi dapagliflozin + metformin, menunjukkan efikasi saxagliptin + dapaglifozin + metformin yang lebih baik dibandingkan dengan placebo + dapagliflozin + metformin berdasarkan parameter:
    a) *mean change from baseline HbA1c* (-0.51% vs -0,16%);
    b) *difference in adjusted HbA1c mean change from baseline* (-0,35; 95%CI: -0,52, -0,18; p<0.0001); dan
    c) proporsi subjek yang mencapai target HbA1c <7% (35,3% vs 23,1%).
3. Studi klinik fase 3 (Studi MB102129, n=301), dengan desain *multicenter, randomized, double blind, placebo-controlled, parallel group*, selama 24 bulan pada pasien DM tipe 2 yang sebelumnya mendapatkan terapi saxagliptin + metformin menunjukkan efikasi saxagliptin + dapaglifozin + metformin lebih baik dibandingkan placebo + saxagliptin + metformin berdasarkan parameter:
    a) *mean change from baseline in HbA1c* (-0.82% vs -0.10%);
    b) *difference in adjusted HbA1c mean change from baseline* (-0.72%; 95% CI -0.91, -0.53; p<0.0001);
    c) *mean change from baseline in Fasting Plasma Glucose* (FPG) (-32.7 vs -5.3 mg/dl);
    d) *mean change from baseline in 2 hours Post Prandial Glucose* (PPG) (-73.5 vs -38 mg/dl); dan
    e) *rata-rata perubahan berat badan dari baseline* (-1.91 vs -0.41 kg).
4. Studi klinik fase 3 (CV181169, n=490) dengan desain *multicenter, randomized, double blind, active-controlled, parallel group*, menunjukkan pemberian saxagliptin + dapagliflozin pada pasien DM Tipe 2 yang sebelumnya mendapatkan terapi metformin tunggal (saxa+dapa+met) memiliki kemanfaatan yang lebih baik dibandingkan pemberian plasebo + saxagliptin terhadap metformin tunggal (saxa+met) dan plasebo + dapagliflozin terhadap metformin (dapa+met), berdasarkan parameter:
    a) *adjusted mean reduction from baseline in HbA1c* (-1,47% vs -0,88% vs -1,20%); dan berbeda bermakna secara statistik dibanding kelompok saxa+met (-0.59%; 95% CI: -0.81, -0.37;p<0.0001) dan kelompok dapa+met (-0.27%;95% CI -0.48, -0.05; p=0.0166)
    b) *mean change from baseline in 120 minutes PPG* lebih besar signifikan dibanding kelompok saxa+met (-79.9 vs -35.6 mg/dL; difference -44.0; CI 95% -53.7, -34.3; p<0.0001) namun tidak ada perbedaan dengan kelompok dapa+met (difference -9.1 95% CI -18.8, 0.5; p=0.00639)
    c) rerata perubahan FPG pada minggu ke-24 lebih tinggi dan berbeda bermakna secara statistik dibanding kelompok saxa+met (-37.8 vs -14.0 mg/dL; *difference* -23.8; CI 95% -31.6, -15.9) namun tidak ada perbedaan dengan kelompok dapa+met (*difference* -6.1; 95% CI -13.8, 1.7)
    d) proporsi subjek yang mencapai target glikemik HbA1c <7% lebih tinggi (41.4% vs 18.3% vs 22.2%).
5. Data keamanan berdasarkan studi yang diserahkan menunjukkan pemberian kombinasi saxagliptin + dapagliflozin + metformin dapat ditoleransi dengan baik dan konsisten dengan profil keamanan masing-masing zat aktif. Tidak ada laporan kematian atau malignansi yang terkait dengan pengobatan. Frekuensi kejadian efek samping serius ditemukan lebih banyak pada kelompok saxa+met dibandingkan kelompok saxa+dapa+met (Studi CV181169). Efek samping yang paling umum terjadi adalah infeksi saluran kemih,

nasofaringitis, sakit kepala, influenza (Studi CV181168 dan MB102129); dan arthralgia (Studi CV181169).

KEPUTUSAN

Mempertimbangkan data khasiat dan keamanan tersebut di atas, diputuskan registrasi zat aktif baru QTERN tablet salut selaput diterima dengan perbaikan indikasi sebagai berikut:

Indikasi

QTERN (FDC saxagliptin/dapagliflozin) is indicated for use in combination with metformin as an adjunct to diet and exercise to achieve glycemic control in adults with type 2 diabetes mellitus (T2DM) who are inadequately controlled on metformin plus saxagliptin or metformin plus dapagliflozine.

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PRODUCT INFORMATION

Name of drug	:	QTERN
Dosage form	:	Film-coated tablets
Active substance	:	Each film-coated tablet contains: - Dapagliflozin propanediol 12.3 mg ~ Dapagliflozin 10 mg - Saxagliptin 5 mg
Packaging	:	Box, 2 blisters @ 14 film-coated tablets
Applicant	:	PT. AstraZeneca Indonesia
Manufacturer	:	- ASTRAZENECA PHARMACEUTICALS LP Mount Vernon, United States of America, (Manufacturer, QC Testing) - ASTRAZENECA AB Sodertalje, Sweden (Releaser, Primary Packaging)
Registration Category	:	Registration of a new registered drug with a new combination
Proposed Indication	:	*QTERN is indicated as an adjunct to diet and exercise, in combination with metformin, to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and dapagliflozin is appropriate*.
Proposed posology	:	*The recommended dose of QTERN is one saxagliptin 5 mg/dapagliflozin 10 mg tablet taken once daily at any time of the day, with or without food. Tablet is to be swallowed whole.* *Please refer to Section Special Warnings and Precautions for Use for information regarding combinations not studied.* *Optimal medical management of patients with diabetes also involves attention to diet, exercise, blood glucose monitoring, assessment of complications and co-morbidities. Regular assessment and review of the compliance and benefit/risk of all therapies is recommended.* *Special populations* *<u>Patients with renal impairment</u>* *Assess renal function prior to initiation of QTERN and periodically thereafter. No dose adjustment is required for patients with eGFR ≥ 45 mL/min/1.73 m^2.* *The glycaemic efficacy of dapagliflozin is dependent on renal function. QTERN should not be used in patients with an estimated glomerular filtration rate (eGFR) persistently <45 mL/min/1.73 m^2 as calculated by the Modification of Diet in Renal Disease [MDRD] formula or in patients with end-stage renal disease (ESRD) or patients on dialysis (see Section Special Warnings and Precautions for Use and Section Adverse Effects (Undesirable Effects)).* *<u>Patients with hepatic Impairment</u>* *QTERN may be used in patients with mild or moderate hepatic impairment. QTERN should not be used in patients with severe hepatic impairment (see Section Special Warnings and Precautions for Use).* *<u>Paediatric and adolescent patients</u>* *Safety and effectiveness of QTERN in paediatric and adolescent patients (<18 years of age) have not been established.* *<u>Elderly patients</u>* *In general, no dosage adjustment is recommended based on age.*

Caution should be exercised due to the risk of hypovolaemia. Because elderly patients are more likely to have decreased renal function, care should be taken in the elderly based on renal function. (see Section Special Warnings and Precautions for Use and Section Pharmacological Properties).

Patients at risk for volume depletion
In patients with volume depletion, correcting this condition prior to initiation of QTERN is recommended (see Section Special Warnings and Precautions for Use).

INTRODUCTION

QTERN is a new combination of Saxagliptin and Dapagliflozin. Saxagliptin is an enzyme inhibitor of DPP4, prolonging the inactivation of the increatin hormone *Glucagon-like peptide* (GLP-1) and *Glucose dependent insulinotropic popypeptide* (GIP). Dapagliflozin is a SGLT2 inhibitor that reduces glucose reabsorption in the renal proximal tubule, leading to increased excretion of glucose through the urine. The combination of both can decrease HbA1c to improve glycemic control in type 2 DM patients. Given that the combination of Saxagliptin and Dapagluflozin is a new combination, the evaluation is currently focused on clinical test data, and the quality of the medication for proof of efficacy, security, and the quality of the drug.

QUALITY ASPECT

QTERN (Saxagliptin/Dapagliflozin) is available as a film-coated tablet, containing 10 mg of dapagliflozin and 5 mg of Saxagliptin. It contains excipients that include *microcrystalline cellulose, Lactose anhydrous, Croscarmellose sodium, Silicon dioxide, Magnesium stearate, Opadry II White, Hydrochloric acid, Sodium hydroxide, Opadry II red, Opadry II purple, Opadry II yellow, Opadry II butterscotch, Opacode Blue and Isopropyl Alcohol.*

Active Substance

Both active ingredients, Saxagliptin and Dapagliflozin, used in QTERN, have previously been utilized in other pharmaceutical products approved for distribution in Indonesia. Specifically, Dapagliflozin is found in Forxiga 5 mg and 10 mg film-coated tablets, as well as in Xigduo XR film-coated tablets. Saxagliptin is present in Onglyza film-coated tablets and Kombiglyze XR film-coated tablets. The quality evaluation of these active ingredients is based on the standards established for these products.

Drug Product

The drug product is produced in the form of round, light brown, film-coated tablets.

The Saxagliptin/Dapagliflozin fixed dose combination (FDC) is a formulation combining a dapagliflozin core tablet (similar to Forxiga) with a three-layer film coating containing saxagliptin (similar to Onglyza).

The production process description is submitted with adequate and detailed information. Critical process stages have been identified, and controls along with acceptance ranges have been established. Process validation was conducted on three production-scale batches. The validation results demonstrated the process's capability to produce finished drug products that meet the established acceptance criteria.

The specifications for the drug include description (visual), identification (UHPLC and UV), assay (UHPLC), impurities (UHPLC), uniformity of dosage units (UHPLC), tablet disintegration, moisture content, and microbiological examination. The parameters in the specifications were selected based on the physicochemical characteristics and critical properties of the active ingredients, considering factors such as the results of clinical trial batches and long-term stability data. The analytical methods used have been validated. The batch analysis results met the required specifications.

Stability data for three production-scale batches were obtained under conditions of 30°C/75% RH for 36 months and 40°C/75% RH for 6 months. Additionally, bulk stability was evaluated for 12 months at 30°C/65% RH, with results meeting the required specifications.

Conclusion:

According to quality perspective, QTERN film-coated tablets can be considered for approval.

EFFICACY AND SAFETY ASPECTS

Non-Clinical Studies
There were no new non-clinical studies for the submission of new combinations.

Clinical Studies
Evaluations were conducted on four clinical studies to support the efficacy and safety of Qtern film-coated tablets proposed, comprising 1 phase I study (CV181191, n=42), and 3 phase III studies (CV studies181168, n=315; MB102129 study, n=301; CV181169 study, n=490).

1. The phase 1 clinical study (CV181191 study, n=42), with the open label design, randomized, crossover, 3-priod, 3-treatment, on healthy subjects showed a joint administration of saxagliptin 5 mg + dapagliflozin 10 mg did not affect the pharmacokinetic profile of each single active substance based on 90%CI geometric mean change ratio Cmax and AuC(inf) against dapagliflozin 10 mg (0.943 and 0.984) and saxagliptin 5 mg (0,994 and 1,046). The single administration of saxagliptin 5 mg, dapagliflozin 10 mg and the combination of saxagliptin 5 mg + dapagliflozin 10 mg (co-administered) is safe and well tolerated during the study.
2. A phase 3 clinical study (CV181168 study, n=315), with a multicenter design, randomized, double blind, placebo-controlled, parallel group, for 24 months in Type 2 DM patients who previously had dapagliflozin + metformin therapy, showed better saxagliptin + dapaglifozin + metformin efficacy than placebo + dapagliflozin + metformin based on parameters:
    a) *mean change from baseline HbA1c* (-0.51% vs -0.16%);
    b) *difference in adjusted HbA1c mean change from baseline* (-0.35; 95%CI: -0.52, -0.18; p<0.0001); and
    c) the proportion of subjects reached HbA1c target is <7% (35.3% vs. 23.1%).
3. A phase 3 clinical study (Study MB102129, n=301), with a multicenter design, randomized, double blind, placebo-controlled, parallel group, for 24 months in Type 2 DM patients who had previously received saxagliptin + metformin therapy demonstrated the efficacy of saxagliptin + dapaglifozin + metformin was better than placebo + saxagliptin + metformin based on parameters:
    a) *mean change from baseline in HbA1c* (-0.82% vs -0.10%);
    b) *difference in adjusted HbA1c mean change from baseline* (-0.72%; 95% CI -0.91, -0.53; p<0.0001);
    c) *mean change from baseline in Fasting Plasma Glucose* (FPG) (-32.7 vs -5.3 mg/dl);
    d) *mean change from baseline in 2 hours Post Prandial Glucose* (PPG) (-73.5 vs -38 mg/dl); and
    e) *the average weight change from the baseline* (-1.91 vs -0.41 kg).
4. A phase 3 clinical study (CV181169, n=490) with a multicenter, randomized, double blind, active-controlled, parallel group design showed that saxagliptin + dapagliflozin administering in Type 2 DM patients who had previously had a single metformin therapy (saxa+dapa+met) had better benefits than giving the placebo + saxagliptin to a single metformin (saxa+met) and placebo + dapagliflozin against meformin (dapa+met), based on parameters:
    a) *adjusted mean reduction from baseline in HbA1c* (-1.47% vs -0.88% vs -1.20%); and it is statistically different from saxa+met (-0.59%; 95% CI: -0.81, -0.37;p<0.0001) and dapa+met group (-0.27%;95% CI -0.48, -0.05; p=0.0166)
    b) *mean change from baseline in 120 minutes PPG is* more significant than the saxa+met group (-79.9 vs -35.6 mg/dL; difference -44.0; CI 95% -53.7, -34.3; p<0.0001) but there is no difference to the dapa+met group (difference -9.1 95% CI -18.8, 0.5; p=0.00639)
    c) the average FPG change in the 24th week is statistically different from that of saxa+met (-37.8 vs -14.0 mg/dL; *difference* -23.8; CI 95% -31.6, -15.9) but there is no difference to the dapa+met group (*difference* -6.1; 95% CI -13.8, 1.7)
    d) the proportion of subjects achieving the HbA1c glycemic target is <7% higher (41.4% vs. 18.3% vs. 22.2%).
5. Safety data based on the submitted studies show that the giving of the combination of saxagliptin + dapagliflozin + metformin can be well tolerated and consistent with the security profile of each active substance. There are no reports of deaths or malignancy associated with medications. The frequency of serious side effect events is found more in saxa+met groups than saxa+dapa+met groups (study

CV181169). The most common side effects are urinary tract infections, nasopharyngeitis, headache, influenza (Study CV181168 and MB102129); and arthralgia (Study CV181169).

DECISION

Considering the safety and efficacy data mentioned above, the decision was made to register the new active substance QTERN film-coated tablet followed by an improved indication as follows:

Indication

QTERN (FDC saxagliptin/dapagliflozin) is indicated for use in combination with metformin as an adjunct to diet and exercise to achieve glycemic control in adults with type 2 diabetes mellitus (T2DM) who are inadequately controlled on metformin plus saxagliptin or metformin plus dapagliflozin.