Public Assessment Report
NEXIUM

PRODUCT INFORMATION

Name of the drug	:	**NEXIUM**
Dosage form	:	Granules
Active substances	:	Esomeprazole Magnesium Trihydrate ~ Esomeprazole 10mg
Packaging	:	Dus, 28 sachets @ 3g
Applicant	:	AstraZeneca Indonesia
Manufacturer	:	AstraZeneca AB, Sodertalje, Sweden
Category Registration	:	New dosage forms
Proposed Indication	:	*Nexium oral suspension is primarily indicated for:* *Paediatric population* *Children 1-11 years old* *Gastroesophageal Reflux Disease (GERD)* - *treatment of endoscopically proven erosive reflux esophagitis* - *symptomatic treatment of gastroesophageal reflux disease (GERD)* *Children over 4 years of age* *In combination with antibiotics in treatment of duodenal ulcer caused by Helicobacter pylori* *Adults and adolescents from the age of 12 years* *For indications in patients from the age of 12 years reference is made to the Nexium gastro- resistant tablet product information.* *Nexium oral suspension may also be used by patients having difficulty swallowing dispersed Nexium gastro-resistant tablets*
Proposed posology	:	Attached

INTRODUCTION

Esomeprazole is an S-isomer of omeprazole, which acts specifically to inhibit the production of gastric acid in the late stages, that is, it inhibits the ATP pump of H+/K+ parietal cells that secrete gastric acid.

The active substance Esomeprazole has been approved in Indonesia with dosage forms of injectable powder (Nexium), 20 mg and 40 mg film-coated tablets (Nexium mups) and enteric coated tablets 20 mg and 40 mg (S-omevell). The currently approved indication is for GERD in adult patients.

Currently the applicant applies for registration of the active substance esomeprazole 10 mg with a granular gastro-resistant dosage form for oral suspension for the treatment of GERD in children 1-11 years and *duodenal ulcer* caused by H. pylori for children aged 4 years and older). The purpose of the development of this granular preparation is for patients who have difficulty swallowing tablets .

QUALITY ASPECTS

Nexium has a granular dosage form, where this dosage form consists of 2 intermediates, namely Esomeprazole pellets and excipient granules. The constituent components of Esomeprazole pellets are Esomeprazole magnesium trihydrate, glycerol monostearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methacrylic acid copolymer type C, polysorbate 80, sugar spheres, talc, triethyl citrate, purified water while the granule constituent components are glucose anhydrous, xanthan gum, polyvinylpyrrolidrolidone crosslinked, citric acid anhydrous, iron oxide yellow, hydroxypropyl cellulose, ethanol 95%

Active substances

Esomeprazole magnesium trihydrate is a white to slightly colored crystalline powder, has a solubility of 1.5 mg/ml at pH 10.0, is non-hygroscopic. Based on X-ray diffraction, Esomeprazole magnesium trihydrate has a high level of crystallinity.

Structure characterization of Esomeprazole magnesium trihydrate was shown based on *mass spectrum assay, elemental analysis, IR spectrum, UV spectrum, Optical rotation and enantiomeric purity, X-ray, NMR.*

A monograph of Esomperazole magnesium trihydrate is contained in the European Pharmacopoeia compendia. The specifications and test methods used in active substance testing refer to the European Pharmacopoeia with additional specifications in the form *of absorbance of solution* and *residual solvents* .

An active substance stability test has been performed and shows the drug is stable when stored at 25°C for 36 months.

Drug Product

Nexium granular preparations are formulated with the aim of providing a preparation suitable for all patient ages, in line with the addition of indications proposed for children. Nexium granules consist of 2 intermediate products, namely Esomeprazole pellets and additive granules. Esomeprazole is formulated in pellet form because it is labile to acidic conditions. Esomeprazole pellets rapidly precipitate, so excipients are required that provide a viscous suspension. The granules function of this additive to make esomeprazole dispersible evenly before administration

The manufacturing process of Nexium granules consists of 3 main stages, namely the production of Esomeprazole pellets, the preparation of additive granules, and the manufacture of esomeprazole sachets. Nexium granula is a product that has been circulating for a long time in several countries in Europe. The evaluation of the process's capabilities in producing products with consistent quality is evaluated through the data presented in the annual product review. The results of the evaluation at theAnnual product review show that the production process of Nexium granules consistently produces product quality that meets the specified specifications.
The drug product specification of Nexium granules includes test parameters identification, assay, uniformity of dosage unit by content uniformity, dissolution, organic impurities, and microbiological quality. The batch analysis results provide results in accordance with the specifications.

Nexium granules are packaged in sachet packaging made of laminated aluminum with a laminated composition of PET-Aluminum-LDPE. The part in contact with the product is the LDPE component. Stability data from Nexium packaged in such sachets showed that the drug product was stable in storage at 30°C /75% RH for 36 months

EFFICACY AND SAFETY ASPECTS

Non Clinical Studies

N/A
There are no non clinics submitted to support this submission

Clinical Studies

There are several clinical studies submitted to support this submission. Bioequivalence studies (D9612C00032) to demonstrate equivalence of pharmacokinetic profiles, 2 phase 1 pharmacokinetic studies (studies D9614C00099 and D961TC000022), 1 phase 2 study (study SH-NEC-0001), 1 pivotal phase 3 study (study D9614C00097) and 2 pharmacoepidemiological studies (D9612N00014 and D9612N00016) to support the indication of GERD in children aged 1-11 years, as well as the CF-OMG-0005 study and a published journal to support indications for the treatment of duodenal ulcers caused by H.pylori

Bioequivalence studies (D9612C00032) show administration of esomeprazole 40 mg granules, tablets and capsules have a similar pharmacokinetic profile and are well tolerated thus the administration of esomeprazole granules in adult and adolescent patients may refer to indications and posology of pre-approved esomeprazole tablets.

<u>Indications for GERD pad of children aged 1-11 years</u>

- Pharmacokinetic data of esomeprazole administration in children aged 1-11 years (D9614C00099, n=27) show dose-dependent and age-dependent plasma concentrations
- Studies in children 2 years of age and younger (SH-NEC-0001, n=45) showed efficacy of increasing percentage of time with intragastric pH > 4 at esomeprazole doses of 0.25 mg/kg (from 30.5% to 47.91%) and doses of 1 mg/kg (from 28.6% to 69.25%).
- Phase 3 pivotal study (study D9614C00097, n=101), administration of esomeprazole 5-10 mg to children with body weight (BB) < 20 kg (ages 1-5 years) and esomeprazole 10-20 mg to BB > 20 kg (ages 6-11 years) for 8 weeks showed improvement in GERD symptoms based on Physician Global Assessments at baseline and final visits in 74.3% of subjects and 88.9% of subjects subjects with esophageal erosion (EE) are declared cured.
- Safety data indicate the administration of esomeprazole 10 mg and 20 mg is well tolerated. There are no new security issues. Treatment-related adverse events reported < 5% were diarrhea, abdominal pain, photosensitivity reactions, somnolence, headache, (2-3%); flatulence, nausea, vomiting, asthenia, viral infection, arthralgia (respectively < 1%) (studies D961TC00002, D9614C00097).
- Pharmacoepidemiological studies (D9612N00014 and D9612N00016) showed only the profile of esomeprazole use in paediatric patients in the UK (n=24 patients) and the Netherlands (n=2820 patients), as well as reports of adverse events occurring in the form of gastroenteritis (2%), convulsion/seizure (1%), pneumonia (1%)

<u>Indications for the treatment of duodenal ulcer caused by H. pylori in children 4 years and older:</u>

- Supporting data regarding the use of esomeprazole in the form of 1 published article with a single arm design, without comparator, the number of subjects is small and therefore considered insufficient to prove efficacy and safety for the proposed indications although study data show an eradication rate of H. pylori at 92% (49/53 subjects) of total subjects aged 2-18 years. (Arenz et al. 2006; n = 53).
- Another study (CF-OMG-0005, n=63) used another test drug (omeprazole) and was conducted with a limited number of subjects and at different age ranges than those proposed (ages 11-15 years)

DECISION

Considering the above efficacy and safety data, the submission of a new dosage form of Nexium granules can be accepted according to the indications proposed for the indication of GERD in children aged 1 -11 years, and rejected for the indication of treatment of duodenal ulcer caused by H.plyori in children > 4 years of age.

Recommended indication suggested are:

Pediatric population

Children 1-11 years old

Gastroesophageal Reflux Disease (GERD)

- *treatment of endoscopically proven erosive reflux esophagitis*
- *symptomatic treatment of gastroesophageal reflux disease (GERD)*

Adults and adolescents from the age of 12 years

For indications in patients from the age of 12 years reference is made to the Nexium gastro-resistant tablet SmPC.

Nexium oral suspension may also be used by patients having difficulty swallowing dispersed Nexium gastro-resistant tablets

Appendix I
Posology
Children 1 – 11 years with a bodyweight of ≥10 kg
Gastroesophageal Reflux Disease (GERD)
- Treatment of endoscopically proven erosive reflux esophagitis
  • Weight ≥10 -<20 kg: 10 mg once daily for 8 weeks.
  • weight ≥20 kg: 10 mg or 20 mg once daily for 8 weeks.
- Symptomatic treatment of gastroesophageal reflux disease (GERD) 10 mg once daily for up to 8 weeks.

Doses over 1 mg/kg/day have not been studied

Children below the age of 1 year
The experience of treatment with esomeprazole in infants < 1 year is limited and treatment is therefore not recommended.

Adults and adolescent from the age of 12 years
For posology in patients from the age of 12 years reference is made to the Nexium gastro resistant tablet

Public Assessment Report
NEXIUM

INFORMASI PRODUK

Nama obat	:	**NEXIUM**
Bentuk sediaan	:	Granula
Zat aktif	:	Esomeprazole magnesium trihydrate ~ Esomeprazole 10 mg
Kemasan	:	Dus, 28 sachet @ 3 g
Pendaftar	:	AstraZeneca Indonesia
Produsen	:	AstraZeneca AB, Sodertalje, Swedia
Kategori Registrasi	:	Bentuk sediaan baru
Indikasi yang diajukan	:	*Nexium oral suspension is primarily indicated for:* *Paediatric population* *Children 1-11 years old* *Gastroesophageal Reflux Disease (GERD)* - *treatment of endoscopically proven erosive reflux esophagitis* - *symptomatic treatment of gastroesophageal reflux disease (GERD)* *Children over 4 years of age* *In combination with antibiotics in treatment of duodenal ulcer caused by Helicobacter pylori* *Adults and adolescents from the age of 12 years* *For indications in patients from the age of 12 years reference is made to the Nexium gastro- resistant tablet product information.* *Nexium oral suspension may also be used by patients having difficulty swallowing dispersed Nexium gastro-resistant tablets.*
Posologi yang diajukan	:	Terlampir

PENGANTAR

Esomeprazole merupakan S-isomer dari omeprazole, yang bekerja secara spesifik menghambat produksi asam lambung pada tahap akhir, yaitu menghambat pompa ATP H+/K+ sel parietal yang mensekresi asam lambung.

Zat aktif Esomeprazole telah disetujui di Indonesia dengan bentuk sediaan serbuk injeksi (Nexium), tablet salut selaput 20 mg dan 40 mg (Nexium mups) dan tablet salut enteric 20 mg dan 40 mg (S-omevell). Indikasi yang disetujui saat ini yaitu untuk GERD pada pasien dewasa.

Saat ini Pendaftar mengajukan registrasi zat aktif esomeprazole 10 mg dengan bentuk sediaan gastro-resistant granul untuk suspensi oral untuk pengobatan GERD pada anak 1-11 tahun dan dan *duodenal ulcer* caused by H. pylori untuk anak usia 4 tahun ke atas). Tujuan pengembangan sediaan granul ini yaitu untuk pasien yang mengalami kesulitan menelan tablet.

ASPEK MUTU

Nexium memiliki bentuk sediaan granula, dimana bentuk sediaan ini tersusun dari 2 intermediate, yaitu pellet Esomeprazole dan granula zat tambahan. Komponen penyusun pellet *Esomeprazole adalah Esomeprazole magnesium trihydrate, glycerol monostearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methacrylic acid copolymer type C, polysorbate 80, sugar spheres, talc, triethyl citrate, purified water* sedangkan komponen penyusun granula zat tambahan adalah *glucose anhydrous, xanthan gum, polyvinylpyrrolidone crosslinked, citric acid anhydrous, iron oxide yellow, hydroxypropyl cellulose, ethanol 95%*

Zat aktif

Esomeprazole magnesium trihydrate merupakan serbuk kristalin berwarna putih sampai sedikit berwarna, memiliki kelarutan 1,5 mg/ml pada pH 10.0, bersifat non higroskopik. Berdasarkan difraksi X-ray, Esomeprazole magnesium trihydrate memiliki tingkat kristalinitas yang tinggi.

Karakterisasi struktur Esomeprazole magnesium trihydrate ditunjukkan berdasarkan uji *mass spectrum, elemental analysis, IR spectrum, UV spectrum, Optical rotation and enantiomeric purity, X-ray, NMR.*

Monografi Esomperazole magnesium trihydrate terdapat pada kompendia European Pharmacopoeia. Spesifikasi dan metode uji yang digunakan pada pengujian zat aktif mengacu pada European Pharmacopoeia dengan spesifikasi tambahan berupa *absorbance of solution* dan *residual solvents.*

Uji stabilitas zat aktif telah dilakukan dan menunjukkan obat stabil ketika disimpan pada suhu 25°C selama 36 bulan.

Obat jadi

Sediaan Nexium granula diformulasi dengan tujuan agar memberikan sediaan yang sesuai untuk semua umur pasien, hal ini sejalan dengan penambahan indikasi yang diajukan untuk anak – anak. Nexium granula terdiri dari 2 produk intermediate, yaitu pellet Esomeprazole dan granula zat tambahan. Esomeprazole diformulasikan dalam bentuk pellet karena labil terhadap kondisi asam. Esomeprazole pellet secara cepat mengendap, sehingga diperlukan eksipien yang memberikan suspensi yang kental. Fungsi granula zat tambahan ini untuk membuat esomeprazole dapat terdispersi merata sebelum pemberian

Proses pembuatan Nexium granula terdiri dari 3 tahapan utama, yaitu pembuatan pellet Esomeprazole, pembuatan granul zat tambahan, serta pembuatan esomeprazole sachet. Nexium granula merupakan produk yang sudah lama beredar di beberapa negara di Eropa. Evaluasi kapabilitas proses dalam menghasilkan produk dengan mutu yang konsisten dievaluasi melalui data yang tersaji dalam *annual product review*. Hasil evaluasi pada *Annual product review* menunjukkan bahwa proses produksi Nexium granula secara konsisten menghasilkan mutu produk yang sesuai dengan spesifikasi yang ditetapkan

Spesifikasi obat jadi dari Nexium granula memuat parameter uji *identification, assay, uniformity of dosage unit by content uniformity, dissolution, organic impurities,* dan *microbiological quality*. Hasil analisis bets memberikan hasil sesuai dengan spesifikasi.

Nexium granula dikemas dalam kemasan sachet yang terbuat dari aluminium terlaminasi dengan komposisi laminasi PET-Aluminium-LDPE. Bagian yang kontak dengan produk adalah komponen LDPE. Data stabilitas dari Nexium yang dikemas dalam kemasan sachet tersebut menunjukkan bahwa produk obat stabil dalam penyimpanan 30°C /75% RH selama 36 bulan

ASPEK KHASIAT DAN KEAMANAN

Studi Non Klinik

NA

Tidak diserahkan data non klinik dalam pengajuan ini

Studi Klinik

Terdapat beberapa studi klinik yang diserahkan untuk mendukung pengajuan ini. Studi Bioekivalensi (D9612C00032) untuk menunjukkan kesetaraan profil farmakokinetika, 2 studi farmakokinetik fase 1 (studi D9614C00099 dan D961TC000022), 1 studi fase 2 (studi SH-NEC-0001), 1 studi pivotal fase 3 (studi D9614C00097) dan 2 studi farmakoepidemiologi (D9612N00014 dan D9612N00016) untuk mendukung indikasi GERD pada anak usia 1-11 tahun, serta studi CF-OMG-0005 dan jurnal terpublikasi untuk mendukung indikasi pengobatan duodenal ulcer yang disebabkan oleh H.pylori

Studi bioekivalensi (D9612C00032) menunjukkan pemberian esomeprazole 40 mg granula, tablet dan kapsul memiliki profil farmakokinetik yang similar dan dapat ditoleransi dengan baik sehingga pemberian esomeprazole granula pada pasien dewasa dan remaja dapat mengacu pada indikasi dan posologi esomeprazole tablet yang telah disetujui sebelumnya.

<u>Indikasi GERD pad anak usia 1-11 tahun</u>

- Data farmakokinetik pemberian esomeprazole pada anak usia 1-11 tahun (D9614C00099, n=27) menunjukkan konsentrasi dalam plasma bergantung pada dosis (dose dependent) dan usia (age dependent)
- Studi pada anak usia 2 tahun ke bawah (SH-NEC-0001, n=45) menunjukkan efikasi peningkatan percentage of time with intragastric pH>4 pada esomeprazole dosis 0,25 mg/kg (dari 30.5% menjadi 47.91%) dan dosis 1 mg/kg (dari 28.6% menjadi 69.25%).
- Studi pivotal fase 3 (studi D9614C00097, n=101), pemberian esomeprazole 5-10 mg untuk anak dengan berat badan (BB) <20 kg (usia 1- 5 tahun) dan esomeprazole 10-20 mg untuk BB >20 kg (usia 6-11 tahun) selama 8 minggu menunjukkan perbaikan gejala GERD (improvement) berdasarkan penilaian Physician Global Assessments saat baseline dan final visit pada 74,3% subjek dan sebanyak 88,9% subjek dengan esophageal erosion (EE) dinyatakan sembuh .
- Data keamanan menunjukkan pemberian esomeprazole 10 mg dan 20 mg dapat ditoleransi dengan baik. Tidak terdapat isu keamanan baru. Adverse events terkait pengobatan dilaporkan <5% yaitu diare, abdominal pain, reaksi fotosensitivitas, somnolence, sakit kepala, (2-3%); flatulence, mual, muntah, asthenia, viral infection, arthralgia (masing-masing <1%) (studi D961TC00002, D9614C00097).
- Studi farmakoepidemiologi (D9612N00014 dan D9612N00016) hanya menunjukkan profil penggunaan esomeprazole pada pasien anak di Inggris (n=24 pasien) dan Belanda (n=2820 pasien), serta pelaporan efek samping yang terjadi berupa gastroenteritis (2%), convulsion/seizure (1%), pneumonia (1%)

<u>Indikasi pengobatan duodenal ulcer yang disebabkan oleh H. pylori pada anak usia 4 tahun ke atas:</u>

- Data pendukung penggunaan esomeprazole berupa 1 artikel terpublikasi dengan desain single arm, tanpa pembanding, jumlah subjek kecil sehingga dipertimbangkan tidak memadai untuk membuktikan khasiat dan keamanan untuk indikasi yang diajukan walaupun data studi menunjukkan eradication rate H. Pylori sebesar 92% (49/53 subjek) total subjek usia 2-18 tahun.(Arenz et al. 2006; n = 53).
- Studi lain (CF-OMG-0005, n=63) menggunakan obat uji lain (omeprazole) serta dilakukan dengan jumlah subyek yang terbatas dan pada rentang usia yang berbeda dari yang diajukan (usia 11-15 tahun)

KEPUTUSAN

Mempertimbangkan data khasiat dan keamanan tersebut di atas, maka pengajuan bentuk sediaan baru Nexium granula dapat diterima sesuai indikasi yang diajukan untuk indikasi GERD pada anak usia 1 -11 tahun, dan ditolak untuk indikasi pengobatan duodenal ulcer caused by H.plyori pada anak usia > 4 tahun.

Perbaikan indikasi yang direkomendasikan adalah:

Pediatric population
Children 1-11 years old
Gastroesophageal Reflux Disease (GERD)

- *treatment of endoscopically proven erosive reflux esophagitis*
- *symptomatic treatment of gastroesophageal reflux disease (GERD)*

Adults and adolescents from the age of 12 years
For indications in patients from the age of 12 years reference is made to the Nexium gastro-resistant tablet SmPC.
Nexium oral suspension may also be used by patients having difficulty swallowing dispersed Nexium gastro-resistant tablets

Lampiran I
Posologi

Children 1 – 11 years with a bodyweight of ≥10 kg
Gastroesophageal Reflux Disease (GERD)
- Treatment of endoscopically proven erosive reflux esophagitis
  • Weight ≥10 -<20 kg: 10 mg once daily for 8 weeks.
  • weight ≥20 kg: 10 mg or 20 mg once daily for 8 weeks.
- Symptomatic treatment of gastroesophageal reflux disease (GERD) 10 mg once daily for up to 8 weeks.

Doses over 1 mg/kg/day have not been studied

Children below the age of 1 year
The experience of treatment with esomeprazole in infants < 1 year is limited and treatment is therefore not recommended.

Adults and adolescent from the age of 12 years
For posology in patients from the age of 12 years reference is made to the Nexium gastro resistant tablet.