Public Assessment Report
SAXENDA®

INFORMASI PRODUK

Nama obat	:	Saxenda®
Bentuk sediaan	:	Larutan Injeksi
Zat aktif	:	Liraglutide 6 mg/mL
Kemasan	:	Dus, 3 *cartridge* @ 3 mL *in pre-filled pen*
Pendaftar	:	PT Beta Pharmacon, Karawang
Produsen	:	Novo Nordisk A/S, Bagsvaerd, Denmark
Kategori Registrasi	:	Penambahan indikasi dan posologi baru
Indikasi yang diajukan:	:	*Adults* *Saxenda® is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial Body Mass Index (BMI) of* • *≥ 30 kg/m² (obesity), or* • *≥ 27 kg/m² to < 30 kg/m² (overweight) in the presence of at least one weight-related comorbidity such as dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia or obstructive sleep apnoea.* *Treatment with Saxenda® should be discontinued after 12 weeks on the 3.0 mg/day dose if patients have not lost at least 5% of their initial body weight.* ***Adolescents (≥12 years)*** ***Saxenda® can be used as an adjunct to a healthy nutrition and increased physical activity for weight management in adolescent patients from the age of 12 years and above with:*** • ***obesity (BMI corresponding to ≥ 30 kg/m² for adults by international cut-off points)* and*** • ***body weight above 60 kg.*** ***Treatment with Saxenda® should be discontinued and re-evaluated if patients have not lost at least 4% of their BMI or BMI z score after 12 weeks on the 3.0 mg/day or maximum tolerated dose.*** ****IOTF BMI cut-off points for obesity by sex between 12– 18 years (see table 1):*** ***Table 1 IOTF BMI cut-off points for obesity by sex between 12–18 years***

Age (years)	BMI corresponding to 30 kg/m² for adults by international cut-off points	
	Males	Females
12	26.02	26.67
12.5	26.43	27.24
13	26.84	27.76
13.5	27.25	28.20
14	27.63	28.57
14.5	27.98	28.87
15	28.30	29.11
15.5	28.60	29.29
16	28.88	29.43

16.5	**29.14**	**29.56**
17	**29.41**	**29.69**
17.5	**29.70**	**29.84**
18	**30.00**	**30.0**

Posologi yang diajukan :

Posology and method of administration

Posology

Adults

The starting dose is 0.6 mg once daily. The dose should be increased to 3.0 mg once daily in increments of 0.6 mg with at least one week intervals to improve gastro-intestinal tolerability (see table 2). If escalation to the next dose step is not tolerated for two consecutive weeks, consider discontinuing treatment. Daily doses higher than 3.0 mg are not recommended.

Table 2. Dose escalation schedule

	Dose	Weeks
Dose escalation 4 weeks	0.6 mg	1
	1.2 mg	1
	1.8 mg	1
	2.4 mg	1
Maintenance dose	3.0 mg	

Adolescents (≥12 years)

For adolescents from the age of 12 to below 18 years old a similar dose escalation schedule as for adults should be applied (see table 2). The dose should be increased until 3.0 mg (maintenance dose) or maximum tolerated dose has been reached. Daily doses higher than 3.0 mg are not recommended.

Missed doses

If a dose is missed within 12 hours from when it is usually taken, the patient should take the dose as soon as possible. If there is less than 12 hours to the next dose, the patient should not take the missed dose and resume the once-daily regimen with the next scheduled dose. An extra dose or increase in dose should not be taken to make up for the missed dose.

Patients with type 2 diabetes mellitus

Saxenda® should not be used in combination with another GLP-1 receptor agonist.

When initiating Saxenda®, it should be considered to reduce the dose of concomitantly administered insulin or insulin secretagogues (such as sulfonylureas) to reduce the risk of hypoglycaemia. Blood glucose self-monitoring is necessary to adjust the dose of insulin or insulin-secretagogues (see section 4.4).

Special populations

Elderly (≥65 years old)

No dose adjustment is required based on age. Therapeutic experience in patients ≥75 years of age is limited and use in these patients is not recommended (see sections 4.4 and 5.2).

Renal impairment

No dose adjustment is required for patients with mild or moderate renal impairment (creatinine clearance ≥30 mL/min). Saxenda® is not

recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min) including patients with end-stage renal disease (see sections 4.4, 4.8 and 5.2).

Hepatic impairment
No dose adjustment is recommended for patients with mild or moderate hepatic impairment. Saxenda® is not recommended for use in patients with severe hepatic impairment and should be used cautiously in patients with mild or moderate hepatic impairment (see sections 4.4 and 5.2).

Paediatric population
No dose adjustment is required for adolescents from the age of 12 years and above. The safety and efficacy of Saxenda® in children below 12 years of age has not been established (see section 5.1).

Method of administration
Saxenda® is for subcutaneous use only. It must not be administered intravenously or intramuscularly.
Saxenda® is administered once daily at any time, independent of meals. It should be injected in the abdomen, thigh or upper arm. The injection site and timing can be changed without dose adjustment. However, it is preferable that Saxenda® is injected around the same time of the day, when the most convenient time of the day has been chosen.
For further instructions on administration, see section 6.6.

PENGANTAR

Saxenda mengandung zat aktif liragutide yang merupakan analog *glucagon-like peptide-1* (GLP-1) manusia dengan homologi sebesar 97%. Saxenda diproduksi menggunakan teknologi DNA rekombinan di dalam *Saccharomyces cerevisiae*. Saxenda telah disetujui untuk *weight management* pada usia dewasa (≥ 18 tahun) dan saat ini diajukan untuk usia remaja (≥ 12 tahun hingga < 18 tahun).

ASPEK KHASIAT DAN KEAMANAN

Penggunaan Saxenda untuk usia remaja didukung oleh 3 studi klinik sebagai berikut.

1. Studi NN8022-3967, merupakan studi klinik fase 1 selama 5-6 minggu dengan tujuan untuk mengevaluasi keamanan, tolerabilitas dan farmakokinetik liraglutide dosis hingga 3 mg pada populasi remaja obesitas berusia 12−17 tahun dan *pubertal development* Tanner stadium 2−5.
2. Studi NN8022-4179, merupakan studi klinik fase 3a dengan tujuan untuk membandingkan efikasi liraglutide versus plasebo terkait penurunan berat badan pada anak berusia 12 hingga < 18 tahun (Tanner stadium 2-5) dan 6 hingga <12 tahun (Tanner stadium <2) dengan obesitas dan *Prader-Willi Syndrome* (PWS) pada minggu ke-16 dan dibandingkan tanpa pengobatan pada minggu ke-52.
3. Studi NN8022-4180, merupakan studi klinik fase 3a dengan tujuan untuk membandingkan efikasi liraglutide versus plasebo terkait penurunan berat badan pada remaja dengan obesitas berusia 12 hingga <18 tahun dan *pubertal development* Tanner stadium 2-5 setelah 56 minggu pengobatan.

Hasil studi klinik menunjukkan bahwa:

1. Studi NN8022-3967
   Hasil studi NN8022-3967 yang dilakukan pada subjek remaja dengan obesitas usia 12-17 tahun dan *pubertal development* Tanner stadium 2-5 (n = 21) menunjukkan profil farmakokinetik liraglutide yang sebanding dengan profil farmakokinetik yang diamati pada subjek dewasa dari studi NN8022-3630. Profil keamanan liraglutide pada subjek remaja dapat ditoleransi dengan baik.

2. Studi NN8022-4179

Hasil studi klinik NN8022-4179 pada subjek berusia 12 hingga <18 tahun dan 6 hingga <12 tahun dengan obesitas dan PWS yang membandingkan liraglutide vs plasebo menunjukkan:

- Efikasi
  - Subjek usia 12 hingga <18 tahun (liraglutide n=19 vs plasebo n=12): Pada parameter perubahan BMI *Standard Deviation Score* (SDS) dari baseline menunjukkan liraglutide tidak berbeda bermakna dibandingkan dengan plasebo hingga pengamatan minggu ke 16 (perbedaan -0.07; 95%CI: -0.23, 0.09; p-value 0.3787) dan pengamatan hingga minggu ke 52 (perbedaan -0.14; 95%CI: -0.62, 0.34; p-value 0.5665).
  - Pada parameter proporsi subjek (usia 12 hingga <18 tahun) dengan penurunan berat badan di atas 5% menunjukkan lebih besar pada kelompok liraglutide dibandingkan kelompok plasebo hingga pengamatan minggu ke 16 (odds ratio 11.71; 95%CI: 0,45, 305.66; p-value 0.1393) dan pengamatan hingga minggu ke 52 (odds ratio 2.69; 95%CI: 0.32, 22.95; p-value 0.3646). Ditinjau dari aspek penurunan berat badan, kelompok liraglutide usia 12 hingga <18 tahun menunjukkan penurunan berat badan lebih baik dibanding usia 6 hingga <12 tahun.
- Keamanan
  - Angka kejadian AE dan SAE pada kelompok liraglutide sebanding dengan plasebo, meskipun demikian angka kejadian AEs *severe* lebih tinggi dibandingkan kelompok plasebo. AEs lebih banyak terjadi pada kelompok liraglutide usia 6 hingga <12 tahun.

3. Studi NN8022-4180

Hasil studi klinik NN8022-4180 pada pasien obesitas usia 12 hingga<18 tahun yang membandingkan liraglutide (n=125) vs plasebo (n=126) menunjukkan:

- Efikasi
  - Penurunan BMI SDS pada kelompok liraglutide berbeda bermakna dibandingkan kelompok plasebo pada evaluasi minggu ke-30 (perbedaan -7.04; 95%CI: -9.98, -4.09; p-value <0.0001) dan minggu ke-56 (perbedaan -7.64; 95%CI: -12.41, -2.87; p-value 0.0017).
  - Penurunan BMI SDS bermakna (P<0.05) pada kelompok liraglutide secara gradual hingga minggu ke-30. Penurunan ini mulai stagnan pada minggu 30-42 dan diikuti oleh peningkatan berat badan pada minggu 42-56. Meskipun penurunan bermakna secara statistik, penurunan rata-rata secara klinis tidak terlalu besar.
    - *Body weight* (kg):
      - -3.9 kg vs. +0.4 kg (minggu ke-30)
      - -2.7 kg vs. +2.1 kg (minggu ke-56)
    - *Body weight* (%):
      - -4.3% vs. +0.4% (minggu ke-30)
      - -3.2% vs. +2.2% (minggu ke-56)
- Keamanan

  Secara umum profil keamanan dan tolerabilitas cukup baik hingga minggu ke-56 penggunaan dan minggu ke-82 *follow up*.

4. Target usia dari penggunaan liraglutide yang diajukan dipertimbangkan masih tergolong dalam masa pertumbuhan. Belum ada data keamanan jangka panjang terhadap masa pertumbuhan pada pediatrik.

KEPUTUSAN

Mempertimbangkan data khasiat dan keamanan di atas, diputuskan registrasi penambahan indikasi dan posologi Saxenda larutan injeksi **diterima sesuai dengan indikasi dan posologi yang diajukan**.

Indication

Adults

Saxenda® is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial Body Mass Index (BMI) of

- *≥ 30 kg/m² (obesity), or*
- *≥ 27 kg/m² to < 30 kg/m² (overweight) in the presence of at least one weight-related comorbidity such as dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia or obstructive sleep apnoea.*

Treatment with Saxenda® should be discontinued after 12 weeks on the 3.0 mg/day dose if patients have not lost at least 5% of their initial body weight.

Adolescents (≥12 years)

Saxenda® can be used as an adjunct to a healthy nutrition and increased physical activity for weight management in adolescent patients from the age of 12 years and above with:

- ***obesity (BMI corresponding to ≥ 30 kg/m² for adults by international cut-off points)* and***
- ***body weight above 60 kg.***

Treatment with Saxenda® should be discontinued and re-evaluated if patients have not lost at least 4% of their BMI or BMI z score after 12 weeks on the 3.0 mg/day or maximum tolerated dose.

****IOTF BMI cut-off points for obesity by sex between 12– 18 years (see table 1):***

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Dirilis Badan POM tanggal 8 Maret 2023