IMPORTANT INFORMATION NOTE AGREED WITH THE ITALIAN MEDICINES AGENCY (AIFA)

27 March 2024

Norditropin NordiFlex® (somatropin, human growth hormone)

Recommendation for the transfer of patients treated with Norditropin NordiFlex® (somatropin, human growth hormone) to alternative medicinal products due to the discontinuation of the following packages: 15 mg/1.5 ml, solution for injection in pre-filled pen (AIC 027686118) and 5 mg/1.5 ml, solution for injection in pre-filled pen (AIC 027686094).

Dear Doctor,

The Italian Medicines Agency, in agreement with Novo Nordisk S.p.A., intends to provide an update on the medicinal product Norditropin NordiFlex®. As of April 2023, a shortage of Norditropin Nordiflex® 15mg/1.5ml solution for injection (AIC 027686118) has been declared, as per the information note published on the AIFA website on 6 February 2023. We hereby inform you that the marketing of the medicinal product, in all authorized packaging, will be definitively discontinued.

Specifically:
- Norditropin NordiFlex 15 mg/1.5 ml, solution for injection in pre-filled pen (AIC 027686118): definitively discontinued on the market starting from 22/02/2024.
- Norditropin NordiFlex 5 mg/1.5 ml, solution for injection in pre-filled pen (AIC 027686094): in quota distribution presumably until 15/04/2024; subsequently, periods of total shortage and quota distribution will alternate until the definitive marketing cessation, during 2025.

For any updates, please refer to the Lists of Medicines in Shortage, which are periodically updated and published at the following link: https://www.aifa.gov.it/farmaci-carenti
It should be noted that the marketing cessations in question are not related to any defect in the quality of the medicinal products or to safety concerns.

Summary and background information

Norditropin NordiFlex® contains somatropin, a biosynthetic human growth hormone approved for use in several growth hormone-related disorders[1] including:

Children:

- Growth failure due to growth hormone deficiency (GHD)
- Growth failure in girls due to gonadal dysgenesis (Turner syndrome)
- Growth retardation in prepubertal children due to chronic renal disease
- Growth disturbance (current height SDS < -2.5 and parental adjusted height SDS < -1) in short children born small for gestational age (SGA), with a birth weight and/or length below -2 SD, who failed to show catch-up growth (HV SDS < 0 during the last year) by 4 years of age or later.
- Growth failure due to Noonan syndrome.

Adults:

- Childhood onset growth hormone deficiency:

Patients with childhood onset GHD should be re-evaluated for growth hormone secretory capacity after growth completion. Testing is not required for those with more than three pituitary hormone deficits, with severe GHD due to a defined genetic cause, due to structural hypothalamic pituitary abnormalities, due to central nervous system tumours or due to high-dose cranial irradiation, or with GHD secondary to a pituitary/hypothalamic disease or insult, if measurements of serum insulin-like growth factor 1 (IGF-1) is < -2 SDS after at least four weeks off growth hormone treatment.

In all other patients an IGF-1 measurement and one growth hormone stimulation test is required.

- Adult onset growth hormone deficiency:

Pronounced GHD in known hypothalamic-pituitary disease, cranial irradiation and traumatic brain injury. GHD should be associated with one other deficient axis, other than prolactin. GHD should be demonstrated by one provocative test after institution of adequate replacement therapy for any other deficient axis.

In adults, the insulin tolerance test is the provocative test of choice. When the insulin tolerance test is contraindicated, alternative provocative tests must be used. The combined arginine-growth hormone releasing hormone is recommended. An arginine or glucagon test may also be considered; however, these tests have less established diagnostic value than the insulin tolerance test.

Mitigation Actions:
Healthcare professionals are advised to ensure that patients using Norditropin NordiFlex® 15 mg/1.5 mL (AIC 027686118) and Norditropin NordiFlex® 5mg/1.5 mL (AIC 027686094) are informed of this issue and to safely transfer patients to alternative growth hormone therapy at their own discretion, based on their clinical judgment and any relevant local regulations and/or institutional and professional guidance.
Physicians are advised not to initiate new patients on Norditropin NordiFlex® therapy.

Considering that Norditropin Nordiflex® is the only somatropin-based medicinal product authorised in Italy for the treatment of patients suffering from growth failure due to Noonan Syndrome, AIFA has included the medicinal product Somatropin for this indication in the list established pursuant to Law no. 648/96 (Determination no. 99173 of 02/08/2023 - GU no. 186 of 10/08/2023).
Therefore, Somatropin can be prescribed, at the total expense of the National Health System (NHS), for the treatment of growth failure due to Noonan Syndrome according to the criteria established by AIFA note 39. The prescription of the medicine should be authorised by the regional centres.
Please refer to the full text of the Determination available at the following link: https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2023-08-10&atto.codiceRedazionale=23A04511&elenco30giorni=false

Additional information for specialists

In the event of interruption of treatment, it is not possible to list exhaustively all the implications; however, it should be taken into account that:

- In children, treatment is usually discontinued, without dose reduction once normal height is reached in adulthood [2]. The risk associated with early discontinuation of therapy is related to the decrease in the

efficacy of treatment in terms of growth and worsening of body composition, directly derived from studies aimed at assessing non-adherence to growth hormone treatment, even for short periods.[3.4]

- In adults, the benefits of growth hormone become appreciable with long-term treatment[5]. For this reason, no immediate/serious consequences are expected in the event of interruption of treatment for a short period. The consequences of discontinuing for a long period, on the other hand, could lead to complications related to body mass composition, metabolism, and heart health with a possible impact on general health, quality of life and mental well-being[6].

Switching to alternative treatment:

- the main risk from a security point of view is represented by the change of the device;
- the available literature on the possible consequences of switching medicinal products during treatment with recombinant human growth hormone reports concerns regarding dosing errors and treatment interruptions due to the need to learn how to use a new device and reduced adherence related to patient and family frustration and anxiety[7];
- to mitigate the above risks, additional guidance is required for patients until they can properly handle their new device.

Adverse Event Reporting

Adverse events, including medication errors, related to Norditropin NordiFlex® should be reported to the Italian Medicines Agency via the following link https://www.aifa.gov.it/web/guest/content/segnalazioni-reazioni-avverse and to Novo Nordisk S.p.A.

AIFA takes this opportunity to remind all Healthcare Professionals of the importance of reporting suspected adverse drug reactions, as an indispensable tool to confirm a favorable benefit-risk ratio in real conditions of use.

Reports of Suspected Adverse Drug Reactions must be sent to the Pharmacovigilance Manager of the Facility to which the Operator belongs.

This Information Note is also published on the AIFA website (https://www.aifa.gov.it/web/guest) whose regular consultation is recommended for the best professional information and service to the citizen.

Company Contacts

Further information on the marketing cessation of medicinal products and medical information can be obtained by contacting Novo Nordisk SpA, via Giorgio Ribotta 35, 00144 Rome, Italy - +39 06 500881- Website https://www.novonordisk.it/

Bibliography

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