IMPORTANT INFORMATION NOTE

AGREED WITH THE ITALIAN MEDICINES AGENCY (AIFA)

2 July 2025

RE: Minirin/DDAVP (desmopressin) 50mcg/ml nasal spray, solution: Discontinuation from the Italian market.

Dear Health Care Professional,

the company Ferring S.p.A in agreement with the Italian Medicines Agency (AIFA), would like to inform you of the following:

1 *Summary*

- **MINIRIN/DDAVP 50 mcg/ml nasal spray, solution, will be discontinued from the Italian market and it is expected to be not available on the market starting approximately from September 2025.**
- **MINIRIN/DDAVP 50 mcg/ml nasal spray, solution, AIC 023892033 contains the active substance desmopressin, and is indicated for the treatment of: pituitary diabetes insipidus, idiopathic or symptomatic, post-surgical polyuria and polydipsia, for testing of renal concentration capacity, and for the differential diagnosis of diabetes insipidus.**
- **Desmopressin is critically important in treatment of central diabetes insipidus.**
- **Other medicinal product formulations, containing desmopressin, are available in Italy for the same indications as MINIRIN 50 mcg/ml nasal spray, solution.**
- **When transitioning patients to other formulations, the appropriate dose should be determined by individual titration.**

2 *Background information for marketing discontinuation*

Minirin/DDAVP 50 mcg/ml nasal spray, solution contains the stabilizing agent chlorobutanol.

In 2021, the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) requested a risk assessment for medicinal products containing the preservative chlorobutanol at levels exceeding a permitted daily exposure (PDE) of 0.5 mg/day due to a potential risk of cardiotoxicity and reproductive toxicity.

Preclinical in vitro studies on cardiotoxicity and post marketing safety data on intravenous (IV) drug formulations containing chlorobutanol indicate that chlorobutanol may have a potential for prolonging the QT-interval, which may, particularly together with other substances capable of QT-prolongation, lead to a risk of arrythmia. Furthermore, preclinical in vitro and in vivo studies have indicated that high, repeated doses

of chlorobutanol may cause reproductive toxicity[1]. The extent to which chlorobutanol is absorbed following intranasal administration is unknown, but if fully absorbed the estimated exposure would exceed the permitted daily exposure (PDE) threshold of 0.5 mg/day.

A Direct Healthcare Professional Communication (DHPC) informing about the safety concern was disseminated in Italy 30 March 2023 and available at the address: https://www.aifa.gov.it/-/nota-informativa-importante-minirin-ddavp-desmopressina

The EU national competent authorities' (AIFA for Italy) conclusion on the risk assessment for Ferring desmopressin nasal products was that systemic exposure to chlorobutanol might exceed the levels corresponding to 0.5 mg/day given by intravenous route, and the products are therefore not acceptable to retain on the market as is.

3 *Discontinuation of the marketing of MINIRIN 50 mcg/ml AIC 023892033 in Italy:*

In accordance with Ferring's commitment to CMDh and AIFA in the context of the risk assessment of chlorobutanol, the manufacturing of MINIRIN/DDAVP 50 mcg/ml nasal spray, solution AIC 023892033 has been discontinued. The last batch of MINIRIN/DDAVP 50 mcg/ml nasal spray, solution AIC 023892033 on the Italian market will expire March 2026, and considering national distribution dynamics (a minimum 6-month remaining shelf-life), the product will no longer be available for purchase starting from September 2025.

4 *Recommendations for the management of patients currently using MINIRIN 50 mcg/ml nasal spray AIC 023892033*

MINIRIN 50 mcg/ml nasal spray, solution AIC 023892033 is indicated for the treatment of pituitary diabetes insipidus, idiopathic or symptomatic, post-surgical polyuria and polydipsia, for testing of renal concentration capacity, and for the differential diagnosis of diabetes insipidus.

Ferring continues, however, to manufacture and supply authorised medicinal products containing the active ingredient desmopressin in different formulations, with similar indications as MINIRIN 50 mcg/ml nasal spray, solution AIC 023892033.

Based on the publication by Oiso, 2013[2], patients could be referred to treatment with other desmopressin-based medicinal products authorised and marketed on the Italian market, in different formulations and with similar indications as MINIRIN 50 mcg/ml nasal spray, solution AIC 023892033 both owned by Ferring S.p.A. and by other marketing authorization holders.

Whenever changing formulations, it is recommended to start with a low dose and closely monitor fluid balance and serum sodium. Transitioning of patients to oral formulations requires careful individual titration according to antidiuretic response and safety (serum sodium) due to significant interindividual variability.

Desmopressin is critically important in treatment of central diabetes insipidus. Patients treated with desmopressin for central diabetes insipidus should be aware that stopping medication may lead to polyuria, which may lead to dehydration and hypernatremia (higher than normal serum sodium levels) if water deficit is not corrected.

Healthcare professionals are, therefore, urged to ensure that patients using MINIRIN 50 mcg/ml nasal spray, solution, AIC 023892033 are informed of this issue and to safely transfer patients to an appropriate alternative therapy according to their clinical judgement.

Call for the reporting of adverse events

Si ricorda agli Operatori Sanitari di continuare a segnalare le reazioni avverse sospette associate all'utilizzo di desmopressina in conformità al sistema nazionale di segnalazione spontanea, tramite l'Agenzia Italiana del Farmaco, sito web: https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse

AIFA takes this opportunity to remind all Healthcare Professionals of the importance of reporting suspected adverse drug reactions, as an indispensable tool for confirming a favourable benefit-risk relationship under actual 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 (http://www.aifa.gov.it), whose regular consultation is recommended for the best professional information and service to citizens..

Company contact point

If you require further information, please contact:

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References:

1) *SWP response to CMDh questions on chlorobutanol, 17-March 2021, EMA/CHMP/SWP/482438/2020 corr. 1** https://www.ema.europa.eu/en/documents/scientific-guideline/chmp-safety-working-partysresponse-cmdh-questions-chlorobutanol_en.p

2) *Yutaka Oiso, Gary L. Robertson, Jens Peter Nørgaard, and Kristian Vinter Juul. Treatment of Neurohypophyseal Diabetes Insipidus. J Clin Endocrinol Metab, October 2013, 98(10):3958–3967*