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Minirin/DDAVP (desmopressin) 50mcg/ml nasal spray, solution: Introduction of warnings about potential risk of arrythmia and reproductive toxicity from exposure to the excipient chlorobutanol.

Dear Healthcare professional,

Ferring S.p.A in agreement with *l'Agenzia Italiana del Farmaco (AIFA),* would like to inform you of the following:

1 Summary

- **Minirin/DDAVP 50mcg/ml nasal spray, solution contains the stabilising agent CHLOROBUTANOL**
- **Chlorobutanol exposure has been associated with prolongation of the QT-interval leading to a potential risk of arrythmia**
- **Preclinical studies have indicated that chlorobutanol may cause reproductive toxicity**
- **It is not known to what extent chlorobutanol is systemically available following administration of Minirin/DDAVP 50mcg/ml nasal spray but if fully absorbed the estimated exposure is exceeding the permitted daily exposure threshold (0.5 mg/day).**
- **Although no safety concerns regarding cardiotoxicity or reproductive toxicity have been identified from post-marketing safety data on Minirin/DDAVP 50mcg/ml nasal spray, solution the product information has been updated due to the severity of the potential detrimental effects following chlorobutanol exposure and the uncertainty about systemic availability following nasal exposure. ,**
- **Minirin/DDAVP 50mcg/ml nasal spray, solution should only be considered in situations when alternative desmopressin formulations without chlorobutanol are unavailable or else.**

2 Background on the safety concern

Minirin/DDAVP 50mcg/ml nasal spray, solution is indicated for the treatment of central diabetes insipidus, reversible or permanent post-surgical polyuria and polydipsia, for testing of renal concentration capacity, for the differential diagnosis of diabetes insipidus.

Minirin/DDAVP 50mcg/ml nasal spray, solution contains the stabilising agent chlorobutanol. No human data from controlled studies of pharmacologic/toxicologic effects of chlorobutanol are available in the public domain. 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.

To avoid potential detrimental effects following exposure to chlorobutanol, Minirin/DDAVP 50mcg/ml nasal spray, solution should only be considered in situations when alternative desmopressin formulations without chlorobutanol are unavailable or else.

Minirin/DDAVP 50mcg/ml has 40 years of marketing experience with desmopressin nasal formulations containing chlorobutanol and during that time has not identified any safety concerns regarding cardiotoxicity or reproductive toxicity. However, based on post-marketing and published data for medicinal IV formulations containing chlorobutanol and preclinical studies, the product information has precautionarily been updated with the potential effects of the excipient chlorobutanol:

- Update of section 4.4 (Special warning and precautions of use) of the Summary of Product Characteristics (SmPC) to emphasize the potential risks of QT-prolongation and reproductive toxicity following exposure to chlorobutanol and to highlight that Minirin/DDAVP 50mcg/ml nasal spray, solution should only be considered in situations when alternative desmopressin formulations without chlorobutanol are unavailable or else.

- Update of section 4.6 (Pregnancy and lactation) of the SmPC to emphasize that Minirin/DDAVP 50mcg/ml nasal spray, solution containing chlorobutanol is not recommended for use during pregnancy or in women intending to become pregnant.

- Update of section 5.3 (Preclinical safety data) of the SmPC with information about the preclinical data on reproductive toxicity in rats following high, repeated doses of chlorobutanol.

The Package Leaflet is updated accordingly.

Desmopressin is critically important in treatment of central diabetes insipidus. According to the SmPC, desmopressin nasal formulations should only be used in patients where orally administered formulations are not feasible. Therefore, despite the potential risk of QT-prolongation and associated risk of arrythmia, and the possible reproductive toxicity of the excipient chlorobutanol, the benefits of administering Minirin/DDAVP 50mcg/ml nasal spray, solution to patients not capable of obtaining optimal titration with the desmopressin oral formulations continues to outweigh these potential risks.

3 Call for reporting

Healthcare Professionals are reminded to continue to report suspected adverse reactions associated with the use of desmopressin in accordance with the national spontaneous reporting system, via the Italian Medicines Agency, website:

https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse

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-partys-response-cmdh-questions-chlorobutanol_en.pdf