KEMENTERIAN KESIHATAN MALAYSIA
(*Ministry of Health Malaysia*)
Bahagian Amalan & Perkembangan Farmasi
(Pharmacy Practice & Development Division)
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Ruj. Tuan :
Ruj. Kami : KKM.600-35/1/5 Jld. 3 (35)
Tarikh : 7 Jun 2018

SEPERTI SENARAI EDARAN

Tuan/Puan,

MAKLUMAN BERHUBUNG PERUBAHAN MAKLUMAT PADA PEMBUNGKUSAN DAN SISIP BUNGKUSAN PRODUK *APPROVED PRODUCTS PURCHASE LIST* (APPL) 2017 - 2019

NAMA PRODUK	: DESMOPRESSIN 100 MCG/ML NASAL SPRAY
JENAMA	: MINIRIN NASAL SPRAY 0.1 MG / ML
NOMBOR PENDAFTARAN	: MAL19984346ARZ

Saya dengan hormatnya merujuk kepada perkara tersebut di atas.

2. Untuk makluman, pembekal kontrak APPL 2017-2019, Ferring Sdn Bhd (Ferring) telah memaklumkan bahawa terdapat perubahan pada rekaan grafik, maklumat pada kotak pembungkusan dan sisip bungkusan produk tersebut di atas. Berikut adalah perbezaan maklumat yang terlibat:

Perkara	Maklumat Asal	Maklumat Baru
Suhu	*Do not store above 25°C*	*Do not store above 30°C*
Tempoh jangka hayat	36 bulan	24 bulan
Nombor Pendaftaran	MAL19984346A	MAL19984346ARZ

3. Produk dengan maklumat-maklumat baru ini telah mula dibekalkan oleh pihak Pharmaniaga Logistics Sdn Bhd (Pharmaniaga) pada pertengahan bulan April 2018. Bersama-sama ini disertakan sesalinan *artwork* kotak pembungkusan dan sisip bungkusan baru pada **LAMPIRAN A** dan **LAMPIRAN B** untuk makluman dan tindakan pihak tuan/ puan selanjutnya. Mohon supaya perkara ini dipanjangkan kepada hospital dan klinik kesihatan di bawah jagaan pihak tuan/puan.

Tarikh : 7 Jun 2018
Ruj. Kami : KKM.600-35/1/5 Jld. 3 (35)

Kerjasama dan perhatian daripada pihak tuan/ puan dalam perkara ini adalah amat dihargai.

Sekian, terima kasih.

"BERKHIDMAT UNTUK NEGARA"

Saya yang menurut perintah,

(DR. KAMARUZAMAN BIN SALEH) RPh.931
Pengarah Amalan & Perkembangan Farmasi
Kementerian Kesihatan Malaysia
FAR/*mmz*

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s.k.:

1. Setiausaha Bahagian
   Bahagian Perolehan dan Penswastaan, KKM

2. Pengarah Edaran dan Logistik,
   Pharmaniaga Logistics Sdn Bhd

SENARAI EDARAN

1. Timbalan Pengarah Kesihatan Negeri (Farmasi)
   Bahagian Perkhidmatan Farmasi,
   Jabatan Kesihatan Negeri Johor.

2. Timbalan Pengarah Kesihatan Negeri (Farmasi)
   Bahagian Perkhidmatan Farmasi,
   Jabatan Kesihatan Negeri Kedah.

3. Timbalan Pengarah Kesihatan Negeri (Farmasi)
   Bahagian Perkhidmatan Farmasi,
   Jabatan Kesihatan Negeri Kelantan.

4. Timbalan Pengarah Kesihatan Negeri (Farmasi)
   Bahagian Perkhidmatan Farmasi,
   Jabatan Kesihatan Negeri Melaka.

5. Timbalan Pengarah Kesihatan Negeri (Farmasi)
   Bahagian Perkhidmatan Farmasi,
   Jabatan Kesihatan Negeri Negeri Sembilan.

6. Timbalan Pengarah Kesihatan Negeri (Farmasi)
   Bahagian Perkhidmatan Farmasi,
   Jabatan Kesihatan Negeri Pahang.

7. Timbalan Pengarah Kesihatan Negeri (Farmasi)
   Bahagian Perkhidmatan Farmasi,
   Jabatan Kesihatan Negeri Perak.

8. Timbalan Pengarah Kesihatan Negeri (Farmasi)
   Bahagian Perkhidmatan Farmasi,
   Jabatan Kesihatan Negeri Perlis.

9. Timbalan Pengarah Kesihatan Negeri (Farmasi)
   Bahagian Perkhidmatan Farmasi,
   Jabatan Kesihatan Negeri Pulau Pinang.

10. Timbalan Pengarah Kesihatan Negeri (Farmasi)
    Bahagian Perkhidmatan Farmasi,
    Jabatan Kesihatan Negeri Sabah.

11. Timbalan Pengarah Kesihatan Negeri (Farmasi)
    Bahagian Perkhidmatan Farmasi,
    Jabatan Kesihatan Negeri Sarawak.

12. Timbalan Pengarah Kesihatan Negeri (Farmasi)
    Bahagian Perkhidmatan Farmasi,
    Jabatan Kesihatan Negeri Selangor.

13. Timbalan Pengarah Kesihatan Negeri (Farmasi)
    Bahagian Perkhidmatan Farmasi,
    Jabatan Kesihatan Negeri Terengganu.

14. Timbalan Pengarah Kesihatan Negeri (Farmasi)
    Bahagian Perkhidmatan Farmasi,
    Jabatan Kesihatan W.P Kuala Lumpur & Putrajaya.

15. Timbalan Pengarah Kesihatan Negeri (Farmasi)
    Bahagian Perkhidmatan Farmasi,
    Jabatan Kesihatan W.P Labuan.

16. Ketua Pegawai Farmasi,
    Hospital Kuala Lumpur.

17. Ketua Pegawai Farmasi
    Institut Kanser Negara.

Malaysia MINIRIN spray 2.5ml carton 05-C-MY-03.01 size 34.5x27.5x97mm
Created by JIWO (28-12-2016) - 30oC + revised brandbox design

Proposed packaging material		
Code	05,36-I-MY-02.02	
Size	180x250, 180x300, 180x370, 180x420	
Submission	☐NDA ☐Renewal ☒Variation change detail no.: Deficiency email by NPRA dated 20-2-2017	
Code of previous version	05,36-I-MY-02.01	
Changes	Revised Section Special Warnings and precautions for use : putting it as point form, requested by PV unit, NPRA	
	☐CCDS version:	☐SPC country/version/date:
	☐Core PIL version:	☒LAC no.: 633 (approved indication and dosage unchanged)
Name & Date	JIWO, 22-Feb-2017	

MINIRIN®

Nasal Spray 10mcrog/dose (0.1 mg/ml)

QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 0.1 mg desmopressin acetate equivalent to 89 µg desmopressin, and 0.1 mg benzalkonium chloride. Excipients: Benzalkonium chloride (solution), sodium chloride, citric acid monohydrate (E 330), disodium phosphate dihydrate, and purified water.

PHARMACEUTICAL FORM

Nasal spray, solution.

THERAPEUTIC INDICATIONS

Central diabetes insipidus

The use of MINIRIN® in patients with an established diagnosis will result in a reduction in urinary output with concomitant increase in urine osmolality and decrease in plasma osmolality. This will result in decreased urinary frequency and decreased nocturia.

Renal concentrating capacity test

MINIRIN® can be used to test the capacity of the kidneys to concentrate urine; as a diagnostic aid in the examination of the kidney function. This is especially useful in the differential diagnosis between level of urinary tract infections. Cystitis will opposite to pyelonephritis not cause a subnormal ability to concentrate urine.

POSOLOGY AND METHOD OF ADMINISTRATION

General

1 dose of the spray provides 0.1 ml, which corresponds to 10 µg desmopressin acetate.

MINIRIN® nasal formulations should be used only when treatment with oral formulations is inappropriate and always start at the lowest dose (see section Special warnings and precautions for use).

Fluid restriction should be observed (see indication specific instructions in section Special warnings and precautions for use).

If signs of water retention and/or hyponatraemia (headache, nausea/vomiting, weight gain and in serious cases convulsions) develop, treatment should be discontinued until the patient has recovered completely. Fluid intake should be strictly limited when treatment is reinstated (see section Special warnings and precautions for use).

Indication specific

Central diabetes insipidus:

Dosage is individual but clinical experience has shown that the normal daily dose for adults is 10-20 µg 1-2 times daily and for children 5-10 µg 1-2 times daily.

Renal concentrating capacity test:

Normal adult dose is 40 µg. For children over 12 months the dose is 20 µg. For children under 12 months the dose is 10 µg. After administration of MINIRIN® any urine collected within 1 hour is discarded. During the next 8 hours 2 portions of urine are collected for osmolality testing.

The reference level for normal urine osmolality after MINIRIN® administration is 800 mOsm/kg for most patients. With values under this level, the test should be repeated. A similar low result indicates an impaired ability to concentrate urine and the patient should be referred for further examination into the underlying cause of the malfunction.

Special Populations

Elderly: see section Special warnings and precautions for use.
Renal Impairment: see section Contraindications.
Hepatic Impairment: see section Interaction with other medicinal products and other forms of interaction.
Paediatric Population: MINIRIN® is indicated in children with central diabetes insipidus and for testing of renal concentration capacity, see section Special warnings and precautions for use and Undesirable effects.

CONTRAINDICATIONS

MINIRIN® must NOT be used in:

- habitual or psychogenic polydipsia (resulting in a urine production exceeding 40 ml/kg/24 hours);
- syndrome of inappropriate ADH secretion (SIADH);
- known hyponatraemia;
- known or suspected cardiac insufficiency and other conditions requiring treatment with diuretics;
- moderate and severe renal insufficiency (creatinine clearance below 50 ml/min);
- hypersensitivity to the active substances or to any of the excipients.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

MINIRIN® nasal formulations should be used only when treatment with oral formulations is inappropriate.

When MINIRIN® is prescribed it is recommended to:
- start with the lowest dose
- ensure compliance with fluid restriction instructions
- increase dose progressively, with caution
- ensure that children administration is under adult supervision in order to control the dose intake

MINIRIN® should be used with caution in:
- the treatment of small children and elderly patients
- fluid and/or electrolyte imbalance
- risk of increased intracranial pressure

Without simultaneous reduction in fluid intake, treatment can lead to water retention and/or hyponatraemia (headache, nausea/vomiting, weight gain and in serious cases convulsions).

Elderly patients, patients with low plasma sodium levels and patients with high 24-hour urine volumes (above 2.8 to 3 litres) have an increased risk of developing hyponatraemia.

In patients with:
- urgency/urge incontinence
- organic causes for increased micturition frequency or nocturia (e.g. benign prostatic hyperplasia, urinary tract infection, bladder stones/tumours),
- polydipsia or poorly controlled diabetes mellitus
The specific cause of the symptoms should be dealt with primarily.

To prevent hyponatraemia, caution must be exercised and particular attention should be paid to fluid retention and frequent checks made of sodium plasma levels in the following circumstances;
- concomitant treatment with drugs that are known to induce inappropriate ADH secretion syndrome (SIADH), e.g. tricyclic antidepressants, SSRIs, chloropromazine and carbamazepine as well as some antidiabetics of the sulfonylurea group such as glibenclamide.
- concomitant treatment with NSAID preparations.

Treatment with desmopressin should be carefully adjusted during acute illness characterized by fluid and/or electrolyte imbalance such as systemic infections, fever and gastroenteritis.

Experience from clinical use indicates a risk of severe hyponatraemia in association with the nasal formulations of desmopressin, when it is used in the treatment of central diabetes insipidus.

MINIRIN® 0.1 mg/ml nasal spray may cause bronchospasm due to the presence of benzalkonium chloride in this product.

At testing of renal concentration capacity
When used diagnostically, fluid intake should be restricted to a maximum of 0.5 L to satisfy thirst for 1 hour before administration until 8 hours after administration. Renal concentration capacity testing in children below 1 year of age should only be performed in hospital and under careful supervision.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Substances that are known to induce inappropriate ADH secretion, e.g. tricyclic antidepressants, SSRIs, chloropromazine and carbamazepine as well as some antidiabetics of the sulfonylurea group such as glibenclamide may cause an additive antidiuretic effect with an increased risk of fluid retention, see section Special warnings and precautions for use.
NSAID preparations may induce water retention/hyponatraemia, see section Special warnings and precautions for use.

It is unlikely that desmopressin interacts with pharmaceuticals affecting hepatic metabolism, since desmopressin has not been shown to undergo any significant liver metabolism in *in vitro* studies with human microsomes. However, formal interaction studies *in vivo* have not been performed.

PREGNANCY AND LACTATION

Fertility
Fertility studies have not been carried out. *In vitro* analysis of human cotyledon models have shown that there is no transplacental transport of desmopressin when administered at therapeutic concentrations corresponding to recommended doses.

Pregnancy
Data on a limited number (n=53) of pregnant women who were treated for diabetes insipidus as well as data on a limited number (n=54) of exposed pregnancies in women with von Willebrand disease indicate no adverse effects of desmopressin on pregnancy or on the health of the foetus/newborn. No other relevant epidemiological data are available. Animal studies do not indicate direct or indirect adverse effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development.

Caution should be exercised when administering MINIRIN® to pregnant women.

Lactation
Results from analyses of milk from nursing mothers receiving high doses of desmopressin (300 µg intranasally), indicate that desmopressin is transferred to the breast milk but that the amount of desmopressin that may be transferred to the child is low and probably less than the amounts required to influence diuresis.
Whether desmopressin will accumulate in breast milk upon repeated doses has not been studied.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

MINIRIN® has no or negligible influence on the ability to drive and use machines.

UNDESIRABLE EFFECTS

Summary of the safety profile
The most serious adverse reaction with desmopressin is hyponatraemia, see below under "Description of selected adverse reactions".

The most commonly reported adverse reactions during treatment were nasal congestion (27%), high body temperature (15%) and rhinitis (12%). Other common adverse reactions were headache (9%), upper respiratory tract infection (9%), gastroenteritis (7%), abdominal pain (5%). Anaphylactic reactions have not been seen in clinical trials but spontaneous reports have been received.

Tabulated summary of adverse reactions
The below table is based on the frequency of adverse drug reactions reported in clinical trials with nasal MINIRIN® conducted in children and adults for treatment of central diabetes insipidus, primary nocturnal enuresis and at testing of renal concentration capacity (N=745) combined with the post marketing experience for all indications. Reactions only reported post-marketing or for other desmopressin formulations have been added in the "Not known" frequency column.

MedDRA Organ Class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**	**Not known (cannot be estimated from available data)**
Immune system disorders				Allergic reaction
Metabolism and nutrition disorders			Hyponatraemia	Dehydration***
Psychiatric disorders		Insomnia, Affect lability**, Nightmare**, Anxiety**, Aggression**		Confusional state*

Nervous system disorders		Headache*		Convulsions*, Coma *, Dizziness*, Somnolence
Vascular disorders				Hypertension
Respiratory, thoracic and mediastinal disorders	Nasal congestion, Rhinitis,	Nosebleed, Upper respiratory tract infection**		Dyspnoea
Gastrointestinal disorders		Gastroenteritis, Nausea*, Abdominal pain*	Vomiting*	Diarrhoea
Skin and subcutaneous tissue disorders				Pruritus, Rash, Urticaria
Musculoskeletal and connective tissue disorders				Muscle spasms*
General disorders and administration site conditions				Fatigue*, Peripheral oedema*, Chest pain, Chills
Investigations				Weight increased*

*Reported in connection with hyponatraemia.
** Above all reported in children and adolescents.
*** Reported for central diabetes insipidus indication.

Description of selected adverse reactions
The most serious adverse reaction with desmopressin is hyponatraemia, which may give symptoms like headache, nausea, vomiting, weight increase, malaise, abdominal pain, muscle spasms, dizziness, confusion, decreased consciousness and in serious cases convulsions and coma. The cause of the potential hyponatraemia is the anticipated antidiuretic effect.

Paediatric population
Hyponatraemia is reversible and in children it is often seen to occur in relation to changes in daily routines affecting fluid intake and/or perspiration.
Special precautions should be observed in children, see section Special warnings and precautions for use.

Special populations
Elderly patients and patients with low serum sodium levels may have an increased risk of developing hyponatraemia (see section Special warnings and precautions for use).

OVERDOSE
Toxicity
Overdosage leads to prolonged duration of action with an increased risk of fluid retention and hyponatraemia. Even normal doses may cause water intoxication in association with a high fluid intake. Doses exceeding 0.3 µg/kg i.v. and 2.4 µg/kg intranasally have together with fluid intake caused hyponatraemia and convulsions in children and adults. However, 40 µg administered intranasally to a 5-month-old baby and 80 µg administered intranasally to a 5-year-old produced no symptoms. 4 µg administered parenterally to a newborn produced oliguria and weight-gain.

Symptoms
The same symptoms as for water intoxication. Headache, nausea. Fluid retention, hyponatraemia, hypoosmolality, oliguria, CNS depression, convulsions, pulmonary oedema. See also section Undesirable effects.

Treatment
The treatment of hyponatraemia must be tailored to the individual, but the following general recommendations may be given.
Hyponatremia is treated by discontinuing the desmopressin treatment and restricting fluids. If the patient has symptoms, an infusion of isotonic or hypertonic sodium chloride may be given. When the fluid retention is serious (convulsions and loss of consciousness), treat with furosemide.

PHARMACODYNAMIC PROPETIES
Pharmacotherapeutic group: vasopressin and analogues.
ATC code: H01B A02.

MINIRIN® contains desmopressin, a structural analogue of the natural pituitary hormone arginine vasopressin. The difference lies in that the amino group in cysteine has been removed and L-arginine has been substituted by D-arginine. This results in a considerably longer duration of action with intranasal administration and a complete lack of pressor effect in the dosages used clinically.

PHARMACOKINETIC PROPERTIES

Absorption: Bioavailability is approx. 3-5%. The maximum plasma concentration is reached after approx. one hour and does not increase in proportion to the administered dose. One intranasal dose of 10-20 µg produces an antidiuretic effect for 8-12 hours.

Distribution: The distribution volume during the elimination phase is 0.3-0.5 L/kg. Desmopressin does not cross the blood-brain barrier.

Metabolism: In vitro studies with human liver microsomes have shown that an insignificant amount of desmopressin is metabolised in the liver microsomes. It is therefore unlikely that desmopressin is metabolised in the liver in humans. Desmopressin does not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 *in vitro* and thus should desmopressin not affect the pharmacokinetics of other drugs metabolized by CYP enzymes.

Elimination: The total clearance of desmopressin has been calculated to 7.6 L/h. The half-life for desmopressin in the elimination phase is 2.8 hours in average. In healthy subjects the fraction excreted unchanged in urine is 52%.

No sex-related differences have been observed regarding the pharmacokinetics of desmopressin.

INCOMPATIBILITIES

Not applicable.

SHELF LIFE

2 years.

SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30°C.

NATURE AND CONTENTS OF CONTAINER

MINIRIN® nasal spray is propelled by a manual dose pump without propellant gas. The spray pump is constructed to administer 100 µl solution (= 10 µg desmopressin acetate) per spray dose.

Pack size: 1 x 2.5 ml; 1 x 5 ml
Not all pack sizes may be marketed.

SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

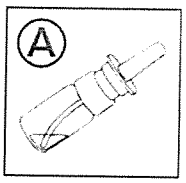
Before MINIRIN® nasal spray is used for the first time, the pump should be primed by pressing it downwards 4 times, or until an even spray is obtained. If the spray has not been used during the previous week, the pump must be primed again by pressing once or until an even spray is obtained.

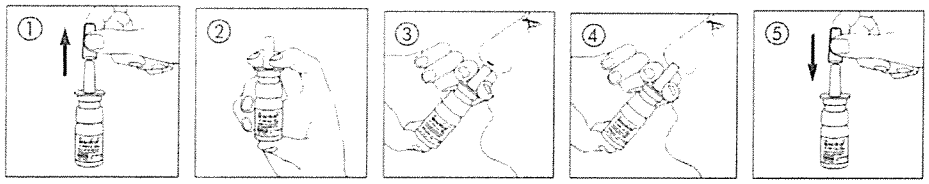
IMPORTANT! The lower end of the tube must always be submerged in the liquid when you use the spray (see figure A).

At the least hesitation whether correct dose is administered, no further spray dose should be given until the next time for administration. In small children the administration should be monitored by an adult to ensure correct dosing.

Instructions for use:

1. Remove the protective cap.
2. Hold the bottle according to the figure.
3. Tilt your head slightly backwards. Insert the nasal applicator into one nostril as shown in figure 3. Hold your breath and spray once.
4. If you are prescribed more than one dose, repeat the administration in the other nostril. For every further dose, change nostrils and repeat according to instructions.
5. Replace the protective cap. Always store the bottle upright.





MANUFACTURER
Ferring GmbH
Kiel, Germany

Date of revision: Feb 2017