SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

MIGRANAL 4mg/ml nasal spray solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml nasal spray solution contains 4.0 mg dihydroergotamine mesilate.
Each metered dose delivers 0.5mg dihydroergotamine mesilate.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Nasal spray, solution.

MIGRANAL Nasal Spray is a liquid dosage form for local application using a spray device. The liquid is a clear, colourless to faintly yellow, brownish-yellow or greenish-yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of acute attacks of migraine with or without aura

4.2 Posology and method of administration

The solution in the vial was developed especially for intranasal administration and must not be injected.

Posology
One spray (0.5 mg) of MIGRANAL Nasal Spray should be administered in each nostril at the onset of the migraine headache.

Fifteen minutes later, in patients in whom the first dose of MIGRANAL Nasal Spray (1.0 mg) was not sufficient, one additional spray (0.5 mg) can be administered in each nostril for a total dosage of four sprays (2.0 mg) of MIGRANAL Nasal Spray per attack.

The following recommendations must be observed:
The maximum dose of MIGRANAL Nasal Spray allowed within 24 hours is 2 mg (= 4 sprays) and the maximum weekly dose is 8 mg (= 16 sprays).

Following the treatment of a migraine attack with MIGRANAL Nasal Spray, an interval of at least 24 hours should be observed before treating any further attack with MIGRANAL Nasal Spray, Dihydergot injections, any ergotamine-containing preparations, sumatriptan or other agonists of the 5-hydroxytryptamine$_1$(5-HT$_1$) receptors.

The assembled nasal spray should be discarded after the treatment of a single migraine attack as described above (1 mg or 2 mg, respectively).

Elderly
MIGRANAL Nasal Spray is not recommended for use in patients aged over 65 years due to a lack of data on safety and efficacy.

Hepatic impairment

Caution is recommended in patients with mild to moderate hepatic impairment, especially in patients with cholestatic hepatitis (see sections 4.4 and 5.2). MIGRANAL Nasal Spray is contraindicated in patients with severe hepatic impairment (see section 4.3).

Paediatric population
MIGRANAL Nasal Spray is not recommended for use in children aged below 16 years due to a lack of data on safety and efficacy.

Method of administration
Only prepare the nasal spray when you feel an attack of migraine starting. Once the spray device is assembled, it should be used within 8 hours.

1. Pull back the blue seal by lifting up at the lip, but do not break the blue seal off the metal collar.

2. Tear off the whole cap and metal collar. The blue seal and metal collar should come off in one piece. If the blue seal snaps off, continue to remove the metal collar but take extra care as the edges of the metal collar may be sharp.

3. Carefully remove the rubber stopper from the bottle.

4. Gently remove the plastic protective cap from the bottom of the pump unit.

5. Insert the nasal spray pump unit into the open bottle and turn the pump clockwise to tighten.

6. Holding the bottle upright, gently remove the blue protective cap from the top of the nozzle.

7. The pump unit must be primed before first use. To do this hold the nasal spray upright and press down firmly on the pump 4 times. Do not worry if a small amount of medicine sprays out during the priming process, this is normal.

8. Holding the spray upright, insert the nozzle and spray once into each nostril. Sniff vigorously several times to prevent the solution from running out of your nose. Do not blow your nose immediately after taking a dose.

Replace the blue cap and keep the spray unit handy in case you need it again later. You do not need to reprime the pump.

4.3 Contraindications

- Hypersensitivity to ergot alkaloids or any of the excipients listed in section 6.1.
- Conditions predisposing to vasospastic reactions: coronary heart disease (in particular unstable or vasospastic angina), septic conditions, shock, obliterative vascular disease, peripheral vascular diseases such as Raynaud's syndrome, past history of transitory ischaemic attack or cerebral injury as well as inadequately controlled hypertension.
- Temporal arteritis
- Treatment of familial hemiplegic migraine.
- Treatment of basilar migraine.
- Pregnancy and breast-feeding (see section 4.6).
- Patients with severely impaired hepatic function.
- Concomitant treatment with potent CYP 3A inhibitors, such as macrolide antibiotics, HIV-protease inhibitors, azole antifungals and other medications (see section 4.5).

Concomitant treatment with peripheral vasoconstrictive agents including ergot-containing preparations, sumatriptan and other agonists of the 5-hydroxytryptamine1 (5-HT1) receptors (see section 4.5).

4.4 Special warnings and precautions for use

MIGRANAL Nasal Spray is not intended for use as a prophylactic treatment for migraine nor should it be used continually in the long term due to the risk of serious side effects and complications of use.

Dihydroergotamine can have serious side effects, called fibrosis, including retroperitoneal, cardiac, pulmonary and pleural fibrosis and ergotism (including severe cases of symptoms of constriction of peripheral blood vessels) with possible fatal outcome.

Patients with a history of drug induced fibrotic disorders such as retroperitoneal and pleural fibrosis should be monitored with caution.

Prolonged use of dihydroergotamine or other ergot derivatives must be avoided because it may lead to drug dependence.

Chronic daily use of MIGRANAL Nasal Spray or its use in excess of the recommended doses should be avoided, since it may cause vasospasm.

Chronic abuse of MIGRANAL Nasal Spray may cause rebound headache. If such a condition is suspected, the treatment should be discontinued.

In rare cases, vascular spasms may occur, particularly in the lower extremities. If signs of vascular spasms are observed, MIGRANAL Nasal Spray should be discontinued and treatment with a peripheral vasodilator initiated (see section 4.9).

Patients who are being treated with MIGRANAL Nasal Spray should be informed of the maximal allowed doses and of the first symptoms of overdosage: paraesthesia (e.g. numbness, tingling) in the fingers and toes, non-migraine-related nausea and vomiting, and symptoms of myocardial ischaemia and chest pain. Should

signs of overdosage occur, treatment must be discontinued and patients should consult their physician at once.

Caution is recommended in patients with rhinitis, nasal congestion and allergic rhinitis as well as in patients with mild to moderate hepatic impairment, especially in patients with cholestatic hepatitis.

Note:
The solution contained in the amber glass vials is specially formulated for intranasal administration and must not be injected.

4.5 Interaction with other medicinal products and other forms of interaction

Strong CYP3A4 inhibitors

The concomitant use of potent cytochrome P450 3A (CYP3A) inhibitors together with MIGRANAL Nasal Spray is contraindicated. Potent CYP3A inhibitors include tetracycline, macrolide antibiotics (e.g. erythromycin, clarithromycin, troleandomycin, telithromycin, josamycin), HIV protease inhibitors (e.g. indinavir, nelfinavir, fosamprenavir, ritonavir, amprenavir, atazanavir), reverse transcriptase inhibitors (e.g. delavirdine, efavirenz), imidazole , antifungals (e.g. ketoconazole, miconazole), triazoles (e.g. itraconazole, voriconazole) must be avoided (see section 4.3), since this can result in an elevated exposure to dihydroergotamine and ergot toxicity (vasospasm, ischaemia and possible necrosis of the extremities and other tissues).

Vasoconstrictors

Concurrent use of vasoconstrictive agents including ergotamine-containing preparations, other ergot alkaloids and sympathomimetics is contraindicated since this may result in enhanced vasoconstriction, ischaemia and possible necrosis of the extremities and other tissues (see section 4.3).

In view of its vasoconstrictor properties, caution is advised with concomitant use of nicotine (e.g. heavy smoking, nicotine replacement therapy)

MIGRANAL Nasal Spray should not be taken for at least 24 hours before or 6 hours after sumatriptan, almotriptan, rizatriptan and zolmitriptan. . In addition, concurrent use with eletriptan, frovatriptan or naratriptan should be separated by at least 24 hours due to the risk of additive vasoconstriction.

Moderate/weak CYP3A4 inhibitors

Moderate to weak CYP3A4 inhibitors such as grapefruit juice, saquinavir, cimetidine, metronidazole, quinupristin/dalfopristin, clotrimazole, fluconazole, nefazodone, fluoxetine, fluvoxamine, zileuton can also increase the exposure to ergotamine and caution is required for their concomitant use

There are no other known pharmacokinetic interactions with other P450 isoenzymes.

Although the combination of β-adrenergic blocking agents (e.g. propranolol) and MIGRANAL Nasal Spray is usually well tolerated, caution is required in patients with impaired peripheral circulation.

4.6 Fertility, pregnancy and lactation

Pregnancy

MIGRANAL Nasal Spray is contraindicated during pregnancy.

Clinical practice with parenteral administration of dihydroergotamine suggests that because of uterotonic activity and vasoconstrictive effects on the placenta and umbilical cord, dihydroergotamine may be hazardous for the foetus.

Studies in animals have shown reproductive toxicity (see section 5.3).

Breast-feeding

It is likely that dihydroergotamine is excreted in breast milk. MIGRANAL Nasal Spray is therefore contraindicated for nursing mothers.

Fertility

No data on the effect of dihydroergotamine on fertility in humans are available. In rats, no effects of on male and female fertility were observed following intranasal and oral administration of dihydroergotamine at doses higher than the maximum recommended human daily dose.

4.7 Effects on ability to drive and use machines

Patients who experience dizziness or other central nervous system disturbances, including visual disturbances, following use of MIGRANAL Nasal Spray should not drive or operate machinery.

4.8 Undesirable effects

The most frequently reported adverse reactions are rhinitis, nausea and vomiting, altered sense of taste, dose-dependent application-site reactions such as runny nose, nasal congestion, diarrhoea, pharyngitis, dizziness and flushing.

Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and Not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Immune system disorders	
Rare	Hypersensitivity reactions (such as skin rash, face oedema, urticaria and dyspnoea)
Nervous system disorders	
Uncommon	Paraesthesia/hypoaesthesia, dizziness, taste disturbance
Cardiac disorders	
Rare	Symptoms of myocardial ischaemia
Vascular disorders	
Uncommon	Flushing
Rare	Arterial spasm (particularly in the lower extremities) (see sections 4.4 and 4.9)
Respiratory, thoracic and mediastinal disorders	
Uncommon	Nasal congestion, rhinitis
Rare	Pharyngitis, dyspnoea
Not known	Epistaxis
Gastrointestinal disorders	
Uncommon	Nausea, vomiting
Rare	Diarrhoea
Not known	Abdominal pain
Skin and subcutaneous tissue disorders	
Rare	Rash, face oedema, urticaria
Musculoskeletal and connective tissue disorders	
Not known	Muscular spasms
General disorders and administration site conditions	
Uncommon	Application site reactions
Rare	Chest pain

In some patients who have taken Oral dihydroergotamine continuously over years ergotism can result. The development of fibrotic changes, in particular of the pleura and the retroperitoneum have been observed. There have been reports of fibrotic changes of the cardiac valves (see section 4.4). Chronic use can lead to dependence (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

No case of overdosage with MIGRANAL Nasal Spray is known. One may, however, expect the symptoms to be similar to those observed after an excessive oral dose, i.e.: nausea, vomiting, headache, tachycardia, vertigo, peripheral signs and symptoms of vasospasm (e.g. numbness, tingling and pain in the extremities) symptoms of myocardial ischaemia, chest pain and coma. It should be noted that symptoms of vasospasm can be delayed up to 24 hours after drug administration.

Management

After discontinuation of use, the treatment of overdose is symptomatic, under close monitoring of the cardiovascular system.

In the event of severe vasospastic reactions, intravenous administration of a peripheral vasodilator such as nitroprusside, phentolamine or dihydralazine, local application of warmth to the affected area and nursing care to prevent tissue damage are recommended. In the case of coronary constriction, appropriate treatment such as nitroglycerin should be initiated.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ergot alkaloids, ATC code: N02CA01

Mechanism of action
Dihydroergotamine displays moderate to high affinity for various serotonin receptor subtypes. It displays particularly potent agonist activity at the 5-HT_{1D} receptor, which is believed to underlie its antimigraine efficacy. This agonistic effect produces a reduction in 5-HT neuronal function and thereby influences elements of the cranial vasculature and/or prevents neurogenic inflammation and the resultant stimulation of nociceptors.

The administration of MIGRANAL Nasal Spray provides a rapid onset of action. In acute migraine attacks of mild to severe intensity, MIGRANAL Nasal Spray reduces headache pain and associated symptoms such as phonophobia and photophobia.

5.2 Pharmacokinetic properties

Absorption
Intranasally administered dihydroergotamine is rapidly absorbed (t_{max} approx. 45 min). The absolute bioavailability of dihydroergotamine via the intranasal route is about 43 ± 24%.

Distribution
Dihydroergotamine is 93% bound to plasma proteins. Its apparent steady-state volume of distribution is about 800 litres.

Biotransformation
Between 70 and 80% of the plasma concentration is related to unchanged drug pointing to a lower metabolism of parent drug than that obtained with oral administration.

Elimination
Total body clearance is about 1.5 litres/minute, reflecting mainly hepatic clearance. Elimination from the plasma is biphasic, with a terminal half-life of about 10 hours. The major route of excretion is via the bile in the faeces. After intranasal administration, the urinary excretion of parent substance and metabolites amounts to about 2%.

5.3 Preclinical safety data

Reproductive toxicity

Dihydroergotamine at oral doses of up to 30 mg/kg per day was not teratogenic to pregnant rats or rabbits, and had no effect on perinatal or postnatal development in rats and rabbits. Oral administration of 5 mg/kg per day to pregnant monkeys was not teratogenic. However, following intravenous and nasal administration, developmental toxicity (decreased fetal body weights and/or delayed skeletal ossification) was observed in experimental animals. This observation has been attributed to reduced uteroplacental blood flow resulting from prolonged vasoconstriction of the uterine vessels and/or increased myometrial tone induced by dihydroergotamine.

Genotoxicity

Mutagenicity tests in vitro provided contradictory results. In vivo models showed no evidence of mutagenic activity of dihydroergotamine, and therefore it is considered devoid of genotoxic potential.

Carcinogenicity

Carcinogenicity studies in rats (dosed intranasally with 0.08, 0.24 or 0.8 mg per day) and mice (dosed subcutaneously with 0.5, 1.5 or 5 mg/kg per day) led to the conclusion that dihydroergotamine has no carcinogenic activity. An increased incidence of fibrosarcomas at the injection site in the mouse study (at 5 mg/kg per day) was considered to be related to the mode of administration (subcutaneously) without relevance for the intermittent use in man.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Caffeine
Glucose, anhydrous
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

Once opened, the vial solution has an in-use shelf-life of 8 hours.

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

MIGRANAL Nasal Spray is available in packs containing 1 ml solution in a 3.5 ml vial made of hydrolytic type I amber glass and a spray device consisting of a pump unit with a blue nozzle cover and a dip tube cover. The vial is closed with a rubber stopper sealed by a plastic flip-tear cap affixed to an aluminium metal collar.

After properly priming the spray device, MIGRANAL Nasal Spray contains at least 4 metered doses each of 0.125 ml spray solution.

Spray devices/vials are provided in cartons of 1,2 and 6. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Amdipharm UK Limited
Dashwood House,
69 Old Broad Street,
London, EC2M 1QS,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20072/0216

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/01/2007

10 DATE OF REVISION OF THE TEXT

26/01/2024