For the use of a registered medical practitioner.

℞

Apomorphine Hydrochloride Injection 10 mg/ml

APOSAN®

FOR SUBCUTANEOUS USE ONLY

COMPOSITION:
Each ml contains:
Apomorphine Hydrochloride Hemihydrate EP equivalent to
anhydrous Apomorphine Hydrochloride ……10 mg
Excipients ……..... q.s.
Water for Injections IP……..…….…..... q.s.

DESCRIPTION
A clear colorless to pale yellow colour solution.

PHARMACODYNAMICS
Pharmacotherapeutic group: Dopamine agonists
ATC Classification: N04BC07

Apomorphine Hydrochloride is a direct stimulant of dopamine receptors and while possessing both D1 and D2 receptor agonist properties does not share transport or metabolic pathways with levodopa.

Although in intact experimental animals, administration of apomorphine suppresses the rate of firing of nigro-striatal cells and in low dose has been found to produce a reduction in locomotor activity (thought to represent pre-synaptic inhibition of endogenous dopamine release) its actions on parkinsonian motor disability are likely to be mediated at post-synaptic receptor sites. This biphasic effect is also seen in humans.

Pharmacokinetics: After subcutaneous injection of apomorphine its fate can be described by a two-compartment model, with a distribution half-life of 5 (±1.1) minutes and an elimination half-life of 33 (±3.9) minutes. Clinical response correlates well with levels of apomorphine in the cerebrospinal fluid; the active substance distribution being best described by a two-compartment model. Apomorphine is rapidly and completely absorbed from subcutaneous tissue, correlating with the rapid onset of clinical effects (4-12 minutes), and that the brief duration of clinical action of the active substance (about 1 hour) is explained by its rapid clearance. The metabolism of apomorphine is by glucuronidation and sulphonation to at least ten per cent of the total; other pathways have not been described.

INDICATION
For treatment of disabling motor fluctuations ("on-off" phenomena) in patients with Parkinson's disease which persist despite individually titrated treatment with levodopa (with a peripheral decarboxylase inhibitor) and/or other dopamine agonists.

POSOLOGY AND METHOD OF ADMINISTRATION
Posology and method of administration
Selection of Patients suitable for APOSAN®:
Patients selected for treatment with Apomorphine should be able to recognise the onset of their 'off' symptoms and be capable of injecting themselves or else have a responsible carer able to inject for them when required.

Patients treated with apomorphine will usually need to start domperidone at least two days prior to initiation of therapy. The domperidone dose should be titrated to the lowest effective dose and discontinued as soon as possible. Before the decision to initiate domperidone and apomorphine treatment, risk factors for QT interval prolongation in the individual patient should be carefully assessed to ensure that the benefit outweighs the risk.

Apomorphine should be initiated in the controlled environment of a specialist clinic. The patient should be supervised by a physician experienced in the treatment of Parkinson's disease (e.g. neurologist). The patient's treatment with levodopa, with or without dopamine agonists, should be optimised before starting Apomorphine treatment.

Adults
Administration
APOSAN® is for subcutaneous use by intermittent injection.
Apomorphine must not be used via the intravenous route.
Do not use if the solution has turned green. The solution should be inspected visually prior to use. Only clear, colourless and particle free solution should be used.

Determination of the threshold dose.
The appropriate dose for each patient is established by incremental dosing schedules. The following schedule is suggested:-

1mg of apomorphine HCl (0.1ml), that is approximately 15-20 micrograms/kg, may be injected subcutaneously during a hypokinetic or 'off' period and the patient is observed over 30 minutes for a motor response.

If no response, or an inadequate response, is obtained a second dose of 2 mg of apomorphine HCl (0.2ml) is injected subcutaneously and the patient observed for an adequate response for a further 30 minutes.

The dosage may be increased by incremental injections with at least a forty minute interval between succeeding injections, until a satisfactory motor response is obtained.

Establishment of treatment.
Once the appropriate dose is determined, a single subcutaneous injection may be given into the lower abdomen or outer thigh at the first signs of an 'off' episode. It cannot be excluded that absorption may differ with different injection sites within a single individual. Accordingly, the patient should then be observed for the next hour to assess the quality of their response to treatment. Alterations in dosage may be made according to the patient's response.

The optimal dosage of apomorphine hydrochloride varies between individuals but, once established, remains relatively constant for each patient.

Precautions on continuing treatment.
The daily dose of Apomorphine varies widely between patients, typically within the range of 3-30 mg, given as 1-10 injections and sometimes as many as 12 separate injections per day.

It is recommended that the total daily dose of apomorphine HCl should not exceed 100 mg and that individual bolus injections should not exceed 10 mg.

In clinical studies it has usually been possible to make some reduction in the dose of levodopa; this effect varies considerably between patients and needs to be carefully managed by an experienced physician.

Once treatment has been established, domperidone therapy may be gradually reduced in some patients but successfully eliminated only in a few, without any vomiting or hypotension.

Children and adolescents:
APOSAN® is contraindicated for children and adolescents under 18 years of age.

Elderly:
The elderly are well represented in the population of patients with Parkinson's disease and constitute a high proportion of those studied in clinical trials of Apomorphine. The management of elderly patients treated with Apomorphine has not differed from that of younger patients. However, extra caution is recommended during initiation of therapy in elderly patients because of the risk of postural hypotension.

Renal impairment:
A dose schedule similar to that recommended for adults, and the elderly, can be followed for patients with renal impairment.

Contraindications
In patients with respiratory depression, dementia, psychotic diseases or hepatic insufficiency.

APOSAN® must not be administered to patients who have an 'on' response to levodopa which is marred by severe dyskinesia or dystonia.

Apomorphine should not be administered to patients who have a known hypersensitivity to apomorphine or any excipients of the medicinal product.

Apomorphine is contraindicated for children and adolescents under 18 years of age.

WARNINGS AND PRECAUTIONS
APOSAN® should be given with caution to patients with renal, pulmonary or cardiovascular disease and persons prone to nausea and vomiting.

Extra caution is recommended during initiation of therapy in elderly and/or debilitated patients.

Since apomorphine may produce hypotension, even when given with domperidone pretreatment, care should be exercised in patients with pre-existing cardiac disease or in patients taking vasoactive medicinal products such as anti-hypertensives, and especially in patients with pre-existing postural hypotension.

Since apomorphine, especially at high dose, may have the potential for QT prolongation, caution should be exercised when treating patients at risk for torsades de pointes arrhythmia.

When used in combination with domperidone, risk factors in the individual patient should be carefully assessed. This should be done before treatment initiation, and during treatment. Important risk factors include serious underlying heart conditions such as congestive cardiac failure, severe hepatic impairment or significant electrolyte disturbance. Also medication possibly affecting electrolyte balance, CYP3A4 metabolism or QT interval should be assessed. Monitoring for an effect on the QTc interval is advisable. An ECG should be performed:

- Prior to treatment with domperidone
- During the treatment initiation phase
- As clinically indicated thereafter

The patient should be instructed to report possible cardiac symptoms including palpitations, syncope, or near-syncope. They should also report clinical changes that could lead to hypokalaemia, such as gastroenteritis or the initiation of diuretic therapy.

At each medical visit, risk factors should be revisited.

Apomorphine is associated with local subcutaneous effects. These can sometimes be reduced by the rotation of injection sites or possibly by the use of ultrasound (if available) in order to avoid areas of nodularity and in duration.

Haemolytic anaemia and thrombocytopenia have been reported in patients treated with apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa, when given concomitantly with apomorphine.

Caution is advised when combining apomorphine with other medicinal products, especially those with a narrow therapeutic range.

Neuropsychiatric problems co-exist in many patients with advanced Parkinson's disease. There is evidence that for some patients neuropsychiatric disturbances may be exacerbated by apomorphine. Special care should be exercised when apomorphine is used in these patients.

Apomorphine has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution whilst driving or operating machines during treatment with apomorphine. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore, a reduction of dosage or termination of therapy may be considered.

Impulse control disorders
Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including apomorphine. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

Dopamine dysregulation Syndrome (DDS) is an addictive disorder resulting in excessive use of the product seen in some patients treated with apomorphine. Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing DDS.

APOSAN ® contains sodium metabisulphite which may rarely cause severe allergic reactions and bronchospasm.

This medicinal product contains less than 1 mmol sodium (23mg) per 10ml, i.e. essentially "sodium-free".

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonist for Parkinson's disease, including apomorphine.

INTERACTIONS WITH OTHER MEDICAMENTS
Patients selected for treatment with Apomorphine are almost certain to be taking concomitant medications for their Parkinson's disease. In the initial stages of Apomorphine Injection therapy, the patient should be monitored for unusual side-effects or signs of potentiation of effect.

Neuroleptic medicinal products may have an antagonistic effect if used with apomorphine. There is a potential interaction between clozapine and apomorphine, however clozapine may also be used to reduce the symptoms of neuropsychiatric complications.

If neuroleptic medicinal products have to be used in patients with Parkinson's disease treated by dopamine agonists, a gradual reduction in apomorphine dose may be considered when administration is by minipump and/or syringe-driver (symptoms suggestive of neuroleptic malignant syndrome have been reported rarely with abrupt withdrawal of dopaminergic therapy).

The possible effects of apomorphine on the plasma concentrations of other medicinal products have not been studied. Therefore caution is advised when combining apomorphine with other medicinal products, especially those with a narrow therapeutic range.

Antihypertensive and Cardiac Active Medicinal Products
Even when co-administered with domperidone, apomorphine may potentiate the antihypertensive effects of these medicinal products.

It is recommended to avoid the administration of apomorphine with other drugs known to prolong the QT interval.

PREGNANCY AND LACTATION
There is no experience of apomorphine usage in pregnant women.

Animal reproduction studies do not indicate any teratogenic effects, but doses given to rats which are toxic to the mother can lead to failure to breathe in the newborn. The potential risk for humans is unknown.

Apomorphine Injection should not be used during pregnancy unless clearly necessary.

It is not known whether apomorphine is excreted in breast milk. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with Apomorphine Injection should be made taking into account the benefit of breast-feeding to the child and the benefit of Apomorphine Injection to the woman.

UNDESIRABLE EFFECTS:
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
For the evaluation of adverse effects the following frequency specification will be used:
Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1000 to <1/100)
Rare (≥ 1/10,000 to <1/1000), Very rare (< 1/10,000), Not known (cannot be estimated from available data).

System organ class	Frequency	Adverse event
Blood and lymphatic system disorders	Uncommon	Haemolytic anaemia and thrombocytopenia have been reported in patients treated with apomorphine.
	Rare:	Eosinophilia has rarely occurred during treatment with apomorphine Hcl.
Immune system disorders	Rare	Due to the presence of sodium metabisulphite, allergic reactions (including anaphylaxis and bronchospasm) may occur.
Psychiatric disorders	Common	Neuropsychiatric disturbances are common in parkinsonian patients. Apomorphine should be used with special caution in these patients. Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine Hcl therapy.
Nervous system disorders	Not known	**Impulse control disorders** Pathological gambling, increased libido, hypersexuality; compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including apomorphine hydrochloride.
	Common	Transient sedation with each dose of apomorphine HCl at the start of therapy may occur; this usually resolves over the first few weeks. Apomorphine is associated with somnolence. Dizziness/light-headedness have also been reported.
	Uncommon	Apomorphine may induce dyskinesias during 'on' periods, which can be severe in some cases, and in a few patients may result in cessation of therapy.
Vascular disorders	Uncommon:	Postural hypotension is seen infrequently and is usually transient.
Respiratory, thoracic and mediastinal disorders	Common	Yawning has been reported during apomorphine therapy.
	Uncommon	Breathing difficulties have been reported.
Gastrointestinal disorders	Common:	Nausea and vomiting, particularly when apomorphine treatment is first initiated, usually as a result of the omission of domperidone.
Skin and subcutaneous tissue disorders	Uncommon	Local and generalised rashes have been reported.
General disorders and administration site conditions	Very common	Most patients experience injection site reactions, particularly with continuous use. These may include subcutaneous nodules, induration, erythema, tenderness and panniculitis. Various other local reactions (such as irritation, itching, bruising and pain) may also occur.
	Uncommon	Injection site necrosis and ulceration have been reported.
	Not Known	Peripheral oedema has been reported.
Investigations	Uncommon	Positive Coombs' tests have been reported for patients receiving apomorphine.

SYMPTOMS AND TREATMENT OF OVERDOSAGE
There is little clinical experience of overdose with apomorphine by this route of administration. Symptoms of overdose may be treated empirically as suggested below:-
- Excessive emesis may be treated with domperidone.
- Respiratory depression may be treated with naloxone.
- Hypotension: appropriate measures should be taken, e.g. raising the foot of the bed.
- Bradycardia may be treated with atropine.

STORAGE CONDITION
Do not store above 25°C. Do not freeze. Store ampoules in the outer carton. Protect from light.
Keep out of reach of children.

PRECAUTION FOR USE AND DISPOSAL
Do not use if the solution has turned green.

Withdraw contents immediately after opening and discard the ampoule.

Caution: Take care not to spill apomorphine on clothing or household surfaces and textiles as spillages may turn green.

No special precautions for Disposal.

Nature and content of container

Clear Transparent USP type I glass ampoule.

Manufacturing License No.: 22/UA/SC/P-2008

PRESENTATION
2ml ampoule, Such 5 ampoules packed in Plastic tray and then in Inner carton.
5ml ampoule, Such 5 ampoules packed in Plastic tray and then in Inner carton.

Rūsan

Manufactured by: **Rusan Pharma Ltd.**
Khasra No. 122 MI, Central Hope Town, Selaqui, Dehradun - 248 197, Uttarakhand, India.
H.O.: 58-D, Govt. Ind. Estate, Charkop, Kandivali (W), Mumbai - 400 067, India.
Marketed by: **Rusan Healthcare Pvt. Ltd.**
Mumbai - 400 067, India.
Website: www.aposan.in | Email: aposan@rhcpl.com
Toll Free No.: 1800 103 0475

PACKAGE LEAFLET: INFORMATION FOR THE USER

Rx Apomorphine Hydrochloride Injection 10 mg/ml

APOSAN®

FOR SUBCUTANEOUS USE ONLY

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not give it to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What APOSAN® is and what it is used for

APOSAN® contains Apomorphine Hydrochloride solution for injection. Apomorphine belongs to a group of medicines called dopamine agonists. It is used to treat Parkinson's disease in patients who are already being treated with other dopamine agonists and/or levodopa. Apomorphine helps to reduce the amount of time spent in an "off" state (periods of immobility). Your doctor or nurse will help you to recognize when you need to use this medicine. Despite the name, Apomorphine does not contain morphine, and is not a controlled substance.

2. What you need to know before you use APOSAN®

Do not use APOSAN®:

- If you are under 18 years of age
- If you are allergic to Apomorphine hydrochloride or any of the other ingredients in the medicine.
- If you have breathing difficulties
- If you have dementia or Alzheimer's disease
- If you have psychotic diseases (group of serious illnesses that affect the mind)
- If you have hepatic insufficiency.
- If you have any disorder, other than Parkinson's disease, which affects the brain or spinal cord.

2.1 Talk to your doctor before using Apomorphine:

- If you have kidney, lung or heart disease
- If you suffer from nausea and vomiting
- If you have neuropsychiatric problems (confusion, hallucinations)

2.2 Check with your doctor before taking your medicine if:

- You are using medicines that are known to affect the way your heart beats. This includes medicines used for heart rhythm problems (such as quinidine and amiodarone), for depression (including tricyclic antidepressants such as amitriptyline and imipramine) and for bacterial infections ('macrolide' antibiotics such as erythromycin, azithromycin and clarithromycin) and domperidone.

2.3 Other medicines and APOSAN®. Please refer section '*Interactions with other medicaments'.*

2.4 Pregnancy and breast-feeding. Please refer section *'Pregnancy and Lactation'.*

2.5 Driving and using machines: APOSAN® can cause drowsiness and a strong desire to sleep. Do not drive or use any tools or machinery if this medicine affects you in this way. APOSAN® can affect your ability to drive. Do not drive whilst taking this medicine until you know how this medicine affects you.

Caution: Take care not to spill APOSAN® on clothing or household surfaces and textiles as spillages may turn green.

3. How to use APOSAN®

Before you use APOSAN®, your doctor will ensure that you tolerate the medicine and an antiemetic medicine will be prescribed simultaneously.

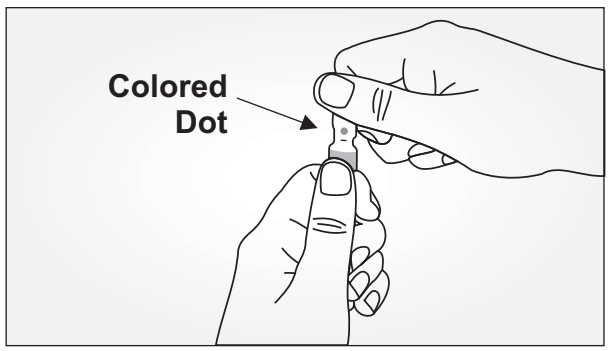
Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

It is essential that you have already taken domperidone to stop the nausea and vomiting.

3.1 To Inject APOSAN®, you will need:

- One syringe and needle.
- Needles, glass ampoules and syringes should be disposed safely in an appropriate manner.
- Your Doctor or Nurse will show you how to break the ampoules and use the equipment to administer your medicine.

3.2 Breaking the APOSAN® Ampoules:



- Locate the colored dot on the region above the neck of the ampoule. This indicates breaking point of the ampoule.
- Hold the bottom of the ampoule in one hand.
- Grasp the neck of the ampoule at the colored dot.
- Apply pressure in a backward direction. This will snap off the top of the ampoule.
- Carefully dispose of the top of the ampoule.

3.3. How much to use

Your doctor will discuss this with you and tell you how much of your medicine you should inject and how often. The amount that will work best for you will have been determined during your visit to the specialist clinic.

- The recommended dose is in the range of 3 mg (0.3ml) to 30 (3ml) mg per day, injected 1 to 10 times a day at the first sign of an unpredictable "off" period.
- You should NOT exceed a total daily dose of 100 mg (10ml)
- Do not inject more than 10 mg (1ml) at any one time, unless advised by your doctor.

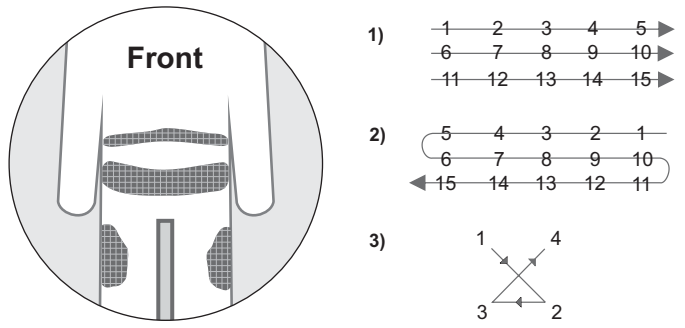
If your symptoms are not controlled well enough with separate injections or if you find that you are requiring more than 10 injections per day, you may require a continuous infusion. Your doctor will decide if you need this form of treatment and which dose is best for you.

3.4 How and where to inject APOSAN®:

- Place the needle firmly on the end of the syringe
- Ensure the site of injection is clean and sterile before you inject
- Inject your medicine as shown by your doctor or nurse into an area under the skin (subcutaneously)
- Intermittent subcutaneous injections should be administered in the lower abdominal wall, below the umbilicus, the upper outer aspects of the thighs. The injection site should be rotated for each injection.
- Discard used syringes, needles and ampoules in a "Sharps" bin (available from your doctor or pharmacist) or other suitable container, such as an empty coffee jar

If you have any further questions about the use of this medicine, ask your doctor or nurse.

The recommended pattern for the injection site is shown in the image below. Any one of the following patterns can be followed as instructed by the doctor.



3.5 When choosing injection site

- It is at least 2.5 cm (1 inch) away from a previous Injection site.
- It is at least 2.5 cm (1 inch) away from the belly button.
- Do not inject APOSAN® into a vein.

3.6 If you use more APOSAN® than you should

- Tell your doctor or contact your nearest hospital emergency department immediately
- You may experience a slow heart rate, excessive sickness, excessive sleepiness and/or difficulty breathing. You may also feel faint or dizzy particularly when you stand up, due to low blood pressure. Lying down and raising your feet may help you to feel better.

3.7 If you forget to use APOSAN®

Take it when you next require it. Do not take a double dose to make up for a forgotten dose.

3.8 If you stop using APOSAN®

Do NOT stop your treatment suddenly; you may get symptoms of muscular rigidity, high fever, changes in mental function (neuroleptic malignant syndrome).

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

If you get any side effects (as mentioned in the *'undesirable effects'* section), talk to your doctor or nurse.

5. How to store APOSAN®

Do not store above 25°C. Do not freeze. Store ampoules in the outer carton. Protect from light. Keep out of reach of children.

Once opened APOSAN® should be used immediately. Full contents of ampoule should be drawn in the syringe. Use the required amount of dose. Put the needle protection cap on after use. Store the filled syringe at the temperature below 25°C and protect from light. Needle needs to be changed every time you inject.

5.1 Do not use this medicine if:

- The solution has turned green
- The solution is cloudy or you can see particles in it

6. Contents of the pack and other information

What APOSAN® contains

The active substance is Apomorphine Hydrochloride.
Each ml contains 10 mg Apomorphine Hydrochloride.
2ml ampoule contains 20mg Apomorphine Hydrochloride.
5ml ampoule contains 50mg Apomorphine Hydrochloride.

6.1 What APOSAN® looks like

APOSAN® is a solution for injection. It is a clear, colorless to pale yellow colour solution.

Aposan Hope Program™

The *Hope* Nurse and coordinators can help you understand with any product information, safe administration, dosing and any support required for the effective use of **APOSAN®** therapy.

The *Hope* number: **1800 103 0475**

* TM Trademark applied