8th January 2019

Clexane (enoxaparin) 4,000 IU (40mg)/0.4ml Pre-Filled Syringes out of stock announcement

Sanofi is facing increasing global demand for Clexane (enoxaparin) solution for injection. In the UK, there has also been an increased use of Clexane due to recent shortages of some of the other low molecular weight heparins in the marketplace. This has put pressure on Sanofi's usual supply of Clexane to the UK.

On the 7th January 2019, Sanofi UK were informed that a batch of Clexane 4,000 IU (40mg)/0.4ml Pre-Filled Syringes planned to be delivered on 8th January 2019 had failed a quality release test. Delivery has now been placed on hold pending further investigation and re-testing. The anticipated delivery date of the failed batch is now early February, and the next scheduled delivery after that is the 18th February 2019.

Despite Sanofi doing all it can to match supply with demand, in the UK there will now be a shortage of Clexane 4,000 IU (40mg)/0.4ml Pre-Filled Syringes. As stock levels are already low we expect depots to start to go out of stock from the 8th January 2019, with all depots out of stock by Friday 11th January 2019. We expect this situation to last between 3-4 weeks if the failed batch passes further testing and is released. If this is not possible, the out of stock situation is likely to last until 18th February 2019.

In order to reduce the impact of this supply issue Sanofi will release Italian batches of 4,000 IU (40mg)/0.4ml Clexane Syringes from the 23rd January 2019 PIP code: 409-6202. This is supplied as a UK licensed product, supplied under a batch specific variation to cover the fact that it remains in Italian packaging. Each pack will contain an English Patient Information Leaflet.

We apologise for the inconvenience that this situation will cause. Sanofi remains committed to doing all that it can to improve supply to the UK and ensuring that patients requiring Clexane can continue to be treated with as little disruption as feasible.

Q&A

**Q1. What are the main differences between the Italian Clexane and regular UK Clexane?**

A1. Below is a table that highlights the differences between the two batches

| Comparative table of PREVENTIS and ERIS devices features | CLEXANE ITALY PREVENTIS | CLEXANE UK ERIS |
|---|---|---|
| Single use 40mg/0.4ml dose | ✓ | ✓ |
| Blistered pre-filled syringes | ✓ | ✓ |
| Auto-Activated ERIS needle protective sleeve | ✗ | ✓ |
| User activated PREVENTIS needle protective sleeve | ✓ | ✗ |
| Audible click when activating the safety device | ✓ | ✓ |
| Plunger colour | Yellow | White |
| Number of Syringes per pack | 6 | 10 |
| Pack dimensions (mm) | 63 x 86 x 169 | 138 x 84 x 162 |

The most important difference between the Italian and UK preparations is the difference in the needle guard device. To deploy the Preventis needle shield on the Italian syringes, users will need to firmly push the plunger after completing the injection. The user will hear an audible "click" to confirm the activation of the protective sleeve and the protective sleeve will automatically cover the needle. Patients and HCPs will need to be trained on this new device; instructions for use can also be found within the PIL attached to each pack of the syringes.

**Q2. Why are Sanofi introducing Italian stock?**

A2. A number of factors are currently putting greater pressure on supply of Clexane 4000 IU (40mg)/0.4ml prefilled syringes. Due to changes in packaging (including addition of serialization required as part of the Falsified Medicines Directive), the manufacturing site has had to close an existing production line to transition to the new packaging which allows inclusion of these extra requirements. Sanofi is committed to finding solutions to try to ensure that those Trusts which use Clexane can remain supplied during this temporary interruption in supply as far is possible.

**Q3. Is the Italian version of Clexane licenced in the UK?**

A3. Yes, this particular presentation is approved in the same product licence as the presentation normally supplied in the UK. A Batch Specific Variation has been approved permitting the use of Italian packs as a means to address this temporary interruption in supply.

**Q4. What support is available for our Trust?**

A4. Sanofi are providing the following:

1. Dear Healthcare Professional Communication (DHPC) letter to all Trusts impacted
2. English Patient Information Leaflet (PIL) in each box.
3. Ward posters highlighting the difference between regular UK Clexane and Italian Clexane packs

- All these items above are available in print and electronically.

4. Sanofi Sales representatives to support individual trusts.

| Region | Name | Contact number | Email |
|---|---|---|---|
| North of England | Owen Dixon | 07764 624691 | Owen.Dixon@sanofi.com |
| Midlands and East | Lianne Rai | 07834 794508 | Lianne.Rai2@sanofi.com |
| London | Bali Bassi | 07921 054950 | Balli.Bassi@sanofi.com |
| South of England | Samantha Clark | 07935 503425 | Samantha.Clark@sanofi.com |
| Wales & N Ireland | Rebecca Slater | 07740 935165 | Rebecca.Slater@sanofi.com |
| Scotland | Jo Graham | 07841 051959 | Joanne.Graham@sanofi.com |

**Q5. What is the price of the Italian Clexane pack?**

A5. List price is £18.16 for a pack of 6 x 4,000 IU (40mg)/0.4ml prefilled syringes. **Contract prices will be pro-rota based on the current contract price for Clexane 40mg.**

**Q6. Who do I contact for further information?**

A6. For questions relating to supply of stock please contact our customer service team on email: GB-CustomerServices@sanofi.com or telephone 0800 854 430

For medical enquiries, please contact our medical information team on email uk-medicalinformation@sanofi.com or telephone 0845 372 7101;

**Prescribing Information: Clexane® Syringes, Clexane® Forte Syringes, and Clexane® Multidose Vial**

**Presentations:** Clexane® Syringes: single dose pre-filled syringes containing either: 2,000 IU (20mg) enoxaparin sodium in 0.2ml, 4,000 IU (40mg) enoxaparin sodium in 0.4ml, 6,000 IU (60mg) enoxaparin sodium in 0.6ml, 8,000 IU (80mg) enoxaparin sodium in 0.8ml or 10,000 IU (100mg) enoxaparin sodium in 1ml. Clexane® Forte Syringes: single dose pre-filled syringes containing either: 12,000 IU (120mg) enoxaparin sodium in 0.8ml or 15,000 IU (150mg) enoxaparin sodium in 1ml. Clexane® Multidose vial: Vial containing 30,000 IU (300mg) enoxaparin sodium in 3.0ml solution for injection for single patient use.

**Indications:** In adults for: prophylaxis of venous thromboembolic disease in moderate and high risk surgical patients, in particular those undergoing orthopaedic or general surgery including cancer surgery; prophylaxis of venous thromboembolic disease in medical patients with an acute illness and reduced mobility at increased risk of venous thromboembolism (VTE); treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), excluding PE likely to require thrombolytic therapy or surgery; prevention of thrombus formation in extra corporeal circulation during haemodialysis; treatment of unstable angina and non ST-segment elevation myocardial infarction (NSTEMI), in combination with oral acetylsalicylic acid; treatment of acute ST-segment elevation myocardial infarction (STEMI) including patients to be managed medically or with subsequent percutaneous coronary intervention (PCI).

**Dosage & Administration:** ***Prophylaxis in Surgical Patients:*** With moderate risk of thromboembolism, recommended dose of enoxaparin sodium is 2,000 IU (20mg) once daily by subcutaneous (SC) injection. Initiation 2 hours before surgery was proven effective and safe in moderate risk surgery. Treatment should be maintained for at least 7-10 days and until the patient no longer has significantly reduced mobility. In patients at high risk of thromboembolism, the recommended dose of enoxaparin sodium is 4,000 IU (40 mg) once daily by SC injection preferably started 12 hours before surgery. If there is a need for earlier than 12 hours enoxaparin sodium preoperative prophylactic initiation (e.g. high risk patient waiting for a deferred orthopaedic surgery), the last injection should be administered no later than 12 hours prior to surgery and resumed 12 hours after surgery. For patients undergoing major orthopaedic surgery an extended thromboprophylaxis up to 5 weeks is recommended. For patients with high risk of VTE undergoing abdominal or pelvic surgery for cancer, extended thromboprophylaxis up to 4 weeks is recommended. ***Prophylaxis in Medical Patients:*** Recommended dose of enoxaparin sodium is 4,000 IU (40 mg) once daily by SC injection. Treatment with enoxaparin sodium is prescribed for at least 6 to 14 days. Benefit is not established for treatment longer than 14 days. ***Treatment of VTE:*** 150 IU/kg (1.5 mg/kg) administered SC once-daily should be used in uncomplicated patients with low risk of VTE recurrence. 100 IU/kg (1 mg/kg) twice-daily should be used in all other patients such as those with obesity, symptomatic PE, cancer, recurrent VTE or proximal (vena iliaca) thrombosis. The regimen should be selected based on individual assessment including evaluation of the thromboembolic risk and risk of bleeding. Enoxaparin sodium treatment is prescribed for an average period of 10 days. Oral anticoagulant therapy should be initiated when appropriate. ***Treatment of Acute Coronary Syndromes:*** For treatment of unstable angina and NSTEMI, the recommended dose of enoxaparin sodium is 100 IU/kg (1 mg/kg) every 12 hours by SC injection administered in combination with antiplatelet therapy. Treatment should be for a minimum of 2 days and until clinical stabilization (usual duration 2 to 8 days). Acetylsalicylic acid recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (in acetylsalicylic acid-naive patients) and a maintenance dose of 75–325 mg/day long-term. For treatment of acute STEMI, recommended dose of enoxaparin sodium is a single intravenous (IV) bolus of 3,000 IU (30 mg) plus a 100 IU/kg (1 mg/kg) SC dose followed by 100 IU/kg (1 mg/kg) administered SC every 12 hours (maximum 10,000 IU (100 mg) for each of the first two SC doses). Appropriate antiplatelet therapy such as oral acetylsalicylic acid (75 mg to 325 mg once daily) should be administered concomitantly unless contraindicated. Recommended duration of treatment is 8 days or until hospital discharge. When administered in conjunction with a thrombolytic (fibrin specific or non-fibrin specific), enoxaparin sodium should be given between 15 minutes before and 30 minutes after the start of fibrinolytic therapy. For patients managed with PCI, if the last dose of enoxaparin sodium SC was given less than 8 hours before balloon inflation, no additional dosing needed. If the last SC administration was given more than 8 hours before balloon inflation, an IV bolus of 30 IU/kg (0.3 mg/kg) enoxaparin sodium should be administered. ***During haemodialysis:*** 1mg/kg (100 IU/kg) Clexane® introduced into arterial line of the circuit at beginning of dialysis. This dose is usually sufficient for a 4 hour session. If fibrin rings are found, e.g. after a longer session, a further 0.5 to 1mg/kg (50 to 100 IU/kg) may be given. In patients with high risk of haemorrhage reduce the dose to 0.5mg/kg (50 IU/kg) (double vascular access) or 0.75mg/kg (75IU/kg) (single vascular access). ***Elderly:*** For treatment of acute STEMI in elderly patients ≥75 years of age, an initial IV bolus must not be used. Initiate dosing with 75 IU/kg (0.75 mg/kg) SC every 12 hours (maximum 7,500 IU (75 mg) for each of the first two SC doses only, followed by 75 IU/kg (0.75 mg/kg) SC dosing for the remaining doses). ***Children:*** Safety and efficacy not established. ***Renal impairment:*** Not recommended for patients with end stage renal disease Dosage adjustment required for patients with severe renal impairment. ***Hepatic Impairment***: Limited data in this population therefore caution should be used.

**Contraindications:** Hypersensitivity to enoxaparin sodium, heparin or its derivatives, including low

molecular weight heparins (LMWH) or any of the excipients. Recent (<100 days) history of immune mediated heparin-induced thrombocytopenia (HIT) or in the presence of circulating antibodies. Active clinically significant bleeding and conditions with a high risk of haemorrhage, including recent haemorrhagic stroke, gastrointestinal ulcer, presence of malignant neoplasm at high risk of bleeding, recent brain, spinal or ophthalmic surgery, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities. ***Multiple dose vials containing benzyl alcohol***: Hypersensitivity to benzyl alcohol. Newborns or premature neonates.

**Warnings and Precautions.** Do not use interchangeably (unit for unit) with other LMWHs. Use with extreme caution in patients with a history (>100 days) of HIT without circulating antibodies, only after careful benefit-risk assessment and after non-heparin alternative treatments are considered; platelet counts should be measured before and regularly thereafter during the treatment and patients should be warned of symptoms. Use with caution in conditions with increased potential for bleeding (e.g. impaired haemostasis, history of peptic ulcer, recent ischemic stroke, severe arterial hypertension, recent diabetic retinopathy, neuro- or ophthalmologic surgery). Increases in activated partial thromboplastin time (aPTT), and activated clotting time (ACT) may occur at higher doses but not linearly correlated with dose. Spinal/epidural anaesthesia or lumbar puncture must not be performed within 24 hours of administration of therapeutic doses of enoxaparin sodium; placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of enoxaparin sodium is low. Skin necrosis and cutaneous vasculitis have been reported with LMWHs and should lead to prompt treatment discontinuation. Following vascular instrumentation during the treatment of unstable angina, NSTEMI and acute STEMI: adhere precisely to the recommended dosing intervals; in case a closure device is used, the sheath can be removed immediately; If a manual compression method is used, sheath should be removed 6 hours after the last IV/SC enoxaparin sodium injection; The site should be observed for signs of bleeding or hematoma. Use of heparin is usually not recommended in patients with acute infective endocarditis. Enoxaparin sodium has not been adequately studied for thromboprophylaxis in patients (including in pregnancy) with mechanical prosthetic heart valves. Elderly patients may be at increased risk of bleeding at treatment doses. Low body weight patients are at increased risk of bleeding at prophylactic and treatment dose ranges. Obese patients are at higher risk for thromboembolism however there is no consensus for dose adjustment; these patients should be observed carefully. Heparins can suppress adrenal secretion of aldosterone leading to hyperkalaemia, particularly in patients such as those with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, taking medicinal products known to increase potassium; plasma potassium should be monitored regularly especially in patients at risk. **Pregnancy:** Enoxaparin sodium should be used during pregnancy only if the physician has established a clear need. As benzyl alcohol may cross the placenta, it is recommended to use a formulation that does not contain benzyl alcohol. **Interactions***. **Not Recommended:*** Systemic salicylates, acetylsalicylic acid at anti-inflammatory doses, and NSAIDs including ketorolac. Other thrombolytics (e.g. alteplase, reteplase, streptokinase, tenecteplase, urokinase) and anticoagulants. ***Caution:*** Platelet aggregation inhibitors including acetylsalicylic acid used at anti-aggregant dose (cardioprotection), clopidogrel, ticlopidine, and glycoprotein IIb/IIIa antagonists indicated in acute coronary syndrome due to the risk of bleeding. Dextran 40. Systemic glucocorticoids. Medicinal products increasing potassium levels.

**Adverse Reactions:** *Very Common:* Hepatic enzyme increases (mainly transaminases > 3 times the upper limit of normality), haemorrhage, thrombocytosis (platelet increase >400 G/L). *Common:* haemorrhagic anaemia, thrombocytopenia, allergic reaction, headache, urticarial, pruritus, erythema, injection site haematoma / pain / other reaction (such as oedema, haemorrhage, hypersensitivity, inflammation, mass, pain, or reaction). *Uncommon:* hepatocellular liver injury, skin necrosis at injection site, intracranial haemorrhage. *Rare:* Retroperitoneal haemorrhage, eosinophilia, cases of immuno-allergic thrombocytopenia with thrombosis (in some cases thrombosis was complicated by organ infarction or limb ischaemia), anaphylactic/anaphylactoid reactions including shock, spinal/neuraxial haematoma resulting in varying degrees of neurologic injuries including long-term or permanent paralysis, cholestatic liver injury, Osteoporosis following therapy > 3 months, hyperkalaemia. *For a full list of undesirable effects please refer to the Summaries of Product Characteristics.* **Pharmaceutical Precautions:** Do not mix with other products. Do not store above 25°C. Do not refrigerate or freeze. The contents of the multidose vial should be used within 28 days of opening. **Legal Category:** POM; PL04425/0187: Clexane® Syringes; PL04425/0185: Clexane® Forte Syringes; PL 04425/0186: Clexane® Multidose Vials **Basic NHS cost for 10 pre-filled syringes:** 2,000 IU - £20.86, 4,000 IU - £30.27, 6,000 IU - £39.26, 8,000 IU - £55.13, 10,000 IU - £72.30, 12,000 IU - £87.93, 15,000 IU - £99.91. **Basic NHS cost for 6 pre-filled syringes:** 4,000 IU - £18.16. **NHS cost for one Multidose Vial** - £21.33. **Date of Revision:** December 2018 ® denotes a Registered Trade Mark. Further information is available on request from Sanofi, One Onslow St, Guildford, Surrey, GU1 4SY 0845 372 7101.

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