Core Safety Profile

Active substance: Nadroparin Calcium
Pharmaceutical form(s)/strength: 0.3ml; 0.4ml; 0.6ml; 0.8ml; and 0.6ml; 0.8ml; 1ml, respectively
P-RMS: ES/H/PSUR/0015/002
Date of FAR: 24.05.2013
Proposed Core Safety Profile (CSP) for EU PSUR Worksharing Scheme

Active:
Nadroparin Calcium

Formulations/Indications:

Nadroparin calcium solution for injection (9,500 anti-Xa IU Ph.Eur./ml) (FRAXIPARINE, FRAXIPARINE MULTI)

Pre-filled syringes:
- 0.2 ml of solution equivalent to 1,900 anti-Xa IU
- 0.3 ml of solution equivalent to 2,850 anti-Xa IU
- 0.4 ml of solution equivalent to 3,800 anti-Xa IU.

Graduated pre-filled syringes:
- 0.6 ml of solution equivalent to 5,700 anti-Xa IU
- 0.8 ml of solution equivalent to 7,600 anti-Xa IU
- 1 ml of solution equivalent to 9,500 anti-Xa IU.

Multi Dose Vials:
- 2 ml of solution equivalent to 19,000 anti-Xa IU
- 5 ml of solution equivalent to 47,500 anti-Xa IU
- 15 ml of solution equivalent to 142,500 anti-Xa IU.

Nadroparin calcium Double Strength solution for injection (19,000 anti-Xa IU Ph.Eur./ml) (FRAXODI, FRAXIPARINE FORTE, FRAXIPARINE Tx)

Graduated pre-filled syringe:
- 0.6 ml of solution equivalent to 11,400 anti-Xa IU
- 0.8 ml of solution equivalent to 15,200 anti-Xa IU
- 1 ml of solution equivalent to 19,000 anti-Xa IU.
**Multi-dose Vials:**
- 5 ml of solution equivalent to 95,000 anti-Xa IU.
- 15 ml of solution equivalent to 285,000 anti-Xa IU.

**Nadroparin calcium solution for injection (9,500 anti-Xa IU/ml)**
- The prophylaxis of thromboembolic disorders, such as:
  - those associated with general or orthopaedic surgery
  - those in high risk medical patients (respiratory failure and/or respiratory infection and/or cardiac failure), hospitalised in intensive care unit.
- The treatment of thromboembolic disorders.
- The prevention of clotting during haemodialysis.
- The treatment of unstable angina and non-Q wave myocardial infarction.

**Nadroparin calcium Double Strength solution for injection (19,000 anti-Xa IU/ml)**
- The treatment of thromboembolic disorders.

**ATC Code:** B01AB06

**Period covered by the submitted PSUR(s):**
01 April 2008 to 31 March 2009

**Introduction:**
This proposed CSP is based on GlaxoSmithKline’s Company Core Data Sheet (CCDS) (16 November 2010) updated with subsequent changes to the CCDS.

National labels may be subject to on-going variations to align with the CCDS, and/or may contain amendments requested by national regulatory authorities.

This document is formatted as a SmPC but contains only sections 4.3, 4.4, 4.5, 4.6, 4.7, 4.8 and 4.9, Core Safety Information (CSI) from sections 4.2 and 5 are also included. All Core Safety Information (CSI) is highlighted in shaded text.
4.2 Posology and method of administration

Particular attention should be paid to the specific dosing instructions for each proprietary Low Molecular Weight Heparin (LMWH), as different units of measurement (units or mg) are used to express doses. Nadroparin should therefore not be used interchangeably with other low molecular weight heparins during ongoing treatment. In addition, care should be taken to use the correct formulation of nadroparin, either single or double strength, as this will affect the dosing regimen.

Graduated syringes are intended for use when dose adjustment for body weight is necessary.

Nadroparin is not intended for intramuscular injection.

Platelet count must be monitored throughout nadroparin treatment (see Section 4.4).

Specific recommendations regarding the timing of nadroparin dosing surrounding spinal/epidural anaesthesia and spinal lumbar puncture should be followed (see Section 4.4).

Subcutaneous injection technique:

The usual site for subcutaneous injection is on the right or left side of the abdominal wall, but the thigh may be used as an alternative. To avoid loss of the solution when using pre-filled syringes, the air bubble should not be expelled from the syringe before the injection. The needle should be inserted perpendicularly into a pinched-up fold of skin which should be held gently but firmly until injection has been completed. The injection site should not be rubbed.

Populations

- Adults

PROPHYLAXIS OF THROMBOEMBOLIC DISORDERS

Nadroparin calcium solution for injection (9,500 anti-Xa IU/ml)

- General Surgery

The recommended dose of nadroparin is 0.3 ml (2,850 anti-Xa IU) administered subcutaneously 2 to 4 hours before surgery, and then once daily on subsequent days.
Treatment should be continued for at least seven days, and throughout the risk period, until the patient is ambulant.

- Orthopaedic Surgery

Nadroparin is administered subcutaneously and the dose is adjusted for body weight according to the table below. This is based on a target dose of 38 anti-Xa IU per kg body weight, and is increased by 50% on the fourth post-operative day. The initial dose is administered 12 hours before surgery and a second dose 12 hours after the end of surgery. Treatment is then continued once daily throughout the risk period and until the patient is ambulant. The minimum treatment period is 10 days.

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>12 hours before and after surgery, and then once daily to the third post-operative day</th>
<th>From the fourth post-operative day onwards</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Volume injected (ml)</td>
<td>Anti-Xa IU</td>
</tr>
<tr>
<td>&lt;50</td>
<td>0.2</td>
<td>1,900</td>
</tr>
<tr>
<td>50-69</td>
<td>0.3</td>
<td>2,850</td>
</tr>
<tr>
<td>≥70</td>
<td>0.4</td>
<td>3,800</td>
</tr>
</tbody>
</table>

high-risk medical patients in intensive care (respiratory failure and/or respiratory infection and/or cardiac failure)

Nadroparin is administered subcutaneously once daily. The dose should be adjusted for body weight according to the table below. Treatment should be continued throughout the risk period of thromboembolism.

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Volume injected (ml)</td>
</tr>
<tr>
<td>≤70</td>
<td>0.4</td>
</tr>
<tr>
<td>&gt;70</td>
<td>0.6</td>
</tr>
</tbody>
</table>

TREATMENT OF THROMBOEMBOLIC DISORDERS

In the treatment of thromboembolic disorders, oral anti-coagulant therapy should be initiated as soon as possible unless contraindicated. Treatment with nadroparin should not be stopped before the International Normalised Ratio target is reached.

Nadroparin calcium solution for injection (9,500 anti-Xa IU/ml)

It is recommended that nadroparin is administered subcutaneously twice daily (every 12 hours) for a usual duration of 10 days. The dose should be adjusted for body weight according to the table below, which is based on a target dose of 86 anti-Xa IU per kg body weight.
**Nadroparin calcium Double Strength solution for injection (19,000 anti-Xa IU/ml)**

It is recommended that nadroparin is administered subcutaneously once daily for a usual duration of 10 days. The dose is adjusted to the patient’s weight according to the table below, which is based on 171 anti-Xa IU per kg body weight.

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Twice daily for a usual duration of 10 days</th>
<th>Volume injected (ml)</th>
<th>Anti-Xa IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td></td>
<td>0.4</td>
<td>3,800</td>
</tr>
<tr>
<td>50-59</td>
<td></td>
<td>0.5</td>
<td>4,750</td>
</tr>
<tr>
<td>60-69</td>
<td></td>
<td>0.6</td>
<td>5,700</td>
</tr>
<tr>
<td>70-79</td>
<td></td>
<td>0.7</td>
<td>6,650</td>
</tr>
<tr>
<td>80-89</td>
<td></td>
<td>0.8</td>
<td>7,600</td>
</tr>
<tr>
<td>≥90</td>
<td></td>
<td>0.9</td>
<td>8,550</td>
</tr>
</tbody>
</table>

**PREVENTION OF CLOTTING DURING HAEMODIALYSIS**

**Nadroparin calcium solution for injection (9,500 anti-Xa IU/ml)**

In the prevention of clotting during haemodialysis, the dose of nadroparin must be optimised for each individual patient, also taking into account the technical conditions of the dialysis.

Nadroparin is usually given as a single dose into the arterial line at the start of each session. For patients without increased risk of haemorrhage the following initial doses are suggested according to body weight and are usually sufficient for a four hour session:

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Injected into the arterial line at the start of dialysis</th>
<th>Volume injected (ml)</th>
<th>Anti-Xa IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td></td>
<td>0.3</td>
<td>2,850</td>
</tr>
<tr>
<td>50-69</td>
<td></td>
<td>0.4</td>
<td>3,800</td>
</tr>
<tr>
<td>≥70</td>
<td></td>
<td>0.6</td>
<td>5,700</td>
</tr>
</tbody>
</table>
Doses should be halved in patients with an increased risk of haemorrhage.

An additional smaller dose may be given during dialysis for sessions lasting longer than four hours. The dose in subsequent dialysis sessions should be adjusted as necessary according to the observed effect.

Patients should be carefully monitored throughout each dialysis session for signs of bleeding or clotting in the dialysis circuit.

**TREATMENT OF UNSTABLE ANGINA AND NON-Q WAVE MYOCARDIAL INFARCTION**

*Nadroparin calcium solution for injection (9,500 anti-Xa IU/ml)*

It is recommended that nadroparin is administered subcutaneously twice daily (every 12 hours). The usual duration of treatment is six days. In clinical studies in patients with unstable angina and non-Q wave myocardial infarction, nadroparin was administered in combination with up to 325 mg aspirin per day.

The initial dose is administered as a bolus injection intravenous (i.v.) and subsequent doses given by subcutaneous injection. The dose should be adjusted for body weight according to the table below, which is based on a target dose of 86 anti-Xa IU per kg body weight.

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Initial i.v. bolus</th>
<th>Subcutaneous injection (every 12 hours)</th>
<th>Anti-Xa IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>0.4 ml</td>
<td>0.4 ml</td>
<td>3,800</td>
</tr>
<tr>
<td>50-59</td>
<td>0.5 ml</td>
<td>0.5 ml</td>
<td>4,750</td>
</tr>
<tr>
<td>60-69</td>
<td>0.6 ml</td>
<td>0.6 ml</td>
<td>5,700</td>
</tr>
<tr>
<td>70-79</td>
<td>0.7 ml</td>
<td>0.7 ml</td>
<td>6,650</td>
</tr>
<tr>
<td>80-89</td>
<td>0.8 ml</td>
<td>0.8 ml</td>
<td>7,600</td>
</tr>
<tr>
<td>90-99</td>
<td>0.9 ml</td>
<td>0.9 ml</td>
<td>8,550</td>
</tr>
<tr>
<td>≥ 100</td>
<td>1.0 ml</td>
<td>1.0 ml</td>
<td>9,500</td>
</tr>
</tbody>
</table>

**Children and Adolescents**

Nadroparin is not recommended in children and adolescents as there are insufficient safety and efficacy data to establish dosage in patients aged less than 18 years.

**Elderly**

No dosage adjustment is necessary in the elderly, unless renal function is impaired. It is recommended that renal function is assessed before initiating treatment (see Renal Impairment below, and Section 5.2).
- Renal Impairment

**Prophylaxis of thromboembolic disorders**

Dose reduction is not required in patients with mild renal impairment (creatinine clearance greater than or equal to 50 ml/min).

Moderate and severe renal impairment is associated with increased exposure to nadroparin. These patients are at increased risk of thromboembolism and haemorrhage.

If a dose reduction is considered appropriate by the prescribing physician, taking into account the individual risk factors for haemorrhage and thromboembolism in patients with moderate renal impairment (creatinine clearance greater than or equal to 30 ml/min and less than 50 ml/min) the dose should be reduced by 25 to 33% (see Section 4.4 and 5.2).

The dose should be reduced by 25 to 33% in patients with severe renal impairment (creatinine clearance less than 30 ml/min) (see Section 4.4 and 5.2).

**Treatment of thromboembolic disorders, unstable angina and non-Q wave myocardial infarction**

Dose reduction is not required in patients with mild renal impairment (creatinine clearance greater than or equal to 50 ml/min).

Moderate and severe renal impairment is associated with increased exposure to nadroparin. These patients are at increased risk of thromboembolism and haemorrhage.

If a dose reduction is considered appropriate by the prescribing physician, taking into account the individual risk factors for haemorrhage and thromboembolism in patients with moderate renal impairment (creatinine clearance greater than or equal to 30 ml/min and less than 50 ml/min) the dose should be reduced by 25 to 33% (see Section 4.4 and 5.2).

Nadroparin is contraindicated in patients with severe renal impairment (see Section 4.4 and 5.2).

- Hepatic impairment

There have been no studies conducted in patients with hepatic impairment.

**4.3 Contraindications**

Nadroparin is contraindicated in cases of:

- hypersensitivity to nadroparin or any of the excipients of nadroparin injections
- history of thrombocytopenia with nadroparin (see Section 4.4)
active bleeding or increased risk of haemorrhage, in relation to haemostasis disorders, except for disseminated intravascular coagulation not induced by heparin

- organic lesion likely to bleed (such as active peptic ulceration)

- haemorrhagic cerebrovascular accident

- acute infectious endocarditis

- severe renal impairment (creatinine clearance less than 30 ml/min) in patients receiving treatment for thromboembolic disorders, unstable angina, and non-Q wave myocardial infarction

- multi-dose vials contain benzyl alcohol and therefore should not be used in children under 3 years.

- Locoregional anesthesia in elective surgical procedures is contra-indicated when a LMWH is given for therapeutic use.

4.4 Special warnings and precautions for use

*Heparin-induced Thrombocytopenia*

Because of the possibility of heparin-induced thrombocytopenia, **platelet count should be monitored throughout the course of treatment with nadroparin.**

Rare cases of heparin-induced thrombocytopenia, occasionally severe, have been reported, which may be associated with arterial or venous thrombosis. Such diagnosis should be considered in the following situations:

- thrombocytopenia

- any significant reduction in platelet level (30 to 50% compared with the baseline value)

- worsening of the initial thrombosis while on therapy

- thrombosis occurring on treatment

- disseminated intra-vascular coagulation.

In this event, nadroparin treatment must be discontinued.

These effects are probably of an immuno-allergic nature and in the case of a first treatment are reported mainly between the 5th and the 21st day of therapy, but may occur much earlier if there is a history of heparin-induced thrombocytopenia.
If there is a history of thrombocytopenia occurring with heparin (either standard or low molecular weight heparin), treatment with nadroparin may be considered if necessary. In such cases, careful clinical monitoring and assessment of platelet count should be performed at least daily. If thrombocytopenia occurs, treatment should be discontinued immediately.

When thrombocytopenia occurs with heparin (either standard or low molecular weight heparin), substitution with a different anti-thrombotic class should be considered. If not available, then substitution with another low molecular weight heparin may be considered if the administration of heparin is necessary. In such cases, platelet count monitoring should be performed at least daily and the treatment should be discontinued as soon as possible, since cases of initial thrombocytopenia continuing after substitution have been described (see Section 4.3).

*In vitro* platelet aggregation tests are only of limited value in the diagnosis of heparin-induced thrombocytopenia.

**Caution should be exercised when nadroparin is administered in the following situations as they may be associated with an increased risk of bleeding:**

- hepatic failure
- severe arterial hypertension
- history of peptic ulceration or other organic lesion likely to bleed
- vascular disorder of the chorio-retina
- during the post-operative period following surgery of the brain, spinal cord or eye.

**Renal Impairment**

Nadroparin is known to be mainly excreted by the kidney, which results in increased nadroparin exposure in patients with renal impairment (see Section 5.2). Patients with impaired renal function are at increased risk of bleeding and should be treated with caution.

The decision on whether a dose reduction is appropriate for patients with creatinine clearance 30 to 50 ml/min should be based on the physician’s assessment of an individual patient’s risk of bleeding versus the risk of thromboembolism (see Section 4.2).

**Elderly**

It is recommended that renal function is assessed before initiating treatment (see Section 4.3).

**Hyperkalaemia**

Heparin can suppress adrenal secretion of aldosterone leading to hyperkalaemia, particularly in patients with raised plasma potassium, or at risk of increased plasma
potassium levels, such as patients with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis or those taking drugs that may cause hyperkalaemia (e.g. angiotensin-converting enzyme (ACE) inhibitors, Nonsteroidal anti-inflammatory drugs (NSAIDs)).

The risk of hyperkalaemia appears to increase with duration of therapy but is usually reversible.

Plasma potassium should be monitored in patients at risk.

**Spinal/epidural anaesthesia/spinal lumbar puncture and concomitant drugs**

In patients undergoing spinal or epidural anaesthesia, the use of LMWH may be rarely associated with hematomas, which can result in prolonged or permanent paralysis. The risk of spinal/epidural haematomas is increased by in-dwelling epidural catheters or by the concomitant use of other drugs which may affect haemostasis, such as NSAIDs, platelet inhibitors, or other anti-coagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal lumbar puncture.

Therefore, the concomitant prescription of a neuraxial blockade and of an anti-coagulant therapy should be decided after careful individual benefit / risk assessment in the following situations:

- in patients already treated with anti-coagulants, the benefits of a neuraxial blockade must be carefully balanced against the risks.
- in patients planned to undergo elective surgery with neuraxial blockade, the benefits of anti-coagulant therapy must be carefully balanced against the risks.

In the case of patients with spinal lumbar puncture, spinal anaesthesia or epidural anaesthesia, a minimum of 12 hours should elapse between the nadroparin injection at prophylactic doses or 24 hours at treatment doses and the insertion or the removal of the spinal/epidural catheter or needle, taking product characteristics and patient profile into account. For patients with renal impairment longer intervals may be considered. Subsequent dose should not take place before at least four hours have elapsed. Re-administration of nadroparin should be delayed until the surgical procedure is completed.

Patients should be frequently monitored for signs and symptoms of neurological impairment, such as back pain, sensory and motor deficits (numbness and weakness in lower limbs), bowel and/or bladder dysfunction. If neurological compromise is noted, urgent treatment is necessary. Nurses should be trained to detect such signs and symptoms. Patients should be instructed to inform their physician immediately if they experience any of these.

If signs or symptoms of spinal haematoma are suspected, urgent diagnosis and treatment including spinal cord decompression should be initiated.

If significant or overt bleeding has occurred during catheter placement, a careful benefit/risk assessment should take place prior to commencing/resuming heparin therapy.
Salicylates, non-steroidal anti-inflammatory and anti-platelet drugs

In the prophylaxis or treatment of venous thromboembolic disorders and in the prevention of clotting during haemodialysis, the concomitant use of aspirin, other salicylates, NSAIDs, and anti-platelet agents is not recommended, as they may increase the risk of bleeding. Where such combinations cannot be avoided, careful clinical and biological monitoring should be undertaken.

In clinical studies for the treatment of unstable angina and non-Q wave myocardial infarction, nadroparin was administered in combination with up to 325 mg aspirin per day (see Section 4.2 and 4.5).

Cutaneous Necrosis

Cutaneous necrosis has been reported very rarely. It is preceded by purpura or infiltrated or painful erythematous blotches, with or without general signs. In such cases, treatment should be immediately discontinued.

Latex Allergy

The needle shield of the pre-filled syringe may contain dry natural latex rubber that has the potential to cause allergic reactions in latex sensitive individuals.

4.5 Interactions with other medicinal products and other forms of interaction

Nadroparin should be administered with caution in patients receiving oral anti-coagulant agents, systemic (gluco-) corticosteroids and dextrans. When oral anti-coagulant therapy is initiated in patients receiving nadroparin, treatment with nadroparin should be continued until the International Normalisation Ratio (INR) is stabilised at the target value.

The concomitant use of acetylsalicylic acid (or other salicylates), non-steroidal anti-inflammatory drugs, and antiplatelet agents is not recommended as they may increase the risk of bleeding (see section 4.4).

In clinical studies for the treatment of unstable angina and non-Q wave myocardial infarction, nadroparin was administered in combination with up to 325 mg aspirin per day (see Section 4.2 and 4.4).

4.6 Fertility, pregnancy and lactation

There are no clinical studies on the effect of nadroparin on fertility.

Studies in animals have not shown any teratogenic or foetotoxic effects. However, there is only limited clinical data concerning transplacental passage of nadroparin in pregnant
women. Therefore, the use of nadroparin during pregnancy is not advised, unless the therapeutic benefits outweigh the possible risks.

There is limited information on the excretion of nadroparin in breast milk. Therefore, the use of nadroparin during breast feeding is not advised.

4.7 Ability to perform tasks that require judgement, motor or cognitive skills

There are no data on the effects of nadroparin on driving performance or the ability to operate machinery.

4.8 Undesirable effects

Adverse reactions are listed below by system organ class and frequency.

The following convention has been used for the classification of adverse reactions in terms of frequency: 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.

Blood and lymphatic system disorders

Very common: Haemorrhagic manifestations at various sites (including cases of spinal haematoma), more frequent in patients with other risk factors (see Section 4.3 and 4.4).

Rare: Thrombocytopenia (including heparin-induced thrombocytopenia) (see Section 4.4), thrombocytosis.

Very rare: Eosinophilia, reversible following treatment discontinuation.

Immune system disorders

Very rare: Hypersensitivity reactions (including angioedema and cutaneous reactions), anaphylactoid reaction.

Metabolism and nutrition disorders

Very rare: Reversible hyperkalaemia related to heparin-induced aldosterone suppression, particularly in patients at risk (see Section 4.4).

Hepato-biliary disorders
Common: Raised transaminases, usually transient.

Reproductive system and breast disorders
Very rare: Priapism.

Skin and subcutaneous tissue disorders
Rare: Rash, urticaria, erythema, pruritus
Very rare: Cutaneous necrosis, usually occurring at the injection site (see Section 4.4).

General disorders and administration site conditions
Very common: Small haematoma at the injection site.

In some cases, the emergence of firm nodules, which do not indicate an encystment of the heparin may be noted. These nodules usually disappear after a few days.

Common: Injection site reaction.
Rare: Calcinosis at the injection site.

Calcinosis is more frequent in patients with abnormal calcium phosphate product, such as in some cases of chronic renal failure.

4.9 Overdose

Haemorrhage is the major clinical sign of subcutaneous or intravenous overdosage. The platelet count and other coagulation parameters should be measured. Minor bleeding rarely requires specific therapy, and reducing or delaying subsequent doses of nadroparin is usually sufficient.

The use of protamine sulphate should be considered only in serious cases. It largely neutralises the anti-coagulant effect of nadroparin but some anti-Xa activity will remain.

0.6 ml of protamine sulphate neutralises about 950 IU anti-Xa nadroparin. The amount of protamine to be injected, should take into account time elapsed from the injection of heparin, and a dose reduction of protamine may be appropriate.
5.2 Pharmacokinetic properties

Special populations

Renal Impairment

In a clinical study investigating the pharmacokinetics of nadroparin administered intravenously in patients with varying degrees of renal impairment, a correlation was found between nadroparin clearance and the creatinine clearance. In patients with moderate renal impairment (creatinine clearance 36-43 ml/min) both mean AUC and half-life were increased by 52 and 39% respectively compared with healthy volunteers. In these patients, mean plasma clearance of nadroparin was decreased to 63% of normal. Wide inter-individual variability was observed in the study. In subjects with severe renal impairment (creatinine clearance 10-20 ml/min) both mean AUC and half-life were increased by 95 and 112% respectively compared with healthy volunteers. Plasma clearance in patients with severe renal impairment was decreased to 50% of that observed in patients with normal renal function. In subjects with severe renal impairment (creatinine clearance 3-6 ml/min) on haemodialysis, both mean AUC and half-life were increased by 62 and 65% respectively compared with healthy volunteers. Plasma clearance in haemodialysis patients with severe renal impairment was decreased to 67% of that observed in patients with normal renal function (see Section 4.2 and 4.4).